Simplified approach

Mansoura Clinical Pharmacology

For Medical students

Edited by

Staff members of
Clinical Pharmacology Department
Faculty of Medicine
Mansoura University

Volume 1

رقم الإيداع بدار الكتب: 1456 لسنة 2000
بتاريخ 2000/9/6

Preface

Clinical training for undergraduate students often focuses on diagnostic rather than therapeutic skills. Sometimes students are only expected to copy the prescribing behavior of their clinical teachers, or existing standard treatment guidelines, without explanation as to why certain treatment is chosen. Books may not be much help either. Pharmacology reference works and formularies are drug-centered, and although clinical textbooks and treatment guidelines are disease-centered and provide treatment recommendations, they rarely discuss why these therapies are chosen. Different sources may give contradictory advice.

This book in primarily intended for under graduate medical students who are about to enter the clinical phase of their studies. It will provide step by step guidance to the process of rational prescribing together with many illustrative examples. It teaches also skills that are necessary throughout a clinical career. Postgraduate students and practicing doctors may also find it a source of straightforward information.

I wish to acknowledge the ongoing efforts of my contributing authors, and we are deeply grateful to all those who have with such good grace given us their time and energy to supply valuable facts and opinions, they principally include:

- **Prof. Hussein El-Beltagi** who took over the preparation of all books since the 1st edition in 1995 including the revision process, printing control, distribution and selling control.
- **Assist. Prof. Mohamed-Hesham Daba** who took over the revision process and amendments of the last two editions.
- **Assist. Prof. Abdel-Motaal Fouda** who prepared the last two editions in a readable up-to-date text to provide essential information necessary throughout the clinical career.
- **Dr. Sameh Abdel-Ghany** who assisted in the revision process.

Much of any merit this book may have is due to the generosity of those named above.

Gamal M. Dahab (MD, PhD)

Professor Emeritus in Clinical Pharmacology
Mansoura Faculty of Medicine

Mission and Vision

Our mission

The Clinical Pharmacology Department is seeking excellence and leadership in four major core activities: education, research, community service, and faculty and staff development. We are connecting basic medical sciences with clinical care through innovative and disciplined teaching of clinical pharmacology in an integrative manner

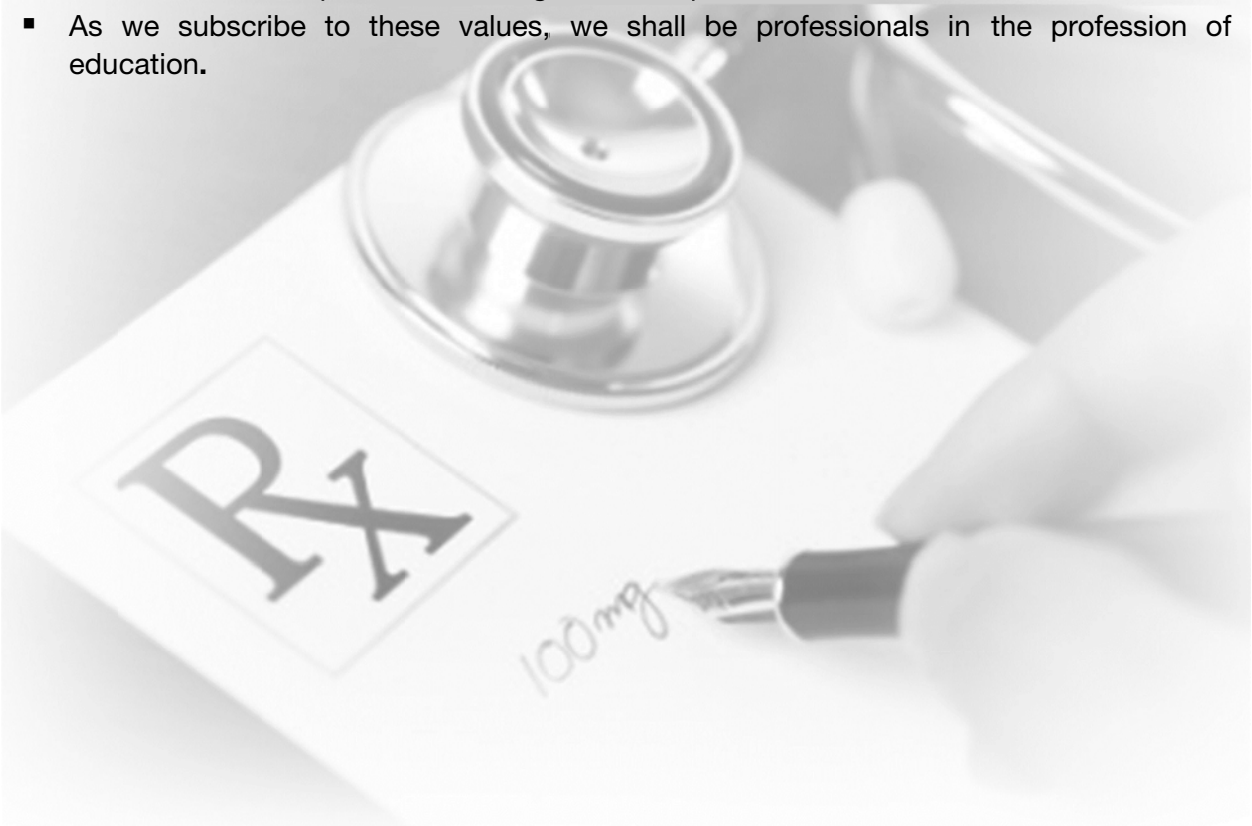
Our vision

The department of Clinical Pharmacology is aiming to be a premier academic model in the field of pharmacology and therapeutics in Egypt and Middle East through promoting use of the best therapeutics and developing newer experimental and clinical research projects.

Values

The guiding principles and beliefs for the department

- Excellence, creativity, innovation, fairness, honesty, transparency, collaboration, teamwork and lifelong learning
- Recognition that our student comes first
- All members of our department must see themselves as integral to the success of our mission and our department as integral to their personal success.
- As we subscribe to these values, we shall be professionals in the profession of education.



Contributers

Effat A. Haroun MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Elhamy M. El-Kholy MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Gamal M. Dahab MD, PhD, MSc (Int.Med)
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Farida M. El-Banna MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Aly M. Gaballah MD, PhD, MSc (int.Med**)**
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Layla T. Hanna MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Mohamed Kheriza MD, PhD, MSc (Int.Med)
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Abdel-Rahman A. Yassin MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Mohmmad A. Attia MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Mohamed Abdel-Ghani MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Hussien M. El-Beltagi MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Karawan M. Abdel-Rahman MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Somaya A. Mokbel MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Amany A. Shalaby MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Amal Abdel-Hamid MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Essam A. Ghyati MD, PhD
Assist. Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Mohamed-Hesham Y. Daba MD, PhD
Assist. Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Abdel-Motaal M. Fouda MD, PhD
Assist. Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Vivian Boshra MD, PhD
Assist. Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Hala A. Al-Ashri MD, PhD
Assist. Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Nageh Rizk MD, PhD
Lecturer in pharmacology
Mansoura Faculty of Medicine

Elsayed A. Hassan MD, PhD
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

Mohamed Abdel-Monem MD, PhD
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

Mahmoud A. Naga MD, PhD
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

Ahmad Hassan MD, PhD
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

Ahlam El-masry MD, PhD
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

Rehab Hamdy MD, PhD
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

Mohamed Abou El-khair MD, PhD
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

Sameh A. Abdel-Ghani MSc.
Assist. Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

Table of Contents

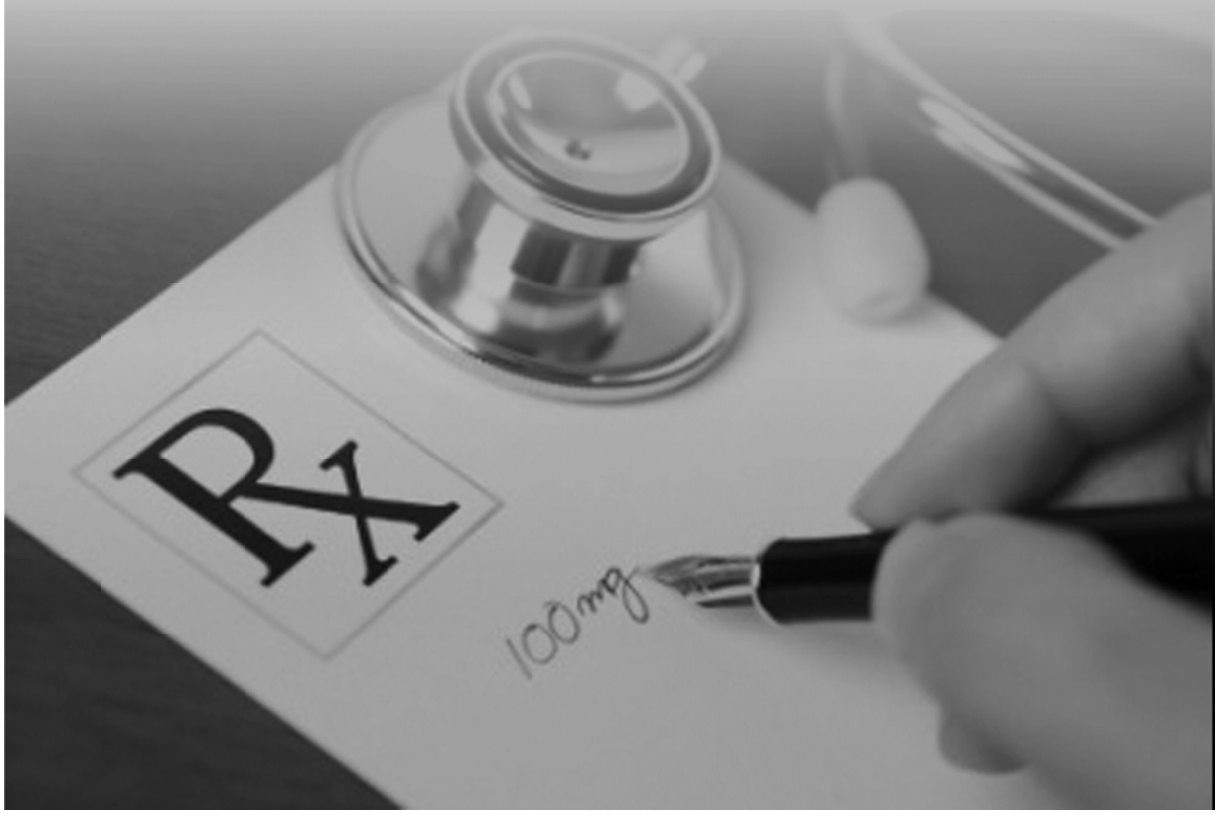
CHAPTER 1: GENERAL PRINCIPLES

CHAPTER 2: AUTONOMIC PHARMACOLOGY

CHAPTER 3: DIURETIC AGENTS AND VOLUME BALANCE

Chapter 1

General Principles



Chapter 1

General Principles

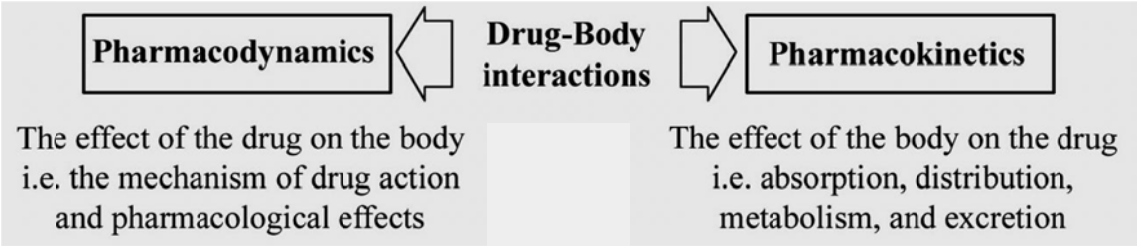
Introductory definitions

Medical pharmacology is a basic science. It the science dealing with small molecules used to prevent, diagnose, or treat diseases.

Clinical pharmacology is the science concerned with the rational, safe and effective use of drugs in humans. It combines elements of basic pharmacology with clinical medicine; in other words, it involves the complex interaction between the **drug** and the **patient**.

A drug is any chemical molecule that can interact with body systems at the molecular level and produce effect.

The drug-body interactions



Part 1: Pharmacodynamics (Mechanism of drug action)

Pharmacodynamics is summarized as what a drug does to the body; a drug may produce its effects through:

- **Interaction with body control systems** (regulatory proteins):
  - (a) Receptors
  - (b) Ion channels
  - (c) Enzymes
  - (d) Carrier molecules
- Direct chemical or physical mechanisms.
- Interaction with certain metabolic pathways.

A. RECEPTORS

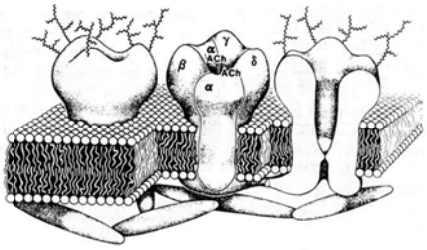
Receptors: they are protein macromolecules. When they combine with a drug, they may be activated or blocked.

Ligand: is any molecule that can combine with the receptors. A ligand that activates the receptor is called **agonist**. A ligand that blocks the receptor is called **antagonist.**

Affinity: it is the empathy of the receptor to the ligand. It determines *the number* of receptors occupied by the drug.

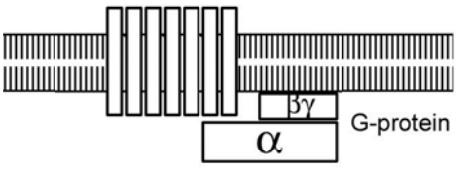
Types of receptors

- **Ion channel-linked receptors (direct ligand-gated ion channels):**

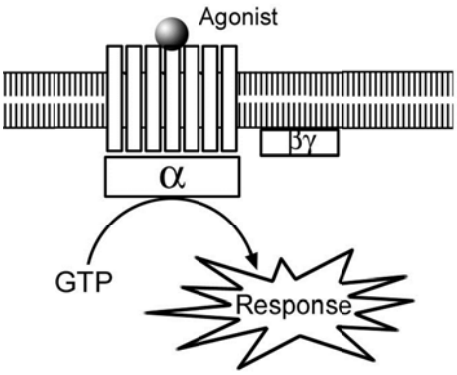


- The receptor is an ion channel consists of **5** transmembrane subunits (α_1, α_2, β, γ, δ).
- Binding of the agonist to the extracellular part of the receptor causes opening of the channel for a specific ion.
- The response of these receptors is very fast and their duration is very short.
- Examples:
  - *Nicotinic Ach receptors in the motor end-plate:* the ion channel opens for Na^+ ions in response to stimulation by Ach.
  - *The Gama aminobuteric acid (GABA) receptors in the brain:* the ion channel opens for Cl^- ions in response to stimulation by GABA.

- **G-protein-linked receptors:**



- The receptor consists of **7** membrane subunits.
- Binding of the agonist to the extracellular part of the receptor causes activation of intracellular G-protein.
- When the G-protein is activated, its α subunit binds to GTP to be phosphorylated and bring stimulatory or inhibitory response.
- Their response is slower than ion channel receptors but their duration is longer.

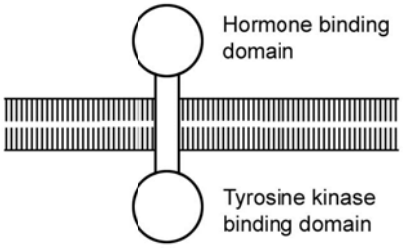


- **Stimulatory G-protein (Gs)** leads to increase *adenyl cyclase enzyme* → ↑ cAMP → activation of specific proteins (protein kinases). Examples of Gs-coupled receptors are the β1 and β2-adrenergic receptors.

- **Inhibitory G-protein (Gi)** leads to decrease *adenyl cyclase enzyme* → ↓ cAMP → inhibition of protein kinases. Examples of Gi-coupled receptors are the α2-adrenergic receptors and M2 muscarinic receptors.

- **Gq-coupled receptors:** they increase inositol triphosphate (IP3) and diacylglycerol (DAG). IP3 increases free intracellular Ca^{2+}. Examples of Gq-coupled receptors are the α1-adrenergic receptors, M1 and M3 muscarinic receptors.

■ Tyrosine kinase (TK)-linked receptors:

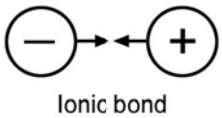


- The receptor consists of 2 large domains: an extracellular hormone-binding domain and an intracellular TK-binding domain connected by a transmembrane segment.
- Binding of the agonist to the hormone-binding domain causes activation of the intracellular domain to activate TK enzyme → activation of several proteins known as *"signaling proteins"*.
- Examples: *insulin receptors.*

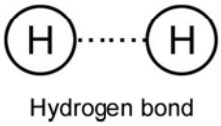
■ Intracellular receptors:

- They are located inside the cell either in the cytoplasm or **directly on the DNA**.
- They regulate transcription of genes in the nucleus or the mitochondria.
- Their agonist must enter inside the cell to reach them.
- They have two important features:
  - Their response is **slow** (time is required for synthesis of new proteins).
  - Their effects persist for **long time** after the agonist is removed.
- Examples: receptors for ***corticosteroids****, sex hormones, thyroxin, etc.*

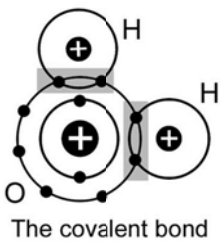
Types of drug-receptor bonds



■ **The ionic bond:**
It is an electrical attraction between two opposing charges. It is strong but reversible.



■ **The hydrogen bond:**
It is an attraction between two hydrogen bonds. It is weak and reversible.



■ **The covalent bond:**
Very strong and irreversible.
If occurred between drug and receptor, the receptor becomes permanently blocked.

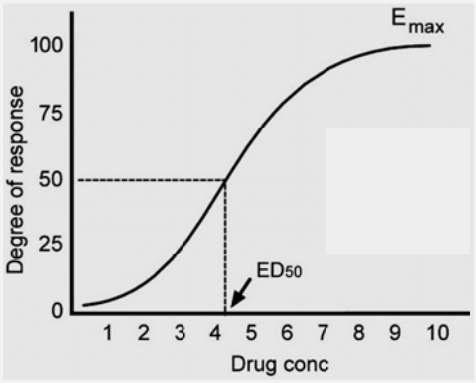
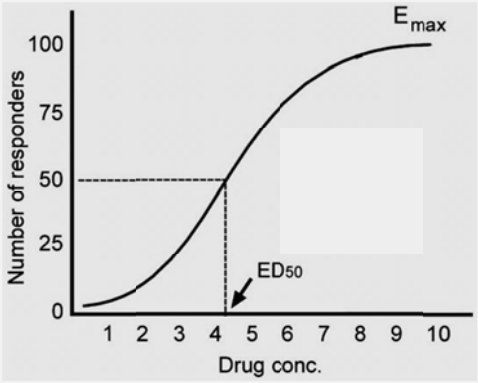
BIOLOGICAL RESPONSE TO DRUG-RECEPTOR BINDING (Dose-response relationship studies)

When a drug combines with a receptor, this may lead to one of the following:

- **Agonist effect:** means that the drug combines with the receptor and gives response.
- **Antagonist effect:** means that the drug combines with the receptor but gives **NO response,** and prevents the receptor from binding to another drug.

Agonist effect

According to the **"dose-response relationship curves"**, there are **2 types** of responses to drugs:

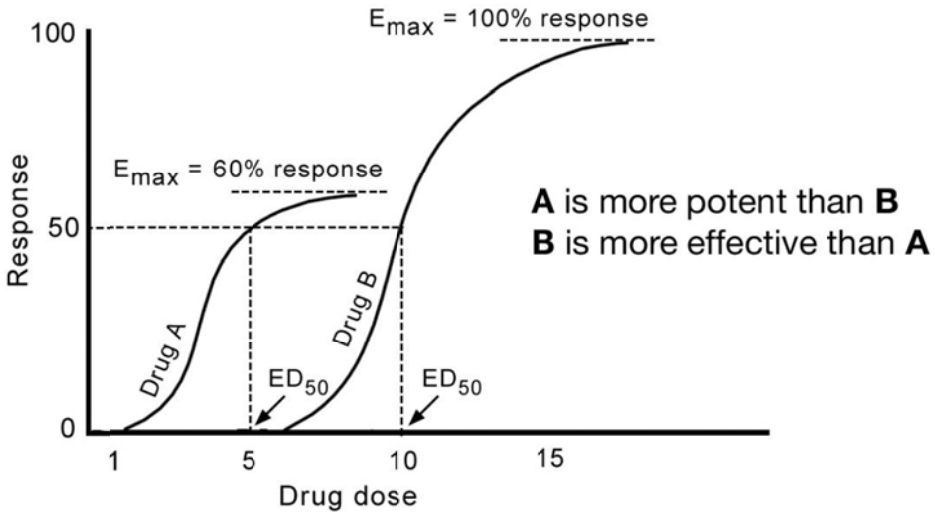
Graded response	Quantal response
– The response is increased **proportionally** to the dose of the agonist e.g. the response of the heart to adrenaline. – It is the response to **most** drugs. – The response could be tested in **one or more** animals.	– The response does not increase proportionally to the agonist but it is **all-or-none** response e.g. prevention of convulsions by antiepileptic drugs – It is response to **few** drugs. – The response could not be tested in one animal and must be tested in a **group** of animals.
	

Effectiveness and safety

- **Efficacy**

– It is the ability of a drug to produce response (effect) after binding to the receptor.
– It is measured by the **Emax** (the maximal response that a drug can elicit at full concentration):

- **Full agonist** is the drug that gives maximal response at full concentration (at full occupancy).
- **Partial agonist** is that agonist gives submaximal response even at full concentration i.e. never gives Emax

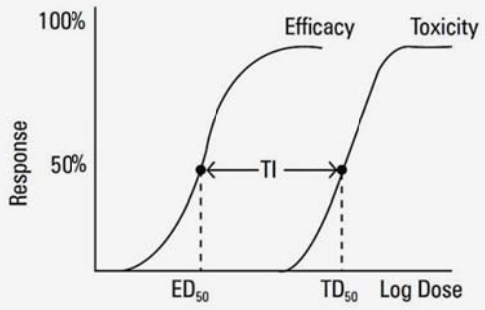


■ Potency

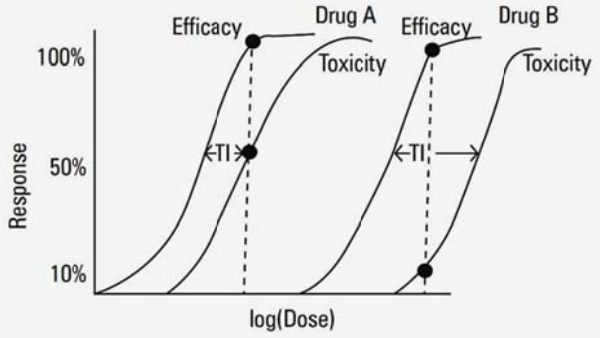
- **ED50 (Effective Dose)** is the dose of the drug that gives 50% of the Emax, or it is the dose that gives the desired effect in 50% of a test population of subjects.
- A drug that gives ED50 by smaller doses is described as **"potent"** drug.
- Potency of drugs is generally **less clinically important** than efficacy because you can increase the dose of a less potent drug to obtain the effect of a more potent one (provided that it is not toxic).

■ Safety

- **TD50 (Toxic Dose)** is the dose of the drug needed to cause a harmful effect in 50% of a test population of subjects.
- **LD50 (Lethal Dose)** is the dose needed to cause death in 50% of a test group of animals. It is experimental term that can be determined in animals.



The therapeutic index (TD_{50}/ED_{50}) is a measure of the margin of safety of a given drug

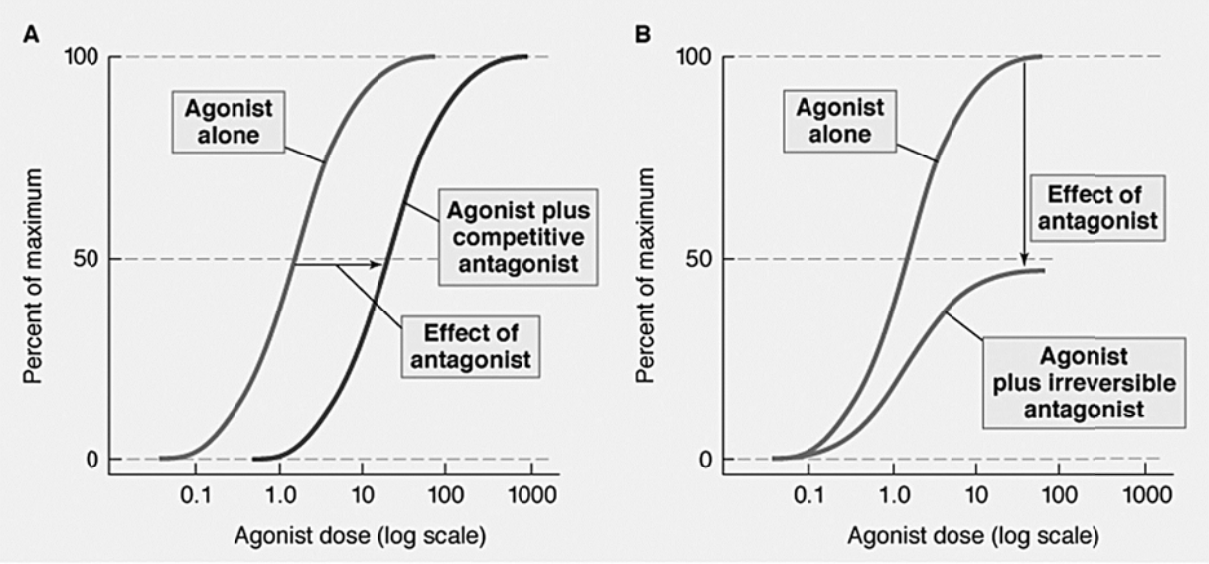


Drug A has a much narrower therapeutic index than Drug B. The dose of Drug A required to achieve a 100% therapeutic response will be toxic in 50% of patients. For Drug B, this is only 10%

- **Therapeutic index (TI) LD50/ED50:**
- It is the ratio between the LD50 and the ED50. It is a measure of safety; if there is a large difference between the dose of a drug that produces the desired effect and the dose that produces a toxic effect, it is said that the drug has a large TI.
- Drugs with high TI are more safe for clinical use, and *vice versa* (e.g. warfarin has a narrow TI and requires careful therapeutic monitoring).

Antagonist effect

- **Antagonist** is the ligand that combines with the receptor and **does not activate it**. It has no intrinsic activity, but may cause a pharmacological response by inhibiting the actions of endogenous substances or other drugs.
- If the antagonist binds to the same site of the agonist on the receptor, it is called **competitive antagonist**. If the antagonist binds to another site on the receptor, and prevented the action of the agonist, it is called **non-competitive antagonist**.
- **Competitive antagonism** may be **reversible** or **irreversible:**
  - **Reversible antagonist** makes **weak** bond with the receptor so as you can overcome the block by giving high doses of the agonist, and even you can get the maximal response in presence of the antagonist (i.e. surmountable effect). The duration of block is short because the antagonist can be easily washed off the receptors.
  - **Irreversible antagonist** makes **covalent** bond with the receptor so as you cannot overcome the block or get the maximal response by increasing the dose of the agonist (i.e. non-surmountable effect). The occupied receptors are permanently blocked, so the duration of block is long, and the body has to synthesize new receptors to regain the original state.

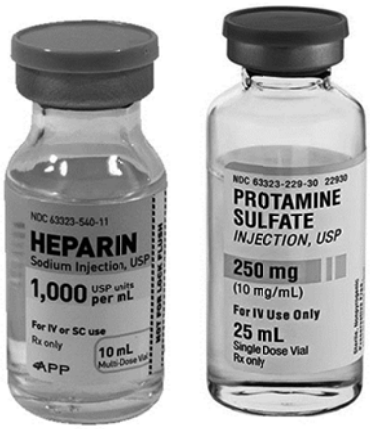


Reversible antagonism | Irreversible antagonism

Other types of drug antagonism

- **Chemical antagonism:** e.g. one **acidic** drug when added to a **basic** drug can cause precipitation of each other's

  Example: the addition of gentamycin (basic drug) to carpenicillin (acidic drug) in the same syringe causes chemical complex.



- **Physical antagonism:** antagonism between two drugs carrying opposite charges.

  Example: **protamine** is used for treatment of **heparin** overdose because protamine carries **+ve** charge while heparin carries **–ve** charge. One mg of protamine can neutralize 100 units of heparin.

- **Physiological antagonism:** antagonism between two drugs producing opposite effects by activation of different receptors.

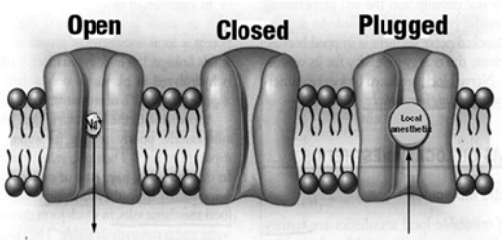
  Example: **adrenaline** is the physiological antagonist of **histamine** because while histamine causes hypotension and bronchoconstriction through activation of histamine H_1 receptors, adrenaline causes hypertension and bronchodilatation through activation of adrenergic α & β receptors respectively.

- **Pharmacokinetic antagonism:** (see drug interactions).

– One drug may **prevent absorption** of another drug e.g. antacids ↓ absorption of iron & aspirin.
– One drug may **increase metabolism** of another drug e.g. rifampicin induces hepatic enzymes and ↑ metabolism of oral contraceptive pills.
– One drug may ↑ **excretion** of another drug e.g. NaHCO3 cause alkalinization of urine and ↑ excretion of acidic drugs like **aspirin**.

B. ION CHANNELS

How drugs could modulate ion channels?



- Physical block: e.g. blocking of Na^+ channels by local anesthetics.
- The ion channel may be part of the receptor e.g. ion channel-linked receptors.
- The ion channel may be modulated by G-protein linked receptors.
- Ion channels may be modulated by intracellular ATP e.g. ATPase sensitive K^+ channels in the pancreatic β cells, rise of intracellular ATP causes closure of pancreatic K^+ channels.

C. ENZYMES

How drugs could affect enzymes?

- The drug may act as a competitive inhibitor of the enzyme e.g. neostigmine on cholinesterase enzyme.
- The drug may act as irreversible inhibitor of the enzyme e.g. organophosphates on cholinesterase enzyme.
- The drug may act as a false substrate for the enzyme e.g. α-methyldopa is a false substrate for *dopa decarboxylase*.
- The drug may induce or inhibit hepatic microsomal enzymes activity (see later).

D. CARRIER MOLECULES

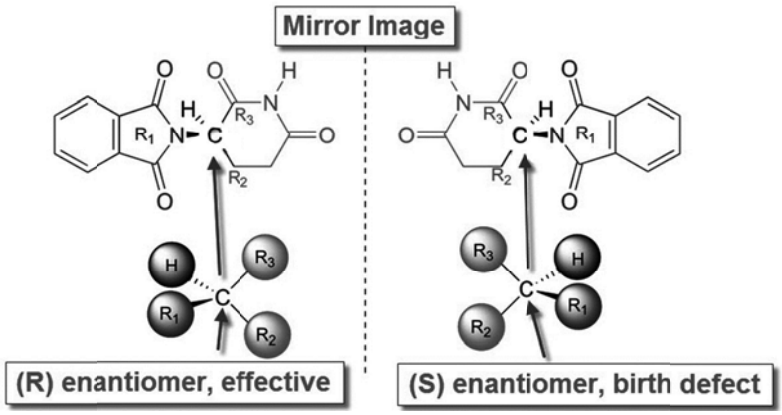
- These are small protein molecules that carry organic molecules across the cell membrane when they are too large or too polar.
- Drugs could affect carrier molecules by blocking their recognition site.

Part 2: Factors affecting dose-response relationship

A. FACTORS RELATED TO THE DRUG

1. Drug shape (stereoisomerism):

- Most drugs have multiple stereoisomers (enantiomers) (e.g. L-thyroxin and D-thyroxin). The receptor site is usually sensitive for one stereoisomer and not suitable for another, like the hand and the glove. This means that one isomer may be hundred times more potent than the other. In other instances one isomer is beneficial while the other is toxic.



- This phenomenon may explain how a single drug could act as agonist and antagonist (i.e. partial agonist) because many drugs are present in **"racemic mixtures"** rather than as pure isomers; or how one isomer is effective and the other isomer is toxic.

2. Molecular weight (MW):

- Most drugs have MW between 100-1000 Da. Drug particles larger than MW 1000 Da cannot be absorbed or distributed. They should be given parenterally.
- Drug particles larger than MW 1000 Da cannot cross placental barrier.

3. Time of drug administration (Chronopharmacology):

- Many body functions (e.g. liver metabolism, RBF, blood pressure, HR, gastric emptying time, etc.) have daily circadian rhythm. Some enzymes responsible for metabolism of drugs are active in the morning or evening.
- Also many diseases (e.g. asthma attacks, myocardial infarction, etc.) are circadian phase dependent.
- *Chronopharmacology* is the science dealing with tailoring drug medication according to the circadian rhythm of the body to get better response and/or to avoid possible side effects.
- Examples:
- Episodes of acute bronchial asthma are common at night due to circadian variation of cortisol and other inflammatory mediators, so it is better to give the anti-asthmatic medications in the evening.
- Blood pressure is at its peak during afternoon, so it is better to give the antihypertensive medications at morning.

4. Drug cumulation:

Cumulation occurs when the rate of drug administration exceeds the rate of its elimination (especially in patients with liver or renal disease). Some drugs are cumulative due to their slow rate of elimination e.g. digoxin.

5. Drug combination:

Drug combination is very common in clinical practice. When two or more drugs are combined together, one of the following may occur:

a) Summation or addition:

- Summation means that the combined effect of two drugs is *equal* to the sum of their individual effects (i.e. 1+1=2). It usually occurs between drugs having the same mechanism, for example, the use of two simple analgesics together.

b) Synergism and potentiation:

- Synergism means that the combined effect of two drugs is *greater* than the sum of their individual effects (i.e. 1+1=3). The two drugs usually have different mechanisms of action, for example, the use of *penicillin* with *aminoglycosides* to exert bactericidal effect.

- Potentiation is similar to synergism but, in potentiation, the effect of one drug itself is greatly increased by intake of another drug without notable effect (i.e. 1+0=2), for example, *Phenobarbitone* has no analgesic action but it can potentiate the analgesic action of *aspirin*.

c) Antagonism:

One drug abolishes the effect of the other i.e. 1+1=0 (see before).

B. FACTORS RELATED TO THE PATIENT

1. Age, sex, and weight.

2. Pathological status:

Liver or kidney diseases significantly alter the response to drugs due to altered metabolism. Also the failing heart is more sensitive to digitalis than the normal heart.

3. Pharmacogenetic factors (idiosyncrasy):

It is abnormal response to drugs due to genetic abnormality in drug metabolism. These are some examples:

Examples of heritable conditions causing EXAGGERATED drug response:

a) Pseudocholinestrase deficiency:

Succinylcholine is a neuromuscular blocker metabolized by *pseudo-cholinestrase* enzyme. Some individuals with deficient PsChE, when they take succinylcholine, severe muscle paralysis occurs due to lack of succinylcholine metabolism, and may lead to death from respiratory paralysis (*succinylcholine apnea)*.

b) Glucose-6-phosphate dehydrogenase (G6PD) deficiency:

- G6PD is the most common human enzyme defect. G6PD enzyme catalyzes the reduction of NADP+ into NADPH which maintains glutathione in the RBCs in its reduced form. Reduced glutathione keeps Hb in the reduced (ferrous) form and prevent formation of methemoglobin and cell membrane injury (hemolysis) by oxidizing drugs.
- Individuals with deficiency of G6PD may suffer acute hemolysis if they are exposed to oxidizing drugs e.g. nitrates, antimalarial drugs, and others.

c) Thiopurine methyltransferase (TPMT) deficiency:

- Thiopurine methyltransferase (TPMT) is an enzyme that methylates thiopurine anticancer drugs (e.g. 6-mercaptopurine and 6-thioguanine) into less toxic compounds.

- Genetic deficiency in TPMT leads to increased conversion of parent thiopurine drugs into more toxic compounds, leading to severe myelotoxicity and bone marrow suppression which may be fatal.
- TPMT deficiency prevalence is 1:300. Screening for TPMT deficiency is necessary in patients treated by thiopurine anticancer drugs.

d) Acetylator phenotypes:

Many drugs are metabolized in the liver by acetylation (e.g. **isoniazid)**. Acetylation reaction is under genetic control and people can be classified according to their rate of acetylation into **rapid** and **slow** acetylators:

- In rapid acetylators: excessive isoniazid toxic metabolites accumulate in the liver causing *hepatocellular necrosis*.
- In slow acetylators: isoniazid accumulates in peripheral tissues causing *peripheral neuropathy* due to interference with pyridoxine metabolism, (so pyridoxine "vit B6" is added to isoniazid therapy to prevent neurotoxicity).
- Some drugs that are metabolized by acetylation can cause systemic lupus erythematosis-like syndrome (SLE) in slow acetylators (see box).

Drug-induced SLE like syndrome

Hydralazine (+++)
Procainamide (++)
Isoniazid (+)
Quinidine (+)
Phenytoin (+)

Examples of heritable conditions causing DECREASED drug response:

a) Resistance to coumarin (warfarin) anticoagulants:

- In normal individuals, warfarin anticoagulant acts by inhibiting the enzyme *vit K epoxide reductase* responsible for reduction of the oxidized vit K (inactive) to its reduced form (active).
- Some individuals have another variant of this enzyme making them needing 20 times the usual dose of coumarin to get the response.

b) Resistance to vit D (vit D-resistant rickets):

Children with *vit D-resistant rickets* need huge doses of vit D to be treated.

c) Resistance to mydriatics:

Dark eyes are genetically less responsive to the effect of **mydriatics**.

4. Hyporeactivity to drugs:
(Tolerance; tachyphylaxis; drug resistance)

Tolerance means progressive decrease in drug response with successive administration. The same response could be obtained by higher doses. It occurs over long period. **Tachyphylaxis** is an acute type of tolerance that occurs very rapidly.

Mechanism of tolerance:

- ***Pharmacodynamic tolerance:*** may occur due to:
  - Receptor desensitization: prolonged exposure to the drug leads to slow conformational changes in the receptors by which the receptor *shape* becomes no longer fitted well with the drug.
  - Receptor down-regulation: prolonged exposure to the drug leads to decrease *number* of the functional receptors.
  - Exhaustion of mediators: e.g. depletion of catecholamines by amphetamine.
- ***Pharmacokinetic tolerance:***
  - Due to ↑ metabolic degradation of a drug by induction of hepatic enzymes e.g. with chronic administration of ethanol.
- ***Behavioral tolerance:***
  - It occurs by a drug independent learning of the brain how to actively overcome a certain drug-induced effect through practice e.g. with psychoactive drugs.

5. Hyperreactivity to drugs:
(Rebound and withdrawal effect)

Rebound effect: is recurring of symptoms in exaggerated form when a drug is suddenly stopped after a long period of administration.

Mechanism: prolonged administration of the **antagonist** leads to up-regulation (increase number) of receptors. When the antagonist is suddenly stopped, severe reaction occurs e.g. severe tachycardia and arrhythmia occurs after sudden stopping of beta-blockers.

Withdrawal effect (syndrome) is recurring of symptoms in exaggerated form plus addition of new symptoms when a drug is suddenly stopped e.g. withdrawal effects that occur after sudden stopping of opioids in opioid addicts.

N.B. Some examples of drugs should not be stopped suddenly:

Drug		Sudden withdrawal can lead to:
Beta-blockers	:	Severe tachycardia, arrhythmia, and even myocardial infarction.
Clonidine	:	Severe hypertension (hypertensive crisis).
Cimetidine	:	Severe hyperacidity and even peptic ulceration.
Corticosteroids	:	Acute Addisonian crisis.
Morphine	:	Withdrawal symptoms (see CNS).
Warfarin	:	Thrombotic catastrophes

Part 3: Clinical pharmacokinetics

Definition: it is the journey of the drug inside the body. It includes 4 processes:

Absorption **D**istribution **M**etabolism **E**xcretion

ABSORPTION OF DRUGS

Definition: it is the passage of drug from the site of administration **t**o the plasma.
The main routes of administration: oral, sublingual, rectal, inhalation, injection, etc.

Factors affecting drug absorption:

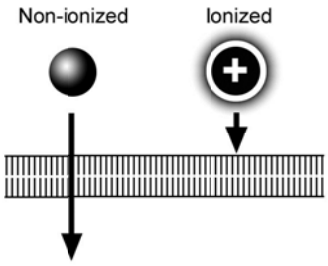
A. Factors related to the drug

- Molecular size: small molecules are absorbed than large molecules.
- Dose: absorption increases with increasing the dose (up to limit).
- Drug formulations: e.g. sustained-release tablets are slow in absorption.
- Local effects of the drug: e.g. drugs producing VC ↓ their own absorption.
- Drug combination: e.g. vit C ↑ absorption of iron.
- Lipid solubility, drug ionization, and the pKa of the drug.

B. Factors related to the absorbing surface:

- Route of administration: i.v. route is the fastest while rectal is the slowest.
- Integrity of the absorbing surface: may ↑ or ↓ absorption.
- Local blood flow: ischemia ↓ absorption.
- Specific factors: e.g. apoferritin system for iron, etc.

The pKa and drug ionization



Principles

- Ionized (polar; charged) drugs are **poorly** absorbed, while unionized (non-polar, non-charged) drugs are **more** absorbed.
- Most drugs are weak acids or **b**ases. They become ionized or non-ionized according to the **pH** around them.
- Acidic drugs (e.g. aspirin) are more ionized in alkaline pH and *vice versa.*
- Basic drugs (e.g. amphetamine) are more ionized in acidic pH and *vice versa*.
- **pKa of a drug: is the pH at which 50% of the drug is ionized and 50% is non-ionized**. *(Where p = inverse log; Ka = association/dissociation constant).*

Example of pH variation and drug kinetics with aspirin:

Aspirin is an acidic drug; its **pKa = 3.5**
The pH of the stomach is **1.5** The pH of the intestine is **8.5**

►When aspirin is put in the stomach:

- Aspirin is acidic drug and becomes more absorbable in acidic pH.
- Log (Unionized /Ionized)* = pKa – pH = 3.5 – 1.5 = 2 (log 2 =10^2).
- This means that the ratio of unionized: ionized = 100/1 (or accurately 0.99 parts are absorbed and 0.01 parts are non-absorbed).

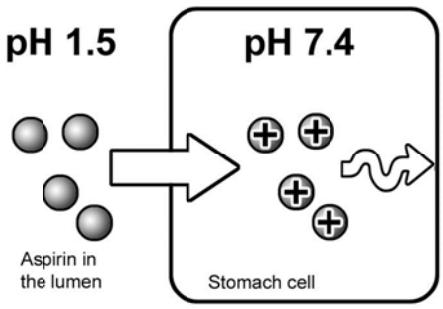
►When aspirin is put in the intestine:

- Aspirin is acidic drug and becomes less absorbable in alkaline pH.
- Log (Unionized/Ionized)* = pKa – pH = 3.5 – 8.5 = – 5 (log -5 =10^{-5}).
- This means that the ratio of unionized/ionized = 1/100000 (or accurately 0.00001 parts are absorbed and 0.99999 parts are non-absorbed).

***N.B.** The above rule applies only to acidic drugs like aspirin. For basic drugs, the ratio would be reversed.

►Ion trapping of aspirin:

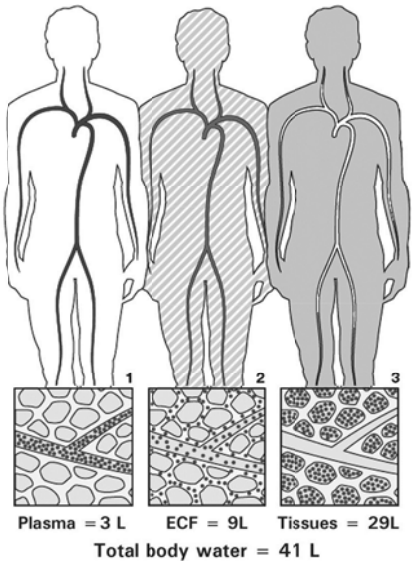
In the stomach, aspirin is more absorbable into stomach cells but once entered the cells, the pH changes from 1.5 outside to 7.4 inside the cell. So aspirin becomes ionized inside the cells and can't diffuse outside them again → gastric ulcer.



Clinical significance of pKa

- Knowing the site of drug absorption from the GIT (see principles).
- Treatment of drug toxicity:
  - Toxicity with acidic drugs (e.g. aspirin) could be treated by alkalinization of urine, which renders this drug more ionized in urine and less reabsorbable.
  - Toxicity with basic drugs (e.g. amphetamine) could be treated by acidification of urine, which renders this drug more ionized in urine and less reabsorbable.
- Ion trapping in breast milk:
  - The pH of the breast milk is 7 i.e. it is considered acidic in relation to plasma (pH 7.4).
  - Basic drugs (with pKa > 7.2) tend to be ionized, and thus trapped, inside breast milk more than acidic drugs; hence, the milk/plasma ratio (M/P ratio) would be high.

DISTRIBUTION OF DRUGS



Sites of drug distribution

- Plasma: 3 liters
- Extracellular water: 9 liters
- Intracellular water: 29 liters

Volume of distribution (Vd)

Definition: The apparent volume of water into which the drug is distributed in the body after distribution equilibrium.

Calculation:

$$Vd = \frac{\text{Total amount of the drug in the body}}{\text{Plasma conc of the drug (after distribution equilibrium)}} \text{ L}$$

Clinical significance:

- Determination of the **site of drug distribution** e.g.:
  - A total Vd < 5 L: means that the drug is confined to the vascular compartment and can be removed by dialysis.
  - A total Vd 5-15 L: means that the drug is restricted to the ECF.
  - A total Vd > 41 L: means that the drug is highly bound to tissue proteins and cannot be removed by dialysis.
- Calculation of **the total amount of drug in the body** by single measurement of plasma concentration (from the equation).
- Calculation of the **loading dose** (LD) needed to attain a desired plasma concentration (Cp): LD = Vd x Cp.
- Calculation of **drug clearance:**

$$\text{Clearance (Cl)} = \frac{0.693 \times Vd}{\text{Half-life } (t_{1/2})}$$

Binding of drugs to plasma proteins

- Most drugs when introduced into the body are bound to plasma proteins.
- Albumin: the most important plasma protein and it can bind –ve or +ve charged drugs.

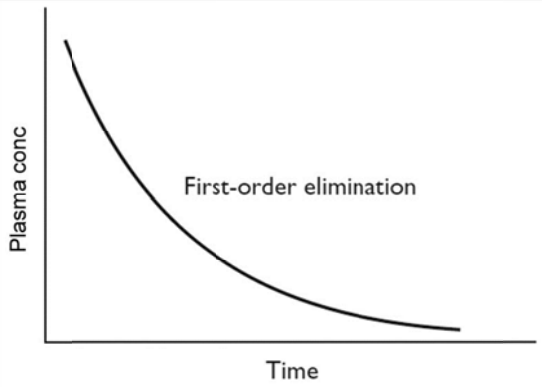
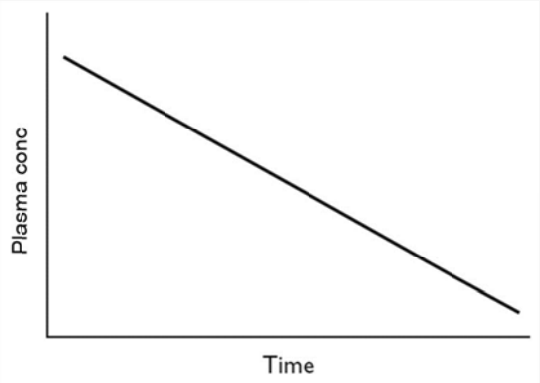
Clinical significance:

- The pharmacological effect of the drug is related only to its **free part** not to its bound part (the bound part acts only as a reservoir from which the drug is slowly released).

- Binding of drugs to plasma proteins **prolongs** their effects.
- When the drug has **high plasma protein binding** (e.g. 99% for warfarin), the free part that exerts the pharmacologic effect is 1%. Any small displacement of the bound part by another drug (say for example another1% is displaced) can lead to dramatic toxicity (doubles the amount of the free part in plasma).
- Many **disease states** (e.g. chronic liver disease, pregnancy, renal failure) can affect the level of albumin and the nature of plasma proteins, thus causing serious problems with some drugs.

EXCRETION AND ELIMINATION OF DRUGS

Elimination of drugs may follow one of 2 processes (orders):

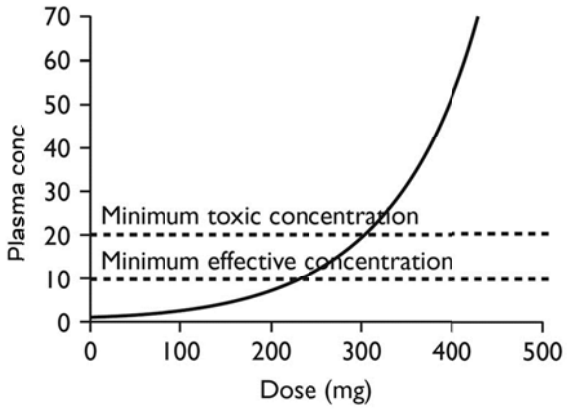
First-order elimination	Zero-order elimination
	
- Occurs to **most** drugs. - Constant **ratio (%)** of the drug is eliminated per unit time i.e. the rate of elimination is **proportional** to plasma concentration. The higher the concentration, the greater the rate of elimination. - Elimination **does not** depend on **saturable enzyme** system. - The $t_{1/2}$ of the drug is constant. - Drug cumulation is not common	- Occurs to **limited** number of drugs. - Constant **amount** of the drug is eliminated per unit time i.e. the rate of elimination is **not proportional** to plasma concentration. A familiar example is ethanol, concentrations of which decline at a constant rate of approximately 15 mg/100 mL/h. - Elimination depends on **saturable enzyme** system. - The $t_{1/2}$ of the drug is not constant. - Drug cumulation is common

Examples of drugs eliminated by zero-order: prednisolone, theophylline.

N.B. Some drugs are eliminated by first-order elimination in **low doses** and by zero-order elimination in **high doses** e.g. aspirin and phenytoin.

Clinical significance of zero-order elimination:

- Modest change in drug dose may produce unexpected toxicity.
- Elimination of drugs or attainment of Cpss takes long time.
- Changes in drug formulation may produce adverse effects.
- Drug cumulation and interactions are common.



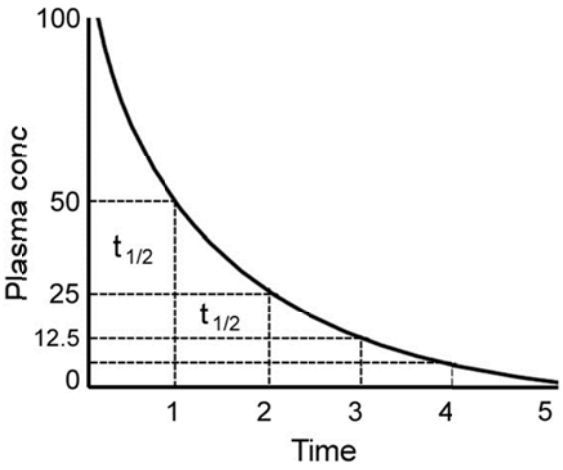
Elimination half-life ($t_{1/2}$)

Definition: It is the time taken for the concentration of a drug in blood to fall half to its original value.

Calculation:

- From the plasma concentration versus time curve.
- From the equation:

$$\text{Clearance (Cl)} = \frac{0.693 \times Vd}{\text{Half-life } (t_{1/2})}$$



Clinical significance:

- Determination of **inter-dosage interval:** drugs are given every $t_{1/2}$ to avoid wide fluctuations of the **peak** level (the highest plasma concentration of the drug) and **trough** level (the lowest plasma concentration).
- **Time-course of drug accumulation:** if a drug is started as a constant infusion, the Cp will accumulate to approach steady-state after 4-5 $t_{1/2}$.
- **Time-course of drug elimination:** If a drug is stopped after an infusion, the Cp will decline to reach complete elimination after 4-5 t1/2.
- Drugs having long $t_{1/2}$ could be given **once daily** to improve patient **compliance.**

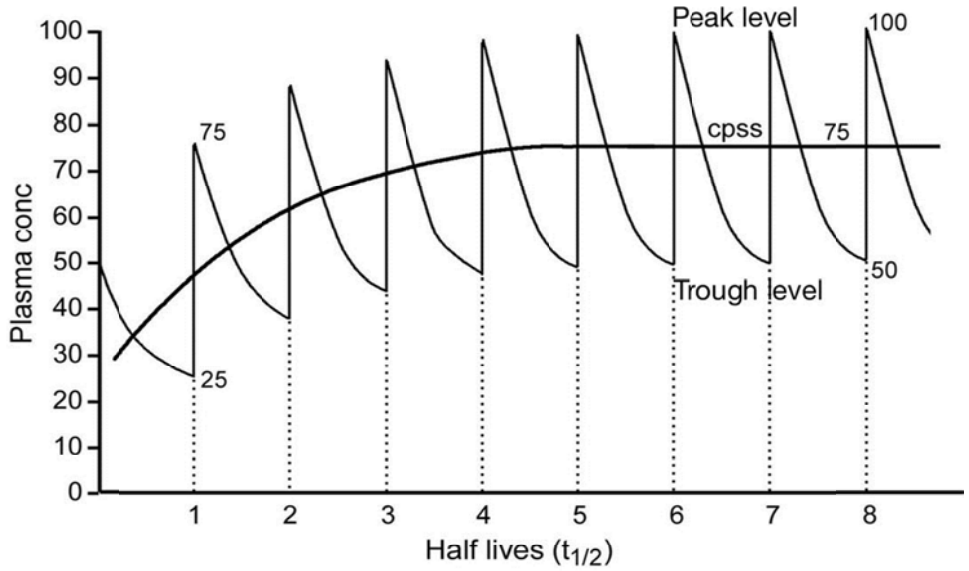
Steady-state plasma concentration (Cpss)

Definition: the steady level of drug in plasma achieved when the rate of administration equals the rate of elimination.

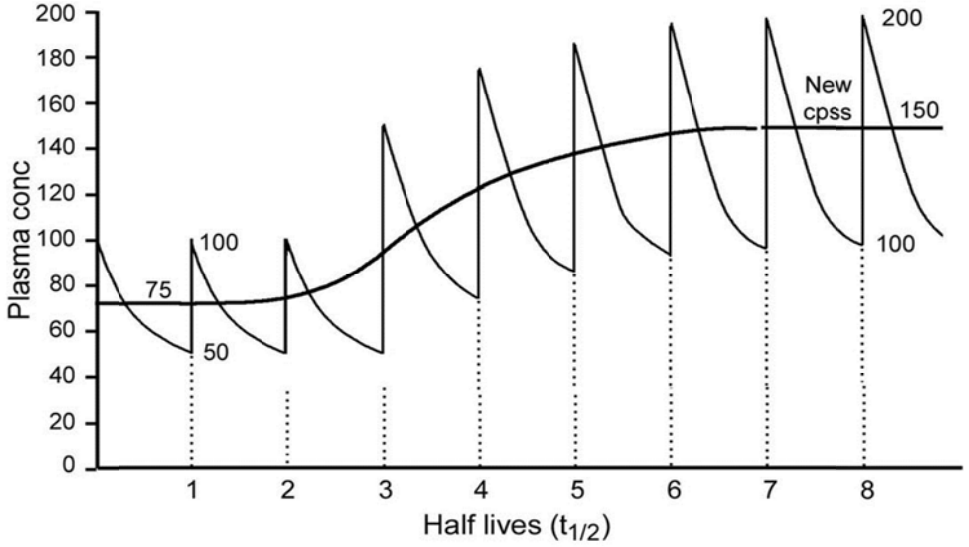
The rule of 5:

- The Cpss is reached after 4-**5** $t_{1/2.}$

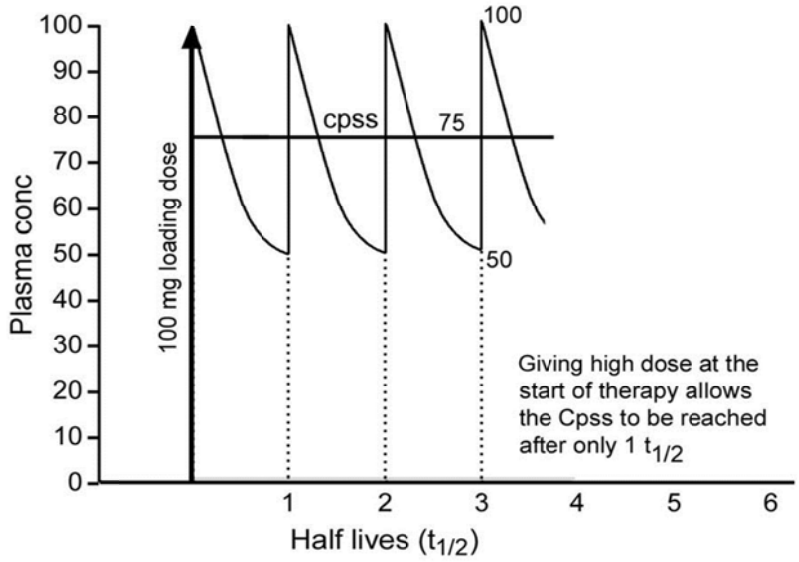
- If we changed the dose, the new Cpss is reached after 4-**5** $t_{1/2.}$
- If dosing stops, complete elimination of drug from plasma occurs after 4-**5** $t_{1/2.}$



Cpss is reached after 5 $t_{1/2}$



New Cpss is reached after 5 $t_{1/2}$



Therapeutic drug monitoring (TDM)

Definition: monitoring of serum drug concentrations to optimize drug therapy.

- Serum drug samples are usually taken when the drug has reached the CPSS (e.g. at the trough level, just before the next dose).
- TDM can be done by monitoring drug effect rather than concentration e.g. in warfarin therapy, TDM is done via monitoring the INR (see blood).

Clinical significance:

- **To avoid toxicity in the following situations:**
  - Drugs with a low 'therapeutic index' e.g. lithium, digoxin, and warfarin.
  - Presence of disease states (e.g. liver or renal dysfunction) that can affect the drug's pharmacokinetics.
- **To improve efficacy** of drugs having pharmacokinetic problems e.g. phenytoin and other drugs with non-linear kinetics.
- **Differentiation between** drug resistance and patient non-compliance.

Clearance as a channel of elimination

Definition: plasma clearance of a substance means the volume of plasma cleared from this substance per minute.

Calculation:

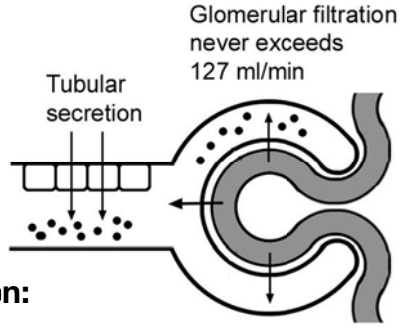
$$\text{Clearance (Cl)} = \frac{0.693 \times Vd}{\text{Half-life } (t_{1/2})}$$

Clinical significance of renal clearance:

If the drug is cleared by the kidney, clearance can help to determine whether this drug is eliminated by renal **filtration** or **secretion:** a drug that is eliminated only by *filtration* cannot exceed 127 ml/min. If clearance > 127 ml/min → the drug is eliminated also by *tubular secretion*.

Routes of elimination:

- Kidney (the major route).
- Bile and liver.
- Lungs, intestine, milk, saliva and sweat.



Clinical importance of knowing the route of elimination:

- Help to adjust the dose to avoid cumulation.
- Avoid drugs eliminated by a diseased organ.
- Targeting therapy: e.g. drugs eliminated by the lung could be used as expectorants.

METABOLISM OF DRUGS (biotransformation)

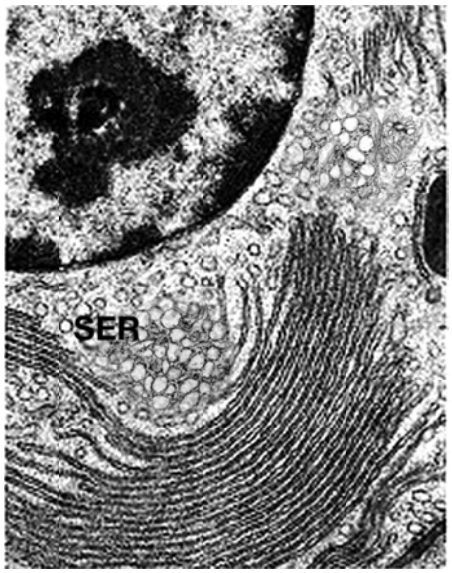
- The **liver** is the major site of drug metabolism but other organs can also metabolize drugs e.g. kidney, lungs, and adrenal glands.
- Many lipid soluble drugs must be converted into a **water-soluble form** (polar) to be excreted.
- Some drugs are not metabolized at all and excreted unchanged (**hard drugs**).
- **Metabolism of drugs may lead to:**
  - Conversion of **active** drug into **inactive** metabolites → termination of drug effect.
  - Conversion of **active** drug into **active** metabolites → prolongation of drug effect e.g. codeine (active drug) is metabolized to morphine (active product).
  - Conversion of **inactive** drug into **active** metabolites (**prodrugs**) e.g. enalapril (inactive drug) is metabolized to enalaprilat (active metabolite).
  - Conversion of **non-toxic** drug into **toxic** metabolites (e.g. paracetamol is converted into the toxic product *N*-acetylbenzoquinone).

Biochemical reactions involved in drug metabolism

The drug must enter **phase I** of chemical reactions be excreted as water-soluble compound. If the drug is not liable to conversion into water-soluble compound by phase I, it must enter **phase II** to increase solubility and enhance elimination.

Phase I reactions

- Phase I reactions include **oxidation, reduction,** and **hydrolysis**.
- Enzymes catalyzing phase I reactions include cytochrome P450, aldehyde and alcohol dehydrogenase, deaminases, esterases, amidases, and epoxide hydratases.
- The majority of phase I reactions is done by the **cytochrome P450** (CYP450) enzyme system located primarily inside membranous vesicles *(microsomes)* on the surface of the smooth endoplasmic reticulum of parenchymal liver cells. CYP450 activity is also present in other tissue e.g. kidney, testis, ovaries and GIT.



- Although this class has more than 50 enzymes, six of them metabolize 90% of drugs. The most important subfamily is CYP3A4 which is responsible for metabolism of over 50% of drugs.
- **Genetic polymorphism** of several clinically important CYP450 enzymes is a source of variability of drug metabolism in humans.
- Drugs may be metabolized by only one CYP450 enzyme (e.g. metoprolol by CYP2D6) or by multiple enzymes (e.g. warfarin).
- Some drugs and environmental substances can **induce** (increase activity) or **inhibit** certain CYP450 enzymes leading to significant drug interactions.
- Other examples of **non-microsomal oxidation** include xanthine oxidase (converts xanthine to uric acid) and monoamine oxidase (MAO) (oxidizes catecholamines and serotonin). Only the microsomal enzymes are subjected to induction or inhibition by drugs.

Microsomal enzyme induction	Microsomal enzyme inhibition
▪ Microsomal inducers ↑ rate of metabolism of some drugs leading to ↓ their serum levels and therapeutic failure. ▪ Induction usually requires prolonged exposure to the inducing drug.	▪ Microsomal inhibitors ↓ rate of metabolism of some drugs leading to ↑ their serum levels and toxicity. ▪ Enzyme inhibition can occur after short period of exposure to the inhibiting drug.
▪ Examples of inducing agents: phenytoin, phenobarbitone, carbamazepine, rifampicin, smoking, chronic alcohol intake, St John's Wort,	▪ Examples of inhibiting agents: macrolide antibiotics (e.g. erythromycin), ciprofloxacin, cimetidine, ketoconazole, ritonavir, grapefruit juice.
▪ Clinical examples: – Rifampicin accelerates metabolism of contraceptive pills leading to failure of contraception. – Phenytoin accelerates metabolism of cyclosporine-A leading to graft rejection.	▪ Clinical examples: – Ciprofloxacin inhibits metabolism of warfarin (anticoagulant) leading to accumulation of warfarin and bleeding. – Erythromycin inhibits metabolism of theophylline leading to toxicity of theophylline (cardiac arrhythmia).

Phase II reactions (conjugation)

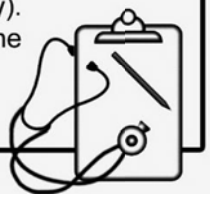
- It involve coupling of a drug or its metabolite to water-soluble substrate (usually glucuronic acid) to form water-soluble conjugate.
- **Glucuronyl transferase** is a set of enzymes that is responsible for the majority of phase II reactions. This set of enzymes is also located **inside liver**

microsomes and is the only phase II reaction that is **inducible by drugs** and is a possible site of drug interactions e.g. phenobarbital induces glucuronidation of thyroid hormone and reduces their plasma levels.

- Some glucuronide conjugates secreted in bile can be hydrolyzed by intestinal bacteria and the free drug can be reabsorbed again (enterohepatic circulation), this can extend the action of some drugs.
- Other examples of **non-glucurounide conjugation** reactions include sulphate conjugation (steroids), glycine conjugation (salicylic acid), and glutathione conjugation (ethacrynic acid).

N.B. Breakthrough pregnancy!!!

- Contraceptive pills contain estrogen, which is metabolized by glucuronide conjugation and excreted in bile as conjugate.
- Intestinal bacteria hydrolyze this conjugate to form free estrogen again which is reabsorbed and attain long duration of action (so contraceptive pills are given once daily).
- If the woman took contraceptive pills with broad-spectrum antibiotics (kills the intestinal bacteria), estrogen will lose its long duration of action and pregnancy can occur.

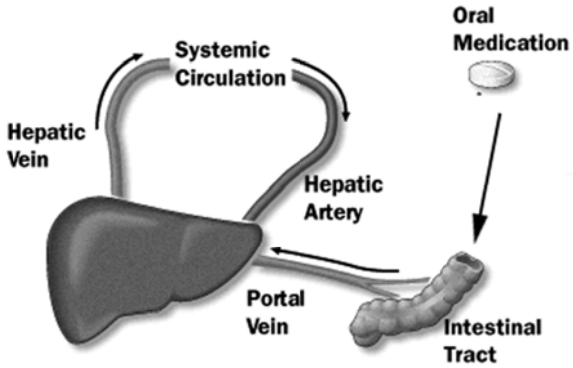


First-pass metabolism (pre-systemic elimination)

Definition: metabolism of drugs at the site of administration before reaching systemic circulation e.g. the liver after oral administration, the lung after inhalation, the skin after topical administration, etc.

Hepatic first-pass metabolism:

- Complete: lidocaine.
- Partial: propranolol, morphine, nitroglycerine
- None: atenolol and mononitrates



How to avoid?

- By increasing the dose of the drug.
- By giving the drug through other routes e.g. sublingual, inhalation, or i.v.

Bioavailability

Definition: it is the fraction of the drug become available for systemic effect after administration. The bioavailability of drugs given i.v. is 100%.

Factors affecting bioavailability:

- Factors affecting absorption.
- Factors affecting metabolism.
- First-pass metabolism.

Part 4: Adverse drug reactions (ADR)

An ADR is any response to a drug which is noxious, unintended, and occurs at doses used in man for prophylaxis, diagnosis or therapy.

Predisposing factors:

- Multiple drug therapy.
- Extremes of age: due to age related changes in pharmacokinetics and dynamics.
- Associated disease: e.g. impaired renal or hepatic function.
- Genetics: can affect the pharmacokinetics.

Classification:

Type A (Augmented):

These reactions are predictable from the known pharmacology of the drug. They may result from an **exaggerated response** (e.g. hypotension from an antihypertensive) or **non-specificity** (e.g. anticholinergic effects with tricyclic antidepressants).

Prevention

- Take a careful history for predisposing factors.
- Use the smallest dose of the drug adequate for the desired effect.
- Adjust dosage to therapeutic end-points, e.g. blood pressure or INR.
- Adjust dosage to optimum plasma concentrations, e.g. digoxin.
- Adjust dosage in relation to renal function, hepatic function, or other drugs.

Type B (Bizarre):

These are less common, less predictable, and may be severe. **Examples are:**

- Immunologic: penicillin allergy
- Genetic: haemolysis in G6PD deficiency
- Disease: amoxycillin rash in glandular fever
- Idiosyncratic: malignant hyperpyrexia in anesthesia.

Prevention

- Take a careful drug history, especially of allergies

- Family history: allergies or genetic disease
- Avoid drugs susceptible to ADRs in particular disease states, e.g. clozapine in bone marrow depression.

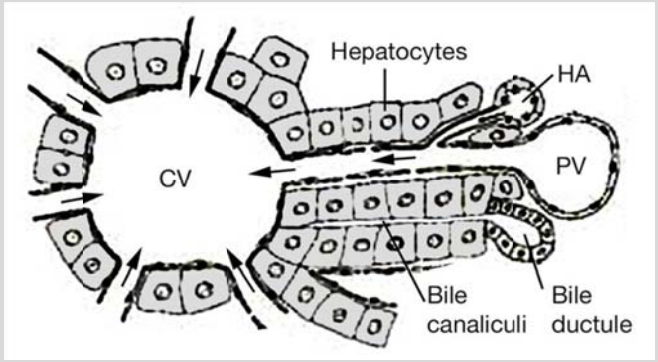
Type A (Augmented)	Type B (Bizarre)
– Predictable	– Unpredictable
– Dose-dependent	– Dose-independent
– High incidence	– Low incidence
– May respond to dose adjustment	– Generally need to stop the drug

Drug-induced liver injury (DILI)

DILI accounts for up to 10% of all adverse drug reactions and may be fatal.
It may be classified into:

- According to **time course**: acute or chronic.
- According to **mechanism**: dose-dependent, idiosynchratic, or immune mediated
- According to **histological finding**: hepatocellular, cholestatic, or mixed picture.

Hepatocellular (cytotoxic) DILI	Cholestatic DILI
Features: – The drug or its metabolites affects parenchymal liver cells leading to cell necrosis and initiation of inflammatory process. – It may be spotty, zonal, or diffuse. – Clinically it resembles viral hepatitis with ↑ ALT and AST.	**Features:** – The drug or its metabolites affect the biliary canaliculi leading to narrowing or destruction of biliary passages. – Clinically it resembles obstructive jaundice with pruritus and ↑ALP.
Common drugs: Paracetamol – methyldopa – amiodarone – isoniazid – valproic acid	**Common drugs:** Chloropromazine – sulfonylureas – oral contraceptive pills – anabolic steroids – macrolides – co-amoxiclav



ADR on pregnancy

Key facts:

- Fetal birth defects represent 2-3% of all births, the majority of which are related do drugs.
- Some fetal defects may be impossible to identify, or can be delayed e.g. the use of diethylstilbesterol (estrogenic compound) during pregnancy is associated with development of adenocarcinoma of girls' vagina at teen age.
- **Three factors** determine the risk of teratogenicity: **dose** of the drug; **duration** of administration; and **stage** of pregnancy.
- Most drugs with a MW <1000 can cross the placental barrier.
- All drugs should be considered harmful until proven otherwise.

Mechanism of teratogenicity according to pregnancy stage:

- **Before implantation: (0-17 day):** The effect is all-or-none i.e. either death of the embryo (abortion) or no effect.

- **Early pregnancy: (3-10 weeks):**
  - It is the most dangerous period because it is period of organogenesis.
  - Selective interference can produce characteristic anatomical abnormality e.g. aminoglycosides cause damage to 8th cranial nerve.

- **Late pregnancy:**
  - Gross anatomical abnormalities are less liable to occur.
  - Functional defects rather than anatomical abnormalities can occur especially in organs having delayed formation e.g. brain, testes, and bone.

Examples of teratogenic drugs:

- **ACE inhibitors** and angiotensin receptor blockers cause fetal pulmonary and renal dysfunction.
- **Antithyroid drugs** can cause fetal goiter and hypothyroidism.
- **Tetracycline** antibiotics inhibit growth of fetal bones and stain teeth.
- **Aminoglycosides** cause fetal 8th cranial nerve damage.
- **Warfarin** can cause fetal intracerebral bleeding.
- **NSAIDs** cause premature closure of ductus arteriosus.
- **Benzodiazepines** cause cleft lip and palate.
- **Sex hormones** can cause inappropriate virilization or feminization.
- **Antiepileptic drugs** cause neural tube defect (spina bifida).
- **Cytotoxic drugs** can cause multiple structural damage.

The FDA pregnancy categories:

Category	Definition	Animal	Human
A	Adequate studies in animal and human did not show a risk to the fetus either in the first or in the late trimesters.	✓	✓
B	Animal studies did not show risk to the fetus but there are no adequate studies in human. **or:** Animal studies showed a fetal risk, but adequate studies in human did not show a risk to the fetus.	✓ ×	? ✓
C	Animal studies showed a risk to the fetus but there are no adequate studies in humans; the benefits from the use of the drug in pregnant women may by acceptable despite its potential risks.	×	? **Benefit > Risk**
D	There is evidence of human fetal risk, but the potential benefit of the drug may outweigh its potential risk.	×	× **Benefit > Risk**
X	Studies in animals and humans showed evidence of fetal risk. The potential risk of use in pregnant women clearly outweighs any potential benefit.	×	× **Risk > Benefit**

Part 5: Principles of drug-drug interactions

Classification:

- **Pharmacokinetics interactions.**
- **Pharmacodynamic interactions.**

PHARMACOKINETIC INTERACTIONS

Drug interactions *in vitro*:

e.g. antipseudomonal penicillins and aminoglycosides form complexes in the infusion fluid (see chemotherapy).

Drug interactions *in vivo*:

Absorption

- **Formation of complexes:**
  - Tetracycline forms complexes with Ca^{2+}, Mg^{2+} and Al^{3+}
  - Cholestyramine forms complexes with digitalis and thyroxin.
- **Absorption can be blocked:**
  - Adrenaline ↓ absorption of local anesthetics due to VC.
  - Colchicine ↓ absorption of vitamin B12
- **Change in intestinal motility:**
  - Anticholinergic drugs ⇓intestinal motility → ↑ absorption of some drugs.
  - Prokinetic drugs ↑ intestinal motility → ↓ absorption of some drugs.
- **Changes in gastric pH:**
  - Antacids ↓absorption of salicylates.
  - Ketoconazole is poorly absorbed in absence of gastric acidity.

Distribution

- Sulfonamides displace bilirubin from pl pr in premature infants → kernicterus.
- Phenylbutazone displaces warfarin → excessive bleeding.

Metabolism

- **Inhibition or induction of microsomal metabolism** (see before).
- **Inhibition of non-microsomal enzymes:**
  - MAO inhibitors ↓ metabolism of some drugs e.g. benzodiazepines, serotonin and norepinephrine.
  - Disulfiram inhibits *acetaldehyde dehydrogenase* enzyme → ↓ metabolism of acetaldehyde → accumulation of acetaldehyde causes flushing, nausea, vomiting, and tachycardia.

Excretion

- **Reduction in urinary elimination:**
  - Probenecid ↓ renal excretion of penicillin.
  - Quinidine ↓ renal excretion of digoxin.
- **Changes in urinary pH:**
  - Alkalinization of urine (e.g. sodium bicarbonate) ↑ excretion of weak acids
  - Acidification of urine (e.g. ammonium chloride) ↑ excretion of weak bases.

- **Changes in urinary volume:**
  Diuretics can increase toxicity of some drugs by reducing plasma volume e.g. thiazide can increase lithium toxicity.

- **Stimulation of biliary excretion:**
  Phenobarbital ↑ biliary excretion of many drugs by increasing both bile flow and the synthesis of conjugating proteins.

PHARMACODYNAMIC INTERACTIONS

- **Antagonism:** competitive, non-competitive, chemical, physical, etc.
- **Synergism:** e.g. MAO inhibitors can cause toxic synergism with TCA.
- **Potentiation:** e.g. ethanol can enhance CNS depression caused by opioids
- **Changes in the intracellular or extracellular environment:** e.g. diuretic-induced hypokalemia can ↑ digitalis toxicity.

Notes

Notes

Review Questions

Define the following pharmacokinetic parameters:

- Volume of distribution
- pKa of drugs
- Elimination half life
- First-pass metabolism
- Bioavailability

Mention the clinical significance of each of the following:

- Volume of distribution
- pKa of drugs
- Plasma protein binding of drugs
- Elimination half-life
- Zero-order elimination
- Microsomal enzyme induction
- Hepatic conjugation of drugs

Mention the main differences between:

- Reversible and irreversible antagonism.
- Graded response and quantal response.
- First order elimination and zero order elimination.
- Potency and efficacy.
- Physical and physiological antagonism.
- Habituation and addiction.
- Oxidation and conjugation of drugs.

Discuss 2 pharmacogenetic conditions associated with toxic drug response

Discuss 2 pharmacogenetic conditions associated with reduced drug response

Write short account on antagonism between drugs

Of each of the following questions, select ONE BEST answer:

1. A drug may act by all the following mechanisms EXCEPT:

A. Interaction with protein macromolecules embedded in the cell membranes
B. Interaction with cell membrane ion channels
C. Interaction with intracellular enzymes
D. Interaction with cell membrane phospholipids
E. Interaction with gene functions

2. Ion-channel-linked receptors (direct ligand-gated ion channels) are characterized by:

A. They are the type of receptors principally present in autonomic ganglia and skeletal ms motor end plate
B. They are the type of receptors principally present in vascular endothelium
C. They are rosette-shaped structures consist of 7 membrane subunits
D. Their response is slower than other receptors
E. Activation of these receptors leads to activation of a second messenger

3. Which of the following is classified as belonging to the tyrosine kinase family of receptors:

A. GABA receptors
B. β-Adrenergic receptors
C. Insulin receptors
D. Nicotinic acetylcholine receptors
E. Hydrocortisone receptors

4. All the following are true for intracellular (DNA-linked) receptors EXCEPT:

A. They regulate transcription of genes inside the nucleus
B. Their response is very fast but persists for long time
C. Their agonists must enter inside the cell to reach them inside the nucleus
D. Sex hormones act on these types of receptors
E. Corticosteroids act on these types of receptors

5. The following statements are true for graded dose-response relationship EXCEPT:

A. It is the response to most drugs
B. The response is directly proportional to drug concentration (linear relation)
C. It could be tested in one animal
D. It can be used for comparing the potencies and efficacies of drugs
E. It can be used for calculation of the LD_{50} of drugs

6. The following statements are true for quantal dose-response relationship EXCEPT:

A. It is the response to anticonvulsant and antiarrhythmic drugs
B. The response to the drug is not directly proportional to drug concentration (all-or-none)
C. It could be tested in one animal
D. It helps in calculation of the ED50 and LD50 of drugs
E. It helps in estimation of the degree of drug safety

7. When a drug has a steep dose-response curve, this means:

A. The drug is lethal
B. The drug is expensive
C. The drug is efficacious
D. The drug is safe
E. Minimal change in the dose can lead to dramatic effect.

8. The following statements are true for drug's therapeutic index EXCEPT:

A. It is the relation between the lethal dose in 50% of animals to the curative dose in 50% of them
B. The lower the TI, the safer will be the drug.
C. It should be done to any drug before it's being approved for human use

D. For theoretically useful drugs, it must be greater than 1
E. It could be applied in animal testing

9. The following is true for competitive antagonism:
A. It never occurs with enzymes
B. Is the same as physiological antagonism
C. The agonist can never abolish the effect of the antagonist
D. Is best exemplified by the use of neostigmine to treat curare toxicity
E. Best described as non-surmountable process

10. A drug is said to be reversible antagonist when:
A. It blocks the receptors by making covalent bonds with them
B. The duration of blockade is too long
C. Increasing the dose of the agonist will reverse the block
D. The response curve of the agonist in presence of this drug is not parallel to that of the agonist alone
E. Termination of the drug effect depends on synthesis of new receptors

11. The interaction that may occur between acidic and basic drugs is called:
A. Chemical antagonism
B. Physical antagonism
C. Physiological antagonism
D. Biological antagonism
E. Receptor antagonism

12. The following is true for interactions between drugs:
A. Is not harmful if occurred between drugs having steep dose-response curves
B. Is not harmful if occurred between drugs having narrow therapeutic ratios
C. Is not harmful if occurred between drugs undergoing zero-order kinetics
D. May lead to valuable therapeutic effects
E. Is described as addition if the action of one drug abolishes the effects of another

13. A drug may interact with ion channels by all of the following mechanisms EXCEPT:
A. The drug may change the ion channel structure
B. The drug may block the channel physically
C. The drug may change an intracellular ATP on which the channel depends
D. The ion channel may be part of ion channel-linked receptors
E. The ion channel may be modulated by G-protein linked receptors

14. Failure of the patient to breath after surgical operation may be due to:
A. Pseudocholinestrase deficiency
B. Methemoglobin reductase deficiency
C. G-6-PD deficiency
D. Vitamin K epoxide reductase deficiency
E. Monoamine oxidase deficiency

15. Hemolysis that may occur with sulfonamides therapy may be due to:
A. Pseudocholinestrase deficiency
B. Methemoglobin reductase deficiency
C. G-6-PD deficiency
D. Vitamin K epoxide reductase deficiency
E. Monoamine oxidase deficiency

16. Severe myelosuppression following 6-mercaptopurine therapy is most likely due to:
A. Pseudocholinestrase deficiency
B. Methemoglobin reductase deficiency
C. G-6-PD deficiency
D. Vitamin K epoxide reductase deficiency
E. Thiopurine methyltransferase deficiency

17. Hepatic toxicity that may accompany isoniazide therapy may be due to:

A. Defective oxidation reaction
B. Defective conjugation reaction
C. Defective deamination reaction
D. Slow acetylation reaction
E. Rapid acetylation reaction

18. Failure of some children with rickets to respond to therapeutic doses of vitamin D is most likely to be due to:
A. Differences in sex
B. Differences in body weight
C. Genetic variation
D. Tolerance
E. Intolerance

19. The following are true for overshot phenomenon (drug intolerance) EXCEPT:
A. It occurs due to down-regulation of receptors
B. It occurs after sudden stoppage of some drugs given for long time
C. It may lead to serious withdrawal effects
D. It can be avoided by gradual cessation of drugs
E. It is best exemplified by occurrence of severe tachycardia after sudden stopping of beta blockers.

20. The following statements are true for pKa of drugs EXCEPT:
A. Ionized drugs are poorly absorbed while unionized drugs are more absorbed
B. Ionization of most drugs depends on the pH of the medium around them
C. pKa of drugs can help knowing the site of drug absorption.
D. Acidic drugs become more absorbable in alkaline pH
E. Basic drugs become more reabsorbable in alkaline urine

21. Which of the following drugs will be absorbed to the LEAST extent in the stomach:
A. Ampicillin (pKa = 2.5)
B. Aspirin (pKa = 3.5)
C. Warfarin (pKa = 5.0)
D. Phenobarbital (pKa = 7.4)
E. Propranolol (pKa = 9.4)

22. The following statements are true for Vd of drugs EXCEPT:
A. It can exceed the volume of water in the body
B. Drugs with large Vd can be removed by dialysis
C. Would be expected to be 5L if the drug is confined to the blood.
D. Highly lipid-soluble drugs would be expected to have large Vd
E. It can help in the calculation of the total amount of the drug in the body

23. The plasma half-life ($t_{1/2}$) of drugs:
A. Is expressed as the percentage that remains ½ hour after administration
B. Will be short if the drug gets into the enterohepatic circulation
C. Cannot be calculated if the drug is excreted through the bile
D. Is constant for drugs having zero-order elimination
E. Can be prolonged by slowing the rate of drug elimination

24. The bioavailability of a drug:
A. Is defined as the actual blood concentration required to produce a pharmacological effect
B. Will be unaffected by changes in formulation
C. May be affected by liver damage
D. Must be 100% for a drug given by mouth and is completely absorbed
E. Is a term applied only to oral administration

25. All the following are phase I biotransformation reactions EXCEPT:
A. Sulfate conjugation
B. Xanthine oxidation
C. Nitroreduction
D. Ester hydrolysis
E. Oxidative deamination

26. Metabolism (biotransformation) of drugs can lead to all the following results EXCEPT:

A. Conversion of active compound into inactive metabolites
B. Conversion of active compound into active metabolites
C. Conversion of inactive compound into active metabolites
D. Conversion of non-toxic compound into toxic metabolites
E. Conversion of water-soluble compound into lipid-soluble metabolites

27. All the following statements are true for First-order kinetics EXCEPT:

A. Apply to most drugs in clinical use
B. Apply to salicylate (aspirin) metabolism within small dose.
C. The concentration versus time curve is non-linear.
D. The rate of elimination depends on plasma concentration of the drug
E. Steady state plasma concentration can be reached after 5 half lives

28. All the following statements are true for zero-order kinetics EXCEPT:

A. Elimination rate is independent of the dose
B. Elimination depends on saturable enzyme system
C. Plasma concentration of the drug cannot be expected at any time
D. The t1/2 of the drug is not constant
E. There is no fear from drug cumulation or interactions

29. Drugs X and Y have the same mechanism of diuretic action. Drug X in a dose of 5mg produces the same magnitude of diuresis as 500 mg of drug Y. This suggests that:

A. Drug Y is less efficacious than drug X
B. Drug X is about 100 times more potent than drug Y.
C. Toxicity of drug X is less than that of drug Y.
D. Drug X is a safer drug than drug Y.
E. Drug X will have a shorter duration of action than drug Y because less of drug X is present for a given effect.

30. Which of the following terms best describes the antagonism of leukotriene's bronchoconstrictor effect (mediated at leukotriene receptors) by terbutaline (acting at adrenoceptors) in a patient with asthma?

A. Pharmacologic antagonist.
B. Partial agonist.
C. Physiologic antagonist.
D. Chemical antagonist.
E. Noncompetitive antagonist.

31. Which of the following provides information about the variation in sensitivity to the drug within the population studied?

A. Maximal efficacy.
B. Therapeutic index.
C. Drug potency.
D. Graded dose-response curve.
E. Quantal dose-response curve.

32. Which of the following provides information about the largest response a drug can produce, regardless of dose?

A. Drug potency.
B. Maximal efficacy.
C. Mechanism of receptor action.
D. Therapeutic index.
E. Therapeutic window.

33. A pro-drug is:

A. The prototype member of a class of drugs.
B. The oldest member of a class of drugs
C. An inactive drug that is transformed in the body to an active metabolite.
D. A drug that is stored in the body tissues and is then gradually released in the circulation.
E. Ionized drug trapped in breast milk.

34. If the rate of infusion of a drug were doubled, what response in the steady

state concentration would be expected?

A. Remain unchanged
B. Doubled
C. Increase 50%
D. Decrease 50%
E. Decrease 100%

35. Half-life of a drug may be helpful to determine:

A. Elimination of the drug
B. Level of absorption
C. Rate of absorption through the GIT
D. Time to reach the steady state
E. Distribution into body systems.

36. What determines the degree of movement of a drug between body compartments?

A. Partition constant
B. Degree of ionization
C. pH
D. Molecular size
E. All of the above

37. For intravenous (IV) dosages, what is the bioavailability assumed to be?

A. 0%
B. 25%
C. 50%
D. 75%
E. 100%

38. Which of the following can produce a therapeutic response? A drug that is:

A. Bound to plasma albumin
B. Concentrated in the bile
C. Concentrated in the urine
D. Not absorbed from the GI tract
E. Unbound to plasma proteins

39. Aspirin is a weak organic acid with a pKa of 3.5. What percentage of a given dose will be in the lipid-soluble form at a stomach pH of 1.5?

A. About 1%
B. About 10%
C. About 50%
D. About 90%
E. About 99%

40. Concerning the renal excretion of drugs:

A. Drugs that are ionized in the renal tubules are more likely to undergo passive reabsorption.
B. Low MW drugs are much more likely to be actively secreted than filtered.
C. Only the fraction of the drug that is unbound (free) to plasma proteins is filtered by the glomerulus.
D. Decreasing urinary pH enhance excretion of weakly acidic drugs.
E. Renal clearance cannot exceed the GFR (125 ml/min).

41. In which of the following cases could a graded dose-response curve be constructed?

A. Prevention of convulsions
B. Prevention of arrhythmias
C. Reduction of death
D. Reduction of fever
E. Relief of insomnia

42. Which of the following can be used as a relative indicator of the margin of safety of a drug?

A. T.I.
B. LD50
C. ED50
D. EC50
E. TD50

43. Flurazepam has a pKa of 8.2. What percentage of flurazepam will be ionized at a urine pH of 5.2?

A. 0.1%
B. 1.0%
C. 50%
D. 99%
E. 99.9%

44. Which route of administration is most likely to subject a drug to first pass metabolism?

A. Intravenous
B. Sublingual
C. Oral

D. Inhalation
E. Intramuscular

45. If a drug was given by a constant infusion rate, which of the following factors determines how long it will take for the drug to reach a steady-state concentration (Cpss) in the blood?
A. Apparent volume of distribution
B. Bioavailability
C. Clearance
D. Half-life
E. Infusion rate (mg of drug/min)

46. Which of the following best describes what the term "tachyphylaxis" means?
A. An increase in the rate of the response, for example, an increase of the rate of muscle contraction
B. Immediate hypersensitivity reactions (i.e., anaphylaxis)
C. Prompt conformational changes of the receptor such that agonists, but not antagonists, are able to bind and cause a response
D. Quick and progressive rises in the intensity of drug response, with repeated administration, even when the doses are unchanged
E. Rapid development of tolerance to the drug's effects

47. Drug A undergoes a series of Phase I metabolic reactions before being eliminated. Which of the following statements best describes the characteristics of Drug A, or the role of Phase I reactions in its metabolism?
A. Complete metabolism of Drug A by Phase I will yield products that are less likely to undergo renal tubular reabsorption
B. Drug A is a very polar substance
C. Drug A will be biologically inactive until it is metabolized
D. Phase I metabolism of Drug A involves conjugation with glucuronic acid or sulfate
E. Phase I metabolism of Drug A will increase its intracellular access and actions

48. The FDA assigns the letters A, B, C, D, and X to drugs approved for human use. To which of the following does this classification apply?
A. Amount of dosage reduction needed as serum creatinine clearances fall
B. Fetal risk when given to pregnant women
C. Amount of dosage reduction needed in presence of liver dysfunction
D. Relative margins of safety/therapeutic index
E. The number of unlabeled uses for a drug

49. Which effect may lead to toxic reactions when a drug is taken continuously or repeatedly?
A. Refractoriness
B. Cumulative effect
C. Tolerance
D. Tachyphylaxis
E. Intolerance

50. Tolerance and drug resistance can be a consequence of:
A. Change in receptors, loss of them or exhaustion of mediators
B. Increased receptor sensitivity
C. Decreased metabolic degradation
D. Decreased renal tubular secretion
E. Activation of a drug after hepatic first-pass

51. If two drugs with the same effect, taken together, produce an effect that is equal in magnitude to the sum of the effects of the drugs given individually, it is called as:
A. Antagonism
B. Potentiation
C. Synergism
D. Additive effect
E. Supersensitivity

52. All of the following statements about efficacy and potency are true EXCEPT:

A. Efficacy is usually a more important clinical consideration than potency

B. Efficacy is the maximum effect of a drug

C. Potent drugs usually given in small dose.

D. Potency is a comparative measure, refers to the different doses of two drugs that are needed to produce the same effect

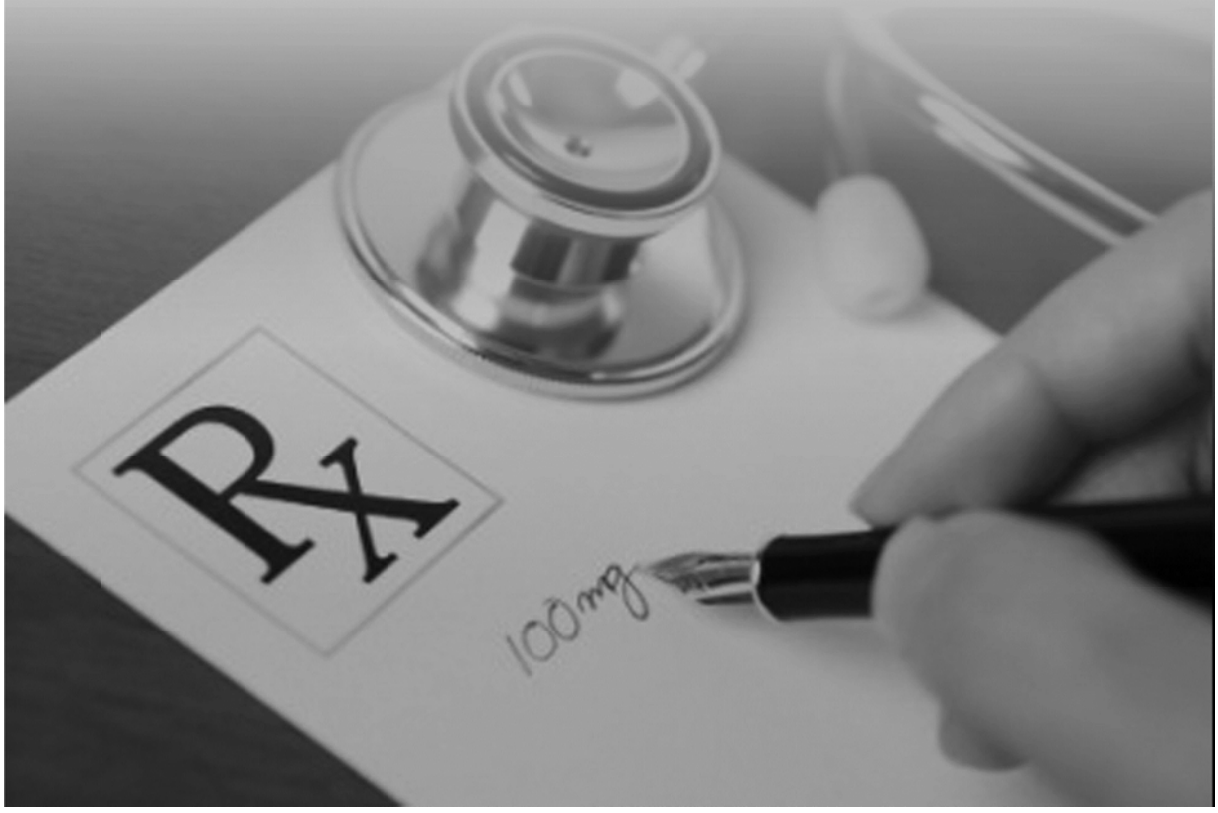
E. The ED50 is a measure of drug's efficacy

Answers

1 D	11 A	21 E	31 E	41 D
2 A	12 D	22 B	32 B	42 A
3 C	13 A	23 E	33 C	43 E
4 B	14 A	24 C	34 B	44 C
5 E	15 C	25 A	35 D	45 D
6 C	16 E	26 E	36 E	46 E
7 E	17 E	27 C	37 E	47 A
8 B	18 C	28 E	38 E	48 B
9 D	19 A	29 B	39 E	49 B
10 C	20 D	30 C	40 C	50 A
				51 D
				52 E

Chapter 2

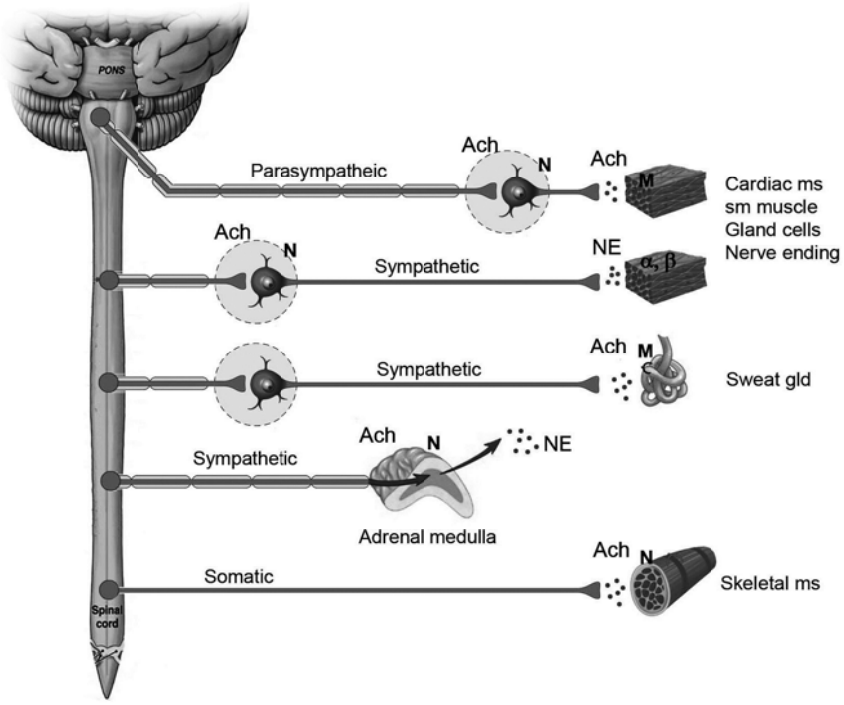
Autonomic Pharmacology



Chapter 2
Autonomic Pharmacology

Part 1: Basic information

The autonomic nervous system controls **involuntary activity** (Fig 1, table 1).



Sympathetic nervous system (SNS)

- Short preganglionic axons originate from thoracic and lumbar areas of the spinal cord and synapse in ganglia located close to the spinal cord.
- The adrenal medulla is considered a *modified ganglion* and is innervated by sympathetic fibers.
- Thermoregulatory **sweat glands** are anatomically sympathetic, but the postganglionic nerve fibers release acetylcholine (ACh) *(i.e. sympathetic cholinergic)*.

Parasympathetic nervous system (PNS)

- Long preganglionic axons originate from cranial and sacral areas of the spinal cord and synapse in ganglia located **close to** or **within** the innervated organ (with few exceptions).
- Short postganglionic axons innervate many tissues and organs as the SNS.
- Parasympathetic innervation predominates over sympathetic innervation of most organs **except blood vessels** *(have only sympathetic supply)*.

Enteric nervous system (ENS)

- The ENS is considered the third division of the ANS.
- It is a collection of neurons inside the wall of the GIT that controls the motility, exocrine and endocrine secretions of the GI tract.
- Nerve terminals contain peptides and purines as neurotransmitters.
- This system functions independently of the CNS and is modulated by both SNS and PNS.

The somatic nervous system controls voluntary activity**:**

- Long axons originate in the spinal cord and directly innervate **skeletal muscles** (no ganglia).
- Nerve terminals in the **neuromuscular junction** release **Ach** as the neurotransmitter.

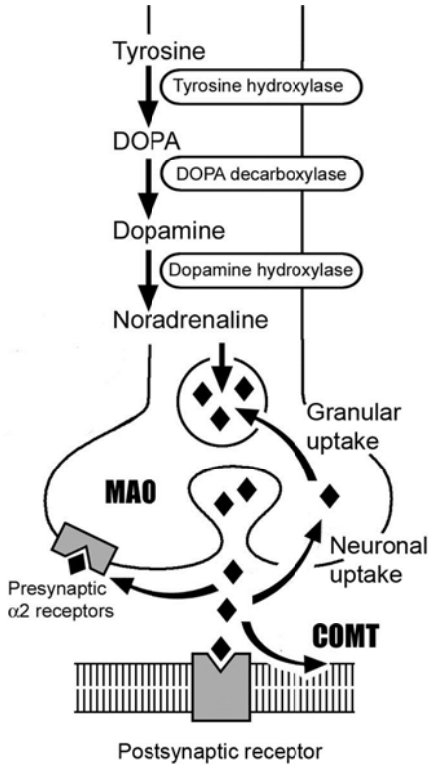
Neurotransmitters of the ANS

1. Norepinephrine and epinephrine

They are **catecholamines,** having catechol nucleus.

Biosynthesis of catecholamines:

- In nerve endings, tyrosine is hydroxylated by *tyrosine hydroxylase* to form (dopa); dopa is then decarboxylated to form dopamine which is hydroxylated into norepinephrine inside storage vesicles.
- In certain areas of the brain and in the adrenal medulla, norepinephrine is methylated by *N-methyltransferase* to form epinephrine.



Storage and release:

- Norepinephrine is stored in vesicles in nerve terminals.
- Norepinephrine also exists in a non-vesicular cytoplasmic pool that is released by indirectly acting sympathomimetics (e.g., **tyramine, amphetamine**).

Termination:

- **Re-uptake (80%):** mainly in the form of:
  - Neuronal uptake (into neuronal cytoplasm).
  - Granular uptake (into storage vesicles).
- **Metabolism (18-20%):**

- **Monoamine oxidase (MAO) enzyme:** metabolizes norepinephrine in neuronal cytoplasm.
  - MAO-A: present in the brain and peripheral tissues (e.g. liver & intestine).
  - MAO-B: present mainly in the **B**rain and more active on **dopamine**. It has little effect on norepinephrine and serotonin.
- **Catechol-O-methyl transferase (COMT):** metabolizes norepinephrine in synaptic space.

N.B. The end-product of catecholamine metabolism is *vanillyl mandelic acid (VMA)*. The normal urinary level of VMA is 4-8 mg/day. Higher levels indicate tumor in suprarenal medulla **(pheochromocytoma,** Fig 3).

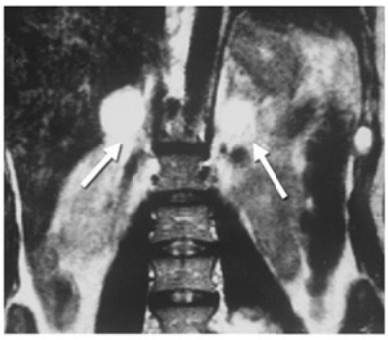


Figure 3. MRI abdomen showing bilateral suprarenal masses typical with pheochromocytoma

Clinical correlates:

Depression is associated with decreased activity of NA and/or serotonin at the level of synapse. Tricyclic antidepressant drugs act by inhibition of neuronal uptake of NA and serotonin while MAO inhibiting drugs act by inhibition of their metabolism. Both mechanisms lead to accumulation of NA and serotonin at the synaptic levels.

Parkinsonism is associated with deficiency of dopamine in the negrostriatal pathway. Inhibition of MAO-B enzyme (selegiline) and COMT enzyme (tolcapone) leads to accumulation of dopamine and improvement of bradykinesia.

2. Acetylcholine (ACh)

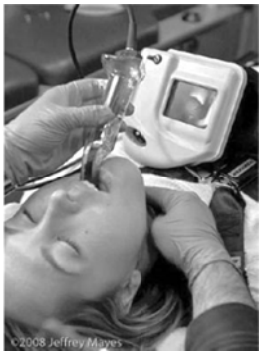
- ACh is synthesized in nerve terminals from acetyl co-A and choline. Synthesized ACh is stored in vesicles in nerve terminal.
- **Botulinum toxin** blocks Ach release and causes skeletal muscle paralysis.
- The main fate of ACh is rapid hydrolysis by **cholinesterase** (ChE) enzyme; there are **two isoforms**:

True ChE	Pseudo ChE
– Present in CNS, ganglia, NMJ.	– Present in plasma and liver.
– Specific for Ach.	– Not specific for Ach
– Deficiency is fatal.	– Deficiency is Not fatal
– Regenerates in 2-3 months.	– Regenerates in 2-3 weeks.

Clinical correlates:

Congenital PsChE deficiency (succinylcholine apnea):

Succinylcholine is a neuromuscular blocker that is metabolized by PsChE enzyme. Some individuals have congenital deficiency of PsChE, when they take succinylcholine to produce muscle relaxation before surgery, severe muscle paralysis occurs due to lack of succinylcholine metabolism. Death may occur from paralysis of respiratory muscles. Urgent blood transfusion and artificial respiration may be required.



3. Co-transmitters

A number of **Non-adrenergic-Non-cholinergic** (NANC) transmitters may be found in association with NA or Ach in the autonomic nerve terminals. **T**hey are released with the primary transmitter to play a **regulatory function**. Examples include: *neuropeptide Y; encephalin; histamine; 5HT; ATP; PGs; and nitric oxide (NO)*.

Table 1. Distribution and functions of **autonomic receptors.**

Tissue	SYMPATHETIC		PARASYMPATHETIC	
	R	**Effect**	**R**	**Effect**
Heart	β_1	↑ all cardiac properties (tachycardia, ↑A-V conduction, ↑contractility, etc)	M_2	↓ SA node activity and AV conduction (NOT **atrial conduction)**
Blood vessels	α_1 β_2	VC of most BV VD of skeletal muscle BVs, and coronary artery.	M_3*	VD of most BV (through release of EDRF). ***N.B.*** *Most vascular M3 receptors are non-innervated*
Bronchi				
Smooth ms Glands	β_2 α_1	Relaxation (Bronchodilatation) ↓ Bronchial secretion	M_3 M_3	Contraction (Bronchoconstriction) ↑ Bronchial secretion
GIT				
Wall	α, β_2	Relaxation (↓ motility)	M_3	Contraction (↑ motility)
Sphincters	α_1	Contraction	M_3	Relaxation
Salivary gld	α_1	↑ enzyme secretion (viscid saliva)	M_3	↑ water secretion (salivation)
Liver	β_2	Glycogenolysis		–
Stomach HCl		–	M_1	↑ HCl secretion
U bladder				
Detrusor ms	β_2	Relaxation	M_3	Contraction
Sphincter	α_1	Contraction (urine retention)	M_3	Relaxation (urine flow)
Uterus	β_2 α_1	Relaxation Contraction		–
♂ **organs**	α_1	Ejaculation	M_3	Erection
Kidney	β_1	↑ Renin secretion		–
Skeletal ms	β_2	Tremors and enhancement of neuromuscular transmission		–
Eye				
Iris ms	α_1	Pupil dilatation (mydriasis)	M_3	Pupil constriction (miosis)
Ciliary ms	β_2	Relaxation (distant vision)	M_3	Contraction (near vision)
IOP	β_2	↑ aq humor secretion (↑ IOP)	M_3	↑ aq humor **drainage** (↓ IOP)
Lacrimal gld		–	M_3	↑ lacrimal secretion
Sweat gld	α_1	↑ sympathetic sweating (forehead & palms)	M_3	↑ Thermoregulatory sweating (cholinergic sweating)
Fat cells	**β_3**	**Lipolysis**		–
Mast cells	β_2*	↓ histamine release		–
Plasma K^+	β_2	Decrease plasma K^+		–
Nerve terminals	α_2 β_2	↓ NA release ↑ NA release		–

* = **Non-innervated receptors** i.e. receptors are found in the organ but have **no** autonomic nerve supply. They can respond only to circulating or administered agonists.
EDFR = endothelial derived relaxing factor = nitric oxide (NO).

Table 2. Summary of adrenergic receptors

	α_1	α_2	β_1	β_2	β_3
2nd msngr	G_q (↑ IP3 & ↑ DAG) →↑ Ca^{2+}	G_i (↓ cAMP)	G_s (↑ cAMP)	G_s (↑ cAMP)	G_s (↑cAMP)
Sites and function	1. VC of **most** bl vessels (α_{1A}) 2. Contraction of all sphincters (GIT, urinary). 3. Contraction of dilator pupillae ms (mydriasis) 4. Contraction of uterus 5. Relaxation of GIT & UB walls 6. Adrenergic sweating (forehead & palm)	1. **Presynaptic** nerve endings **(↓ NA release)** 2. **Central:** ↓ central sympathetic outflow 3. Relaxation of GIT & UB walls	1. ↑ all cardiac properties 2. ↑ renin release (kidney)	1. **Presynaptic** nerve endings **(↑ NA release**) 2. **Central:** ↑ central sympathetic outflow 3. VD of sk ms bl vessels and coronary artery 4. Bronchodilatation 5. Relaxation of GIT & UB walls 6. Relaxation of uterus 7. Skeletal muscle tremors 8. ↑ aqueous humor secretion 9. ↑ liver glycogenolysis 10. ↓ plasma K^+	↑ lipolysis (adipose tissue)
Sel. agonist	Phenylepherine	Clonidine	Dobutamine	Salbutamol	
Selective antagonist	Prazosin	Yohimbine	Atenolol	Butoxamine *(not used clinically)*	
Non-selec agonist	Adrenaline Ephedrine				
Non-selec antagonist	Phenoxybenzamine Ergot alkaloids		Propranolol Timolol		

- β_4 and β_5 are also present but still under investigation.
- In most smooth muscles, the α1 receptors mediate contraction through activation of Ca^{2+} dependent *myosin light chain kinase* but in the GIT smooth muscles, they mediate relaxation through hyperpolarization caused by opening of Ca^{2+} dependent K^+ channels.
- **α1** receptors have 3 subtypes, A, B, and D; **α2** receptors have three subtypes: A, B, and C.

Table 3. Summary of cholinergic receptors

	M_1	M_2	M_3	N_n	N_m
2nd msngr	**G_q** (↑ IP3 & ↑ DAG) →↑ **Ca^{2+}**	**G_i** (↓cAMP)	**G_q** (↑ IP3 & ↑ DAG) →↑ **Ca^{2+}**	**Ion channel**	**Ion channel**
Sites and function	1. **CNS** 2. **Stomach** → ↑ HCL secretion	↓↓ SAN activity and AV conduction *(not atrial conduction)*	1. **VD** of most **BV** through synthesis of *endothelial-derived relaxing factor* (EDRF) → ↓ **blood pressure.** 2. **Contraction** of all wall smooth muscles (bronchi, GIT, UB) and **relaxation** of all sphincters. 3. ↑↑ **all body secretions** (sweating, salivation, lacrimation, etc). 4. **Eye:** → miosis & ciliary muscle contraction (accommodation for near vision).	**All autonomic ganglia** and adrenal medulla	**NMJ** → skeletal muscle contraction
Selective antagonist	Pyrenzepine	Gallamine	---------	Trimetaphan	d-tubocurarine
Non-selec agonist	Acetylcholine				
Non-selec antagonist	Atropine - hyoscine				

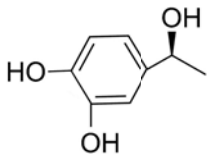
N.B.

- **M4** and **M5** are also present in the **CNS.**
- **M1 – M3 – M5** are linked to Gq (↑ IP3 & ↑ DAG).
- **M2 – M4** are linked to Gi (↓ cAMP)

Part 2: Adrenergic agonists (Sympathomimetics)

Actions and chemical structure

- These drugs act either **directly** or **indirectly** (by release of norepinephrine stored), to activate adrenergic receptors and mimic the effects of endogenous catecholamines.
- Not all sympathomimetic drugs activate the adrenergic receptors by the same degree; some drugs have higher affinity towards certain receptor class (**selectivity)** depending on the **ultrastructure** of these receptors; however, in **large doses, this selectivity is lost**.
- Chemically, these drugs may contain catechol nucleus, **(i.e. catecholamines)** or not **(non-catecholamines)**.
- Catecholamines *(e.g. epinephrine, norepinephrine, isoproterenol,* and *dopamine)* are **characterized by:**
  - They are **not absorbed** orally and **cannot pass** the BBB.
  - They have very **short duration** due to **rapid inactivation** by MAO and COMT.



atechol

DIRECT- ACTING SYMPATHOMIMETIC DRUGS

1. Epinephrine (Adrenaline)

Chemistry and pharmacokinetics

- Epinephrine is a natural catecholamine neurotransmitter. Synthetic epinephrine is **poorly absorbed** from the GI tract and **does not pass BBB** to any extent.
- It is administered **parenterally** (i.m. and s.c.). The s.c. absorption is slow due to local VC.
- Nebulized forms (inhalation) are also available.
- It is metabolized rapidly by COMT and MAO. Metabolites are excreted in urine.

Mechanism and pharmacological effects

- Epinephrine activates **all α and β-**adrenoceptors.
- **β** receptors mediate their effects through increase intracellular cAMP.
- **α1** receptors mediate their effects through increase intracellular **I**P3 and DAG.

CVS (The major action)

- Increase **rate** (chronotropic effect) and **force** (inotropic effect) of the cardiac muscle (β1); it may precipitate angina in patients with coronary insufficiency.
- **Increases systolic pressure** due to positive inotropic and

chronotropic effects (β1), and **decreases diastolic pressure** (because VD of skeletal muscle blood vessels (β2) overcomes the VC produced by α1 receptors in skin and splanchnic vascular beds).

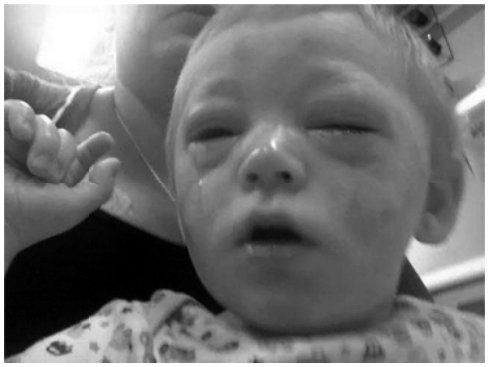
- At high doses, VC (α1) of **all vascular beds** predominates leading to **increase both** systolic and diastolic BP.
- Increase coronary blood flow due to increased cardiac work (accumulation of metabolites), and β2 stimulation (VD).

Respiratory system
- Relaxation of bronchial smooth muscle (β2).
- Decrease bronchial secretions (α1).

Eye
- Mydriasis due to contraction of dilator pupillae muscle (α1)

Metabolic effects
- Hyperglycemia due to stimulation of hepatic glycogenolysis (β2).
- Lipolysis and increase free fatty acids in blood.

Therapeutic uses (emergency conditions)



- **Anaphylactic shock:**
  - It is a life-threatening condition (acute hypersensitivity reaction) resulting from massive release of histamine from inflammatory cells in response to exposure to allergic substance (e.g. penicillin). Histamine causes severe hypotension and bronchoconstriction by its effect on histamine (H1) receptors.
  - Injection of epinephrine immediately dilates the bronchi (β2), decreases bronchial secretions (α1), and elevates BP (VC); so, epinephrine is considered the "**physiological antidote"** of histamine as it can reverse all its effects by actions on different receptors.
  - It is given 0.5 ml (1:1000) i.m. (ideally in the lateral thigh muscles) and could be repeated /5 min if no response.

- **Acute bronchospasm:** within minutes after s.c. administration, epinephrine induces bronchodilation (β2) and decrease airway edema (α1); however, short-acting selective β2 agonists could be used with fewer CVS side effects.

- **Cardiac arrest:** early i.v. epinephrine administration, during cardiopulmonary resuscitation (CPR), can restore cardiac activity (β1) and improve vascular tone collapse (α1). Recommended dose is 1 ml of 1:1000 i.v. or 10 ml 1:10000 i.v.

- **With local anesthetics:** diluted concentrations of epinephrine (1:10000) or norepinephrine are sometimes added to local anesthetics to produce local VC; this will prolong the duration of the anesthetic (due to ↓ absorption of the anesthetic) and reduce bleeding.

Adverse effects

- Cerebral hemorrhage: due to marked elevation of BP.
- Anginal pain from excessive cardiac work and strain.
- Cardiac arrhythmia: especially if given with digoxin, or if given i.v. (i.v. epinephrine can produce fatal ventricular fibrillation).
- Acute pulmonary edema: due to increase both systemic and pulmonary pressures, this cause acute rise of intrapulmonary hydrostatic pressure with hydrostatic flux of fluid.

Contraindications

- **Presence of hypertension:** as it may cause cerebral hemorrhage.
- **Ischemic heart disease.**
- **Cardiac arrhythmia or with digitalis:** epinephrine can worsen the arrhythmia and even precipitate ventricular fibrillation.
- **Cardiac outflow obstruction** (e.g. severe aortic stenosis, severe pulmonary hypertension, hypertrophic obstructive cardiomyopathy). In these conditions, epinephrine will increase contractility of the cardiac muscle against a narrow outlet, so it can precipitate acute pump failure.
- **Thyrotoxicosis:** because patients with thyrotoxicosis have increased sympathetic overactivity (tachycardia, tremors, anxiety, etc) due to **increased sensitivity** of β receptors.

2. Norepinephrine

- It activates **α (mainly) and β1-receptors** leading to increase both systolic and diastolic BP with **reflex bradycardia**.
- It has little activity on β2-receptors.
- It is used as VC (by slow i.v. infusion) in acute hypotensive states.

3. Dopamine

- It is a natural catecholamine given by i.v. infusion because it has very short duration of action (2 min).
- **In low doses:** stimulates dopamine **D1** receptors in renal and mesenteric vascular beds leading to **VD** and increase renal and hepatic blood flow.

The baroreceptor reflex

- It is a physiological reflex concerned with regulation of BP.
- Sudden increase of BP → activation of stretch receptors in the carotid sinus and aortic arch → afferent impulses through the vagus to the CVS centers in the medulla→ decrease HR and vascular tone. Hypotension has opposite effect.
- These receptors begin to respond at pressures ≥170 mm Hg.
- In chronic hypertension, this set point is shifted to higher level.
- Baroreflex is blocked by **atropine.**

- **In intermediate doses:** stimulates **cardiac β1** receptors leading to increase contractility and COP.
- **In large doses:** stimulates **vascular α1** receptors leading to VC and ↑↑ **BP**.

Therapeutic uses

- **Shock states:**

– Shock is a complex state of hypotension associated with impaired tissue perfusion of the vital organs (brain, liver, kidney, etc.).
– Dopamine, given by continuous i.v. infusion, restores adequate tissue perfusion by increasing COP (β1), and increasing renal blood flow (RBF) and glomerular filtration rate (GFR; D1). In high doses, it also stimulates vascular α1 receptors leading to improvement of vascular tone collapse and elevation of BP.
– **N.B.** If vasopressors (e.g. noradrenaline) are given alone, they will elevate BP but aggravate tissue ischemia due to VC.

4. β-adrenoceptor agonists:

a. Selective β1 agonist: Dobutamine

- Dobutamine is a synthetic catecholamine that is related to dopamine. It is administered by i.v. infusion because of its short duration (2 min).
- It activates mainly **cardiac β1**-receptors with **no effect** on dopamine receptors leading to increase COP with little or no vascular effects.
- It is given by continuous i.v. infusion in **cardiogenic shock** (a complication of left ventricular infarction), to reverse myocardial depression and increase COP (β1).

Dopamine	Dobutamine
– Natural catecholamine – Stimulates D > β1 > α1 – Used for treatment of most cases of shock	– Synthetic catecholamine – Stimulates β1 only – Used mainly for treatment of cardiogenic shock

b. Selective β2 agonists:
Salbutamol, terbutaline, salmetrol, formoterol, ritodrine

- They are synthetic non-catecholamines.
- Salbutamol and terbutaline have **short** duration – salmetrol and formoterol have **long** duration.
- They have greater selectivity at **β2** receptors leading to relaxation of bronchial and uterine smooth muscles, and decrease peripheral resistance (VD).
- **In high doses**, selectivity on β2 receptors is **lost,** leading **tachycardia** and even **arrhythmia** (β1).

Therapeutic uses:

- Treatment of **bronchial asthma** (see respiratory for more details).
- **Ritodrine** is commonly used to induce uterine relaxation and delay preterm labor.

Adverse effects

- High doses can cause hypotension (from VD), tachycardia and **arrhythmia** due to loss of selectivity.
- **Tremors:** β2 receptors in skeletal muscles neuromuscular junction facilitate neuromuscular transmission and induce tremors.

c. Non-selective β agonist: Isoproterenol (Isoprenaline)

- Synthetic catecholamine that predominantly stimulates **both β1& β2** receptors.
- It increases HR and contractility, and relax bronchial smooth muscles.
- It is used as a bronchodilator; however, its **nonselectivity** is one of the major drawbacks that makes it **rarely used therapeutically**.

5. α-adrenoceptor agonists:

a. Phenylephrine, methoxamine, and medodrine

- They are non-catecholamines having long duration of action.
- They selectively stimulate **α1**-receptors leading to VC, and increased both systolic and diastolic pressures with **reflex bradycardia**.
- They are used as vasopressors to correct hypotension.
- They could be used **locally** as eye or **nose drops** to produce VC and relieve congestion (i.e. nasal decongestants).

b. Xylometazoline and oxymetazoline

- These drugs stimulate both **α1 and α2** receptors but with slight selectivity toward **α1** receptors.
- They are primarily used **locally** as eye or **nose drops** to produce VC **(nasal decongestants)**.

Adverse effects and precautions

- Sufficient concentrations may be absorbed systemically and produce severe **hypertension** (even stroke); so they must be avoided in hypertensive patients.
- Prolonged and continuous use (> 3 weeks) may lead to **atrophy** of the nasal mucosa (due to VC); so they should be used for the minimum duration.
- Repeated local application leads to **rebound** severe congestion, so they must be used with the minimal dose and for the shortest duration.

c. Clonidine

- It is a centrally acting **α2** agonist leading to **decrease central sympathetic outflow** and **blood pressure** (see page 55).

d. Tizanidine

- It is another centrally acting **α2** agonist (congener of clonidine) with greater effect on presynaptic α2 in the **spinal cord,** so it inhibits neurotransmission and reduces muscle spasm with minimal effect on blood pressure.
- It is used as **skeletal muscle relaxant** in various spastic conditions such as multiple sclerosis, back pain, and spine injuries.

6. Dopamine receptor agonists: Fenoldopam

- It stimulates peripheral dopamine (**D1)** receptors in renal and mesenteric arteries, leading to VD and decrease peripheral resistance.
- It is used parenterally as a **rapid-acting vasodilator** to treat **emergency hypertension** in hospitalized patients.

INDIRECT- ACTING SYMPATHOMIMETIC DRUGS

1. Amphetamine and its derivatives

- Amphetamine and its derivatives are **indirect-acting** adrenergic drugs. They mediates their primarily action by **blocking neuronal uptake** of dopamine and norepinephrine and **promoting their release** from store sites in the CNS and synapses.
- Amphetamine **stimulates** the entire CNS, cortex, brainstem, and medulla. This leads to increased alertness, decreased fatigue, depressed appetite, and insomnia.

Therapeutic uses

– **Methylphenidate** is an amphetamine derivative used in the treatment of attention-deficit/ hyperactivity disorder (ADHD) of children.
– **Modafenil** is another derivative used for treatment of narcolepsy.

Attention deficit hyperactivity disorder (ADHD)

It is a neuropsychiatric disorder appears after the age 6 years. The child is hyperkinetic and lacks attention in addition to poor school performance.

The amphetamine derivative **methylphenidate** is a CNS stimulant that can improve attention spans allowing better function in school, and reduces hyperkinesia associated with this syndrome.

Adverse effects

– High doses cause anxiety, seizures, hypertension, chest pain, and life-threatening arrhythmia.
– Psychosis, hallucinations, and drug dependence.

Narcolepsy is a chronic neurological disorder characterized by intermittent, uncontrollable episodes of falling asleep during the daytime. These sudden sleep attacks may occur during any type of activity at any time of the day.

2. Cocaine

- Cocaine is an alkaloid derived from the coca plant. It is widely **abused** as a recreational stimulant.
- It **inhibits neuronal uptake** of norepinephrine, dopamine, and serotonin leading to their accumulation in the synaptic spaces with profound **CNS stimulation**.
- Adverse effects: similar to amphetamine
- Manifestations of cocaine toxicity is managed by benzodiazepines.

MIXED-ACTING SYMPATHOMIMETIC DRUGS

Ephedrine

- Ephedrine is a **plant alkaloid** effective orally and, unlike catecholamines, penetrates the brain and can produce **CNS stimulation**.
- Ephedrine acts by **both**:
  – Release of norepinephrine from nerve endings.
  – Direct stimulation of **α and β** receptors (weak and prolonged).
- **Tolerance** develops to ephedrine after continuous administration.

Therapeutic uses

– Ephedrine is used as bronchodilator and CNS stimulant, but its clinical use is now **declining** because of the availability of better, more potent agents with fewer side effects.
– **Pseudoephedrine** is one of the four isomers of ephedrine. It is present in many nasal decongestant mixtures.

Chronic orthostatic hypotension

On standing, venous return is reduced by the effect of gravity. Normally, BP decrease is prevented by reflex sympathetic activation with increased HR, and peripheral VC.

Impairment of autonomic reflexes that regulate BP can lead to chronic orthostatic hypotension. This might be caused by drugs that impair autonomic function (e.g., tricyclic antidepressants and α blockers), diabetes, and autonomic neuropathy.

Drugs that activate **α1** receptors (e.g. **Midodrine)** can be used for this indication. **Ephedrine** can be also used (rarely).

Table 4. Selected therapeutic uses of adrenoceptor agonists (sympathomimetics)

Clinical condition	Agonist	Receptor
Cardiac arrest	Epinephrine	β1 – α1
Anaphylactic shock	Epinephrine	β2 – α1
Shock (most types)	Dopamine	D1 - β1
Cardiogenic shock	Dobutamine	β1
Chronic orthostatic hypotension	Midodrine, phenylephrine	α1
Bronchial asthma	Salbutamol, terbutaline, salmetrol	β2
Premature uterine contractions	Ritodrine	β2
Running nose (rhinitis)	Oxymetazoline, xylometazoline	α1
ADHD	Methylphenidate	?
Narcolepsy	Modafenil	?

Part 3: Adrenergic receptor antagonists

These drugs interact with either α- or β-adrenoceptors to prevent or reverse the actions of endogenously released catecholamines or exogenously administered sympathomimetics.

α- ADRENERGIC BLOCKERS

- **Non-selective α-receptor blockers:** phenoxybenzamine, phentolamine
- **Selective α1-receptor blockers:** prazosin , terazosin, doxazosin
- **Selective α2-receptor blockers:** yohimbine
- **The ergot alkaloids.**

1. Non-selective α- blockers: Phenoxybenzamine

- Phenoxybenzamine is a noncompetitive, **irreversible** antagonist at both **α1 and α2** receptors. It binds **covalently** with α receptors, resulting in **long-lasting** blockade (15 –50 h).
- Blockade of α receptors leads to **orthostatic hypotension** and reflex tachycardia.

Therapeutic uses

- **Management of pheochromocytoma**

– Phenoxybenzamine or phentolamine are used for long-term management of inoperable tumors.

– β-receptor antagonists are often given after α-blockers to prevent the cardiac effects of excessive catecholamines (see box).

Adverse effects

– Orthostatic hypotension and reflex tachycardia.
– Impairment of ejaculation.
– Miosis.

2. Selective α1- blockers: Prazosin, terazosin, doxazosin, tamsulosin

- Prazosin is the prototype drug.
- All of these agents decrease peripheral resistance and lower arterial BP by:
  – α1- receptor blockade.
  – Direct VD of both arterial and venous smooth muscles.
- They cause minimal changes in COP, RBF, and the GFR.
- They don't trigger reflex tachycardia by the same degree as the non-selective blockers.
- They improve plasma **lipid profile** and decrease LDL and TGs.
- Doxazosin has the longest duration of action (22 h).

Pheochromocytoma

It is tumor of the adrenal medulla that secretes excess catecholamines → headache, hypertension, palpitations, sweating, and dyspnea. 10% of the tumors are malignant.

Diagnosis:
- CT scan.
- High levels of VMA in urine

Treatment:
- Surgical excision of the tumor.
- Combined **α and β lockers** to block all adrenergic receptors:
  – Phenoxybenzamine 100 mg /day + propranolol 50 mg/day.
  – Start first with phenoxybenzamine to control BP then add β-blocker.
  – **If α-blockers are used alone**, the elevated catecholamines will act on unopposed β-receptors leading to severe palpitations, arrhythmia, etc.
  – **If β-blockers are used alone**, the elevated catecholamines will act on unopposed α-receptors leading to severe hypertension.
- **Labetalol** is a combined **α and β lockers** that could be used alone.

Therapeutic uses

- **Treatment of mild-to-moderate hypertension:** especially in patients with renal failure because it does not decrease RBF or GFR.
- **Treatment of congestive heart failure** because they decrease both the afterload and preload through combined arteriolo- and veno- dilatation (see CVS).
- **Benign prostatic hyperplasia (BPH) and impaired bladder emptying** because blockade of α1 receptors in smooth muscles of the bladder neck and prostate leads to decrease resistance to urine flow. The old drug prazosin is no longer recommended for this indication.

Tamsulosin is the most commonly used for treatment of **BPH** because:

- It has high affinity for α1A & α1D, the 2 receptor subtypes responsible for mediating smooth muscle contraction in prostatic tissue.
- It has little effect on standing BP compared with other α1-blockers.

Salt and water retention induced by BP lowering drugs

- It occurs as a compensatory response after long duration of antihypertensive therapy in the form of ankle edema and slight weight gain.
- Hypotension leads to reflex stimulation of the renin-angiotensin-aldosterone system which causes fluid retention.
- Diuretics are often prescribed with BP lowering drugs to minimize this effect.

Adverse effects

- **First dose hypotension (syncope)**
  - Occurs more frequently with **prazosin**. It starts 30-90 min after the first dose.
  - It occurs more frequently in salt and water depleted patients.
  - Prevention: start with a small dose at bedtime then increase the dose gradually.
- **F**luid retention (salt and water retention): (see box).
- **F**alse positive test for antinuclear factor of rheumatoid arthritis.
- α- blockers can worsen incontinence in women with pelvic floor pathology.

3. Selective α2- blockers: Yohimbine

- Selective presynaptic **α2-blocker** that leads to increase norepinephrine release.
- It is sometimes used as **aphrodisiac** (enhance sexual desire) without clinical evidence.

4. The ergot alkaloids

Chemistry and pharmacokinetics

- Ergots are a wide variety of compounds that are produced by the fungus *Claviceps purpurea.* These agents have a strong structural similarity to norepinephrine, dopamine, and serotonin.
- They may be natural or semi-synthetic:

Natural alkaloids	Semi-synthetic alkaloids
▪ Ergotamine ▪ Ergometrine ▪ Ergotoxine: a mixture of three other alkaloids. It is very toxic and not used clinically.	▪ Dihydroergotamine ▪ Methylergometrine ▪ Dihydroergotoxin ▪ Bromocryptine

- Ergots may be administered parenterally, rectally, or orally, and vary widely in their degree and speed of absorption.
- The absorption of ergotamine is increased by **caffeine**.
- Ergots are extensively metabolized to compounds of varying activity and half-life.

Mechanism and pharmacological effects

- Ergots act as **agonist, antagonist** or **partial agonists** at three receptor types: α-, dopamine, and serotonin receptors.
- The pharmacologic use of ergots is determined by the relative effect of each member on these receptors.

Drug	Receptor	Main effect	Main uses
Ergotamine	Partial agonist at α- and 5-HT receptors	Direct VC with greater effect on cerebral BVs	Acute migraine attacks
Methlyergometrine	α-receptors agonist	Uterine smooth muscle contraction	Postpartum hemorrhage
Dihydroergotoxin	α-receptors antagonist	VD with greater effect on cerebral BVs	Senile cerebral insufficiency
Bromocryptine	Dopamine agonist	Pituitary and nigrostriatal pathway	Suppress lactation and ttt of parkinsonism

Therapeutic uses

- **Ergotamine: acute migraine**
  - The major effect of ergotamine is cerebral VC by a direct action; it reverses the rebound VD that is the probable cause of pain.
  - It should be given at the start of aura because it has slow onset. It is better to be combined with **caffeine** because caffeine increases its absorption.
  - If given before aura (e.g. for prophylaxis), it can induce cerebral VC and precipitates the acute attack (i.e. contraindicated).
  - The VC induced by ergotamine is long-lasting and cumulative; therefore, patients must not take more than 6 mg of the oral preparation for each attack.

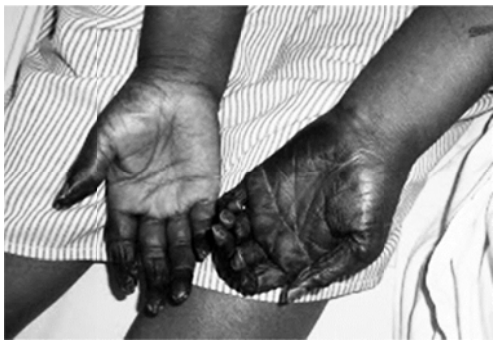
- **Methylergometrine: postpartum hemorrhage**
  - It causes prolonged and forceful contraction of uterine smooth muscles**.**
  - Ergots should **not be used to induce labor**. It should be given at the time of placenta delivery (3rd stage of labor) and never before that. If it is given before delivery of the placenta, it causes severe spasm of uterine smooth muscles and retained placenta.

- **Bromocriptine: hyperprolactinemia**
  - Bromocriptine is a dopamine receptor agonist that causes inhibition of prolactin secretion *(high prolactin levels can induce infertility and amenorrhea in women).*
  - It is used to suppress normal lactation and as a dopamine alternative in Parkinson's disease

- **Dihydroergotoxin:** used as cerebral vasodilator in senile cerebral insufficiency.

Adverse effects of ergot alkaloids

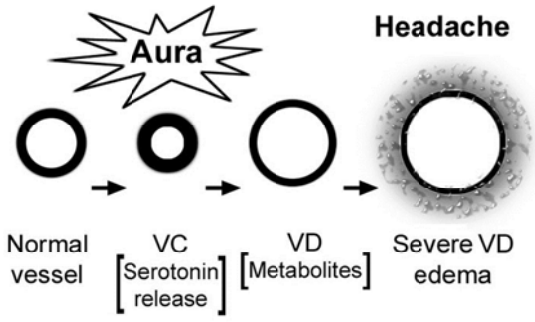
- Nausea and vomiting due to stimulation of CTZ.
- High doses cause VC of small arterioles of fingers leading to cold hands and even gangrene (ergotism).
- VC of coronary artery with anginal pain.
- Uterine contraction and abortion if given during pregnancy.



MIGRAINE AND SOME DRUG TREATMENTS

Migraine is severe unilateral periodic headache characterized by:

- **The stage of aura:** occurs in 15-30% of cases. Sudden release of serotonin (and other mediators) of unknown etiology causing VC of cerebral BV → visual, olfactory or auditory hallucinations.
- **The stage of pain:** prolonged VC leads accumulation of waste metabolites → severe VD → perivascular edema and severe headache.



Pathophysiology of migraine

The exact aetiology of migraine is not clearly understood but the serotonin hypothesis is widely accepted

Drugs used in the acute attack

- **Ergotamine** and **dihydroergotamine** (see before).
- **Triptans: sumatriptan, zolmitriptan**
  - They are agonists at **5-HT$_{1D}$** and **5-HT$_{1B}$** receptors.
  - Activation of **5-HT$_{1D}$** receptors inhibits inflammation of meninges, pain transmission, and release of VD substances e.g. calcitonin gene-related peptide in trigeminal neurons. Activation of **5-HT$_{1B}$** receptors causes VC of the dilated cerebral vessels. About 50%–80% of patients report relief from pain within 2 hours after oral administration.

- 5-HT_{1B} activity can cause **coronary spasm** so; these drugs are contraindicated in patients with ischemic heart disease (IHD).
- Like ergotamine, they are also **contraindicated** for prophylaxis of migraine or in combination with ergotamine because severe hypertension and coronary spasm may occur.

Drugs used for prophylaxis

- Propranolol: the most commonly used drug for prophylaxis.
- Ca^{2+} channel blockers: verapamil (unclear mechanism).
- Clonidine: (unclear mechanism).
- Tricyclic antidepressant (TCA) drugs.

β- ADRENERGIC BLOCKERS

The β-receptor–blocking drugs differ in their relative affinities for β1 and β2 receptors; however, the **selectivity is dose-related** and tends to diminish at higher doses.

- **Non-selective β-blockers:** e.g. propranolol, pindolol, timolol, sotalol, nadolol
- **Cardio-selective β_1-blockers:** e.g. atenolol, metoprolol, bisoprolol, nebivolol.
- **β-blockers with additional VD action:** e.g. dilevalol, carvedilol

  N.B. the VD action comes from either: blocking the vascular **α1** receptors; increasing PGE_2 and PGI_2 synthesis; or by release of endothelial NO.

Chemistry and pharmacokinetics

- **Propranolol** is the prototype β-adrenoreceptor antagonist.
- β-blockers are absorbed well after oral administration, many have **low bioavailability** because of extensive first-pass metabolism.
- **Lipophilic** β-blockers (e.g. **propranolol**) can pass readily to the CNS and are cleared by hepatic metabolism. **Hydrophilic** β-blockers (e.g. **atenolol**) have limited penetration to the CNS and are excreted primarily by the kidney with little hepatic metabolism.
- β-blockers which undergo **hepatic** metabolism usually require **multiple** daily dosing. Drugs eliminated via the **kidney** are suitable for **once** daily administration.

Mechanism and pharmacological effects

CVS effects

- They block cardiac β1 receptors and **decrease all cardiac properties** (↓ contractility and COP, ↓ A-V conduction **"bradycardia"**, ↓ excitability, and automaticity).

- They **block the β2-mediated VD** in peripheral vessels leading to ↓ blood flow to most tissues.
- **They decrease blood pressure through:**
  - ↓↓ COP by their –ve inotropic and chronotropic effects.
  - ↓↓ renin release from the kidney (β1).
  - ↓↓ norepinephrine release and central sympathetic outflow (by blocking presynaptic β2).
  - They cause resetting of baroreceptors to a lower level (see before).
  - Some β-blockers block also vascular α1 receptors.
  - Some β-blockers enhance synthesis of vasodilator PGE_2 and PGI_2.

Respiratory

- β-blockers produce **bronchospasm** as a result of β2-receptor blockade; this effect is more significant in **asthmatic patients**.
- Even **selective** β1 blockers can interact with β2 receptors in high doses and produce bronchospasm, especially in asthmatic patients.

Eye

- ↓ IOP by decreasing aqueous humor secretion from the ciliary epithelium (**timolol** and **betaxolol** have excellent effect).
- Sufficient timolol can be absorbed after topical application to increase airway resistance and decrease HR and contractility.

Metabolic effects

- Inhibition of **glycogenolysis** in the liver (β2) leading to aggravation of hypoglycemic effect of insulin and other hypoglycemic drugs.
- ↑ plasma K^+ (hyperkalemia) in **patients with renal failure**.
- ↑ plasma triglycerides and ↓ HDL.

CNS

- Antianxiety effects.
- Night mares, vivid dreams, and depression.
- Sexual dysfunction through combined central and peripheral mechanisms.

Skeletal ms

- ↓ essential **tremors** due to blocking of β2 in skeletal muscles.

Other specific properties

- **Propranolol** has <u>local anesthetic</u> (membrane stabilizing) action i.e. it can inhibit excitability of the cardiac muscle.
- **Pindolol** is a <u>partial agonist</u> i.e. it doesn't cause excessive bradycardia.
- **Esmolol** is <u>ultrashort acting</u> (t1/2 = 10min) because of extensive hydrolysis by plasma esterases; it is administered by i.v. infusion to control arrhythmia during surgery and emergency situations.
- **Labetalol** blocks β-receptors and α1-receptors (<u>mixed blocker</u>).

- **Carvedilol** has additional antioxidant action.
- **Nebivolol** is the most selective β1 blocker.

Therapeutic uses

- **Treatment of hypertension:** (see the mechanisms above). All beta-blockers, irrespective of their properties, lower BP to a similar extent.

- **Ischemic heart disease (classic angina** and **acute MI)**
  - They decrease contractility, HR, and systolic BP, thus decrease myocardial work and O_2 demand (in acute myocardial infarction (AMI), β-blockers given within 6-12 h can decrease the infarct size).
  - They increase the diastolic (coronary) filling time.
  - They cause redistribution of blood to the ischemic (subendocardial) regions.
  - β-blockers improve myocardial metabolism through metabolic switching from *fat* utilization to *carbohydrates* utilization (cytoprotective effect).

- **Cardiac arrhythmias** (especially thyrotoxic and supraventricular arrhythmia).
  - They decrease A-V conduction, lengthen the refractory periods of the SA node, and suppress automaticity.
  - Propranolol decreases excitability through its membrane stabilizing action.
  - Acute arrhythmia during **surgery** is treated by i.v. **esmolol**.

- **Hypertrophic obstructive cardiomyopathy**
  - It is a congenital thickening of the ventricular wall and interventricular septum. It is the most common cause of sudden death in young athletes. Thickening of the interventricular septum impairs blood flow through the aortic outlet especially during exercise.
  - Drugs having –ve inotropic effect such as β-blockers and verapamil decrease HR and contractility, thus decrease the outflow tract resistance. Drugs with +ve inotropic effects (e.g. digoxin) have the opposite effect.

- **Hyperthyroidism:** propranolol is used to control tachycardia, anxiety, and tremors due to sympathetic overactivity in hyperthyroidism. It also prevents peripheral conversion of T_4 into T_3.

- **Esophageal varices due to liver cirrhosis:** propranolol is used to decrease portal and hepatic blood flow through combined decrease of COP and inducing VC in the splanchnic vascular bed (through an unopposed α-action).

- **Open angel glaucoma:** topical timolol or betaxolol ↓ aq humor secretion.

- **Other uses:** pheochromocytoma (must be combined with alpha-blockers); and prophylaxis of migraine (propranolol has an unclear mechanism).

Adverse effects

- Tiredness and **fatigue** (the most common side effect) due to reduced COP and block of β2-mediated VD in skeletal muscles (mainly non-selective agents).
- **Bradycardia** and impairment of myocardial contractility, so they can precipitate **heart failure** or **heart block** in patients with compromised cardiac function.
- **Bronchospasm** in susceptible individuals due to blockade of β2-receptors which mediate dilation in the bronchi. Asthma is an absolute contraindication for **all** beta-blockers.
- Aggravation of **peripheral ischemia** and cold extremities (mainly non-selective agents). (selective β-blockers are the preferred class if there is associated peripheral vascular disease).
- In diabetic patients, β-blockers (mainly non-selective) can potentiate the **hypoglycemic effect** of insulin and oral hypoglycemic drugs (because they block glycogenolysis), and **mask tachycardia & tremors** resulting from severe hypoglycemia.
- **CNS effects:** vivid dreams, night mares, and depression.
- **Sudden withdrawal** can increase the risk of **angina** and **arrhythmias** due to adrenoceptor "supersensitivity". Gradual withdrawal is recommended.

Heart block

Heart block means block of the electrical conduction at any point in the conducting system e.g. SA nodal block, AV nodal block, or bundle branch block.

N.B.

Excessive **myocardial depression** caused by overdose of β-blockers can be reversed by **i.m. glucagon**. This is because β-blockers decrease intracellular cAMP making all β-agonists acting through cAMP is useless. Glucagon increases **contractility** by a mechanism unrelated to cAMP.

Contraindications

- **Absolute contraindications**
  - Bronchial asthma.
  - Any degree of heart block.
  - Prinzmetal's (vasospastic) angina (see CVS).
  - Sudden withdrawal after long-term use.
- **Relative contraindications**
  - Acute – or severe chronic heart failure.
  - Peripheral vascular diseases (PVD).
  - Diabetes mellitus.
  - In athletes involved in strenuous sports because beta-blockers can interfere with the ability to perform strenuous physical activities.

Part 4: Sympathoplegic drugs

CENTRALLY-ACTING SYMPATHOPLEGIC DRUGS

1. Alpha-methyldopa

Mechanism and pharmacological effects

In the CNS, α-methyldopa competes with dopa for *dopa decarboxylase* enzyme leading to formation of α-methylnorepinephrine, (and also α-methyldopamine), which is a false transmitter. α-methylnorepinephrine stimulates **central α2** receptors leading to reduced central sympathetic outflow and decreased BP.

Therapeutic uses

Methyldopa is the drug of choice to treat arterial **hypertension in pregnancy** because of its long and reliable track record.

Adverse effects

- The most common side effect is **sedation, nightmares,** and **mental depression** due to central deficiency of norepinephrine.
- Mild hyperprolactinemia and extrapyramidal manifestations due to central deficiency of dopamine.
- **Positive Coombs test** and autoimmune hemolytic anemia.
- Autoimmune hepatitis is **rare**.

2. Clonidine

Mechanism and pharmacological effects

- Clonidine is a **central α2-receptor agonist** leading to decreased central sympathetic outflow and reduction in the total peripheral resistance.
- Reduction of BP is **not** associated with changes of the RBF or GFR.

Therapeutic uses

- It is mainly used in the management of **hypertension complicated by renal disease.**
- To **reduce anxiety** accompanying **opiate withdrawal** or surgical operations.

Adverse effects

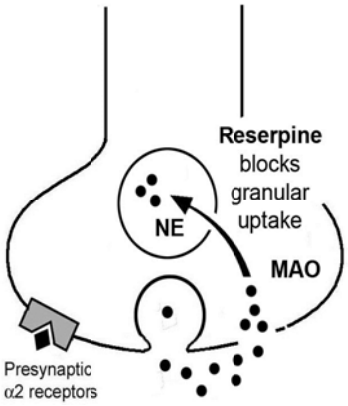
- **S**edation and dry mouth (central effect).
- **S**udden withdrawal of the drug can lead to **rebound hypertension**.
- **S**alt and water retention so it is usually combined with diuretics.

ADRENERGIC NEURON BLOCKERS

Reserpine

Mechanism and pharmacological effects

- Reserpine is a plant alkaloid that blocks **vesicular uptake** of the neurotransmitters norepinephrine, dopamine, and serotonin in both central and peripheral neurons, as well as adrenal medulla.
- These transmitters accumulate in the neuronal cytoplasm and are degraded by MAO enzyme, leading finally to **depletion** of the nervous system from these biogenic amines.
- The effect of reserpine is **slow** and **persists** for many days after discontinuation.



Therapeutic uses

Treatment of mild-to moderate hypertension; however, it is now not considered among the first or second line drugs because of numerous adverse effects.

Adverse effects

- The most important side effect is **sedation, nightmares,** and **mental depression** (2%) due to central depletion of both norepinephrine and serotonin.
- Hyperprolactinemia and extrapyramidal manifestations (parkinsonism) may occur due to central depletion of dopamine.
- GIT symptoms (abdominal cramps, mild diarrhea, increase HCl) are common due to overpredominance of parasympathetic activity.

Part 5: Parasympathomimetic drugs (Cholinomimetics)

- The parent compound of all cholinomimetic drugs is **acetylcholine**.
- **ACh is the natural neurotransmitter in the following sites:**
  - All autonomic ganglia whether sympathetic or parasympathetic.
  - Parasympathetic nerve endings to involuntary organs and exocrine glands.
  - Sympathetic nerve endings to thermoregulatory sweat glands.
  - Sympathetic nerve endings to adrenal medulla.
  - Skeletal muscle motor end plate.
  - Certain tracts within the CNS
- ACh acts on both **muscarinic** and **nicotinic** receptors to produce all the effects listed in **table 1**, and **table 3** (see before).
- ACh is **not used clinically** because: (1) it has very short duration of action (seconds) due to rapid hydrolysis by AChE enzyme; and, (2) it lacks selectivity.
- **Cholinomimetic drugs** are drugs that produce effects similar to ACh or cholinergic nerve stimulation, but with **more selectivity** and **fewer side effects** than ACh.

Classification of cholinomimetic drugs

Direct-acting cholinomimetics	Indirect-acting cholinomimetics
They act by **direct stimulation** of cholinergic receptors	They act by **inhibition of AChE enzyme** leading to accumulation of ACh.
■ **Muscarinic agonists** Bethanecol, carbachol Pilocarpine, cevimeline	■ **Reversible ChE inhibitors:** Physostigmine, neostigmine, pyridostigmine, donepezil
■ **Nicotinic agonists** Nicotine, lobeline	■ **Irreversible ChE inhibitors:** Organophosphate compounds

DIRECT-ACTING PARASYMPATHOMIMETICS

Muscarinic agonists:

Pharmacological effects:

CVS
- ↓ AV conduction and HR (M2).
- VD of all vascular beds through release of EDRF (M3).

Respiratory effects
- Contraction of bronchial smooth muscle (M3).
- ↑ bronchial secretions (M3).

Eye	▪ **Miosis** due to contraction of constrictor pupillae muscle (M3). ▪ Accommodation for **near vision** due to contraction of ciliary muscle (M3). ▪ ↓ IOP (contraction of the ciliary muscle causing opening of the trabecular meshwork and facilitates drainage of aq humor).
GI tract	▪ ↑ motility and relaxation of sphincters (M3). ▪ Salivation (M3) and increase HCl secretion (M1).
Urinary tract	▪ Contraction of bladder smooth muscles (M3). ▪ Relaxation of sphincters (M3).
Exocrine gld	▪ ↑ all exocrine secretions, salivation, lacrimation, sweating, etc.

1. Carbachol

- It is choline ester but resistant to hydrolysis by AChE enzyme.
- It stimulates both **muscarinic** and **nicotinic** receptors.
- It is used as **local eye drops** to ↓ IOP in **glaucoma**. It contracts the ciliary ms causing opening of the trabecular meshwork and facilitates drainage of aq humor.

2. Bethanecol

- It is a choline ester but resistant to hydrolysis by AChE enzyme, so it has long duration of action (2-3 h) as compared to Ach.
- It stimulates **muscarinic** receptors with **no activity on nicotinic receptors**.
- It is used to reverse **post-operative urine retention** and **paralytic ileus** (in absence of organic obstruction).

N.B.

- Bethanechol is administered orally or s.c., **not by i.v. or i.m.,** because parenteral administration may cause **cardiac arrest**.
- Bethanechol is contraindicated to treat urine retention due to **mechanical obstruction** of the bladder or intestine because increasing contraction against a closed outlet can lead to **rupture** of the viscus.

3. Cevimeline and pilocarpine

- Cevimeline is synthetic drug – pilocarpine is a natural plant alkaloid.
- Both drugs act as **muscarinic agonists** with **no nicotinic effects**.
- Both drugs can be given orally to **increase salivary secretion** and decrease symptoms of dry mouth (xerostomia) associated with **Sjögren syndrome.**
- Pilocarpine is used as **local eye drops** to ↓ IOP in **glaucoma**.

Adverse effects of muscarinic agonists

– Most important side effects include nausea, vomiting, sweating, salivation, **bronchoconstriction**, hypotension, and diarrhea; all of which can be blocked by **atropine**.

Contraindications of muscarinic agonists

– Peptic ulcer
– Bronchial asthma
– Heart block.

Nicotinic agonists:

1. Nicotine

- It is a component of cigarette smoke. It is a **poison** with many adverse effects and **no therapeutic** benefit.
- The overall effects of nicotine are complex and result from **mixed** stimulation and inhibition of all autonomic ganglia:
  - ***Small doses*** stimulate autonomic ganglia leading to hypertension, tachycardia, increase GIT peristalsis, increase HCl secretion, and CNS stimulation.
  - ***Toxic doses*** lead to hypotension and CNS depression due to ganglion blockade.
- Nicotine is addictive substance. **Transdermal patches** containing nicotine are used to help smokers stop smoking.

2. Varenicline

- It is nicotinic receptor **partial agonist** used for smoking cessation.
- **Headache** and nausea are the most common adverse effects.
- Contraindicated in **pregnancy** and breast feeding.

How smoking elevates blood pressure?

- Nicotine stimulates sympathetic ganglia and suprerenal medulla causing release of catecholamines with subsequent VC and increase HR.
- Nicotine stimulates ADH (vasopressin) release from posterior pituitary.
- Tobacco smoke cause vascular endothelial dysfunction and accelerates atherogensis.

Smoking cessation

Patients should be offered **nicotine replacement therapy (NRT)** or **varenicline**. The two prescriptions should not be combined together.

Nicotine replacement therapy

These are nicotine containing transdermal patches. It should be started 2 weeks before the target date to stop.

Varenicline

- It should be started 1 week before the target date to stop. The recommended course of treatment is 12 weeks.

INDIRECT-ACTING PARASYMPATHOMIMETICS (Cholinesterase inhibitors)

Mechanism and pharmacological effects

- Indirect-acting parasympathomimetics **inhibit AChE enzyme** resulting in accumulation of ACh and stimulation of both **muscarinic** and **nicotinic** receptors.
- They are classified, according to nature and duration of **AChE inhibition,** into **reversible** and **irreversible** inhibitors.

Reversible AChE inhibitors:

They interact with AChE enzyme by making **reversible bond** allowing duration of inhibition lasting from minutes to hours.

1. Physostigmine

- Natural plant alkaloid (tertiary amine) that is well-absorbed from the GIT and **can pass to CNS**.
- It can reversibly inhibit AChE enzyme for 3-4 hours, leading to:
  - ***Muscarinic effects:*** hypotension, bradycardia, salivation, lacrimation, increased GIT peristalsis (diarrhea and colic), miosis, etc.
  - ***Nicotinic effects:*** skeletal muscle contraction.
  - ***Central effects:*** headache, insomnia, excitation, and convulsions.

Therapeutic uses

- Because of lack of selectivity and harmful CNS effects, it is usually used as **local eye drops** to produce miosis and treat chronic **glaucoma**.
- Physostigmine can be used to reverse the central and peripheral manifestations of **atropine poisoning**.

2. Neostigmine

- Synthetic drug (quaternary amine) that is **poorly absorbed** from the GIT and **cannot pass to CNS**.
- It is similar to physostigmine in mechanism and effects but it has **no CNS actions**.

Therapeutic uses

- To reverse postoperative **urine retention** and **paralytic ileus**. It is contraindicated if there is **mechanical obstruction** (to avoid rupture of the bladder or intestine).

- To reverse postoperative **muscle paralysis** resulting from the use of non-depolarizing neuromuscular blockers.
- Treatment of **myasthenia gravis:**
  - Neostigmine not only increases ACh level in the neuromuscular junction but also can **directly stimulate** nicotinic receptors at the motor end plate.
  - **Atropine** could be given with neostigmine to block the unwanted muscarinic effects caused by excessive ACh.

3. Pyridostigmine

- Reversible AChE inhibitor similar to neostigmine.
- It is more preferred than neostigmine in the chronic treatment of **myasthenia gravis** because:
  - It has more selective action on neuromuscular junction (fewer unwanted muscarinic effects).
  - It has longer duration of action than neostigmine.

4. Edrophonium

- It acts as the same of neostigmine and pyridostigmine but has very short duration of action (5-15 minutes).
- It is used in the **diagnosis of myasthenia gravis** and to differentiate between muscle weakness due to insufficient treatment of myasthenia, or due to excessive treatment with AChE inhibitors (Tensilon test).

Myasthenia gravis

- Myasthenia gravis is an **autoimmune disease** in which antibodies complex with nicotinic receptors at the neuromuscular junction to cause skeletal muscle weakness
- AChE inhibitors, such as **pyridostigmine**, are used to increase ACh levels at the neuromuscular junction to fully activate the remaining receptors.
- Myasthenia gravis can be diagnosed using the **Tensilon test**, which can also assess the adequacy of treatment with AChE inhibitors.

Alzheimer's disease

- Alzheimer's disease is chronic degenerative disease characterized by progressive impairment of memory and cognitive functions.
- Pathologic changes include increased deposits of amyloid β peptide and abnormal protein (tau protein) in the cerebral cortex, leading to cerebral vascular lesions, and progressive loss of **cholinergic neurons**.
- Although evidence for the benefit of AChE inhibitors is statistically significant, the clinical benefit from these drugs is mild and temporary.

- **Tensilon test**: small doses of **edrophonium** improve muscle strength in untreated patients with myasthenia, but worsen muscle weakness if it was due to excessive dose of AChE inhibitors (excessive ACh stimulation at the neuromuscular junction results in muscle weakness due to maintained depolarization).

5. Donepezil and rivastigmine

- They are AChE inhibitors that act more selectively on **central AChE** enzyme.
- They are used to increase ACh levels in the CNS and thus improve memory and cognitive deficit associated with **Alzheimer's disease** (see box).

Irreversible ChE inhibitors: Organophosphate compounds

- They include:
  - **Drugs:** echothiophate eye drops
  - **Insecticides:** parathion and malathion
  - **Nerve gases:** sarin and soman

- Organophosphates are **highly lipid soluble** and rapidly absorbed by all routes including the **skin**. Their **CNS** penetration is rapid and high.
- They interact with AChE enzyme by making **irreversible (covalent) bond** (i.e. phosphorylation of the enzyme).
- As time passes, the strength of the bond increases, (a process called **"aging"**), and AChE becomes **irreversibly** inhibited. *(With most types of organophosphates, 50% of the enzyme undego aging after 3 hrs and 95% after 12 hrs).*
- Once AChE is inhibited, ACh accumulates throughout the nervous system, causing muscarinic and nicotinic symptoms.
- **Echothiophate** is the only non-absorbable organophosphate. It is available as miotic **eye drops** for **glaucoma**. Its effect in the eye lasts for weeks.

Manifestations of organophosphate toxicity:

- **CVS:** hypotension, bradycardia, sweating.
- **Respiratory:** bronchospasm, increase bronchial secretions, respiratory ms paralysis.
- **GIT:** abdominal colic, diarrhea, and salivation.
- **Eye:** severe miosis *(pinpoint pupil)*, lacrimation.
- **CNS:** hallucinations, convulsions, and coma.
- **Skeletal ms:** twitches and fasciculation.
- **The cause of death** is respiratory failure (blocked airway, paralyzed respiratory ms & inhibited RC).

The DUMBELS syndrome:

D: Diarrhea & colic.
U: Urination.
M: Miosis.
B: Bradycardia & Bronchospasm
E: Emesis (vomiting) Excitaion of CNS
L: Lacrimation.
S: Salivation & Sweating. Skeletal ms twitches

Management

- Ensure patent airway and artificial respiration.
- Gastric lavage and skin wash to remove the toxin.

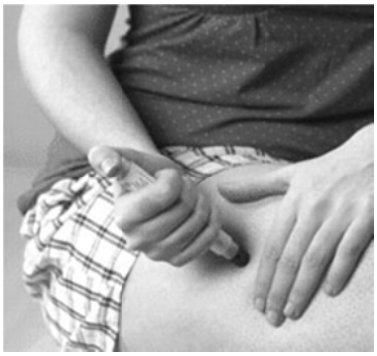
- Intravenous normal saline to raise BP.
- **The triad: atropine – pralidoxime – diazepam**

Atropine (2 mg i.v. bolus)

- Atropine is non-selective muscarinic blocker and can cross BBB to block all muscarinic manifestations of excess ACh **centrally** and **peripherally.**
- Check pulse and BP after 5 min; if no response, repeat the dose of atropine till the HR is > 80 bpm and systolic BP > 80 mmHg.
- The patient should be maintained atropinized for 24-48 hrs because organophosphates are highly lipid soluble. So, it may dissolve in body fat and released again over time.

Pralidoxime (PAM; 2 gm i.v. over 20-30 min)

- It is also available as ready-to-use autoinjector.
- If given early (before aging), it can **reactivate** (dephosphorylate) AChE enzyme especially at the neuromuscular junction.
- Pralidoxime is only effective in organophosphate toxicity (i.e. it does not have an effect if AChE enzyme is carbamylated, as occurs with neostigmine or physostigmine).



Diazepam (10 mg i.v. or i.m.): to control convulsions.

Table 5. Selective therapeutic indications of parasympathomimetics

Clinical condition	Drug	Receptor
Postoperative urine retention and paralytic ileus	Bethanechol (direct) Neostigmine (indirect)	M3 M & N
Glaucoma	Pilocarpine, Carbachol, physostigmine	M3 M & N
Xerostomia	Cevemeline	M3
Alzheimer's disease	Donepezil, rivastigmine	M & N
Myasthenia gravis	Neostigmine, pyridostigmine	Nm
Diagnosis of myasthenia	Edrophonium	Nm
Atropine toxicity	Physostigmine	M & N

Part 6: Muscarinic antagonists

Actions and chemical structure

They are either tertiary amine alkaloids or quaternary amines:

- **Plant alkaloids:** atropine is found in *Atropa belladonna* and scopolamine (hyoscine) is found in *Hyoscyamus niger.* They are tertiary amines (i.e. well absorbed and can pass to **CNS**).
- **Synthetic derivatives:** are either tertiary or quaternary amines (limited **CNS** penetration):
  - Drugs used mainly as **bronchodilators:** Ipratropium
  - Drugs used mainly as **antispasmodics:** Hyoscine butylbromide
  - Drugs used mainly to **decrease HCl secretion:** Pirenzepine
  - Drugs used mainly for **genitourinary system:** Oxybutynin, tolterodine
  - Drugs used mainly as **mydriatics:** Homatropine, tropicamide
  - Drugs used mainly to treat **parkinsonism:** Benztropine

Mechanism and pharmacological effects

Muscarinic-receptor antagonists are **competitive antagonists** of ACh at all muscarinic receptors.

CVS effects	▪ They block M2 receptors in the SA node and **increase HR**. ▪ **No significant effect on the force of contraction** because there are no muscarinic receptors, or parasympathetic innervation of the ventricles. ▪ Blockade of vascular M3 receptors has **no significant clinical value.** ▪ High doses cause **toxic VD** in the facial blush area **(atropine flush)** which is not related to the antagonistic action.
Respiratory	▪ Bronchodilatation and decrease mucus secretion.
GIT	▪ Decrease salivation and HCl secretion. ▪ Decrease motility (antispasmodic action).
Urinary bladder	▪ Relaxation of the bladder smooth muscles and contraction of the sphincters leading to **urine retention**.
Sweat glands	▪ Blocking of muscarinic receptors in thermoregulatory sweat glands (cholinergic) leading to **dry skin** and elevation of body temperature **(atropine fever)**. ▪ **Children** are more sensitive to this effect.
Eye	▪ Passive **mydriasis** due to paralysis of constrictor pupillae muscle.

- **Cycloplegia** (paralysis of ciliary muscle) leading to loss of accommodation for near vision.
- Increase **IOP** due to mydriasis (decrease aqueous humor drainage).

CNS

- **Tertiary amines** can produce sedation, amnesia, delirium, and hallucinations.

Therapeutic uses

CVS:

- **Bradycardia:** parenteral **atropine** is the standard drug for most cases of bradycardia including **reflex** bradycardia caused by vasopressor drugs.

Respiratory:

- **Bronchial asthma: Ipratropium** is a quaternary amine. It has greater selectivity for the bronchial tissue and **limited CNS effects**. It is given by inhalation to dilate the bronchi and reduce secretions in asthma and chronic obstructive pulmonary disease (COPD).
- **Preanesthetic medication:** Preanesthetic injection of **atropine** is used in order to:
  - Prevent bronchoconstriction and reduce bronchial secretions caused by excessive vagal stimulation during anesthesia.
  - Protect the heart from excessive vagal tone (bradycardia) occurred during anaesthesia.

GIT disorders:

- **Peptic ulcer: pirenzepine** has greater selectivity for blocking M1 receptors in the stomach and reduce HCl secretion; however, it is now **rarely used** because of the availability of new and more potent drugs.
- **Diarrhea:** the classic combination of **atropine** with **diphenoxylate**, (a congener of meperidine), is available under many names (e.g, Lomotil). They decrease hypermotility and secretions.
- **Abdominal colic:** e.g. hyoscine butylbromide (Buscoban).

Urinary disorder:

- **Acute cystitis: oxybutynin** is used to decrease bladder spasm and urinary urgency associated with inflammatory bladder disorders.
- **Urine incontinence in adults: tolterodine** is a new muscarinic antagonist used for this indication because it has **greater selectivity** for bladder M3 receptors and has **long duration** of action.

Eye:

- **Funduscopic examination:** muscarinic antagonists are used as eye drops **(cyclopentolate; tropicamide)** to produce mydriasis and cycloplegia and facilitate retinal examination; however, **phenylephrine** (α-agonist) is preferred for simple fundus examination due to its **short duration**.
- **Iridocyclitis:** inflammation of the iris can cause adhesions between the iris and lens (synechia). Long acting **atropine** eye drops is used to produce complete cycloplegia and mydriasis (M3) to prevent this adhesion.

CNS:

- **Parkinson's disease: benztropine** has greater selectivity for blocking the muscarinic receptors in the **basal ganglia** and decrease the excitatory effect of ACh.
- **Motion sickness: scopolamine** (hyoscine) is the standard drug used for this indication. It blocks muscarinic receptors in the **vestibulocerebellar** pathway that are responsible partially for the nausea and vomiting.

Motion sickness

- It is a very common disturbance of the inner ear that is caused by repeated motion such as from the movement of a car or ship.
- Bizarre head movement affects the organs of balance and equilibrium (vestibulocerebellar apparatus) causing nausea and vomiting.
- Overactivity of **muscarinic receptors** is suspected to play an important role in this condition.

Other:

- **Organophosphate toxicity: atropine** is the standard drug (see before).

Adverse effects

- Blurred vision (due to mydriasis and cycloplegia).
- Rise of IOP (**glaucoma**).
- **Dryness** of all body secretions: dry mouth, dry skin, dry eyes, etc..
- **Urine retention** especially in patients with **senile enlarged prostate**.
- Tachycardia.
- **In children:** atropine **fever** (due to blockade of thermoregulatory sweating resulting in hyperthermia) and **flush** . Children are more sensitive to this effect.

Contraindications

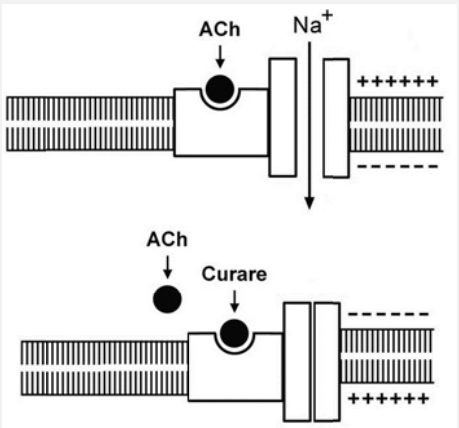
- Narrow angle glaucoma
- Obstructive diseases of the GIT (e.g. pyloric stenosis), paralytic ileus, intestinal atony of the elderly, etc.
- Urine retention due to **senile enlarged prostate**
- It should be used with caution in children.

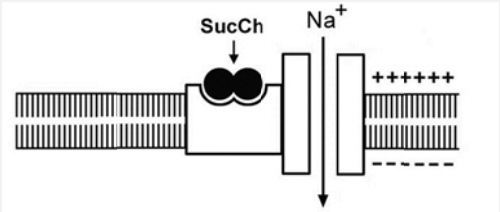
Part 7: Ganglion blocking drugs

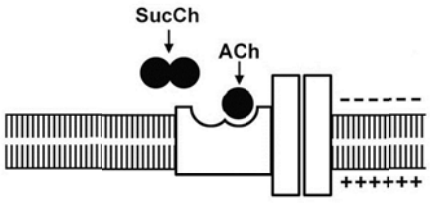
- **Trimethaphan** and **mecamylamine** are competitive blockers of ACh at nicotinic receptors at both sympathetic and parasympathetic ganglia.
- Because of lack of selectivity and **numerous adverse effects**, they are **used rarely** in the clinical setting hypertensive emergencies).

Part 8: Neuromuscular blockers

	Non-depolarizing NMBs	Depolarizing NMBs
members	■ **Tubocurarine** (prototype) is rarely used clinically at this time ■ **Semisynthetic derivatives:** – Mivacurium – Atracurium and *Cis*atracurium – Vecuronium	■ **Succinylcholine** (It is ester of ACh)
Absorption and distribution	– All members are not absorbed orally because they are **polar** compounds (quaternary amines), they must be given **parenterally**. – All cannot cross BBB or placental barrier	
Metabolism	– Atracurium: spontaneous plasma hydrolysis. Breakdown products may cause **seizures.** – Vecuronium: liver.	– By plasma pseudo ChE enzyme
Duration	– Mivacurium: 10-20 min – Atracurium: 20-30 min – Vecuronium: 30 -40 min	– Few minutes.
Mechanism of action	– **Competitive block** of Ach at **Nm** receptors → muscle paralysis. – Muscle paralysis can be reversed by excess Ach (AChE inhibitors).	– **Depolarizing block** of **Nm** receptors → ms paralysis through **2 phases:** ▪ **Phase 1:** initial depolarization → transient ms contraction followed by paralysis due to maintained depolarization

<table>
<tr>
<td></td>
<td></td>
<td>(depolarization block).
▪ Phase 2: the muscle becomes repolarized again but remains insensetive to stimulation by Ach (i.e. it needs ↑ Ach to be stimulated) (desensitization block).</td>
</tr>
<tr>
<td></td>
<td> 

Curare competitively blocks ACh Nm receptors and could be abolished by excess ACh.</td>
<td> 

Phase 1. Initial depolarization resulting in sudden and severe ms contraction


Phase 2. The membrane becomes repolarized again but remains insensetive to stimulation by Ach</td>
</tr>
<tr>
<td>Reversal of block</td>
<td>– Neostigmine can reverse the block by increasing Ach level at NMJ and displace competitive blockers from the receptors.</td>
<td>– Neostigmine increases muscle paralysis during phase 1 (due to increase muscle depolarization), but it can reverse the block in phase 2 (because the receptor is relatively insensetive and needs excess Ach to be stimulated).
– Fresh blood transfusion.</td>
</tr>
<tr>
<td>Therapeutic uses</td>
<td>– To induce sk ms relaxation during surgical operations.
– To control convulsions during electroconvulsive (ECT) therapy</td>
<td>– The same but succinylcholine is preferred for <u>short procedures</u> e.g. endotracheal intubation (has shorter duation).</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>– Histamine release leading to hypotension and</td>
<td>– Sudden rise of IOP due to contraction of the extraocular</td>
</tr>
</table>

	bronchospasm. – Respiratory paralysis in high doses.	muscles in phase 1. – **Acute hyperkalemia** (which may be dangerous and life-threatening). It is due to efflux of muscle K^+ during depolarization. – Postoperative muscle **pain.** – **Bradycardia** due to stimulation of cardiac muscarinic receptors (similar to ACh). – Prolonged **respiratory paralysis (apnea)** may result from **congenital deficiency of PsChE enzyme** (treaed by artificial respiraion and blood ransfusion).
C/I and precautions	– Bronchial asthma: why? – Myasthenia gravis. – With aminoglycosides or quinidine (they can aggravate ms paralysis).	– Glaucoma or recent eye surgery: why? – Congenital deficiency of PsChE enzyme: why?

Notes

Notes

Review Questions

Mention the pharmacodynamic principles underlying the use of:

- Dopamine in shock.
- Adrenaline in acute anaphylactic shock.
- Ritodrine to delay premature labor.
- Sumatriptan in acute migraine.
- Ergometrine in postpartum hemorrhage.
- Tamsulosin in senile enlarged prostate.
- Propranolol (beta-blockers) in hypertension.
- Beta-blockers in obstructive cardiomyopathy.
- Alpha-methyldopa in hypertension of pregnancy.
- Neostigmine in myasthenia gravis.
- Pralidoxime (PAM) in organophosphate toxicity.
- Atropine before surgical operations.
- Tolterodine in urine incontinence in adults.
- Succinylcholine before endotracheal intubation.

Mention the pharmacodynamic principles underlying the contraindication of:

- Ergometrine (or ergotamine) during pregnancy.
- Alpha-blockers (or beta-blockers) alone in pheochromocytoma.
- Propranolol (beta-blockers) in bronchial asthma.
- Reserpine in parkinsonism.
- Bethanechol in urine retention due to senile enlarged prostate.
- Neostigmine to treat ms paralysis of organophosphate intoxicated patient.
- Atropine in closed angle glaucoma.
- Atropine in old patient with senile enlarged prostate.
- Atracurium in bronchial asthma.

Mention the rational of the following combinations:

- Alpha-blockers with beta-blockers in pheochromocytoma
- Atropine with neostigmine in myasthenia gravis.
- Caffeine with ergotamine in acute migraine.

Mention the main differences between:

- Dopamine and dobutamine.
- Ergotamine and ergometrine.
- Propranolol and atenolol.

Of each of the following questions, select ONE BEST answer:

1. Regarding adrenergic α1 receptors, all are true EXCEPT:

A. Molecular techniques revealed the presence of a number of subclasses.
B. Their stimulation can contract the pregnant human uterus.
C. Their stimulation can increase peripheral resistance
D. Their effect is more potent and shorter duration than β2 receptors.
E. Their activation leads to increase intracellular calcium

2. Regarding adrenergic β2 receptors, all are true EXCEPT:

A. Their stimulation can relax the non-pregnant human uterus.
B. Their activation on mast cells leads to stabilization of mast cell membrane.
C. Their activation leads to increase intracellular cAMP.
D. Their selective antagonists have no clinical uses.
E. Continuous and prolonged stimulation can lead to down-regulation

3. Stimulation of cardiac M2 cholinoceptors cause which of the following:

A. Decrease myocardial contractility
B. Decrease SA nodal activity and heart rate
C. Decrease conduction velocity through the Purkinje fibers
D. Decrease coronary blood flow
E. All of the above.

4. Physiological events mediated by stimulation of β1 adrenoceptors include all the following EXCEPT:

A. Increase insulin secretion
B. Increase systolic blood pressure
C. Shorten myocardial cell refractoriness
D. Increase outflow resistance in patients with obstructive cardiomyopathy
E. Increase renin release by juxtaglomerular cells of the kidney

5. Cholinergic stimulation causes:

A. Urine retention
B. Bronchodilatation
C. Sweating
D. Tachycardia
E. Reduced gut motility

6. Nicotinic acetylcholine receptors are found in all the following sites EXCEPT:

A. Sympathetic ganglia
B. Presynaptic nerve endings
C. Central nervous system
D. Skeletal muscles motor end plate
E. Vascular endothelium

7. Increased urinary levels of vanilyl mandelic acid (VMA) above 8 mg/24 hours is diagnostic marker of the following tumors:

A. Pheochromocytoma
B. Carcinoid tumor
C. Leukemia
D. Lymphoma
E. Astrocytoma

8. The actions of norepinephrine at adrenergic receptors are terminated by which of the following:

A. Metabolism by MAO in the liver
B. Reuptake into the nerve terminal
C. Conversion into 5-HIAA
D. Conversion to dopamine
E. None of the above

9. The following is true for true cholinesterase:

A. Is found in autonomic ganglia and myoneural junctions
B. Is found in plasma and liver
C. It needs 2 weeks to be regenerated
D. It can metabolize acetylcholine as well as other choline esters
E. Its presence is not necessary for life

10. Which of the following drugs acts indirectly by releasing norepinephrine?

A. Angiotensin
B. Dopamine

C. Phenylephrine
D. Amphetamine
E. Isoprenaline

11. Attention-deficit hyperactivity disorder in children can be treated by:
A. Ephedrine
B. Modafinil
C. Tizanidine
D. Methylphenidate
E. Midodrine

12. The following is correct about the action of sympathomimetics:
A. Adrenaline has almost exclusively β-adrenoceptor agonist actions
B. Noradrenaline has an approximately equal mix of α-and β-adrenoceptor agonist actions
C. Isoprenaline has predominantly α-adrenoceptor agonist actions
D. Phenylepherine has predominantly β-adrenoceptor agonist actions
E. Dopamine acts on specific D-receptors as well as other adrenoceptors.

13. Epinephrine, all are true EXCEPT:
A. It is a polar (ionized) compound.
B. Is synthesized from norepinephrine within the adrenal medulla
C. Cannot be administered orally.
D. It is available as eye drops for ophthalmic use.
E. The final product of metabolism is vanillylmandelic acid (VMA).

14. The following statements about the action of sympathomimetics (i.v.) are correct EXCEPT:
A. Adrenaline infusion causes rise in both systolic and diastolic blood pressure with tachycardia
B. Noradrenaline infusion causes rise in both systolic and diastolic blood pressure with bradycardia
C. Dopamine infusion causes decrease in renal blood flow and GFR.
D. Salbutamol causes fall of blood pressure with tachycardia
E. Phenylepherine causes rise of blood pressure with bradycardia

15. For the treatment of acute anaphylactic shock, adrenaline must be given by the following route:
A. Inhalation
B. Subcutaneous
C. Intravenous
D. Intramuscular
E. Intracardiac

16. Regarding reflex bradycardia induced by administration of vasopressor drugs:
A. It starts to work as a compensatory response after long time of vasopressor use
B. Reflex is mediated through stretch receptors in the left pulmonary artery
C. The receptors begin to respond at pressure ≥ 150 mmHg
D. In chronic hypertension the set point is shifted to a higher level
E. Beta blockers readjust the set point to a higher level

17. Dobutamine is best indicated for management of which the following shock:
A. Septic shock
B. Cardiogenic shock
C. Anaphylactic shock
D. Hypovolemic shock
E. Neurogenic shock

18. Ritodrine hydrochloride can be used in the management of:
A. Parkinson's disease
B. Bronchial asthma
C. Depression
D. Premature labor
E. Bradycardia

19. Selective α2 agonists that is used to relieve muscle spasm associated with a variety of neurological conditions is:
A. Clonidine
B. Tizanidine
C. Ritodrine

D. Midodrine
E. Alpha methyldopa

20. Nasal decongestants carry the risk of cerebral stroke in which of the following conditions:
A. Arterial hypertension
B. Allergic rhinitis
C. Epistaxis
D. Benign prostatic hypertrophy
E. Sinusitis

21. Oxymetazoline has which of the following actions:
A. Bronchodilation
B. Vasoconstriction
C. Hyperglycemia
D. Tachycardia
E. Inhibition of ejaculation

22. Chronic orthostatic hypotension due to impaired autonomic reflexes can be managed by:
A. Midodrine
B. Ritodrine
C. Amphetamine
D. Modafenil
E. Cocaine

23. 65 year old male requires extensive dental work. In your first session with him you inject lidocaine (2%) plus l: 100,000 epinephrine. Although there was initial anesthesia, you are surprised to discover that after 15 minutes the patient grimaces with pain when you work in the affected area. What is the best possible explanation?
A. The patient is a chronic complainer
B. The injection missed the appropriate nerves
C. The patient metabolizes lidocaine extra rapidly
D. The patient may suffer benign prostatic hypertrophy and is being treated with doxazosin
E. In this patient lidocaine is an ineffective local anesthetic

24. Which of the following drugs will decrease heart rate in a patient with a normal heart but will have no effect on heart rate in a cardiac transplant recipient?
A. Epinephrine
B. Salbutamol
C. Norepinephrine
D. Phenylephrine
E. Dopamine

25. False +ve test for antinuclear factor may be caused by:
A. Phenoxybenzamine
B. Prazosin
C. Reserpine
D. Yohimbine
E. Ergotamine

26. The following alpha blocker is best prescribed to decrease symptoms of urine retention due to senile enlarged prostate:
A. Prazosin
B. Tremazosin
C. Phenoxybenzamine
D. Terazosin
E. Tamsulosin

27. Alpha blockers can worsen which of the following urinary problems:
A. Urine retention due to senile enlarged prostate
B. Urine retention due to atonic bladder
C. Urine retention with over flow due to spinal cord injuries
D. Urine incontinence due to pelvic floor pathology in women
E. Dysuria and frequency associated with bladder inflammation

28. All the following conditions can be effectively treated by beta-blockers EXCEPT:
A. Angina pectoris
B. Essential hypertension
C. Raynaud's disease
D. Open angle glaucoma
E. Supraventricular tachycardia

29. The therapeutic action of beta-blockers in angina pectoris is believed to be primarily due to:

A. Reduced production of catecholamines
B. Dilatation of the coronary vessels
C. Decreased myocardial oxygen requirement
D. Increased peripheral resistance
E. Increased sensitivity to catecholamines

30. Beta-blockers are contraindicated in bronchial asthma because:

A. They produce bradycardia and fall in COP
B. They increase bronchial secretions
C. They decrease pulmonary blood flow
D. They increase airway resistance and narrowing
E. They inhibit the respiratory center and impair ventilation

31. Myocardial depression caused by overdose of beta blockers can be reversed by parenteral administration of:

A. Adrenaline
B. Dopamine
C. Isoprenaline
D. Glucagon
E. Insulin

32. Excessive bradycardia induced by beta-blockers is best treated by:

A. Dopamine
B. Epinephrine
C. Isoprenaline
D. Neostigmine
E. Atropine

33. Essential tremors can be best decreased by which of the following beta blockers?

A. Atenolol
B. Propranolol
C. Betaxolol
D. Nebivolol
E. Bisoprolol

34. The following beta-blocker is preferred to control tachycardia when peripheral vascular disease is also associated:

A. Propranolol
B. Dilevalol
C. Timolol
D. Pindolol
E. Sotalol

35. One of the following drugs is best chosen for the control of hypertension during pregnancy:

A. Captopril
B. Propranolol
C. Reserpine
D. Phenoxybenzamine
E. Alpha methyldopa

36. Positive Coomb's test and hemolytic anemia may follow the administration of:

A. Prazosin
B. Alpha methyldopa
C. Guanithidine
D. Reserpine
E. Clonidine

37. One of the following drugs should be avoided in the control of chronic hypertension associated with peptic ulcer:

A. Reserpine
B. Prazosin
C. Propranolol
D. Clonidine
E. Alpha methyldopa

38. The following statements about pilocarpine are correct EXCEPT:

A. It is a natural plant alkaloid
B. It acts selectively on muscarinic receptors
C. It can block the hypotensive effect of neostigmine
D. It is not metabolized by AChE enzyme
E. It has a clinically useful miotic action

39. The following statements about anti-ChE drugs are correct EXCEPT:

A. Physostigmine lowers IOP
B. Neostigmine may be used with atropine to treat myasthenia gravis
C. Pyridostigmine have fewer visceral side effects than neostigmine.
D. Rivastigmine can be used to treat paralytic ileus
E. Edrophonium has short duration of action

40. A central AChE inhibitor that is used to improve symptoms of Alzheimer's disease is:
A. Pyridostigmine
B. Edrophonium
C. Donepezil
D. Neostigmine
E. Echothiophate

41. A short acting AChE inhibitor used in the diagnosis of myasthenia gravis is:
A. Edrophonium
B. Neostigmine
C. Pyridostigmine
D. Rivastigmine
E. Donepezil

42. Which of the following drugs has the longest duration of AChE inhibition:
A. Echothiophate
B. Neostigmine
C. Physostigmine
D. Pyridostigmine
E. Donepezil

43. The cause of death in organophosphate toxicity is:
A. Bradycardia
B. Increased bronchial secretions
C. Paralysis of the respiratory muscles
D. Depression of the respiratory center
E. All of the above

44. All the following are known contraindications for the use of atropine EXCEPT:
A. Closed angle glaucoma
B. Senile prostatic enlargement
C. Paralytic ileus
D. Postpartum urine retention
E. Acute cystitis

45. Relatively selective muscarinic blocker that is used to treat urine incontinence in adults is:
A. Pyrenzepine
B. Benztropine
C. Ipratropium
D. Tolterodine
E. Oxybutinin

46. The metabolites of which of the following neuromuscular blockers can lead to seizures?
A. d-tubocurarine
B. Atracurium
C. Mivacurium
D. Vecuronium
E. Succinylcholine

47. When succinylcholine is used to provide muscle relaxation during delivery by cesarean section, the following is true:
A. It can cause fetal hypotonia and even fetal paralysis
B. It can relax the uterus and aggravate postpartum hemorrhage
C. It can cause acute hyperkalemia and arrest the heart of the fetus
D. It can cause maternal tachycardia
E. It can decrease the effect of general anesthetics

48. The following statements are true for neuromuscular blockers EXCEPT:
A. Succinylcholine can cause postoperative muscle pain.
B. Atracurium undergoes spontaneous plasma hydrolysis
C. Vecuronium breakdown products may cause seizures.
D. Neostigmine can reverse muscle block caused by competitive blockers
E. Synthetic derivatives are generally preferred than d-tubocurarine

49. A muscarinic blockers that is used as a standard treatment of motion sickness is:

A. Pirenzepine
B. Oxybutinine
C. Atropine
D. Scopolamine
E. Tolterodine

50. Zolmitriptan produce vasoconstriction of cerebral vessels and decrease pain mediators during acute migraine by acting on the following receptor subtypes:

A. 5HT 1B/1D
B. 5HT 1E/1F
C. 5HT 2A/2C
D. 5HT 3
E. 5HT 7

51. Bethanechol, a direct acting muscarinic agonist used for relieving post-operative urine retention in absence of organic obstruction, could not be given parenterally because:

A. It can cause annoying salivation
B. It can cause cardiac arrest
C. It can cause histamine release and severe anaphylaxis
D. It can cause urine leak out of control
E. It can cause undesirable nausea and vomiting

52. A muscarinic agonist given orally to increase salivary secretion and decrease symptoms of dry mouth associated with Sjögren syndrome is:

A. Cevimeline
B. Carbachol
C. Bethanechol
D. Pyridostigmine
E. Rivastigmine

53. Regarding the management of a patient with organophosphate toxicity, the following is true:

A. With most types of organophosphates, 90% of the enzyme undergoes aging within the first 3 hrs.
B. Pralidoxime is completely ineffective for enzyme regeneration after aging of the enzyme.
C. Pralidoxime is effective regardless AChE is phosphorylated (e.g. by organophosphates) or carbamylated (e.g. by neostigmine).
D. Atropine should not be stopped before systolic blood pressure rises above 110 mmHg and pulse rate above 100 bpm.
E. Diazepam should be given to reduce bronchospasm

54. Regarding the management of a patient with iridocyclitis, the following is true:

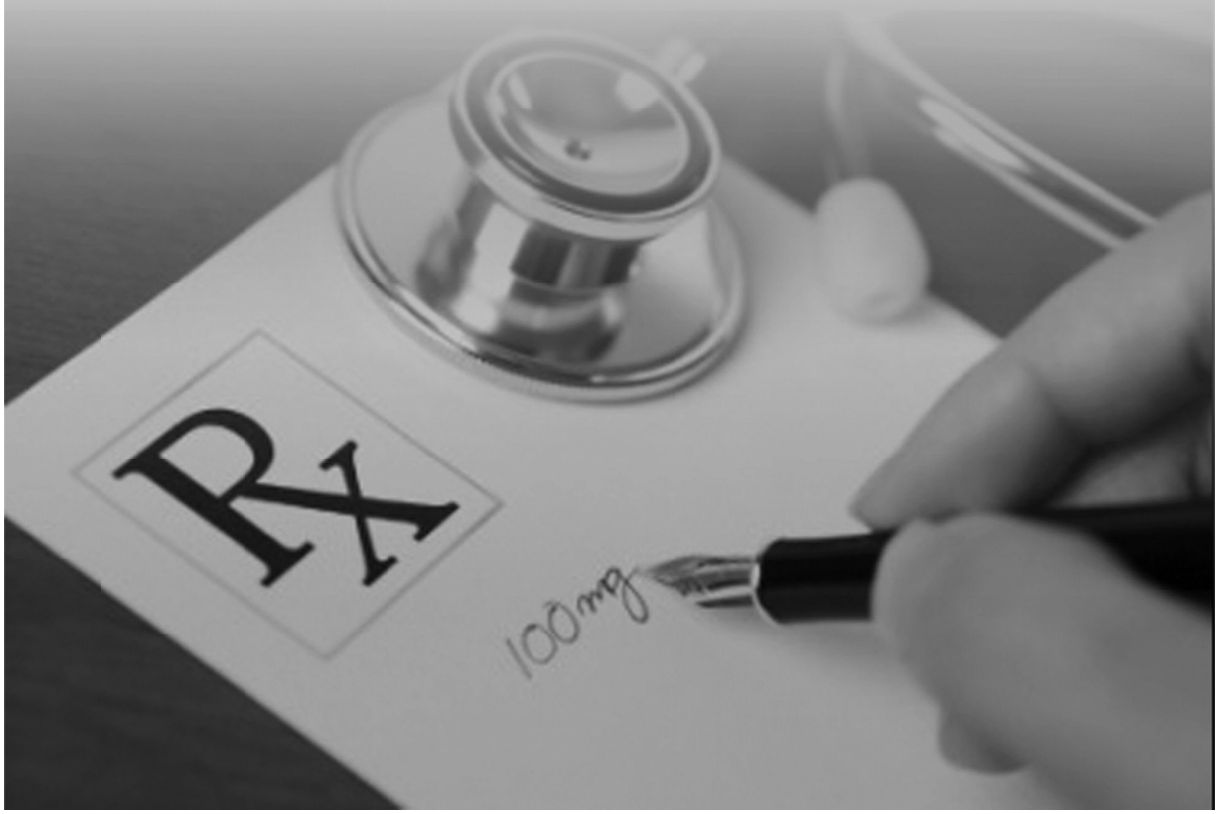
A. Mydriatics are used to help drainage of exudative fluids from the anterior chamber of the eye.
B. Short acting mydriatics such as phenylephrine are preferred to avoid prolonged blurring of vision
C. Atropine is preferred because it produces complete cycloplegia and mydriasis
D. If the patient was a child below 12 years old, atropine eye drops would be contraindicated.
E. Physostigmine eye drops should be used to help drainage of aqueous humor

Answers

1 D	12 E	23 D	34 B	45 D
2 B	13 A	24 D	35 E	46 B
3 B	14 C	25 B	36 B	47 C
4 A	15 D	26 E	37 A	48 C
5 C	16 D	27 D	38 C	49 D
6 E	17 B	28 C	39 D	50 A
7 A	18 D	29 C	40 C	51 B
8 B	19 B	30 D	41 A	52 A
9 A	20 A	31 D	42 A	53 B
10 D	21 B	32 E	43 E	54 C
11 D	22 A	33 B	44 E	

Chapter 3

Diuretic Agents And Volume Balance

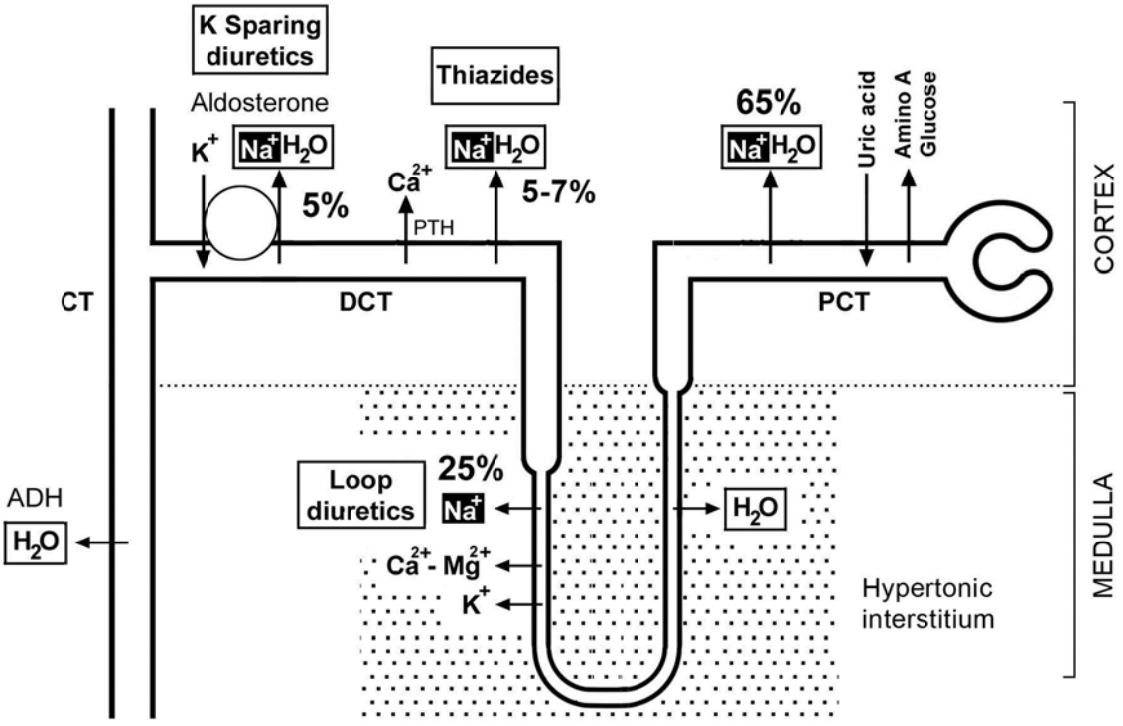


Chapter 3
Diuretic Agents and Volume Balance

Part 1: Basic information

TUBULAR FUNCTION AND URINE FORMATION

- The renal blood flow (RBF) is **1.1 L /min** (~ 22% of COP).
- The glomerular filtration rate (GFR) is **125 ml/min**.
- The capillary tuft filtrates ~ 180 L of fluid per day. 99% of the filtered fluid is reabsorbed again during passage in the renal tubules.
- Water reabsorption is usually **2ry to Na^+ reabsorption** (except in the collecting tubules; 'CT'). Any drug that ↓ Na^+ reabsorption (= ↑ Na^+ loss), also ↓ water reabsorption (= ↑ water loss or 'diuresis').



Tubular reabsorption and sites of action of 3 types of diuretics

- **Proximal convoluted tubules (PCT):**
  - **Reabsorption:** (75% of the glomerular filtrate).
    - Active reabsorption of Na^+ **(~65%).**
    - Passive (2ry to Na^+) reabsorption of equiosmotic amount of water.
    - Reabsorption of all filtered K^+, glucose, amino acids, and drugs.
  - **Secretion:** active secretion and reabsorption of organic acids and bases into tubular fluid.

- **Loop of Henle (LOH):**
  - **Descending limb:** passive reabsorption of water due to hypertonicity of the medullary interstitium.
  - **Ascending limb:** active reabsorption of Na^+ **(~25%)** (this causes hypertonicity of the medullary interstitium), Ca^{2+} and Mg^{2+}.

- **Distal convoluted tubules (DCT):**
  - **Proximal part:**
    - Active reabsorption of Na^+ **(5-7%).**
    - Passive (2ry to Na^+) reabsorption of equiosmotic amount of water.
    - Active reabsorption of **Ca^{2+}** (under the influence of **parathormone 'PTH'**).
  - **Distal part:**
    - Active reabsorption of Na^+ **(2–5%)** in exchange with K^+ (under the influence of **aldosterone**).
    - Passive (2ry to Na^+) reabsorption of equiosmotic amount of water.

- **Collecting tubules (CT):** Reabsorption of water under the influence of **ADH.**

EDEMA AND EDEMATOUS CONDITIONS

- Edema is defined as the accumulation of fluid in the interstitial space due to either:
  - Increased capillary hydrostatic pressure
  - Decreased plasma oncotic pressure.
  - Increased capillary permeability.
- Edema can be either **exudative** (having high protein content) or **transudative** (having low protein content).
- **Exudative edema** results from increased capillary permeability as part of the acute inflammatory response. It is usually localized to the site of inflammation and will not be considered in this chapter.

- **Transudative edema** is usually generalized and is associated with renal Na^+ retention. The three most common clinical causes are:
  - **Congestive heart failure (CHF):** the decreased COP causes renal ischemia which stimulates the renin-angiotensin-aldosterone system (RAAS) → Na^+ and water retention → edema.
  - **Liver cirrhosis:** the cirrhotic liver cannot synthesize sufficient albumin and other plasma proteins → ↓ plasma oncotic pressure. Hypoalbuminemia together with portal hypertension and 2ry stimulation of RAAS cause fluid retention (edema) and accumulation of fluid in the peritoneal cavity (ascites).
  - **Nephrotic syndrome:** glomerular dysfunction causes excessive loss of plasma proteins in urine → ↓ plasma oncotic pressure → edema.

Part 2: Diuretic classes and agents

Diuretics are drugs that increase urine volume and Na^+ excretion.
Natriuretic: a drug that increase Na^+ excretion by the kidney.

Classification of diuretics:

Renal diuretics	Extra-renal diuretics
They act directly on the kidney: ■ **Thiazide diuretics:** act on the proximal part of the DCT *e.g. hydrochlorothiazide.* ■ **Loop diuretics:** act on the ascending limb of loop of Henle *e.g. furosemide.* ■ **K^+ sparing diuretics:** act on the distal part of the DCT *e.g. spironolactone.* ■ **Osmotic diuretics:** substances that ↑ the osmotic pressure of tubular fluid → ↓ water reabsorption by renal tubules *e.g. mannitol.*	They act indirectly on the kidney: ■ **Water diuresis:** ↑ water intake → ↓ ADH release → diuresis. ■ **Digitalis in CHF:** ↑ the COP leading to ↑ RBF → diuresis. ■ **i.v. albumin in ascites or nephrotic edema:** to increase plasma osmotic pressure → mobilization of edema fluid toward the vascular compartment → ↑ RBF → diuresis.

N.B. **Carbonic anhydrase inhibitors** *e.g acetazolamide*: they are weak diuretics that ↓ $NaHCO_3$ reabsorption from the PCT and may cause **metabolic acidosis**. They also ↓ aqueous humor secretion and can be used in the treatment of glaucoma (see pharmacology of the eye).

Loop diuretics

(Furosemide, torsemide, bumetanide , and ethacrynic acid)

Pharmacokinetics

- They are absorbed from the GIT and secreted into the lumen of the PCT by an organic acid excretory system.
- The absorption of furosemide is erratic but bumetanide is complete.
- Diuresis occurs within **5** minutes after i.v. administration and within **30** minutes of oral administration.

Mechanism and pharmacological effects

- Loop diuretics **inhibit $Na^+/K^+/2Cl^-$ co-transport** system in the thick ascending limb of LOH leading to inhibition of the active reabsorption **Na^+**, **Cl^-**, and **K^+**. These ions are excreted with equiosmotic amount of **water**.
  - They also increase **excretion** of **Ca^{2+}**, **Mg^{2+}**, **halides** and **H^+**.
  - Na^+ and water loss at this segment is high, so they are **potent (or high ceiling)** diuretics (i.e., up to 25% of the filtered Na^+ load).
- They ↑ **renal PGE2 and PGI2** production leading to **VD** and ↑ RBF and GFR.
  - Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit PG synthesis and antagonize this effect of loop diuretics.
  - VD of **pulmonary** vascular bed also occurs due to ↑ PG formation.

Therapeutic uses

- **Edematous conditions:** e.g. CHF, nephrotic syndrome, etc.
  - Many patients require fluid and sodium restriction to have the best results.
  - Diuretics are **not used** to treat edema due to lymphatic obstruction (lymphedema) or inflammatory edema (localized edema with high protein content is difficult to be resolved by diuretics).
- **Acute pulmonary edema:** loop diuretic ↓ pulmonary congestion by:
  - They cause venodilatation → ↓ venous return.
  - They cause VD of pulmonary vascular bed even before diuresis occurs.
- **Acute renal failure:** to maintain adequate GFR and enhance K^+ excretion.
- Acute **hypercalcemia** and acute **hyperkalemia**: saline should be given to compensate for Na^+ and water loss.
- **Hypertensive emergencies:** i.v. furosemide is usually given in emergencies:
  - Loop diuretics ↓ plasma volume.
  - They cause peripheral VD due to ↑ PGs production in many vascular beds.
  - Hyponatremia ↓↓ sensitivity of the vascular smooth muscles to circulating catecholamines.

Adverse effects

- **Hypovolemia** and **hypotension.**
- **Electrolyte disturbances:** Hyponatremia, hypokalemia, hypomagnesemia, and hypocalcemia (all need to be properly replaced).
- **Hypokalemic metabolic alkalosis:** due to ↑ tubular secretion of K^+ and H^+.
- **Hyperuricemia** and precipitation of acute gout: This is caused by:
  - Increased uric acid reabsorption in the PCT as a result of hypovolemia (It may be prevented by using lower doses to avoid hypovolemia).
  - Competition with uric acid excretion at the organic acid excretory system in the PCT.
- **Ototoxicity:**
  - It is **reversible** hearing loss. It occurs with very **high** doses.
  - It may be due impairment of **ion transport** in the stria vascularis (inner ear).
  - Occurs more frequent with:
    - Patients with impaired renal function.
    - Ethacrynic acid.
    - Concomitant use of other ototoxic drugs e.g. aminoglycosides.
- **Allergic reactions:** all loop diuretics (except ethacrynic acid) are derivatives of sulfonamides; they cause occasional skin rash, eosinophilia, and less often, interstitial nephritis.

Thiazide diuretics

Classification

- **True thiazides** (they are derivatives of sulfonamides): hydrochlorothiazide, bendroflumethiazide.
- **Thiazide-like diuretics:** metalozone, indapamide, chlorthalidone.

Pharmacokinetics

- Thiazide diuretics are absorbed from the GIT. They are secreted into the lumen of the PCT by an organic acid excretory system.
- They produce diuresis within 1–2 hours.

Mechanism and pharmacological effects

- Thiazides **inhibit Na^+/Cl^- co-transport** system in the proximal part of **DCT** leading to inhibition of the active reabsorption **Na^+**, **Cl^-**. These ions are excreted with equiosmotic amount of **water**.
  - Excess **Na^+** reaching the DCT is reabsorbed in exchange with **K^+** (→ **K^+ loss).**

- They also increase **excretion** of **halides** and **H^+**.
- They ↓ **Ca^{2+} excretion** and enhance its reabsorption.
- Thiazides have **moderate efficacy** (i.e., maximum excretion of filtered Na^+ load is only 5-7%).
- Most thiazides are ineffective if the GFR is < 30-40 ml/min (so it is not useful, or even harmful, in presence of renal failure).

- The action of thiazides also depends on **renal PGs** like loop diuretics but to much less extent.

Therapeutic uses

- **Mild edematous states:** cardiac, hepatic, or renal (same as loop diuretics).
- **Essential hypertension** (mild to moderate)**:**
  - They have the same mechanisms like loop diuretics (mention them).
  - They are often combined with other antihypertensive drugs to enhance their blood pressure-lowering effects.
- **Hypercalcuria and renal Ca^{2+} stones:** to ↓ urinary **Ca^{2+}** excretion.
- **Nephrogenic diabetes inspipidus (DI):**
  - Thiazides can reduce urine volume in some cases of DI. This is called **"paradoxical antidiuretic action"** and it is not clearly understood. It may be due to improvement of ADH receptor sensitivity in the renal collecting tubules.

Adverse effects

- **Hypovolemia** and **hypotension.**
- **Electrolyte disturbances:** Hyponatremia and hypokalemia.
- **Hypokalemic metabolic alkalosis:** due to ↑ tubular secretion of K^+ and H^+.
- **Hyperuricemia** the same as with loop diuretics.
- **Hyperglycemia:** due to both ↓ pancreatic release of insulin and ↓ tissue utilization of glucose.
- **Hyperlipidemia:** due to ↑ cholesterol and LDL (by 5-15%).
- **Allergic reactions:** thiazides are derivatives of sulfonamides; they cause occasional skin rash, dermatitis, and less often, thrombocytopenia.

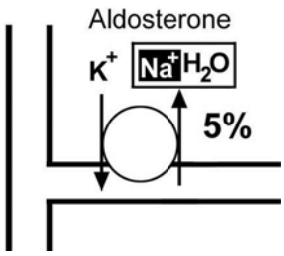
Potassium-sparing diuretics
(Spironolactone – triameterine – amiloride)

- Spironolactone is a **steroid** congener of aldosterone.
- Triamterene and amiloride are synthetic drugs **but not steroids.**

Pharmacokinetics

- All are absorbed from the GIT.
- Spironolactone and triamterene are metabolized by the liver
- Amiloride is excreted unchanged in the urine.
- They have **slow onset** (days).

Mechanism and pharmacological effects



- **Site of action:** the distal part of the DCT where Na^+ is reabsorbed (**2–5%**) in exchange with K^+ under the influence of **aldosterone**.
- **Spironolactone** is a competitive antagonist of aldosterone at its receptor site at the distal part of DCT leading to ↑ Na^+ excretion (with excretion of equiosmotic amount of water) and K^+ retention.
- **Triamterene and amiloride** are **direct inhibitors** of Na^+ channels in the distal part of DCT leading to ↑ Na^+ excretion (with excretion of equiosmotic amount of water) and K^+ retention.

- **The net effect is:**

– Mild Na^+ and water loss (i.e., maximum excretion of filtered Na^+ is only 2-5%)
– Hyperkalemia: due to ↓ K^+ excretion (K^+ will be retained in blood).
– Metabolic acidosis: due to ↓ H^+ ion excretion (H^+ will be retained in blood).

Therapeutic uses

- **All cases of edema due to hyperaldosteronism:**
  - Primary hyperaldosteronism: e.g. Conn's disease.
  - Secondary hyperaldosteronism: e.g. in liver cirrhosis or nephrotic syndrome.
- **Used in combination with loop diuretics or thiazides in order to:**
  - To minimize the risk of electrolyte imbalance:
    Loop diuretics cause hy**po**kalemia while K^+ sparing diuretics cause hy**per**kalemia. Their combination can minimize electrolyte disturbance.
  - To minimize the risk of acid-base imbalance:
    Loop diuretics cause metabolic alkalosis while K^+ sparing diuretics cause metabolic acidosis. Their combination can minimize acid-base imbalance.
  - To make synergism in cases of refractory (resistant) edema.
- **Treatment of female pattern hair loss**:

  Spironolactone is a weak competitive inhibitor of **androgens** at their receptors and ↓ synthesis of testosterone (antianderogenic effect). Some dermatologists use this feature to stop androgen-related frontal hair loss in women.

Adverse effects

- **Hyperkalemia** due to ↓ K^+ excretion.
- **Hyperkalemic metabolic acidosis:** due to ↓ K^+ and ↓ H^+ excretion.
- Spironolactone has **antiandrogenic effects** (gynecomastia and impotence in males).

N.B.

Eplerenone is a similar congener of spironolactone. It has little antiandrogenic effects but more hyperkalemic effects.

Contraindications

- **All cases of hyperkalemia:** especially in the following conditions:
  - Patients with chronic renal failure.
  - With drugs that cause hyperkalemia e.g. ACEIs.
- **Spironolactone should not be given with carbenoxolone** because carbenoxolone has aldosterone-like action and can antagonize the effect of spironolactone.

	Spironolactone	Triamterene - amiloride
Structure	Synthetic steroid	Synthetic non-steroids
Metabolism	Extensive metabolism in the liver	Amiloride is excreted unchanged in urine
Mechanism of action	Competitive antagonism with aldosterone at its receptor site in the DCT	Direct inhibition of Na^+ channels at the distal part of DCT
Antianderogenic efcts	Gynecomastia & impotence	Not present

Osmotic diuretics: Mannitol, Glycerol

They are chemically inert substances given by **i.v. infusion** in **emergency** conditions

Mechanism of action

- First, they ↑ osmotic pressure of plasma leading to withdrawal of transcellular fluid (e.g. aqueous humor, excessive CSF, etc).
- Second, they are freely filtered by the glomerulus and ↑ osmotic pressure of the tubular fluid leading to ↓ water reabsorption by renal tubules.

Therapeutic uses

Acute congestive glaucoma and acute rise in intracranial pressure: they are given by i.v. infusion for rapid ↑ drainage of of aqueous humor or CSF respectively by increasing the osmotic pressure of the plasma before diuresis begins.

Adverse effects: dehydration with hypernatremia is the main adverse effect.

Comparison between the 3 main classes of diuretics

	Loop diuretics	Thiazides	K+ sparing diuretics
Site of action	thick ascending limb of LOH	proximal part of DCT	distal part of DCT
Mechanism	Inhibit $Na^+/K^+/2Cl^-$ co-transport system	inhibit Na^+/Cl^- co-transport system	Spironolactone is a competitive antagonist of aldosterone Triamterene and amiloride are direct inhibitors of Na^+ channels in the distal part of DCT
Efficacy	High	Moderate	Mild
Onset	Rapid (minutes)	Less rapid (hours)	Slow (days)
Serum K+	Hypokalemia	Hypokalemia	Hyperkalemia
Blood pH	Metabolic alkalosis	Metabolic alkalosis	Metabolic acidosis
Ca2+ excretion	↑	↓	--
Use in renal failure	Can be used	Not effective or harmful	Contraindicated
Use in hypertension	Hypertensive emergencies	Mild essential hypertension	In combination with other diuretics
Blood glucose	Little or no effect	Rise	Little or no effect
Plasma lipids	Little or no effect	Rise	Little or no effect
Ototoxicity	Common	Less common	Rare

Part 3: Advantages and disadvantages of diuretics in some edematous conditions

CONGESTIVE HEART FAILURE (CHF)

Patients with CHF have ↓COP due to weak cardiac muscle, fluid retention, and lung congestion. Many patients have also high blood pressure.

Advantages of diuretics:

- Correction of fluid retention.
- Lowering of blood pressure.
- Decrease preload (venodilatation and ↓ venous return) and afterload (due to arterial VD) leads to improvement of cardiac contraction.
- Decrease lung congestion causes improvement of tissue oxygenation.
- Recent evidence showed that **spironolactone** reduces morbidity and mortality rates in patients with advanced heart failure.

Disadvantages of diuretics:

- Excessive hypovolemia can ↓ COP.
- Diuretic-induced acid-base and electrolyte imbalance may impair cardiac function.
- Diuretic-induced **hypokalemia** can predispose to digitalis toxicity and cardiac arrhythmia.

Recommendation: Combination between a K^+ sparing diuretic and loop diuretic is the best choice.

CHRONIC KIDNEY DISEASES

The majority of patients with chronic renal diseases (e.g. chronic renal failure, diabetic nephropathy, etc.) have fluid retention**,** hypertension, hyperkalemia**,** and acidosis.

Advantages of diuretics:

- Correction of fluid retention.
- Reduction of hyperkalemia.
- Reduction of hypertension.

Recommendation: Loop diuretics are best choice.

Disadvantages of diuretics:

- Thiazides are **ineffective** when GFR is <30 ml/min, moreover it may be harmful.
- K^+ sparing diuretics are **contraindicated** because they can exacerbate hyperkalemia and acidosis.
- Carbonic anhydrase inhibitors (acetazolamide) are **contraindicated** because they can exacerbate acidosis.

LIVER CIRRHOSIS

Patients with chronic liver disease have fluid retention, ascites, hyperammonemia and 2ry hyperaldosteronism.

Advantages of diuretics:

- Correction of fluid retention.
- Spironolactone antagonizes aldosterone.

Disadvantages of diuretics:

- Aggressive use of diuretics can precipitate hepatorenal syndrome.
- Aggressive use of diuretics can precipitate hyperammonemia and hepatic **encephalopathy**. **How?**

- Normally, the urine pH is acidic (~5.6). In acidic urine, most of the absorbable **ammonia** (NH3) is converted into the non-absorbable **ammonium** ions (NH4+) and so it is removed out by the kidney (this is known as ammonia trapping).

- Diuretics cause hypokalemia and metabolic alkalosis. This leads to:
  - Systemic alkalosis causes the pH of the urine to become less acidic. This decreases conversion of the urinary absorbable NH3 into the non-absorbable NH4. The excreted NH3 is thus reabsorbed again from urine to blood → **hyperammonemia**.
  - Systemic alkalosis increases the **entry** of NH3 into the brain cells.

Hepatorenal syndrome

- Functional oliguric RF occurring in a patient with advanced liver disease in absence of other causes of RF. The renal histology is normal.

- The pathogenesis of HRS is not fully understood. Disturbance in renal hemodynamics due to imbalance between renal VC and VD mechanisms may be responsible.

- Prognosis is poor.

Recommendation:
Aldosterone antagonists such as spironolactone are suitable choice in hepatic patients to help prevent the formation of ascites. A loop diuretic may need to be added in refractory cases.

LOWER LIMB EDEMA DURING PREGNANCY

- Lower limb edema during late pregnancy is common condition and is usually benign (physiologic). It occurs due to hormonal imbalance, and compression of pelvic veins by the enlarged uterus.
- Unilateral leg edema, redness, warmth, and tenderness require evaluation for deep venous thrombosis (DVT).
- Physiologic edema can be reduced by elevating the lower extremities and wear elastic stockings.

– Diuretics are better avoided during pregnancy because they effectively **reduce maternal plasma volume** and consequently may reduce amniotic fluid and/or placental blood flow.

Part 4: Volume depletion and fluid replacement

- Volume depletion can be caused by loss of blood or other body fluids e.g. vomiting, diarrhea, etc.
- In cases of mild volume depletion, resuscitation can be adequately achieved with oral fluid alone. Sodium chloride tablets and electrolyte-containing solutions are often used.
- In cases of severe dehydration, i.v. fluid therapy is preferred and may be life-saving.
- Water alone is not an appropriate fluid for volume resuscitation since it enters the cells by osmotic effect. Only one third of each administered liter remains in the extracellular space, and only one twelfth of each administered liter remains in the intravascular space.
- When electrolyte disturbances are present, the fluid used for resuscitation should be chosen to correct both volume depletion and electrolyte disturbances.

Crystalloid solutions

■ **Sodium chloride solutions:**

– **Normal saline (0.9% NaCl):** It is the most commonly used solution. It contains 154 mEq sodium per litre, a concentration similar to the sodium concentration of plasma. Due to the relatively high chloride content, normal saline carries a risk of inducing hyperchloraemic metabolic **acidosis** when given in large amounts.

– **Hypotonic saline (0.45% NaCl):** contains 77 mEq sodium per liter, and can be used when there is dehydration with hypernatraemia. In these patients, 5% dextrose in water can be given simultaneously with normal saline.

– **Hypertonic saline (3% NaCl):** contains 513 mEq sodium per liter, and can be used for management of acute hyponatremia.

■ **Lactated Ringer's solution:**

– It is an isotonic solution containing sodium, potassium, chloride, calcium and lactate. The lactate is metabolized by the liver into bicarbonate, which can help correct metabolic **acidosis**. In lactic acidosis and **liver disease** this conversion is impaired, so lactate-containing fluids should be avoided.
– It is **not suitable for maintenance** therapy because the Na^+ and K^+ contents are too low to compensate for daily electrolyte requirement.

■ **Glucose (Dextrose) solutions:**

- Various concentrations are available e.g. 5%, 10% and 25%. The 5% dextrose in water (also known as D5W) is isotonic and is the most commonly used.
- Hypertonic glucose solutions (above 5%) should be infused very slowly and cautiously to avoid **hyperosmolar syndrome** and life-threatening **dehydration**.

Colloid solutions

- Colloids are classified as either natural (**albumin** and **fresh frozen plasma**) or artificial (**starch** and **dextran**).
- They preserve a high colloid **osmotic pressure** in the blood and theoretically designed to increase the intravascular volume with much less effect on tissue water. However, colloid solutions are a less-preferred choice for the management of volume depletion because they are very expensive and have not shown a mortality benefit over isotonic saline.

Oral rehydration therapy (ORT)

- Oral electrolyte solutions are used in **children**, particularly with gastroenteritis. This product contains sodium, potassium, chloride, citrate, and dextrose, and is designed to replace the electrolytes and water that are lost with vomiting or diarrhea.
- Glucose is typically added to these oral replacement solutions to promote uptake of sodium via the intestinal sodium/glucose co-transporter mechanism.

Part 5: Disorders of serum sodium and potassium

Hyponatremia and SIADH

Normal serum Na^+ is **135-145** mEq/L

- Hyponatremia is defined as serum Na^+ <135 mEq/L. It can be caused by any medical illnesses, such as CHF, liver failure, renal failure, pneumonia, or SIADH.
- Severe hyponatremia (Na^+ <120 mEq/L) leads to fall of plasma osmolality, with movement of water from plasma to brain and other cells causing neurological manifestations (altered mental status, weakness, neuromuscular irritability, focal neurologic deficits, coma or seizures).
- ADH (or vasopressin) is released from posterior pituitary in response to high plasma osmolality. It binds to three receptors: **V1a** in the vasculature (VC), **V1b** in the brain, and **V2** in renal collecting ducts (↑ water absorption).
- When the ADH system is working properly, 'the urine should reflect the blood', i.e. concentrated urine occurs when plasma osmolality is high, and vice versa.

- Many factors (including drugs and other non-pharmacological conditions) can stimulate release of ADH irrespective of plasma osmolality, leading to **hyponatremia**, a condition known as **"syndrome of inappropriate ADH secretion"** or **SIADH.**

Drugs that cause SIADH:
Carbamazepine
Chloropropamide
Cytotoxic drugs
Opiates

Management of SIADH

- **Fluid restriction** (1L/d) is the main line.
- **Demeclocycline** and **lithium** may be "rarely" used; they impair the response of the collecting ducts to ADH (by a non-receptor mechanism).
- **Vasopressin receptor antagonists: "Vaptans":**
  - Antagonism of the V2 receptors results in aquaresis, a unique electrolyte-free water excretion by the kidneys.
  - **Conivaptan** is a mixed V1a and V2 antagonist, and **tolvaptan**, a selective V2 antagonist.
  - **Tolvaptan** is approved for treating hyponatremia associated with heart failure, cirrhosis, and SIADH.
  - Recent studies showed that vaptans may be more effective in treating hypervolemia in heart failure than diuretics.

Hypernatremia

- Hypernatremia is defined as a plasma Na^+ >145 mEq/L, and represents a state of hyperosmolality
- Hypernatremia may be caused by a primary **Na+ gain** or a **water loss**, the latter being much more common. **Renal water loss** results from either **osmotic diuresis** or **diabetes insipidus (DI)**.
- Hypernatremia results in contraction of brain cells as water shifts to attenuate the rising ECF osmolality. Thus, the most severe symptoms of hypernatremia are neurological manifestations.

N.B.

Aggressive correction of hyper- or hyponatremia is potentially dangerous. The rapid shift of water into- or- from brain cells increases the risk of seizures or permanent neurologic damage.

Management of symptomatic hypernatremia

- The mainstay of management is the administration of **water**, preferably by mouth or nasogastric tube. Alternatively, 5% dextrose in water (D5W) can be given intravenously.
- Specific therapy of the underlying cause.

Hypokalemia

Normal serum K^+ is 3.5-5 mEq/L

- Potassium is the major intracellular cation. 98% of K^+ in the body is found in the intracellular compartment, leaving 2% in extracellular fluid spaces.
- Renal K^+ excretion occurs from the DCT and is mediated by aldosterone and Na^+ delivery to the distal nephron.
- Hypokalemia is defined as serum K^+ <3.5 mEq/L. It can result from diminished K^+ intake, transcellular shift of K^+, or increased K^+ loss.
- The most common **manifestations** are muscle weakness, cramps, flattened T wave and prolonged QT interval in the ECG.
- Because K^+ is usually exchanged with H^+ at the DCT, hypokalemia is often linked to metabolic alkalosis. Anyone of these two conditions can lead to the other.

Drugs cause transcellular shift of K^+ (from plasma to tissue):
Insulin and beta-2 agonists: they ↑ transmembrane Na^+/K^+-ATPase activity.

Drugs cause renal loss of K^+:
Mineralocorticoids, glucocorticoids, diuretics, amphotericin-B.

Drugs cause GIT loss of K^+: laxatives

Management

- Patients with a K^+ level of **2.5-3.5** mEq/L may need only oral K^+ replacement
- If the K^+ level **< 2.5** mEq/L, intravenous K^+ should be given. The rate of infusion should not exceed 20 mEq/hr, Rapid IV infusion may cause serious arrhythmia or even cardiac arrest.
- Hypomagnesemia is frequently associated with hypokalemia. Concomitant magnesium deficiency aggravates hypokalemia and renders it difficult to treatment by K^+ alone.

Hyperkalemia

- Hyperkalemia is defined as serum K^+ >5 mEq/L. It can result from transcellular shift of K^+, or decreased renal excretion of K^+ (as in chronic renal failure).
- The most common **manifestations** are muscle paralysis, palpitations, high peaked T wave and short QT interval in the ECG.
- Because K^+ is usually exchanged with H^+ at the DCT, hyperkalemia is often linked to metabolic acidosis.

Drugs cause transcellular shift of K^+ (from tissue to plasma):
Insulin deficiency and β-blockers: they ↓ transmembrane Na^+/K^+-ATPase activity.

Drugs that ↓ renal excretion of K^+:
K+ sparing diuretics, ACEIs, NSAIDs, cyclosporins.

Management

- **Mild hyperkalemia:** could be corrected by diuretics and oral cation exchange resins (Polystyrene sulfonate) to promote the exchange of Na^+ for K^+ in the GIT.
- **Severe hyperkalemia with ECG changes:**
  - Intravenous calcium gluconate to reduce cardiac toxicity (↓ membrane excitability). The usual dose is 10 mL of a 10% solution infused over 2 to 3 minutes.
  - Intravenous insulin with glucose: 20 U regular insulin mixed with 500 ml D5W.
  - Correct metabolic acidosis with i.v. NaHCO3 solution.
  - Hemodialysis is reserved for patients with renal failure or with life-threatening hyperkalemia resistant to other treatment.

Part 6: Pharmacological manipulation of the urine pH

Normal urine pH is 5.2-6.5. It is possible, by the use of pharmacological agents, to produce urinary pH values ranging from ~ 5 to 8.5.

Alkalinization of the urine

- **Indications:**
  - To enhance excretion of acidic drugs and organic compounds e.g. aspirin, sulfonamides, and uric acid.
  - To enhance dissolution of uric acid and cystine stones.
  - To relieve dysuria (burning micturition) in some cases of bladder infection.
- **Alkalinizing agents:**
  - **Oral:** sodium and potassium citrate salts: citrate is metabolized into bicarbonate which is excreted in urine.
  - **Intravenous** bicarbonate solution: contains 5% NaHCO3.

Acidification of the urine

- **Indications:**
  - It is rarely used clinically except in a specialized test to discriminate between different kinds of renal tubular acidosis.
  - It can be very dangerous in cases of renal or hepatic impairment.
- **Acidifying agents:**
  - **Oral:** ascorbic acid > 2 g/d.
  - **Intravenous** ammonium chloride (NH4Cl) solution.

Notes

Notes

Review Questions

Mention the pharmacodynamic principles underlying the use of:

- Furosemide in arterial hypertension.
- Furosemide in acute pulmonary edema.
- Thiazides in diabetes insipidus.

Mention the pharmacodynamic principles underlying the contraindication of:

- Furosemide in acute hyperuricemia.
- Thiazides in uncontrolled diabetes mellitus.
- Spironolactone in chronic renal failure.
- Amiloride with ACEIs.
- Ethacrynic acid with aminoglycosides.
- Furosemide with NSAIDs.

Mention the advantages and disadvantages of diuretics in the following conditions:

- Congestive heart failure.
- Chronic kidney disease.
- Chronic liver disease.

Mention the rational of the following combination:

- Furosemide with spironolactone.

Mention 3 differences between:

- Furosemide and spironolactone.

Of each of the following questions, select THE ONE BEST answer:

1. The ascending part of the loop of Henle is the principal site of action of the following diuretics:
A. Hydrochlorothiazide
B. Triamterine
C. Amiloride
D. Bumetanide
E. Spironolactone

2. Hyperkalemia is a contraindication of the following diuretics:
A. Furosemide
B. Bumetanide
C. Ethacrynic acid
D. Chlorothiazide
E. Spironolactone

3. Loop diuretics are clinically useful in the treatment of all the following edematous states EXCEPT:
A. Edema caused by congestive heart failure
B. Edema caused by chronic liver failure
C. Lymphedema
D. Nephrotic syndrome
E. Ankle edema due to chronic hydralazine treatment

4. Intravenous albumin is the ideal choice for treatment of the following conditions:
A. Ascites due to chronic liver disease
B. Edema due to chronic kidney disease
C. Edema due to congestive heart failure
D. Lymphedema
E. Inflammatory edema

5. Vigorous diuretics are contraindicated in resistant ascites due advanced liver disease because:
A. It can lower blood pressure to a critical level
B. It can precipitate hepatorenal syndrome
C. It can lead to severe dehydration
D. It can decrease ascetic fluid suddenly and drastically
E. It aggravate hypoalbuminemia

6. Which of the following diuretics can enhance the parathormone-mediated calcium reabsorption from the distal renal tubules:
A. Hydrochlorothiazide
B. Triamterine
C. Amiloride
D. Bumetanide
E. Spironolactone

7. Idiopathic calcium urolithiasis (hypercalciuria) can be treated by:
A. Hydrochlorothiazide
B. Ethacrynic acid
C. Furosemide
D. Triamterine
E. Bumetanide

8. Spironolactone is characterized by:
A. It interferes with aldosterone synthesis
B. It competitively inhibit aldosterone action in the distal part of the distal renal tubules
C. It inhibits sodium reabsorption in the proximal renal tubules
D. It is more potent diuretic than hydrochlorothiazide
E. It has rapid onset and short duration

9. Hydrochlorothiazide is clinically useful in the treatment of all the following conditions EXCEPT:
A. Edema caused by congestive heart failure
B. Edema caused by chronic liver failure
C. Edema caused by chronic renal failure
D. Hypertension with or without edema
E. Recurrent calcium urolithiasis

10. Adverse reactions associated with thiazide therapy include all the following EXCEPT:
A. Hyperglycemia
B. Hyperuricemia
C. Metabolic acidosis
D. Fluid and electrolyte imbalance
E. Hypotension

11. All the following diuretics can aggravate digitalis toxicity EXCEPT:
A. Hydrochlorothiazide

B. Furosemide
C. Bumetanide
D. Amiloride
E. Ethacrynic acid

12. Adverse effects of loop diuretics include all the following EXCEPT:
A. Magnesium deficiency
B. Sodium deficiency
C. Hypoglycemia
D. Hypovolemia
E. Hyperuricemia

13. Hypokalemia can be caused by all the following drugs EXCEPT:
A. Captopril
B. Salbutamol
C. Thiazides
D. Corticosteroids
E. Insulin

14. The following statements are true concerning the precautions during the use of diuretics in different metabolic disorders EXCEPT:
A. Furosemide may enhance digitalis toxicity in congestive heart failure
B. Furosemide may aggravate hyperammonemia in chronic liver failure
C. Chlorothiazides may aggravate renal impairment in chronic renal failure
D. Thiazides may aggravate hyperglycemia in diabetes mellitus
E. Thiazides may increase formation of urinary uric acid crystals in chronic gout

15. All the following drugs can produce salt and water retention after their prolonged use EXCEPT:
A. Nifedipine
B. Minoxidil
C. Amiloride
D. Prazosin
E. Hydralazine

16. Adverse reactions associated with furosemide therapy include all the following EXCEPT:
A. Hearing loss
B. Hyperuricemia
C. Metabolic alkalosis
D. Fluid and electrolyte imbalance
E. Hypercalcemia

17. Acute pulmonary edema is best treated by i.v. administration of:
A. Hydrochlorthiazide
B. Furosemide
C. Mannitol
D. Amiloride
E. Metalozone

18. Which of the following diuretics has the highest potential to cause ototoxicity:
A. Chlorothiazide
B. Furosemide
C. Ethacrynic acid
D. Acetazolamide
E. Spironolactone

19. All the following are uses of loop diuretics EXCEPT:
A. Acute pulmonary edema
B. Severe hypertension
C. Acute hypercalcemia
D. Acute oliguria
E. Calcium urolithiasis

20. In an addisonian patient, all of the following agents would have diuretic action EXCEPT:
A. Mannitol
B. Chlorothiazide.
C. Bumetanide
D. Furosemide.
E. Spironolactone

21. Gynecomastia may occur with the use of the following diuretics:
A. Chlorothiazide
B. Furosemide
C. Amiloride
D. Acetazolamide
E. Spironolactone

22. The most dangerous complication of injudicious use of diuretics in patients with advanced liver diseases is:

A. Aggravation of hypotension and fatigue
B. Electrolyte imbalance
C. Acid-base imbalance
D. Precipitation of hepatorenal syndrome
E. Marked dehydration

23. Acute congestive glaucoma is best treated by i.v. administration of:
A. Bumetanide
B. Furosemide
C. Mannitol
D. Amiloride
E. Metalozone

24. The following statements concerning hypokalemia are true EXCEPT:
A. It is a side effect predicted with all diuretics
B. It is commonly seen in patients with hyperaldosteronism
C. It can be manifested by ECG changes
D. It could be prevented by the use of K+ sparing diuretics
E. It is a risk factor for digitalis toxicity

25. The best intravenous agent given to patients with advanced liver disease to correct ascites and edema is:
A. Human albumin
B. Mannitol
C. Furosemide
D. Chlorothiazide
E. Spironolactone

26. A 63-year-old man presents to the emergency department with worsening heart failure. Physical exam reveals pitting edema in his ankles. Past medical history is significant for an allergic reaction following exposure to trimethoprim–sulfamethoxazole. Which drug should the physician prescribe to him?
A. Acetazolamide
B. Ethacrynic acid
C. Hydrochlorothiazide
D. Mannitol
E. furosemide

27. A 64-year-old woman with congestive heart failure. She complains of swelling in her legs and ankles. The doctor decides to increase her level of diuretics. What complication should the doctor be most aware of for this patient?
A. Diuretic-induced metabolic acidosis
B. Hepatic encephalopathy
C. Hypercalcemia
D. Hyperkalemia
E. Hypokalemia

28. One of your clinic patients is being treated with spironolactone. Which of the following statements best describes a property of this drug?
A. Contraindicated in heart failure, especially if severe
B. Inhibits Na+ reabsorption in the proximal renal tubule of the nephron
C. Interferes with aldosterone synthesis
D. Is a rational choice for a patient with an adrenal cortical tumor
E. Is more efficacious than hydrochlorothiazide in all patients who receive the drug

29. A patient taking an oral diuretic for about 6 months presents with elevated fasting and postprandial blood glucose levels. You suspect the glycemic problems are diuretic-induced. Which of the following was the most likely cause?
A. Acetazolamide
B. Amiloride
C. Chlorothiazide
D. Spironolactone
E. Triamterene

30. Chlorthalidone and torsemide are members of different diuretic classes, in terms of mechanisms of action, but they share the ability to cause hypokalemia. Which of the following statements best describes the general mechanism by which these drugs cause their effects that lead to net renal loss of potassium?
A. Act as aldosterone receptor agonists, thereby favoring K+ loss

B. Block proximal tubular ATP-dependent secretory pumps for K+
C. Increase delivery of Na+ to principal cells in the distal nephron, where tubular Na+ is transported into the cells via a sodium channel in exchange for K+, which gets eliminated in the urine
D. Inhibit a proximal tubular Na,K-ATPase such that K+ is actively pumped into the urine
E. Lower distal tubular urine osmolality, thereby favoring passive diffusion of K+ into the urine

31. Which of the following is a clinical indication for use of Mannitol?
A. Chronic simple glaucoma
B. Cerebral edema
C. Pulmonary edema
D. Acute heart failure
E. chronic renal failure

32. All the diuretics act from the luminal side of the renal tubule EXCEPT:
A. Torsemide
B. Hydrochlorothiazide
C. Spironolactone
D. Chlorthalidone
E. Furosemide

33. A 55-year-old male with kidney stones has been placed on a diuretic to decrease calcium excretion. However, after a few weeks, he develops an attack of gout. Which diuretic was he taking?
A. Furosemide.
B. Hydrochlorothiazide.
C. Spironolactone.
D. Triamterene
E. Acetazolamide

34. Your 60 year old male hypertensive patient who had a myocardial infarction a year ago is now showing signs of CHF. You therefore add spironolactone to his drug regimen. What side effect should you warn him about?
A. Gynecomastia
B. Hypokalemia
C. Lupus
D. Ototoxicity
E. Hyperuricemia

Answers

1 D	11 D	21 E	31 B
2 E	12 C	22 D	32 C
3 C	13 A	23 C	33 B
4 A	14 E	24 A	34 A
5 B	15 C	25 A	
6 A	16 E	26 B	
7 A	17 B	27 E	
8 B	18 C	28 D	
9 C	19 E	29 C	
10 C	20 E	30 C	

Simplified approach

Mansoura Clinical Pharmacology

For Medical students

Edited by

Staff members of
Clinical Pharmacology Department
Faculty of Medicine
Mansoura University

Volume 2

رقم الإيداع بدار الكتب: 1456 لسنة 2000
بتاريخ 2000/9/6

Preface

Clinical training for undergraduate students often focuses on diagnostic rather than therapeutic skills. Sometimes students are only expected to copy the prescribing behavior of their clinical teachers, or existing standard treatment guidelines, without explanation as to why certain treatment is chosen. Books may not be much help either. Pharmacology reference works and formularies are drug-centered, and although clinical textbooks and treatment guidelines are disease-centered and provide treatment recommendations, they rarely discuss why these therapies are chosen. Different sources may give contradictory advice.

This book in primarily intended for under graduate medical students who are about to enter the clinical phase of their studies. It will provide step by step guidance to the process of rational prescribing together with many illustrative examples. It teaches also skills that are necessary throughout a clinical career. Postgraduate students and practicing doctors may also find it a source of straightforward information.

I wish to acknowledge the ongoing efforts of my contributing authors, and we are deeply grateful to all those who have with such good grace given us their time and energy to supply valuable facts and opinions, they principally include:

- **Prof. Hussein El-Beltagi** who took over the preparation of all books since the 1st edition in 1995 including the revision process, printing control, distribution and selling control.
- **Assist. Prof. Mohamed-Hesham Daba** who took over the revision process and amendments of the last two editions.
- **Assist. Prof. Abdel-Motaal Fouda** who prepared the last two editions in a readable up-to-date text to provide essential information necessary throughout the clinical career.
- **Dr. Sameh Abdel-Ghany** who assisted in the revision process.

Much of any merit this book may have is due to the generosity of those named above.

Gamal M. Dahab (MD, PhD)

Professor Emeritus in Clinical Pharmacology
Mansoura Faculty of Medicine

Mission and Vision

Our mission

The Clinical Pharmacology Department is seeking excellence and leadership in four major core activities: education, research, community service, and faculty and staff development. We are connecting basic medical sciences with clinical care through innovative and disciplined teaching of clinical pharmacology in an integrative manner

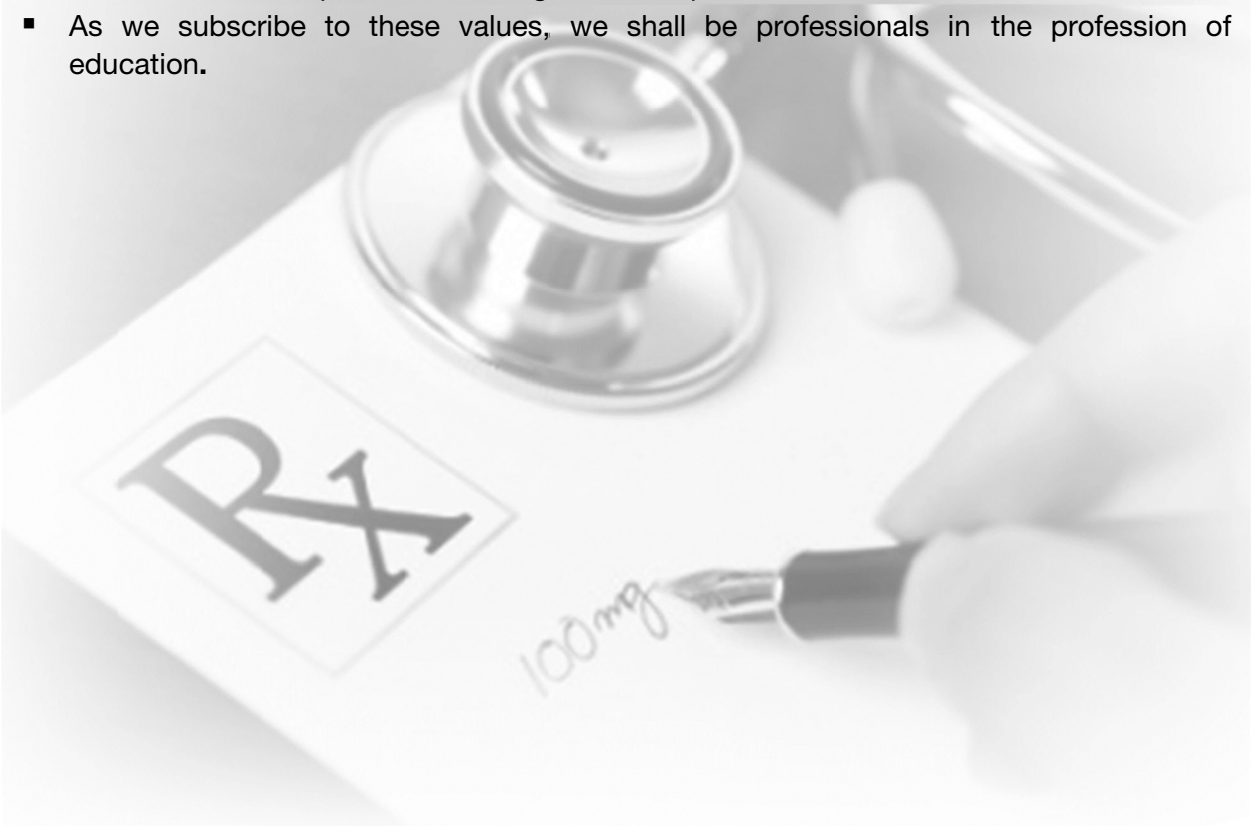
Our vision

The department of Clinical Pharmacology is aiming to be a premier academic model in the field of pharmacology and therapeutics in Egypt and Middle East through promoting use of the best therapeutics and developing newer experimental and clinical research projects.

Values

The guiding principles and beliefs for the department

- Excellence, creativity, innovation, fairness, honesty, transparency, collaboration, teamwork and lifelong learning
- Recognition that our student comes first
- All members of our department must see themselves as integral to the success of our mission and our department as integral to their personal success.
- As we subscribe to these values, we shall be professionals in the profession of education.



Contributers

Effat A. Haroun MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Elhamy M. El-Kholy MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Gamal M. Dahab MD, PhD, MSc (Int.Med)
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Farida M. El-Banna MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Aly M. Gaballah MD, PhD, MSc (int.Med**)**
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Layla T. Hanna MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Mohamed Kheriza MD, PhD, MSc (Int.Med)
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Abdel-Rahman A. Yassin MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Mohmmad A. Attia MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Mohamed Abdel-Ghani MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Hussien M. El-Beltagi MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Karawan M. Abdel-Rahman MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Somaya A. Mokbel MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Amany A. Shalaby MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Amal Abdel-Hamid MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Essam A. Ghyati MD, PhD
Assist. Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Mohamed-Hesham Y. Daba MD, PhD
Assist. Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Abdel-Motaal M. Fouda MD, PhD
Assist. Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Vivian Boshra MD, PhD
Assist. Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Hala A. Al-Ashri MD, PhD
Assist. Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Nageh Rizk MD, PhD
Lecturer in pharmacology
Mansoura Faculty of Medicine

Elsayed A. Hassan MD, PhD
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

Mohamed Abdel-Monem MD, PhD
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

Mahmoud A. Naga MD, PhD
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

Ahmad Hassan MD, PhD
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

Ahlam El-masry MD, PhD
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

Rehab Hamdy MD, PhD
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

Mohamed Abou El-khair MD, PhD
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

Sameh A. Abdel-Ghani MSc.
Assist. Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

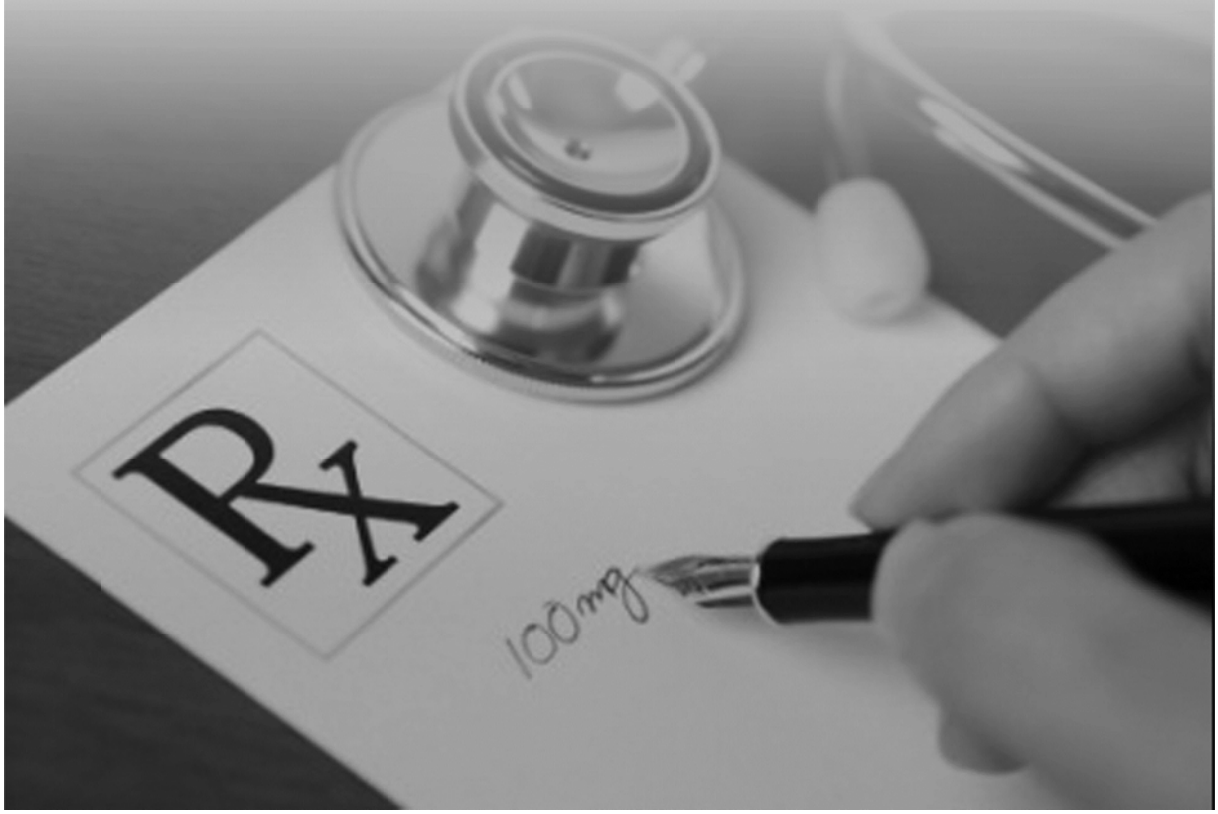
Table of Contents

CHAPTER 4: AUTACOIDS AND ANTI-INFLAMMATORY DRUGS

CHAPTER 5: CARDIOVASCULAR PHARMACOLOGY

Chapter 4

Autacoids And Antiinflammatory Drugs



Chapter 4

Autacoids and Antiinflammatory Drugs

Part 1: Autacoids

Inflammation is the complex biological response of vascular tissues to harmful stimuli. Injury produces locally-acting substances that initiate inflammatory response and activate the repair process. These substances are termed **'autacoids'**.

Examples of autacoids:

- **Amino acid derivatives:** e.g. histamine and 5-HT (serotonin).
- **Vasoactive peptides:** e.g. angiotensin, kinins and endothelins.
- **Fatty acid derivatives:** e.g. prostaglandins, thromboxanes, leukotrienes, etc.
- **The family of cytokines:** e.g. interleukins, interferones, TNF, growth factors, etc.

Histamine

- Histamine is formed from the amino acid histidine by the action of *histidine decarboxylase* and stored mainly in **mast cells**. Non-mast cell histamine is found in several tissues including the **brain**.
- No clinically useful drugs affect the synthesis or metabolism of histamine, but certain drugs can cause **release** of histamine from mast cells as a **side effect**.

Histamine release: can occur through 2 processes:

- **Ca^{2+} dependent mechanism:** by fixation of IgE to the surface of mast cell with subsequent activation of the complement, this causes Ca^{2+} influx and degranulation of mast cells. Many drugs can induce this type e.g. **penicillin**.
- **Ca^{2+} independent mechanism:**
  - Displacement of histamine from storage granules by **drugs**: e.g. morphine, tubocurarine, vancomycin, and amine antibiotics.
  - Mast cell damage: by venoms, or mechanical trauma.

Pharmacological effects of histamine

Histamine acts on at least **4** types of receptors:

R	Postreceptor mechanism	Site	Effect
H1	Gq ↑ IP3 & DAG	CNS	Functions related to appetite and satiety
		Nonvascular smooth ms	Spasm (→ bronchoconstriction, GIT spasm).
		Blood vessels	– VD of microcirculation (arterioles and precapillary sphincters) → ↑ capillary permeability (edema) and fall of BP. – This VD is due to release of NO from vascular endothelium.
		Exocrine glds	↑ exocrine secretions (bronchial, lacrimal, etc)
		Sensory nerves	Pain and itching
H2	Gs ↑ cAMP	Gastric parietal cells	↑ HCl secretion.
		Heart	↑ cardiac contractility and HR.
		Mast cells	↓ histamine release (-ve feed back effect).
H3	Gi ↓ cAMP	CNS and presynaptic nerve endings	Wakefulness and modulation of other neurotransmitters release.
H4	Gi ↓ cAMP	Inflammatory cells	Regulation of the inflammatory response

Clinical uses of histamine

- Histamine itself has **no** clinical applications.
- Some selective agonists are available for **diagnostic** purposes only e.g. test for gastric secretion.

Histamine antagonists

- **Physiological antagonists (adrenaline):** adrenaline reverses all the effects of histamine by action on different receptors (see ANS).
- **Histamine receptor antagonists:**
  - H_1-blockers: e.g. diphenhydramine, loratidine, etc. (see below)
  - H_2-blockers: e.g. cimetidine, ranitidine, famotidine, etc. (see GIT)
  - H_3 and H_4 -blockers: are not yet available for clinical use.
- **Histamine release inhibitors (mast cell stabilizers): ketotifen** and **cromoglycate** They inhibit Ca^{2+} influx into mast cells and prevent mast cell degranulation.

- **Desensitization therapy (immunotherapy):**
  Immunotherapy is a process in which an allergic patient can become **desensitized** to antigens that trigger allergic responses. Small doses of **the allergic substance** are injected weekly. Each week the dose is increased. Gradually a protective antibody (IgG) is formed to block the allergic reaction. Many patients notice an improvement within 6 months.

H1-receptor antagonists

	1st generation H1 blockers	2nd generation H1 blockers
Examples	Diphenhydramine Dimenhydrinate Clemastine Antazoline Cyclizine - Meclizine Chlorpheniramine Promethazine Cyproheptadine	Loratidine Azelastine Cetirizine Fexofenadine Ketotifen is a 2nd gen H1 blocker and mast cell stabilizer (see respiratory pharmacology).
CNS effects	They can cross BBB (more lipophilic) and exert significant CNS actions	Can**not** cross BBB (less lipophilic) and have little or **no** CNS actions
Potency	**Less** potent H1 blockers	**More** potent H1 blockers
Effects related to H1 blocking	– Relief of itching, pain and allergic response. – ↓ capillary permeability and inflammatory edema induced by histamine – ↓ bronchoconstriction, bronchial secretions, lacrimation, etc.	
Other effects	**Sedation:** but excitation or even convulsions may occur in some cases (especially in children or with high doses). **Atropine-like actions:** most of the first generation drugs can block peripheral muscarinic receptors leading to urine retention and blurred vision. **Antiemetic action:** useful in preventing motion sickness. **α-receptor blocking action:**	Not present

	leading to orthostatic (postural) hypotension in susceptible individuals. **5-HT receptor blocking action** *(especially cyproheptadine)*: so it is useful drug for treating carcinoid syndrome.	
Duration of action	3-8 h	3-24 h
Therapeutic uses	■ **Allergic conditions:** – The use of H1-blockers is effective in allergic conditions in which histamine is the primary mediator (e.g. allergic rhinitis and urticaria). – **N.B.** In bronchial asthma, which involves several mediators, the use of H1-blockers is generally ineffective. ■ **Motion sickness and vestibular disturbances:** – The first-generation H1-blockers (especially diphenhydramine and promethazine) are effective in preventing motion sickness, but their efficacy in Ménièrs's disease is not established. – They act by blocking H1 and muscarinic receptors in the vestibulocerebellar pathway. – **N.B.** Scopolamine remains the most effective treatment for motion sickness. ■ **Carcinoid syndrome:** – Carcinoid syndrome is caused by a serotonin-secreting neoplasm of the enterochromaffin cells of the GIT. – When the tumor is not operable, cyproheptadine and other 5-HT blockers can be used to block 5-HT receptors.	
Adverse effects	– **Sedation** with impaired concentration**,** but rarely excitation and convulsions may occur in children after toxic doses. – **Anticholinergic (atropine-like) actions:** this may cause urine retention, dry mouth and blurred vision.	The **second-generation** drugs are metabolized by the hepatic CYP450 enzymes. Some of the early drugs in this group prolonged the QT interval and caused serious **arrhythmia** (*torsade de pointes*) when given with other drugs that **inhibit** CYP450 system (e.g. **ketoconazole**), and in patients

	– **Orthostatic hypotension** due to their **α**-receptor blocking action**.**	with liver disease. These drugs are now withdrawn from the market.
Interactions	These drugs can potentiate the sedative effect of hypnotics, alcohol, etc.	Dangerous **arrhythmia** when given with other drugs that inhibit CYP450 system.

Serotonin (5-hydroxytryptamine; 5-HT)

5-HT is formed from the amino acid tryptophane and stored mainly in the **enterochromaffin** tissue of the GIT (90%) and **platelets** (10%). Serotonin is found also as a **transmitter** in many areas within the CNS. Like histamine, no clinically useful drugs affect the synthesis or metabolism of 5-HT, but many drugs can act on 5-HT receptors as agonists or antagonists.

Pharmacological actions of 5-HT

5-HT acts on at least **7** types of receptors:

	Distribution	Postreceptor mechanism	Effect
5-HT$_{1A}$ **5-HT$_{1B}$** **5-HT$_{1D}$** **5-HT$_{1E}$**	CNS, cranial blood vessels	Gi ↓cAMP	Role in anxiety, cognitive function, appetite, thermoregulation, memory, nociception VC of cranial BV.
5-HT$_{2A}$ **5-HT$_{2B}$** **5-HT$_{2C}$**	Platelets smooth muscle, CNS	Gq ↑ IP3	Platelet aggregation (5HT$_{2A}$) VC and smooth muscle contraction Hallucinations
5-HT$_3$	Area postrema, enteric nervous system	Na^+ ion channel	Nausea and vomiting Nociception (pain)
5-HT$_4$	CNS and enteric nervous system	Gs ↑ cAMP	↑ GIT motility and secretions
5-HT$_{5A}$	CNS	Gi ↓cAMP	?
5-HT$_{6,7}$	CNS	Gs ↑ cAMP	Anxiety, cognitive function, thermoregulation, memory, nociception

Some 5-HT agonists and antagonists in clinical use

5-HT agonists

- **Buspirone:** (see also CNS)

– It activates central **5-HT$_{1A}$** receptors. It is used for treatment of **anxiety** disorders especially in elderly patients.
– Therapeutic effect may take as long as 2 weeks to appear.

- **Triptans: sumatriptan, zolmitriptan, naratriptan** (see also ANS)

– They activate **5-HT$_{1B/1D}$** receptors.
– The major use of triptans is the treatment of **acute migraine**. Activation of **5-HT$_{1D}$** receptors inhibits inflammation of meninges, pain transmission, and release of VD substances e.g. calcitonin gene-related peptide in trigeminal neurons. Activation of 5-HT$_{1B}$ receptors causes VC of the dilated cerebral vessels. About 50%–80% of patients report relief from pain within 2 hours.
– **5-HT$_{1B}$** activity can cause **coronary spasm** so; these drugs are contraindicated in patients with ischemic heart disease (IHD).

Serotonin syndrome

Excess serotonin release in synaptic spaces can cause potentially fatal condition known as "serotonin syndrome". It can occur as a sudden adverse effect of "serotonergic drugs" e.g. MAOIs, tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRIs), tramadol, meperidine, and buspirone (see CNS).

Manifestations: characterized by hypertension, hyperthermia, hyperreflexia, muscle rigidity, diarrhea, and coma.

Treatment: sedation with benzodiazepines + 5-HT blockers.

- **Tegaserod:**

– It is a specific **5-HT$_4$** agonist. It increases GIT motility so it is used for treatment of irritable bowel syndrome with constipation.

5-HT antagonists

- **Cyproheptadine:**

– It blocks **5-HT$_2$**, **H$_1$**, & **muscarinic** receptors.
– It is used for treatment of symptoms of carcinoid tumor and as antiallergic.

- **Atypical antipsychotics: Olanzapine, risperidone** (see also CNS)

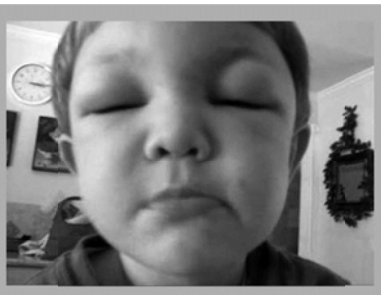
– They block **5-HT$_{2A}$** and dopamine **D$_2$** receptors in the CNS leading to improvement of the negative symptoms of schizophrenia.

- **Ondansetron, granisetron:** (see also GIT)

– They selectively block **5-HT$_3$** receptors centrally (CTZ) and peripherally (GIT).
– It is used for treatment of nausea & vomiting associated with cancer chemotherapy.

Kinins (bradykinin)

- Kinins are potent vasodilator peptides formed from protein substrates called kininogen by the effect of *kallikrein* enzyme.
- Kinins act on at least **2** subtypes of receptors: **B1** and **B2**. Activation of B2 receptors causes VD and ↑ capillary permeability, smooth ms contraction (bronchoconstriction, GIT colic, etc.), and stimulation of sensory nerves causing pain.
- **Icatibant** is a 2nd generation decapeptide which acts as a **selective antagonist** at bradykinin **B2 receptors.** It is given by s.c. injection for the symptomatic treatment of acute attacks of **hereditary angioedema**. It may also be useful in drug-induced angioedema, ascites, and pancreatitis.
- Recently, a 3rd generation of **orally** active B2-receptor antagonists was developed and currently under study.



Hereditary angioedema

HA is a rare autosomal dominant disorder results from deficiency of the C1 esterase inhibitor (C1-INH), a major inhibitor of kallikrein-kinin systems. C1-INH deficiency results in increased formation of bradykinin, which by increasing vascular permeability, causes recurrent episodes of angioedema of the face, airways, GIT, extremities, and genitalia.
HA can be treated with drugs that inhibit the formation or actions of bradykinin.

Endothelins

- Endothelin is a vasoconstricting peptide produced by the endothelium. There are 3 isoforms. **Endothelin-1** (ET-1) is one of the strongest vasoconstrictors currently studied.
- Endothelins act on at least **2** subtypes of receptors: **ET_A** and **ET_B.**
- Most of ET-1 effects are mediated through **ET_A** receptors present in vascular smooth ms and other tissues. Its activation leads to potent VC, vascular smooth ms proliferation, cardiac hypertrophy, and elevation of blood pressure.
- Increased production of ET-1 has been implicated in a variety of CVS diseases, including primary pulmonary hypertension, cardiac hypertrophy, heart failure, atherosclerosis, and coronary artery disease.
- **Bosentan** is orally active nonselective blocker of **ET_A** and **ET_B** receptors, while **ambrisentan** is a selective **ET_A** blocker. Both drugs are approved for treatment of **pulmonary hypertension**.

Purines as mediators

Nucleosides (adenosine) and nucleotides (ADP and ATP) are extracellular chemical mediators. ATP is stored in vesicles and released by exocytosis or through tissue damage. Released ATP is rapidly converted to ADP and adenosine. The three purines act on **three** main families of **purine receptors** and exert a wide range of functions.

R	Postreceptor mechanism	Endogenous ligand	Important sites	Effect
A family (many subtypes)	G-protein coupled	Adenosine	Lung	Bronchoconstriction
			Conducting system of the heart	Inhibits conduction
			Mast cells	Promote mediator release
			CNS	Complex inhibitory functions
P2Y family (many subtypes)	G-protein coupled	ATP ADP UDP	Platelets	Promote aggregation
			CNS	Complex neuropsychiatric effects
			Other tissue	Still unknown functions
P2X family (many subtypes)	Ligand gated ion channel	ATP	Stored intracellular	Regulates vascular sm muscle tone and insulin release through K^+ channels.
			Released by damaged tissue	Promote cytokine release by inflammatory cells.
			Released by nerve terminals	Pain transmission (especially neuropathic pain).

Drugs acting on purine receptors:

Adenosine

It is a short acting purine **A** receptor **agonist**. It is given by **i.v.** route to inhibit AV conduction and converts **supraventricular tachycardia** to the sinus rhythm in non-asthmatic patients (see CVS).

Methylxanthines

Caffeine, aminophylline and theophylline are purine **A1** receptor **antagonists**. They are used as **bronchodilators** and **CNS stimulants** (see respiratory).

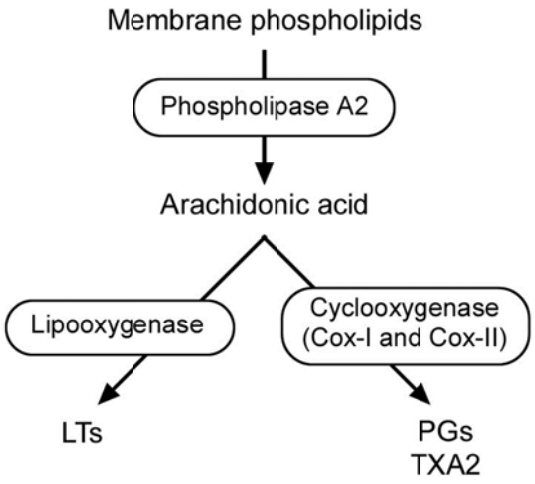
Fatty acid derivatives (eicosanoids)

They are group of fatty acid derivatives derived from arachidonic acid (20 carbons). The family of eicosanoids **includes:**

Prostaglandins (PGs)

PGs are members of fatty acid derivatives. All are derived from arachidonic acid by the action of cyclooxygenase (COX) enzyme which has 3 isoforms:

- **COX-1 (physiological; constitutive):** is involved in synthesis of *protective* PGs (e.g. PGE_2, PGI_2) responsible for protection of stomach from HCl, regulation of RBF, inhibition of platelet aggregation, etc.
- **COX-2 (pathological; inducible):** is involved in synthesis of *undesirable* PGs (e.g. $PGF_{2\alpha}$, PGD_2) involved in inflammatory reactions, bronchoconstriction, etc.
- **COX-3 (central):** it is a variant of COX-2 that found only in the **brain** and may be included in synthesis of PGs responsible for fever and pain sensation. It is selectively inhibited by analgesic/antipyretic drugs e.g. **acetaminophen (paracetamol)** and **dipyrone.**



Thromboxanes (TXs)

- They are also products of cyclooxygenase enzyme.
- They are synthesized in high concentration in platelets.
- They are of 2 forms: **TXA_2** (the *active* form) and **TXB_2** (the *inactive* form).
- **TXA_2** is the most potent endogenous stimulator of *platelet aggregation.*

Leukotrienes (LTs)

- They are derived from arachidonic acid by the action of *lipooxygenase* enzyme.
- They are of 4 main types: **LTB_4, LTC_4, LTD_4, and LTE_4.**
- A mixture of **LTC_4, LTD_4, LTE_4** is termed (the slow-reacting substance of anaphylaxis = SRS-A) that is released during inflammatory response.
- **LTB_4** is powerful **bronchoconstrictor** and **chemotactic** for leukocytes.

Pharmacological actions of eicosanoids

PGs and other eicosanoids act on cell surface **G-protein coupled receptors**. These receptors are termed DP1-2, EP1-4, FP, etc. The following table summarizes the important effects of different eicosanoids:

	PGE_1, PGE_2	PGI_2	$PGF_{2\alpha}$	TXA_2	LTB_4
BV	VD		VC		VD
Edema	+		–		+++
Bronchi	Relaxation		Constriction		Severe constriction
Uterus	Pregnant: contraction Non-pregnant: relaxation		Contraction		Contraction
Kidney	↑ RBF		↓ RBF		?
Platelets		↓aggregation		↑aggregation	
Other effects	– ↓ gastric HCl and ↑ mucus secretion – Hyperpyrexia				Chemotaxis

Therapeutic uses of prostaglandins

- **PGE_1:**
  - PGE1 (Alprostadil) is still available as urethral inserts for treatment of **erectile dysfunction** in men: it produces VD of the vascular smooth muscle of the corpus cavernosum and improves erection.
  - To maintain patency of the **ductus arteriosus** in infants with congenital cyanotic heart diseases until surgical correction is undertaken. The ductus arteriosus in neonates and infants is highly sensitive to VD by PGE1. Patency of the ductus is necessary in those patients to ensure additional oxygenation of the blood until surgical correction of the problem is undertaken.
  - Treatment of **peptic ulcer**: Mesoprostol is approved for use in patients taking high doses of NSAIDs to prevent gastric ulceration.

- **PGE_2:**
  - Induction of **labor near full term** (Dinoprostone).
  - Treatment of **peripheral vascular disease**.

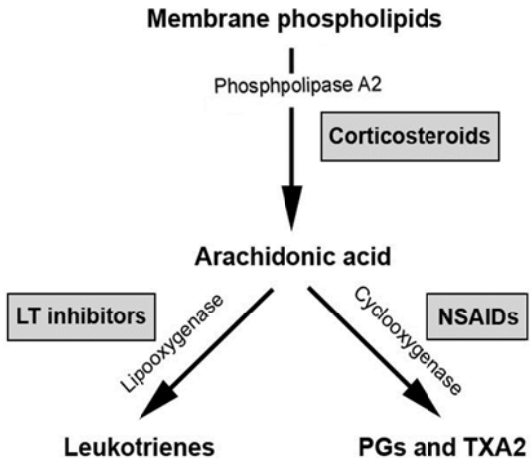
- **PGI_2 (Prostacycline):**
  - To **inhibit platelet aggregation** and prevent thrombosis during cardiopulmonary bypass surgery, hemodialysis, and retinal artery occlusion.
  - Treatment of **pulmonary hypertension** and **peripheral vascular disease**.

- **PGF2α:**
  - Induction of **labor near full term** (Enzaprost).
  - **Therapeutic abortion:** as vaginal suppositories. It may be combined with PGE2 and mifepristone (anti-progesterone) to produce more powerful uterine contraction.
  - Treatment of **open-angle glaucoma**: to *dilate* uveoscleral vessels and enhance uveoscleral outflow (↑ drainage) of aqueous humor (Latanoprost).

- **Thromboxanes and leukotrienes:** they have NO current clinical uses.

INHIBITORS OF EICOSANOIDS

- **Corticosteroids:** they inhibit *phospholipase* A_2 enzyme and consequently inhibit synthesis of **ALL** the eicosanoids family (see endocrine pharmacology).



- **Non-steroidal anti-inflammatory drugs (NSAIDs):** they inhibit cyclooxygenase enzyme:
  - **Classical NSAIDs** (e.g. aspirin) inhibit all COX enzyme non-selectively.
  - **Newer NSAIDs** (e.g. celecoxib) inhibit COX-2 selectively.

- **Leukotriene inhibitors:**

Zafirlukast and Montelukast:

- They block leukotriene *receptors.*
- They are absorbed orally. Zafirlukast it is given twice daily but Montelukast is given once daily.
- **Uses:** LTs receptor antagonists are new drugs to be used in the treatment of **bronchial asthma** and other inflammatory conditions.

Zileuton:

- It inhibits 5-lipooxygenase enzyme leading to decrease LTs *synthesis.*
- **Uses:** treatment of **bronchial asthma** and other inflammatory conditions.

Part 2: Non-steroidal anti-inflammatory drugs (NSAIDs)

Classification

- **Non-selective COX inhibitors (inhibit COX-1 and COX-2):**
  - **Salicylic acid derivatives:** aspirin, aloxiprine, aminosalicylic acid, diflunisal, methyl salicylate, etc.
  - **Acetic acid derivatives:**
    - Carboxylic acetic acid: indomethacin, sulindac, etodolac.
    - Phenyl acetic acid: diclofenac
  - **Propionic acid derivatives:** iboprufen, ketoprofen, fenoprufen, naproxen.
  - **Fenamic acid derivatives:** mefenamic acid, fulfenamic acid.
  - **Pyrazolone derivatives:** phenylbutazone, azapropazone
  - **Oxicams:** piroxicam, tinoxicam.
- **Selective COX-2 inhibitors: celecoxib, etoricoxib, meloxicam.**

Acetylsalicylic acid (Aspirin)

Chemistry and pharmacokinetics

- Oral absorption is complete; most of absorption occurs from the *stomach* and upper GIT.
- Widely distributed to all tissues including CNS.
- Metabolism of salicylates occurs by the hepatic microsomal enzymes.
  - At low doses, elimination is done by the *first-order process.*
  - At high doses, elimination is done by the *zero-order process.*
- Excretion is increased by *alkalinization of urine* (pH 8) because in alkaline urine, most of aspirin is *ionized and less re-absorbable.*

Mechanism and pharmacological effects

Aspirin is **non-selective** and **irreversible** COX inhibitor leading to inhibition of both PGs and TXs. This distinguishes it from other NSAIDs, which **reversibly** inhibit COX enzyme.

Analgesic action: for mild to moderate intensity pain (not severe pain).

Mechanism:
- Peripheral effect: decrease PGs synthesis in the peripheral inflamed tissues.
- Central effect: decrease PGs synthesis in the subcortical sites (thalamus and hypothalamus).

Antipyretic effect:

Aspirin is antipyretic but NOT hypothermic agent i.e. it can lower elevated body temperature but not normal body temperature.

Mechanism:

- Decrease PGE_2 synthesis in the hypothalamus.
- Decrease the hypothalamic response to interleukin-1 (endogenous pyrogen).
- Cutaneous VD and increase sweating.

Anti-inflammatory, anti-immunological and anti-rheumatic effects:

Mechanism:
By inhibition of COX enzyme, it ↓ synthesis of PGs and TXs, and possibly other inflammatory mediators leading to:

- Decrease inflammatory cell activation and chemotaxis.
- Decrease capillary permeability.
- Decrease hyaluronidase enzyme and inhibits spread of inflammation.
- Stabilize lysosomal membranes of inflammatory cells.

Respiratory effects:

- Low toxic doses: produce **metabolic acidosis** → compensatory **hyperventilation** to wash excess CO_2 → prolonged respiratory alkalosis.
- High toxic doses: produce metabolic acidosis together with inhibition of RC → death from severe acidosis.

CVS effects:

- Therapeutic doses: no significant effect on the CVS.
- Toxic doses: inhibit VMC leading to circulatory failure.

GIT effects: salicylates can produce **2 types** of gastric ulcer:

- Acute gastric ulcer: occurs as a result of acute ingestion of large doses of salicylates. The pathogenesis is related to trapping of salicylate ions inside the gastric mucosal cells leading to acute, painful gastric bleeding.
- Chronic gastric ulcer: occurs as a result of chronic ingestion of salicylates. The pathogenesis is related to chronic inhibition of the protective PGE_1, PGE_2 and PGI_2 synthesis leading to chronic ulceration and chronic blood loss.

Hepatic effects: salicylates can produce **2 types** of hepatic injury:

- Mild hepatic injury: it is dose-dependent, reversible and asymptomatic. There may be mild increase in serum transaminases (SGOT and SGPT).

– Severe hepatic injury: **"Reye's syndrome":** it is a rare and fatal condition occurs if aspirin is used to control fever of some viral infections (e.g. chicken pox, influenza, etc.) in **children below 12 years old.** There is severe fatty infiltration of the liver, pancreas, and kidney associated with encephalopathy. The etiology is unknown. Management is supportive.

N.B.

In children, paracetamol or ibuprofen are considered acceptable substitutes

Hematologic effects:

– Antiplatelet action: aspirin inhibit platelet aggregation by:
  – Irreversible inhibition of COX enzyme → ↓ TXA_2 → ↓ platelet *aggregation.*
  – Irreversible acetylation of platelet cell membranes → ↓ platelet *adhesions.*
  – Decrease platelet ADP synthesis → decrease platelet *accumulation.*

– Aspirin in high doses (> 6 gm /day) inhibits hepatic **prothrombin** (factor II) synthesis → prolong bleeding time.

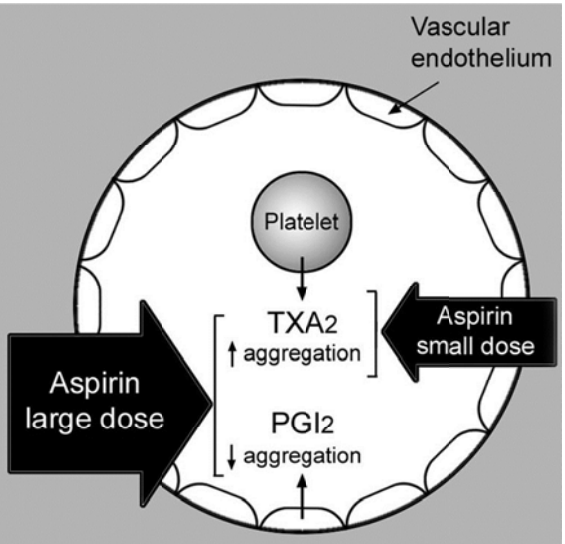
N.B.

Vascular endothelium produces PGI2 (prostacyclin) that causes VD and inhibition of platelet aggregation

Platelets produce TXA2 that causes VC and increase platelet aggregation

In high doses (> 300 mg), aspirin ↓ both vascular PGI2 and platelet TXA2.

In small doses (75-150 mg), aspirin inhibits only platelet TXA2 synthase enzyme → selective antiplatelet action.



Q1: if a patient taking aspirin has to undergo a surgical operation, when must he stop aspirin before the operation?

A: he must stop aspirin at least 7 days before the operation because platelet COX-1 is IRREVERSIBLY inhibited (i.e. platelet aggregation is permanently inhibited) and the patient has to synthesize new platelets (life span of platelets is 7-10 days).

Q2: if this patient needs urgent operation, what is the next step?

A: he must receive fresh blood, or packed platelet transfusion.

Q3: if this patient was taking an NSAID other than aspirin, when must he stop this drug before the operation?

A: any time because all NSAIDs other than aspirin inhibit COX enzyme REVERSIBLY (i.e. platelet aggregation is not permanently inhibited).

Renal effects:

- Analgesic nephropathy: it is chronic renal failure due to chronic abuse of analgesics, which produce chronic renal ischemia due to decrease synthesis of renal PGE_2 and PGI_2.
- Salt and water retention: due to decrease RBF and increase aldosterone
- Antagonize diuretic effect of diuretics and antihypertensive effects of β-blockers: due to decrease synthesis of PGE_2.
- Uric acid excretion: small-to-moderate doses of aspirin can ↓ uric acid excretion and thus contraindicated in patients with gout.

Aspirin in a dose of 75-150mg is not thought to have a significant effect on plasma urate levels - the British Society for Rheumatology recommend it should be continued if required for cardiovascular prophylaxis.

Metabolic effects:

- High doses cause uncoupling of oxidative phosphorylation → tachycardia and hyperpyrexia.

Uterus:

- Prolongation of pregnancy and delay of labor due to inhibition of PGs necessary for uterine contraction during labor. The use of NSAIDs after 20 weeks of pregnancy is not recommended.

Therapeutic uses of salicylates

- **As analgesic and antipyretic:** in mild-to-moderate pain e.g. headache, arthritis, etc. It should not be used routinely as antipyretic because fever may be a normal protective mechanism.
- **As anti-inflammatory and anti-rheumatic:** in rheumatic fever, rheumatoid arthritis, osteoarthritis, etc.
- **As antithrombotic:** see box.

Who should receive prophylactic low-dose aspirin?

- All people with established cardiovascular disease (stroke, TIA, ischemic heart disease, peripheral arterial disease).
- All people with target organ damage from hypertension.
- All people with diabetes mellitus who are ≥ 50 years or who have diabetes + hypertension.
- All people aged ≥ 50 years with a 10-year CVS risk score ≥ 20%.

- **As keratolytic and counter-irritant:**
  - Salicylic acid has keratolytic action and is used for treatment of warts.
  - Methylsalicylic acid is used as a counter-irritant for local rheumatic pain.

Adverse effects of salicylates

GIT:	– Epigastric pain, nausea and vomiting. – Acute and chronic gastric ulcers (why?).
Hepatic:	– Mild reversible hepatic injury in adults. – Severe hepatic injury in children: **"Reye's syndrome".**
Kidney:	– Analgesic nephropathy (why?). – Salt and water retention. – ↓ the diuretic effect of loop diuretics and antihypertensive effects of β-blockers (why?). – Precipitation of acute gout in hyperurecemic patients.
Blood:	– Increase bleeding tendency: (why?). – Displacement of other drugs from plasma proteins.
Uterus:	– Prolongation of pregnancy and delay of labor (why?).
Hypersensitivity reactions:	– Bronchospasm (aspirin asthma) in patients with history of asthma or allergic rhinitis due to accumulation of LTs.

Precautions and contraindications

- **GIT disorders:** peptic ulcer, gastritis, hemorrhagic pancreatitis, etc.
- **Hemorrhagic disorders:** hemophilia, thrombocytopenia, etc.
- **Chronic renal diseases:** aspirin may aggravate renal failure
- **Chronic liver diseases:** (those patients have bleeding tendency).
- **Uncontrolled hypertension:** risk of fatal bleeding.
- **Gout:** small-to moderate doses may inhibit uric acid excretion.
- **Before surgery:** aspirin must be stopped at least 7 days before surgery.
- **Children <12 years old:** fear of Reye's syndrome.

Drug interactions

- Aspirin antagonizes the uricosuric effect of probenecid (see gout).
- Aspirin antagonizes the diuretic effect of diuretics and the antihypertensive effect of antihypertensives (e.g. β-blockers, ACEIs) by inhibition of PGs synthesis.
- Aspirin can **displace** anticoagulants (heparin and warfarin), and other drugs from plasma proteins leading to increase their plasma concentrations.
- Antacids decrease absorption of aspirin.

Acute aspirin toxicity

Aspirin toxicity is dose-dependent and effects are determined by plasma drug levels

Manifestations:

- Tachypnea (hyperventilation) is the **earliest** sign of aspirin toxicity.
- Tinnitus, vomiting, hematemesis.
- Metabolic acidosis.
- Hyperthermia, hypoglycemia, dehydration, and coma.

Treatment:

- Repeated gastric lavage with activated charcoal.
- i.v. fluids and sodium bicarbonate to correct dehydration and acidosis.
- Vit K 10 mg i.m. or slowly i.v. to control hemorrhage.
- Alkalinization of urine: to enhance salicylate excretion.
- Hemodialysis in severe cases (when blood levels > 100 mg/dl).

OTHER NSAIDS

Diclofenac

- One of the most widely used NSAIDs.
- Generally, it is **less gastric irritant** than other NSAIDs but **more nephrotoxic**. A dose of 150 mg/day can impair renal blood flow and GFR.
- It is often combined with PGE analogue misoprostol to decrease gastric ulceration.
- Topical gel is available for local rheumatic pain and osteoarthritis of the knee and hands.

Sulindac and ketorolac

- Both have minimal effect on platelet aggregation.
- Sulindac is a **prodrug** and has long t½.
- Ketorolac is a **potent** analgesic but it can cause **severe GIT bleeding**.

Ibuprofen, fenoprofen, ketoprofen

- They have no reported interactions with oral anticoagulants
- Ibuprofen is a good alternative to aspirin in children with flu fevers.
- Fenoprofen has been reported to induce **nephrotoxic syndrome**
- Long-term use of ibuprofen is associated with an increased incidence of **hypertension** in women.

Indomethacin

- It is a very potent COX inhibitor but relatively **more toxic** than other NSAIDs.
- It is approved to speed the **closure of patent ductus arteriosus** in premature infants (otherwise it is not used in children); it inhibits the production of PGs which prevent closure of the ductus.

Piroxicam

- It has long t½ (~ 45 hours).
- Like aspirin and indomethacin, **bleeding** and ulceration are more likely with piroxicam than with other NSAIDs.

Dysmenorrhea

Dysmenorrhea is a distressing pelvic pain during menstruation. It is common gynecologic complaints.

It can be divided primary (occurring in the absence of pelvic pathology) and secondary (resulting from organic diseases). Primary dysmenorrhea is thought to be due to excessive production of **PGF2α**.

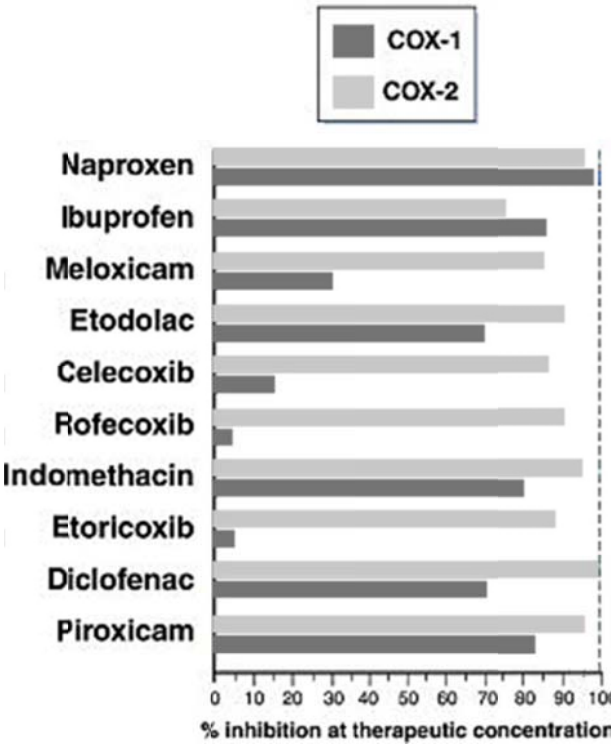
NSAIDs are extremely successful in treatment of both primary and secondary dysmenorrhea. They inhibit PGs synthesis and decrease pelvic congestion.

The FDA approved NSAIDs are in the following order: **diclofenac > ibuprofen > ketoprofen > naproxen.**

Indomethacin should be avoided because it has severe adverse effects.

Selective COX-2 inhibitors:
Celecoxib, etoricoxib, meloxicam

Selective COX-2 inhibitors are newer forms of NSAIDs that directly target COX-2 enzyme responsible for inflammation and pain. Celecoxib is approximately 30 times more potent at inhibiting COX-2 than COX-1. Meloxicam is slightly selective for COX-2 than COX-1 enzyme.



Selectivity for COX-2 reduces the risk of peptic ulceration but does not seem to affect other adverse-effects of NSAIDs (especially the risk of renal failure). Selective COX-2 inhibitors may also increase the risk of **cardiovascular accidents** (myocardial infarction, thrombosis and stroke) due to relative increase in TXA_2 and platelet aggregation (TXA_2 is formed by COX-1 where PGI_2 is formed by COX-2). Rofecoxib (Vioxx®) and valdecoxib were withdrawn from the market in 2004 and 2005 respectively because of these potential adverse effects.

	Non-selective COX inhibitors	Selective COX-2 inhibitors
Mechanism:	They inhibit COX-1 (non-inducible) and COX-2 (inducible) enzymes	They inhibit COX-2 (inducible) enzyme only
Pharmacological effects:	Both classes have equal analgesic and antipyretic effects	
Gastric side effects:	Frequent	Less frequent
Renal side effects:	Frequent	Frequent
Thrombotic complications:	Decreased (due to *decreased* platelet aggregation)	Increased (due to *increased* platelet aggregation)
Hypersensitivity reactions:	Frequent	Less frequent

Part 3: Acute Rheumatic Fever (ARF)

Definition:

It is an inflammatory disease that may develop as a complication of untreated or poorly treated **Group A β-hemolytic streptococcal (GABHS)** infection of the URT. It is caused by antibody cross-reactivity (i.e. autoimmune disease).

Incidence

- Age: 5-15 years (rare 2-5 years - never below 2 years).
- Environmental factors: poor living conditions, overcrowding.
- Genetic factors may play a role.
- No sex difference in the incidence or pathogenesis.

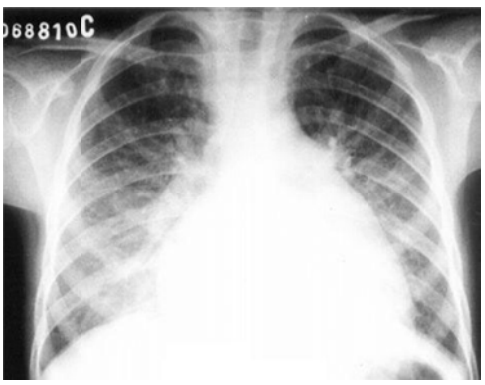
Etiology and pathogenesis

The autoimmune theory (molecular mimicry): the disease usually follows URT infection with GABHS. This *rheumatogenic strain* contain surface antigens *(hyaluronic acid, cell wall polysaccharides, M protein, etc.)* that are immunologically similar to some host's tissue. Antibodies formed against these antigens will later on **cross-react** with connective tissue antigens in the heart, synovial membranes, caudate nucleus, skin and subcutaneous tissue. **Repeated** streptococcal infection is required for **sensitization** of the immune system.

Clinical manifestations: "Jones criteria first published 1944":

Major criteria:

- Polyrthritis (70%): the joints are swollen and tender. It is fleeting (migratory), affects large joints, and subsides without deformity.
- Carditis (50%): murmurs, arrhythmia, cardiomegaly, pericardial rub.
- Rheumatic chorea (10%): jerky limb movements and emotional instability occur more in girls. It is reversible.
- Subcutaneous nodules (5%): painless nodules beside muscle tendons.
- Erythema marginatum (1%): red patches over the limbs and trunk.

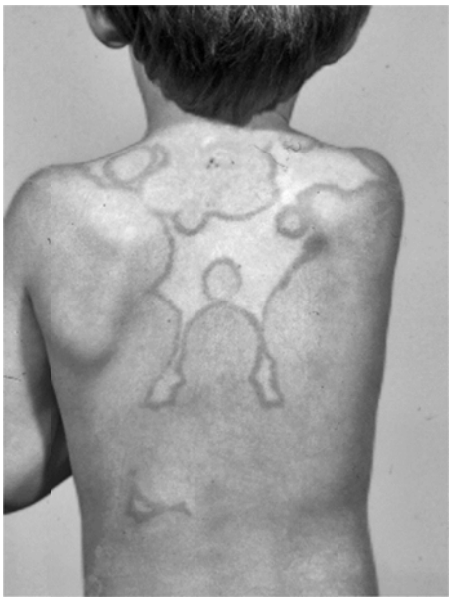


/ears

Minor criteria:

- Fever.
- Arthralgia: pain in the joint.
- ↑ PR interval in the ECG.
- ↑ antistreptolysin O titre (ASO).
- ↑ C-reactive protein and ESR.

Diagnosis: Revised Jones criteria (1992 update):



At least **2 major** criteria must be present **OR 1 major + 2 minor** criteria **PLUS evidence** of previous streptococcal infection:

- History of pharyngitis confirmed by positive throat culture for GABHS.
- Elevated **ASO titer > 400 U** or other streptococcal antibodies.

Management

TREATMENT OF THE ACUTE EPISODE

- **Bed rest:**
  - **2** weeks in absence of carditis.
  - **4** weeks in presence of carditis.
  - **8** weeks in presence of heart failure or cardiomegaly.

N.B.
The most dangerous manifestation is **carditis** because it always leads to permanent valvular lesion
"Rheumatic fever licks the joint but bites the heart".

- **Diet:** Salt and fluid restriction in presence of carditis or heart failure to avoid volume overload.

- **Antibiotics:** to eradicate streptococcal infection
  - First choice: *benzylpenicillin* (**1** million IU/6h i.v. or i.m.).
  - Second choice (in penicillin allergy): *Co-trimoxazole or erythromycin.*

- **Anti-inflammatory drugs:** to suppress acute inflammation

A. RF without carditis: salicylates (aspirin)
Dose: 100 mg/kg/d for 2 weeks (till clinical manifestations subside) then give 75 mg/kg/d for 2 weeks then 50 mg/kg/d for another 2 weeks (Max 16 tabs/d).
- Rapid breathing **(tachypnea)** is the **earliest sign** of aspirin toxicity.
- Naproxen is an alternative for patients who are allergic to aspirin.

B. RF with severe carditis: corticosteroids (prednisolone)
Dose: 2 mg/kg/d for 2 weeks (till clinical manifestations subside) then reduce the dose to 1mg/kg/d for one month.

Why corticosteroids, but not aspirin, in presence of carditis?

- Aspirin produces excellent symptomatic relief of arthritis and fever but exerts non-specific effect on carditis.
- Aspirin cannot prevent pericardial rub or valve deformity, but steroids can prevent them.
- High doses of aspirin increase myocardial O_2 consumption and heart work and so precipitate valvular lesions and CHF.

TREATMENT AFTER THE ACUTE EPISODE (PREVENTION OF RECURRENCE)

- **Long-acting penicillin:** *benzathine penicillin.*
  Dose: 1,200,000 IU / 3-4 weeks by deep i.m. injection

Duration of prophylaxis?

- For mild or no carditis → *for 3 years from last episode.*
- For moderate carditis → prophylaxis *till 21 years.*
- In severe carditis or recurrent episodes of RF → lifelong prophylaxis.

Precaution during treatment of ARF with other disease

ARF with TB	– Avoid using corticosteroids because they are immunosuppressant and cause flaring of TB infection. – If it is necessary to use corticosteroids, it must be used under umbrella of antituberculos drugs.
ARF with CHF	– Fluid and salt restriction – If digoxin is needed, use with caution to avoid arrhythmia (the heart is very sensitive to digoxin during Rh activity).
ARF with diabetes	– If corticosteroids are mandatory, consider adjusting the insulin dose to avoid hyperglycemia. – Consider possible interaction of salicylates with other antidiabetic drugs.
ARF with peptic ulcer	– Give salicylates through multiple routes or as enteric coated preparations to avoid gastric irritation. – Give salicylates after meals with plenty of fluids. – Use H2 blockers or proton pump inhibitors.

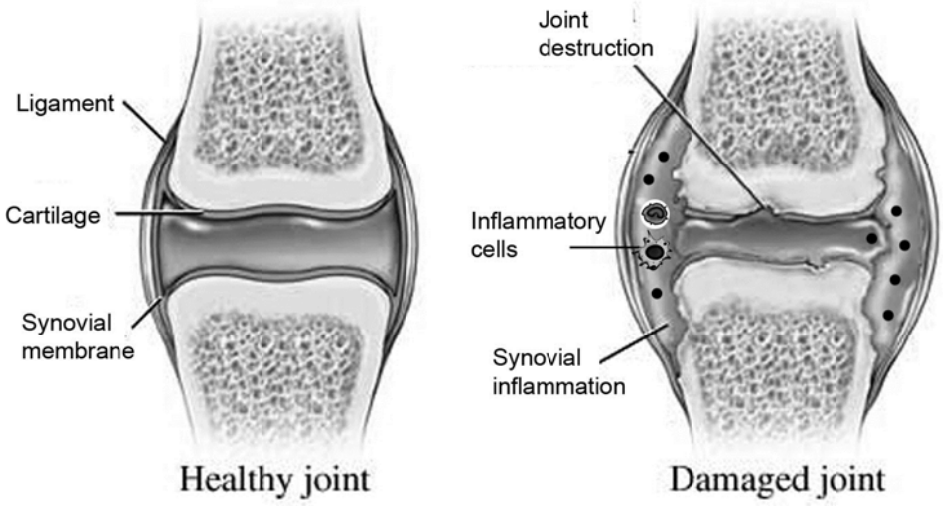
Part 4: Drug therapy of rheumatoid arthritis (RA)

Definition

RA is a chronic inflammatory disease characterized by symmetric small joint inflammation, swelling, and deformity. Extra-articular manifestations are also common.

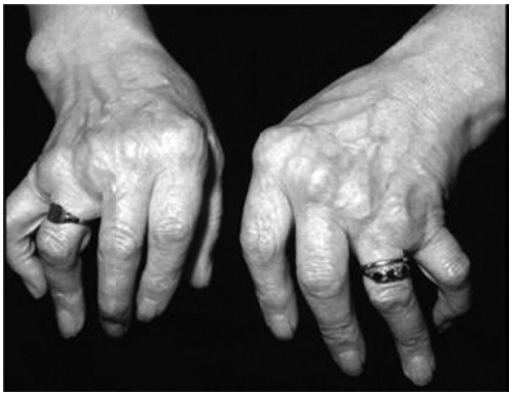
Pathophysiology

The exact aetiology is unclear however; genetic factors play an important role. Activated T cells, B cells, polymorphonuclear leukocytes (PMLs), macrophages, and complement system lead to production of soluble mediators (lysosymes, cytokines, e.g. TNF-α, IL-1, etc.) that cause joint inflammation, cartilage destruction, bone erosion, and deformity. Why the immune system attacks the joint structures as "foreign" antigens, is unknown.



Clinical manifestations

- **Articular manifestations:**
  The disease affects mainly small joints of the hands and toes in a symmetrical fashion. In severe cases, large joints are also affected. Affected joints are swollen, painful and with limited mobility. Symptoms are especially worse in the morning. In late cases, characteristic forms of joint deformity are present.



- **Extra-articular manifestations:**
  The spectrum of clinical manifestations of RA can extend to include systemic organs e.g. pleural effusion, pericarditis, anemia, vasculitis, etc.

Diagnosis

- **Serological:**
  - Abnormal blood antibodies "rheumatoid factor" can be found in 80% of RA patients.
  - Detection of Cyclic Citrullinated Peptide antibodies (anti-CCP antibodies): more specific than RF and can be detected up to 10 years before the development of RA.
- **Joint X-ray** can show joint swelling and bony erosions typical of RA.

Management of RA

Symptomatic treatment

- **NSAIDs:** large doses of NSAIDs are usually required. They offer symptomatic relief of pain and inflammation but don't prevent joint destruction.
- **Corticosteroids:** they are given as short-term therapy till DMARDs give their effect.

Disease-Modifying Antirheumatoid Drugs (DMARDs)

- They are the most important and should be started as **early** as possible because their effect may take 3 weeks to 3 months to be evident.
- They prevent progression of the disease and slow joint destruction by modifying the immune reactions.
- Combinations of two or more DMARDs are more effective than a single drug.

- **Biologic DMARDs: TNF-α inhibitors**

  TNF-α plays a crucial role in the pathogenesis of RA, and these drugs became the most important DMARDs.

  - **Adalimumab** and **infliximab:** they are monoclonal antibodies that complex with TNF-α and prevent its interaction with T cells and macrophages.
  - **Etanercept:** it is a recombinant protein that interferes with TNF-α and prevents it from binding to its receptors.
  - Acute and chronic infections, live virus vaccination, demyelinating disorders, class III or IV heart failure, and recent malignancies are **contraindications** to the use of TNF inhibitors.
  - Because these drugs are expensive, recent guidelines do not recommend their use until at least one nonbiologic DMARD, usually methotrexate, has been administered without sufficient success.

■ Methotrexate

- It is a folic acid antagonist with cytotoxic and immunosuppressant properties. It is one of the first line drugs being used in more than 60% of RA cases.
- It inhibits multiple intracellular enzymes needed for activation of PMLs, T cells, and macrophages.
- It is given once weekly orally. Folic acid 5mg must be given 24h after methotrexate dose to compensate for folic acid deficiency.
- Common **adverse effects**: hepatotoxicity is common (monitoring liver functions is essential), myelosuppression (bone marrow), teratogenicity.

■ Hydroxychloroquine (antimalarial drug)

- It decreases synthesis of DNA and RNA in the inflammatory cells and decrease response of T cells to antigens.
- It also stabilizes lysosomal membranes.

■ Sulfasalazine

It is metabolized into sulfapyridine and 5-aminosalicylic acid. 5-ASA causes inhibition of IgA and IgM production, and suppresses T and B cell functions.

■ Immunosuppressant drugs

- **Cyclophosphamide** and **azathioprine:** suppress immune function by their cytotoxic action through a variety of mechanisms, particularly inhibition of DNA synthesis.
- **Cyclosporine:** It is a potent and specific inhibitor of T cells. It inhibits phosphorylation of calcineurin, a protein that regulates nuclear transcription factors in the T cells.

■ Gold salts

Gold salts could be given i.m. or orally. Gold inhibits the functions of human macrophages and decrease the release of inflammatory cytokines and growth factors from inflammatory cells.

■ Leflunomide

- It suppresses pyrimidine synthesis and suppresses T cell and B cell functions.
- It is effective as methotrexate in inhibition of bone damage.

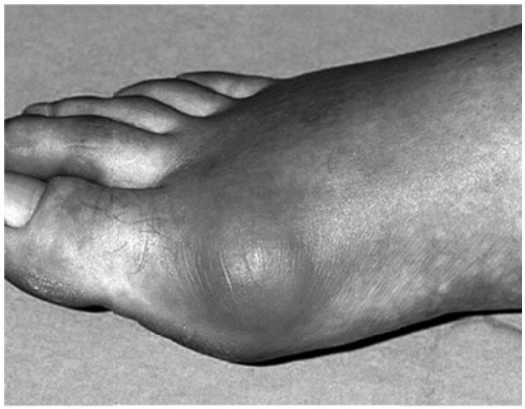
■ Anakinra

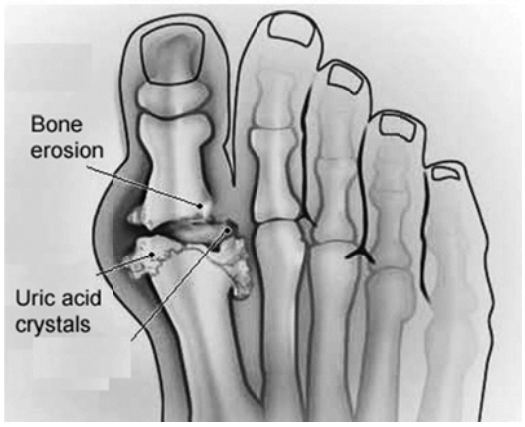
- It is a competitive IL-1 receptor antagonist.
- It has a relatively short half-life and must be administered subcutaneously daily.

Part 5: Drug therapy of gout

Basic information

Gout is a form of inflammatory arthritis due to deposition of monosodium urate crystals in the joint tissue. It is caused by chronic hyperuricemia (uric acid > 7 mg/dl = 0.42 mmol/L).





Biochemistry

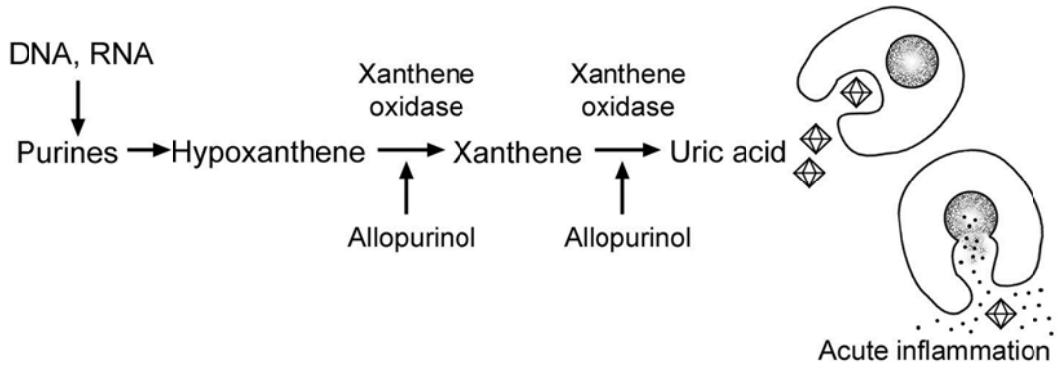
- Uric acid is the end product of purine metabolism by *xanthene oxidase* enzyme.
- The majority of body's uric acid is excreted by the renal PCT. Some drugs (e.g. diuretics) may interfere with excretion of uric acid at this segment leading to its retention.
- The renal excretion of uric acid is enhanced by alkalization of urine.

Causes of hyperuricemia

- **Decreased uric acid excretion:** account for **90%** of cases of primary gout:
  - Drugs: e.g. diuretics, aspirin, pyrazinamide, ethambutol.
  - Kidney diseases.
- **Increased uric acid production:**
  - High protein diet.
  - During treatment of some hematologic malignancies (e.g. leukemia) due to tissue breakdown (tumor lysis syndrome).
  - Sex-linked uricaciduria (Lesch-Nyhan syndrome).
- **Mixed causes:** alcohol.

Pathogenesis of gouty arthritis

- When serum uric acid increases, monosodium urate crystals are selectively precipitated in, and around the joint tissue causing irritation and inflammation.
- PNLs and macrophages come and phagocytose the "foreign" uric acid crystals causing swelling and inflammation of the articular tissue.
- Leukocytes eventually die with the release of proteolytic enzymes and inflammatory mediators (e.g. LTB_4, IL1, PGs, etc) causing severe inflammation.



ANTI-GOUT DRUGS

HYPOURICEMIC DRUGS (For CHRONIC gout)	**ANTI-INFLAMMATORY DRUGS (For ACUTE gout)**
1. ↑ uric acid excretion (uricosuric drugs): Probenecid, Sulfinpyrazone	1. Colchicine 2. Corticosteroids 3. NSAIDs
2. ↓ uric acid synthesis: allopurinol and thiopurinol	
3. ↑ uric acid metabolism: uricase enzyme.	

HYPOURICEMIC DRUGS

Uricosuric drugs: Probenecid

Mechanism of action: it has biphasic action:

- In **S**mall doses: it *inhibits* tubular **S**ecretion of organic acids (e.g. uric acid, penicillin, rifampin) by inhibiting organic acid transporters in tubular cells.
- In la**R**ge doses (≥500 mg twice/day): it *inhibits* tubular **R**eabsorption of uric acid by inhibiting the urate transporter (**URAT1)**, leading to ↑ excretion of uric acid.

Therapeutic uses

- As a uricosuric agent in chronic gout.
- To prolong the t½ of some acidic drugs e.g. penicillin and rifampicin by inhibition of their renal excretion.

Sulphinpyrazone is similar to probenecid with added antiplatelet effect due to decrease TXA2.

Adverse effects

– Gastric irritation, skin rash, and rarely interstitial nephritis and aplastic anemia.

– If given during the acute attack, it can aggravate the inflammation because rapid lowering of serum uric acid during the acute attack causes mobilization of uric acid crystals from the tissue stores and aggravates the acute inflammation.

Precautions during the use of uricosuric drugs

– They should not be used during the acute attack but 2-3 weeks after the acute attack has been subsided.
– Excess fluids and alkalinization of urine help uric acid excretion and prevent stone formation.
– Aspirin may decrease uric acid excretion and antagonize probenecid.

Inhibitors of uric acid synthesis: Allopurinol

Mechanism of action

- Allopurinol is a synthetic purine analogue. It inhibits **xanthine oxidase enzyme** leading to inhibition of uric acid synthesis.
- It has long duration of action because both the parent compound and its metabolite are potent inhibitors of *xanthine oxidase.*

Therapeutic uses

- Recurrent attacks of gout (more than 2 attacks per year): the target uric acid level is 5 mg/dl (0.3 mmol/L). Start with 100 mg once daily then gradually increase the dose every 1-2 weeks to reach 300 mg/d.
- As an adjuvant therapy during treatment of hematologic malignancies (e.g. leukemia) to prevent hyperuricemia resulting from tissue destruction.
- Patients with Lesch-Nyhan syndrome should receive allopurinol for life.

Adverse effects

– Gastric irritation and hypersensitivity reactions (skin rash).
– Precipitation of acute gout at the start of therapy due to mobilization of the deposited uric acid crystals from tissue stores leading to transient hyperuricemia

  Precautions:

  – Do not give allopurinol during the acute attack of gout.
  – Give prophylactic cover with NSAIDs or colchicine to avoid exacerbation of gout at the start of therapy.

Drug interactions

Mercaptopurine, azathioprine, and theophylline are metabolized by xanthine oxidase, and coadministration with allopurinol will dramatically increase levels of these drugs.

Increase uric acid metabolism: Pegloticase

- Pegloticase is a recent recombinant form of porcine **uricase**, the enzyme that converts uric acid into the water-soluble allantoin.
- It is given as 8 mg i.v. /2 weeks. It can lower serum uric acid within 24 hours. .
- It is indicated in **severe gout** not responding to other agents.

ANTI-INFLAMMATORY DRUGS

Colchicine

Mechanism of action

- Colchicine is a plant alkaloid. It binds to intracellular **microtubular system** leading to inhibition of leukocyte motility, phagocytosis, and cell division (mitotic blocker).
- It inhibits the release of **LTB_4** and other mediators by leukocytes.

Therapeutic uses

- Acute attacks of gout:
  - It is specific for gouty arthritis. Other arthritic pains are not relieved by colchicine.
  - It has slower onset than NSAIDs and corticosteroids. Reduction of inflammation and relief from pain occur 12–24 hours after oral administration.
  - Because of its slow onset and high toxicity, it is not a first-choice drug in acute gouty arthritis unless the patient has contraindication for NSAIDs or corticosteroids.
  - The recommended dose is 1.2 mg orally (2 tablets) initially followed by one tablet (0.6 mg)/ 12 hour until the attack resolves.

Familial Mediterranean Fever (FMF)

Also known as (recurrent polyserositis) is an autosomal recessive disorder which typically presents by the second decade. It is characterized by recurrent episodes of abdominal pain (due to peritonitis), pleurisy, pericarditis, arthritis. Attacks typically last 1-3 days.

- Familial Mediterranean fever (FMF): by an unclear mechanism.

Adverse effects

– **The most common: diarrhea.** Why?
Because the GIT epithelium has rapid rate of turnover. High oral doses of colchicine will inhibit this continuous renewal of GIT epithelium (by inhibiting cell

division) leading to accumulation of toxins and bacterial products with diarrhea.

- **The most rare:** alopecia and myopathy.
- **The most serious:** aplastic anemia and agranulocytosis (bone marrow depression).

NSAIDs

Indomethacin and naproxen

- Indomethacin and naproxen are FDA approved NSAIDs for acute gouty arthritis although other NSAIDs can also work (but not aspirin).
- They provide symptomatic relief in acute attacks faster than colchicine.
- Their dose must be reduced if taken with probenecid because probenecid inhibits their renal excretion.

Corticosteroids

- They are used as anti-inflammatory agents when colchicine and NSAIDs are not sufficient to control the acute attacks or when they are contraindicated.
- For more details about the mechanism, see endocrine pharmacology.

Notes

Review Questions

- Mention uses of H1 blockers.
- Mention the main differences between 1st and 2nd generation antihistamines
- Mention the main differences between aspirin and celecoxib.
- Mention the main differences between aspirin and colchicine.
- Mention 2 uses of PGE_1, PGE_2, PGI_2, $PGF_{2\alpha}$.
- Mention side effects of aspirin.
- Mention side effects of colchicine.
- Mention mechanism of aspirin as antiplatelet.
- Mention precautions during the use of antigout drugs.

Discuss on pharmacological basis each of the following:

- Aspirin is contraindicated as antipyretic in children with viral infection.
- Aspirin is contraindicated in chronic liver disease.
- Allopurinol is better to be avoided during acute attack of gout.
- Aspirin (low dose) is contraindicated with uricosuric drugs.
- Diphenhydramine is contraindicated in old males with benign prostatic hypertrophy.

Discuss the pharmacodynamic principles underlying the use of:

- PGI_2 during extracorporeal shunt operations (e.g. hemodialysis).
- PGI_1 during surgical correction of patent ductus arteriosus.
- Colchicine in acute gouty arthritis.
- Methotrexate in rheumatoid arthritis.

Mention the rationale of the following combinations:

- Mesoprostol is advised with diclofenac (NSAID).
- Colchicine is given before allopurinol in acute gout.

Of each of the following questions, select THE BEST SINGLE answer:

1. Which of the following antihistamines has the LEAST sedation at therapeutic dose?
A. Diphenhydramine
B. Loratidine
C. Promethazine
D. Antazoline
E. Cyproheptadine

2. Cyproheptadine is an antagonist at:
A. D_1 and M_1 receptors
B. M_1 and N_n receptors
C. H_1 and 5-HT receptors
D. H_1 and H_2 receptors
E. β_1 and α_1 receptors

3. Sumatriptan is effective for the treatment of acute migraine by acting as:
A. An antagonist at β adrenergic receptors
B. A selective antagonist at H_1 receptors
C. An inhibitor of prostacycline synthesis
D. An agonist at nicotinic receptors
E. A selective agonist at 5-HT_{1D} receptors

4. The pharmacologic effects of acetylsalicylic acid include:
A. Reduction of high body temperature
B. Promotion of platelet aggregation
C. Reduction of pain by stimulation of PGs synthesis
D. Efficacy equals to that of diflunisal as analgesic agent
E. Less gastric irritation than other NSAIDs

5. Aspirin reduces the synthesis of the following eicosanoids EXCEPT:
A. TXA_2
B. PGE_2
C. $PGF_{2\alpha}$
D. LTB_4
E. PGI_2

6. All the following are therapeutic uses of prostaglandins EXCEPT:
A. Medical abortion
B. To produce uterine relaxation during pregnancy
C. Temporary maintenance of the patency of ductus arteriosus in preterm neonates
D. Prevention of gastric ulceration caused by NSAIDs
E. Treatment of open angle glaucoma

7. All the following are effects of serotonin EXCEPT:
A. Increased force of cardiac contraction
B. Vasoconstriction of the arterioles of the pulmonary and renal beds
C. Stimulation of pain response
D. Contraction of bronchial smooth muscles
E. Relaxation of the GIT smooth muscles

8. The following statements about NSAIDs are correct EXCEPT:
A. Diclofenac may cause permanent platelet dysfunction
B. Indomethacin may cause headache
C. Sulindac is a prodrug
D. They may impair renal function
E. Aspirin may displace coumarin anticoagulants from plasma proteins

9. The following statements about aspirin are correct EXCEPT:
A. May cause GIT hemorrhage after a single dose
B. Enteric-coated tablets cause less gastric bleeding
C. May cause metabolic alkalosis in high doses
D. May cause Rye's syndrome in children
E. Its toxicity may require treatment with hemodialysis

10. In the treatment of acute rheumatic fever:
A. Aspirin is used to suppress rheumatic carditis
B. Polyarthritis never resolve without residual deformity
C. Rheumatic chorea requires intensive therapy with corticosteroids
D. Benzathine penicillin is used to prevent recurrent streptococcal infections

E. Erythromycin is considered the first line antibiotic to eradicate streptococcal infection

11. Which one of the following statements concerning Cox-2 inhibitors is correct:
A. They show greater analgesic activity than traditional NSAIDs
B. They show anti-inflammatory activity greater than traditional NSAIDs
C. They increase platelet aggregation
D. They harm the kidney as do non-selective cox inhibitors
E. They are cardio protective

12. Manifestations of acute salicylate intoxication include all of the following EXCEPT:
A. Hyperpyrexia
B. Hyperpnoea
C. Hypertension
D. Convulsions
E. Metabolic acidosis

13. Which of the following NSAID is used to treat patent ductus arteriosus in neonates:
A. Ketoprofen
B. Mefenamic acid
C. Celecoxib
D. Phenylbutazone
E. Indomethacin

14. Leukotrienes:
A. Are used for inducing labor in pregnant women
B. May be inhibited in patients treated with aspirin and similar drugs
C. Are produced from amino acids and stored in granules
D. May participate as SRS-A in asthmatic or anaphylactic reactions
E. LTB4 is powerful platelet aggregator

15. Drugs used in the treatment of gout include all of the following EXCEPT:
A. Indomethacin
B. Allopurinol
C. Colchicine
D. Probenecid
E. Aspirin

16. In the treatment of gout:
A. Aspirin should be combined with a uricosuric
B. Therapy with sulphinpyrazone should be accompanied by high fluid intake and alkalinization of the urine
C. Allopurinol will provide useful relief from an acute attack
D. Colchicine can be used prophylacticaly to prevent recurrence
E. Loop diuretics are indicated to wash the excess uric acid from blood

17. The following is true about allopurinol:
A. It has short duration of action
B. It can act as a uricosuric drug
C. It may worsen acute gout
D. The parent drug but not its metabolites are xanthine oxidase inhibitors
E. Is not recommended for patients treated by anticancer drugs

18. The following is true about PGF2α:
A. It causes bronchodilatation
B. It can be injected in the amniotic sac to induce abortion
C. It increases renal blood flow
D. It increases platelet aggregation
E. It causes hypotension

19. All the following drugs can decrease platelet aggregation EXCEPT:
A. Ketanserine
B. Celecoxib
C. Sulphynpyrazone
D. Aspirin
E. Epoprostenol (prostacyclin)

20. All the following drugs can be used in the treatment of rheumatoid arthritis EXCEPT:
A. Methotrexate
B. Gold
C. Leflunomide
D. Prednisolone
E. Colchicine

21. The most serious side effect of colchicine therapy is:
A. Agranulocytosis
B. Diarrhea
C. Alopecia
D. Amyloidosis
E. Anorexia

22. Which one of the following drugs could significantly impair the ability to drive an automobile?
A. Diphenhydramine.
B. Ergotamine.
C. Fexofenadine.
D. Ranitidine.
E. Sumatriptan.

23. Which one of the following is an action of colchicine?
A. It produce uricosuria
B. It produce constipation
C. It produce polycythemia
D. It stimulates cell division
E. It inhibits leukocyte migration and phagocytosis

24. Which of the following is a uricosuric agent used in chronic gout?
A. Sulfasalazine
B. Sulfinpyrazone
C. Allopurinol
D. Colchicine
E. Chloroquine

25. Which one of the following drugs acts by blocking interleukin-1 receptors?
A. Anakinra
B. Sulfasalazine
C. Gold saults
D. Methotrexate
E. Etanercept

26. Which one of the following drugs acts by blocking soluble receptors of TNF-α?
A. Anakinra
B. Sulfasalazine
C. Gold saults
D. Methotrexate
E. Etanercept

27. Inflammation is a complex tissue reaction that includes the release of cytokines, leukotrienes, prostaglandins, and peptides. Prostaglandins involved in inflammatory processes are produced from arachidonic acid by:
A. Cyclooxygenase 1
B. Cyclooxygenase 2
C. Glutathione – S – transferase
D. Lipoxygenase
E. Phospholipase A2

28. A 60-year-old woman has glaucoma following cataract surgery. Which of the following can be used to reduce intraocular pressure?
A. Leukotriene LTD4 or its analogs
B. Prostaglandin E2 or its analogs
C. Prostaglandin F2α or its analogs
D. Slow-reacting substance of anaplylaxis (SRS-A)
E. Thromboxane A2 or its analogs

29. A 45-year-old surgeon has developed symmetric early morning stiffness in her hands. She wishes to take a nonsteroidal anti-inflammatory drug to relieve these symptoms and wants to avoid gastrointestinal side effects. Which one of the following drugs is most appropriate?
A. Aspirin
B. Celecoxib
C. Ibuprofen
D. Indomethacin
E. Piroxicam

30. The following drug is considered a mast cell stabilizer:
A. Adrenaline
B. Salbutamol
C. Cromoglycate
D. Loratidine
E. Ondansetron

31. The following drug blocks $5HT_{2A}$ receptors in the CNS and is useful in relieving the negative symptoms of schizophrenia:

A. Buspirone
B. Ondansetron
C. Cyproheptadine
D. Olanzapine
E. Alosetron

32. The toxicity spectrum of aspirin does not include:
A. Increased risk of encephalopathy in children with viral infections
B. Increased risk of peptic ulcers
C. Hyperprothrombinemia
D. Metabolic acidosis
E. Respiratory alkalosis

33. Accidental poisonings are common with both aspirin and ibuprofen, the two drugs are available in tasty chewable tablets. In cases of overdose, aspirin is more likely than ibuprofen to cause:
A. Autonomic Instability
B. Hepatic necrosis
C. Metabolic acidosis
D. Thrombocytopenia
E. Ventricular arrhythmias

34. Which of the following compounds is most likely to lower circulating levels of leukotrienes?
A. Zileuton
B. Montelukast
C. Ibuprofen
D. Aspirin
E. Allopurinol

35. The action of aspirin that results in its greater efficacy as an antithrombotic (anti-platelet) drug is its ability to
A. Inhibit lipoxygenase as well as cyclooxygenase
B. Selectively inhibit cyclooxygenase I
C. Inhibit leukocyte migration
D. Promote uric acid excretion
E. Acetylate cyclooxygenase

36. Which of the following statements best describes the usual course of rheumatoid arthritis?
A. It is an acute exacerbation of joint pain treated with short-term anti-inflammatory therapy
B. It is a chronic disease characterized by acute changes within nonsynovial joints
C. It is an acute disease that is characterized by rapid synovial changes due to inflammation
D. It is a chronic disease characterized by acute exacerbations followed by remissions with consequences associated with chronic inflammatory changes
E. It is a joint disease characterized by a marked loss of calcium from the bones and a resultant thinning of the bones

37. All of the following statements concerning an acute gouty arthritis attack are correct EXCEPT
A. The diagonosis of gout is assured by a good therapeutic response to colchicine because no other form of arthritis responds to this drug
B. To be assured of the diagnosis, monosodium urate crystals must be identified in the synovial fluid of the affected joint
C. Attacks frequently occur in the middle of the night
D. An untreated acute attack may last up to 2 weeks
E. The first attack usually involves only one joint, most frequently the big toe (first metatarsophalangeal joint)

38. TNF- α is an example of:
A. Eicosanoids
B. Interleukins
C. Cytotoxic factors
D. Interferons
E. Colony stimulating factors

39. Potential adverse effects associated with aspirin include all of the following EXCEPT
A. Gastrointestinal ulceration
B. Renal dysfunction
C. Enhanced methotrexate toxicity
D. Cardiac arrhythmias

E. Hypersensitivity asthma

40. The cyclooxygenase isoenzymes COX-1 and COX-2 differ from each other in that:

A. They catalyse different pathways in prostanoid biosynthesis
B. COX–1 is inhibited by aspirin but not COX–2
C. COX–2 is inhibited by ibuprofen but not COX–1
D. COX–1 is constitutive while COX–2 is inducible
E. COX–2 is essential for renal function

41. Which one of the following drugs is a selective inhibitor of central COX-3 in the brain?

A. Paracetamol
B. Ibuprofen
C. Aspirin
D. Celecoxib
E. Colchicine

42. Irritable bowel syndrome with constipation can be treated by:

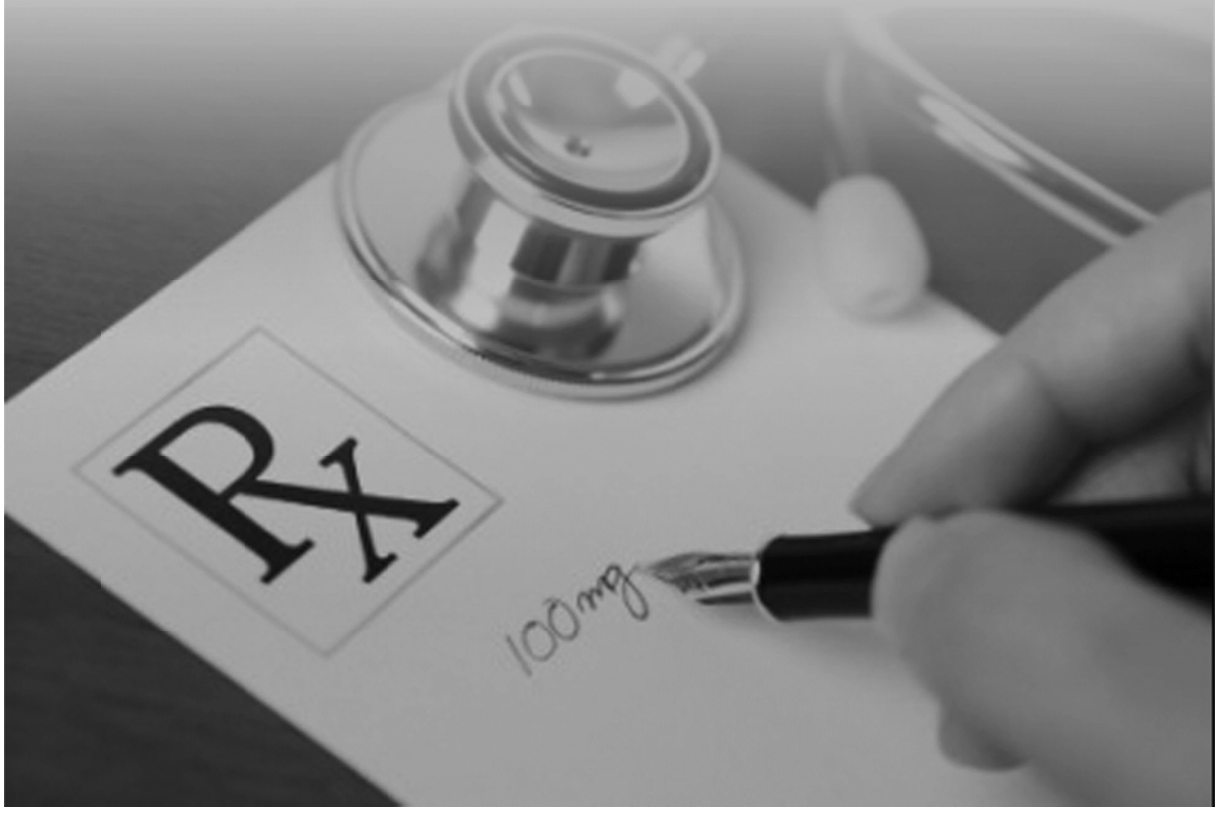
A. Alosetron
B. Tegaserod
C. Ondansetron
D. Olanzapine
E. Buspirone

Answers

1 B	11 C	21 A	31 D	41 A
2 C	12 C	22 A	32 C	42 B
3 E	13 E	23 E	33 C	
4 A	14 D	24 B	34 A	
5 D	15 E	25 A	35 E	
6 B	16 B	26 E	36 D	
7 E	17 C	27 B	37 D	
8 A	18 B	28 C	38 C	
9 C	19 B	29 B	39 D	
10 D	20 E	30 C	40 D	

Chapter 5

Cardiovascular Pharmacology



Chapter 5
Cardiovascular Pharmacology

Part 1: Systemic hypertension and antihypertensive drugs

Basic information

Vascular smooth muscle contraction and relaxation

Vasoconstriction is initiated by opening of voltage gated L-type **Ca^{2+}** channels in the membrane of vascular smooth muscle cells. Increased intracellular **Ca^{2+}** triggers the phosphorylation of *myosin light chain kinase* which initiates contraction.

Vasodilation is initiated by either:

- Activation of guanylyl cyclase → **↑cGMP** → dephosphorylation of *myosin light chain kinase* → smooth ms relaxation.
- **Opening of K^+ channels** in the vascular smooth muscle cell membrane → smooth ms stabilization (hyperpolarization) → relaxation.

The vascular endothelium and local vasomotor control

Beside the neural control of blood vessels through the sympathetic and parasympathetic systems, the **vascular endothelium** produces various compounds that help controlling the vascular tone:

Nitric oxide (NO; or EDRF)	It is a diffusible gas with very short half-life. It causes **VD** by increasing intracellular **cGMP**. It protects against atherosclerosis, high blood pressure, heart failure and thrombosis.
PGI2	It is synergistic to NO. It causes **VD** via specific receptors
Endothelin	Is a 21-amino-acid peptide. By its action on ET_A receptors, it causes severe **VC** and vascular smooth muscle **hypertrophy**.

Angiotensin-converting enzyme (ACE)	Located on the endothelial cell membrane and converts circulating angiotensin-I (synthesized by the action of renin on angiotensinogen) to angiotensin-II. By its action on AT1 receptors, Ang-II causes **VC** and stimulates **aldosterone** release.
Other factors	**Histamine** causes VD, **bradykinin** (synthesized from kininogen) causes VD, and **serotonin** (released by platelets) causes VC.

Management of systemic hypertension

Systemic hypertension is persistent elevation of BP above 140/90.

Classification of hypertension:

- According to etiology: primary (= essential, 90%) or secondary.
- According to type: systolic, diastolic, or mixed.
- According to degree: see table.

Classification of blood pressure levels of the British Hypertension Society

Category	Systolic BP (mmHg)	Diastolic BP (mmHg)
Normal blood pressure	<140	<90
Hypertension		
Stage 1 (mild)	140–159	90–99
Stage 2 (moderate)	160–179	100–109
Stage 3 (severe)	≥180	≥110
Isolated systolic hypertension	>140	<90

N.B. If systolic and diastolic BP fall into different categories, the higher value should be taken for classification.

Target BP:

- For most patients, the **goal of therapy** is to maintain BP **< 140/90** mm Hg.
- In patients with **DM** or **chronic kidney disease**, BP should be **< 130/80** mm Hg.

Non-drug therapy = life style modification:

- Dietary **sodium** restriction and **potassium** and magnesium supplementation.
- Stop **smoking** and avoid **stress**.
- **Weight** reduction alone can correct hypertension in 75% of obese patients.
- Daily physical **exercise** (~30 min/day): it lowers serum cholesterol, improves endothelial functions, and enhances tissue oxygenation.

- Control of **risk factors**: e.g. diabetes mellitus, hyperlipidemia, and obesity.
- Avoid **drugs** that ↑ BP e.g. sympathomimetics, sodium-containing drugs, oral contraceptive pills, corticosteroids.

N.B. Patients failing to normalize BP after **2 weeks** of non-pharmacological therapy should be considered for drug therapy.

Drug therapy (antihypertensive drugs):

First choice groups (commonly used drugs)	Second choice groups (used in special cases):
▪ **A ngiotensin-converting enzyme inhibitors (ACEIs)** ▪ **B eta-blockers** ▪ **C alcium channel blockers** ▪ **D iuretics**	▪ **α_1- blockers:** prazosin and doxasosin. ▪ **Combined α and β-blockers:** labetalol. ▪ **Adrenergic neuron blockers:** α-methyldopa and reserpine. ▪ **Vasodilators: e.g.** hydralazine. ▪ **Central α_2 stimulants:** clonidine. ▪ **Endothelin blockers:** Bosentan. ▪ **Dopamine agonists:** fenoldopam.

Beta-blockers

For detailed mechanism and pharmacology: see chapter 2.

Indications of beta-blockers in hypertension:

- Hypertension associated with cardiac problems e.g. IHD, cardiac arrhythmia, aortic dissection, etc.
- Hypertension associated with thyrotoxicosis.
- Hypertenstion associated with increased sympathetic overactivity.

Diuretics

For detailed mechanism and pharmacology: see chapter 3.

Indications of diuretics in hypertension:

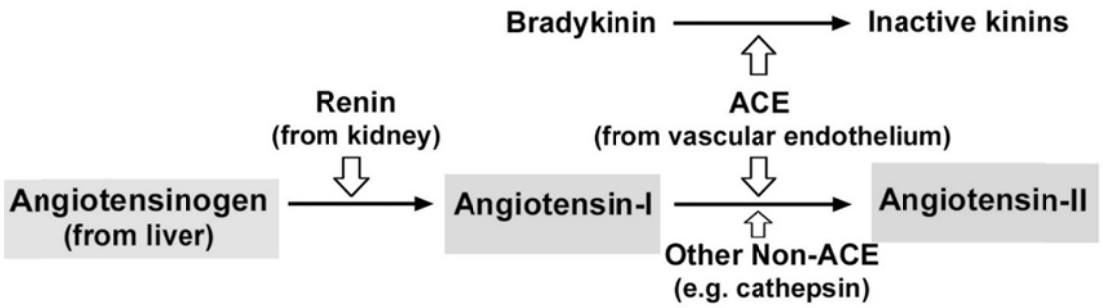
- Thiazides are given as initial therapy in most cases of mild, non-complicated essential hypertension.
- Hypertension associated with volume overload (salt and water retention): e.g. CHF, liver cirrhosis, primary hyperaldosteronism, pulmonary edema, etc.

Angiotensin-converting enzyme inhibitors (ACEIs)

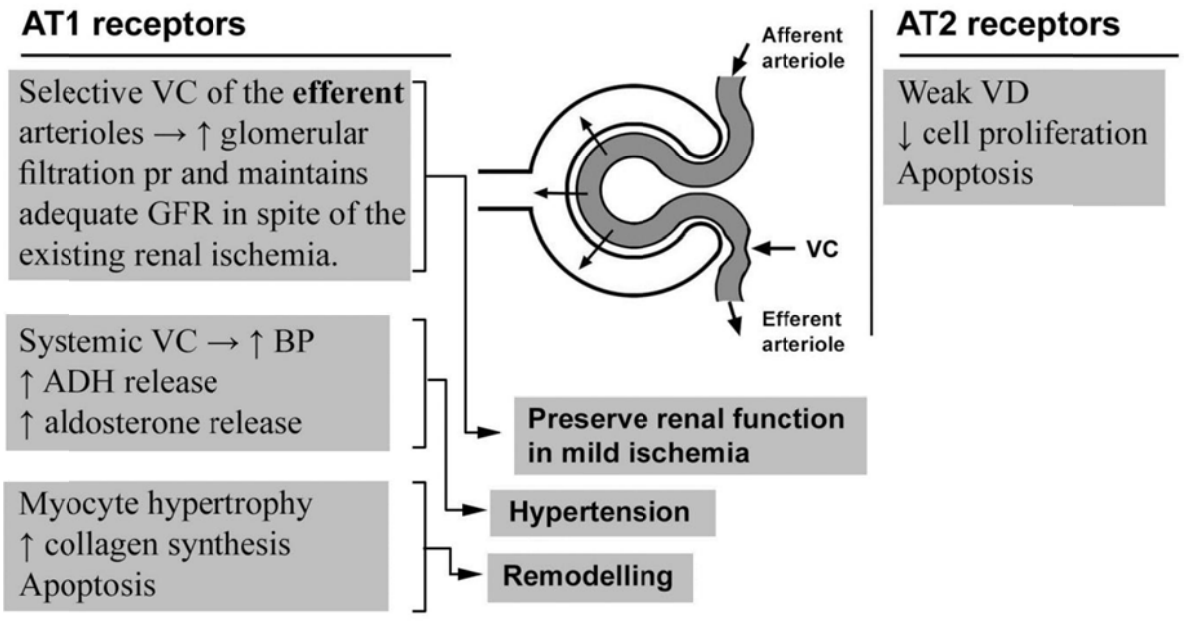
Background

The renin-angiotensin-aldosterone (RAAS) system

- When renal ischemia occurs, there is ↓ RBF and ↓ GFR. This may lead to acute oliguria that may develop to acute tubular necrosis.
- As a compensatory mechanism, **renin** is released from the juxtaglomerular cells of the kidney as a rescue message to initiate stimulation of RAAS as follows:



- Ang-II acts on **AT1** receptors in the **efferent** arterioles of the kidney causing their **VC** and thus maintains adequate GFR in spite of the ↓ RBF.
- Unfortunately, Ang-II acts on AT1 receptors in other vascular beds and tissues causing systemic **VC**, **cell hypertrophy**, and **apoptosis** (i.e. degenerative changes).



Should we inhibit the RAAS?!

- Inhibition of the RAAS will correct the hypertension but also will ↓ GFR and aggravate RF if renal ischemia was grave.
- Normal S. creatinine is 0.3-1.2 mg/dl. If S. creatinine is up to **3 mg/dl** (i.e. mild renal impairment) → you can block RAAS.
- If S. creatinine >**3 mg/dl** (i.e. severe renal impairment) → blocking the RAAS is dangerous and will aggravate RF.

Inhibitors of RAAS

- Inhibitors of **renin release:** β-blockers, α-methyldopa, and clonidine.
- Inhibitors of plasma **renin activity**: aliskiren.
- Inhibitors of **Ang-2 formation:** ACEIs
- **AT1 receptor blockers** (ARBs) e.g. losartan, valsartan

Angiotensin converting enzyme inhibitors

Classification

- **SH-containing drugs:** Captopril, zofenopril, alacepril
- **Non SH-containing drugs:** Enalarpril, fosinopril, lisinopril, benazepril, ramipril

Pharmacological properties of some ACEIs

	Captopril	Fosinopril	Enalapril	Lisinopril	Benazepril
SH group	+	–	–	–	–
Immune S/E	+	–	–	–	–
Prodrug	–	+	+	–	+
Metabolism	Liver, kidney	Liver, kidney	Liver	**No** metabolism	Liver, kidney
Onset	1 – 4 h				
Frequency of administration	/8 h	/12 h	/12 h	/24 h	/24 h
SL dose	25 mg	None	None	None	None

Mechanism of action

They inhibit **Ang-converting enzyme (ACE)** in the vascular endothelium leading to:

- Inhibition of both **Ang-II formation** and **aldosterone release** (→ ↓ both VC and salt & water retention).
- Prevent degradation of **bradykinin** which is a potent VD.
- Most ACEIs have **direct VD action** to both arteries (i.e. ↓ afterload) and veins (i.e. ↓ preload).

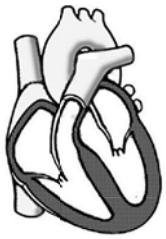
Pharmacological effects

CVS:

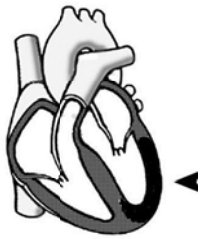
- They ↓ BP mainly by decreasing peripheral resistance **but no reflex tachycardia or changes in the COP can occur**. This may be due to either (1) resetting of baroreceptors; and/or (2) enhanced parasympathetic activity.
- They ↑ **COP** (only in presence of **CHF**) due to reduction of both venous return (preload), and systemic BP (afterload).
- They ↓ myocardial changes complicating acute **myocardial infarction** (ventricular hypertrophy, and dense collagen scar) because they prevent myocyte cell hypertrophy and collagen synthesis **(i.e. prevent cardiac remodeling).**

Other tissue

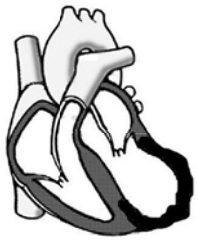
- They ↓ apoptosis, ↓ cell hypertrophy, & ↓ collagen synthesis (i.e. they reduce degenerative changes caused by the action of Ang-II on AT1 receptors).



Normal



MI and necrosis



Ventricular remodeling

Cardiac remodelling means change in the size or shape of the heart due to dilatation, hypertrophy, or excessive formation of collagen scar.

After MI, myocyte cell necrosis triggers stimulation of the RAAS. Ang-II triggers the formation of thick scar and myocyte hypertrophy leading to cardiac remodelling.

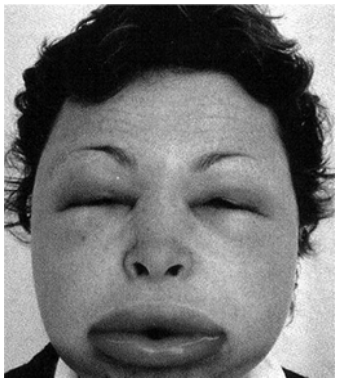
Therapeutic uses

- **Systemic hypertension:**
  - Hyperreninemic hypertension.
  - Normoreninemic hypertension: because they are direct VDs.
- **Congestive heart failure (CHF):**
  - To ↓ afterload and preload through reduction of both systemic vascular resistance, and aldosterone release (↓ Na and H_2O retention).
  - To ↓ myocardial hypertrophy and dilatation (i.e. ↓ remodeling).
- **To prevent LV hypertrophy (remodeling) after acute MI through:**
  - ↓ arterial BP (↓ myocardial strain).
  - ↓ myocyte cell hypertrophy, apoptosis, and collagen synthesis.
- **Diabetic nephropathy & microalbuminuria:**
  - They ↓ renal changes complicating **diabetic nephropathy** (mesangial cell apoptosis, proliferation, and collagen synthesis), thus **reducing microalbuminuria** (provided that renal impairment is **not grave)**.

Adverse effects:

C : **Dry Cough** (the most common): inhibition of ACE leads to accumulation of bradykinin and PGs, which cause bronchial irritation and spasm.
Treatment: stop ACEIs. Cough will resolve after a few days.

A : **Angioedema** (edema of the face, tongue and throat): due to accumulation of bradykinin or due to immune reaction. It may be life threatening.



P : Aggravation of **Proteinuria** in patients with significant renal failure.

T : **Taste changes:** temporary loss of taste (ageusia and dysgeusia).

O : **Orthostatic (First dose) hypotension:** especially in sodium depleted (hypovolemic) patients.
Prevention: start by small at bedtime then increase gradually.

P : **Pregnancy:** teratogenesis (fetal pulmonary hypoplasia and renal dysfunction)

R : **skin Rash**

I : **Increased K^+ (hyperkalemia)** due to ↓ aldosterone release.

L : **Leukopenia** (neutropenia)**:** especially in patients with impaired renal function.

N.B. The sulfhydryl group (-SH) present in captopril may be responsible partially for the immunological side effects e.g. **angioedema, taste changes, skin rash, leukopenia.**

Contraindications

- **Hypotension:** when systolic BP is less than 95 mm Hg.
- **Severe renal failure or bilateral renal artery stenosis** (SCr > 3 mg/dl)**.** Why?
  - In these conditions, the use of ACEIs is dangerous because they ↓ Ang-II → ↓ VC of the efferent arterioles → ↓ glomerular filtration pressure and ↓ GFR → aggravation of renal failure in both kidneys.
  - Dangerous hyperkalemia may occur.
  - Dangerous neutropenia may occur.
- **Pregnancy and lactation:** they may cause fetal pulmonary hypoplasia and growth retardation.
- **Hyperkalemia.**
- **Neutropenia, thrombocytopenia**, or **severe anemia** (ACEIs may cause bone marrow depression).
- **Immune problems:** whether due to autoimmune diseases or due to immunosuppressive drugs.

Precautions

- Initial dose should be **small and at bedtime** to avoid 1st dose hypotension.
- Frequent monitoring of **kidney functions** (S. creatinine) and **potassium** levels one week after treatment and then every 3 months.
- Avoid use of **K^+ sparing diuretics** to avoid severe **hyperkalemia**.
- Remember all other contraindications…

Angiotensin II receptor blockers (ARBs)
(Losartan- Valsartan- Candesartan- Telmisartan)

- They selectively block **AT_1** receptors and they exert most of the pharmacological effects seen with ACEIs.
- They have **no effect on bradykinin** metabolism.
- They have the potential for more complete inhibition of Ang-II action compared with ACE inhibitors because there are **non-ACE enzymes** (cathepsin and chymase) that can convert Ang-I into Ang-II.
- The **adverse effects and contraindications** are similar to those of ACE inhibitors but **cough** and **angioedema** are **less common** than with ACE inhibitors.

	ACE inhibitors	ARBs
Class	Angiotensin converting enzyme inhibitor (ACEI)	Angiotensin receptor blocker (ARB)
Mechanism	Inhibition of ACE leading to: ↓ VC effect of Ang-II ↑ VD bradykinins	Blocking of AT-1 receptors leading to ↓ VC effect of Ang-II
Efficacy in inhibition of RAAS	Less effective because other enzymes rather than ACE can convert Ang-I into Ang-II	More effective because it blocks AT-1 receptor, the final station responsible for Ang-II effects.
Cough and angioedema	Frequent due to ↑ bradykinins	Less frequent (they do not ↑ bradykinins)

Direct renin inhibitors: aliskiren

- Activation of angiotensinogen into Ang-I by renin is the rate limiting step in formation of RAAS.
- Aliskiren is a recently approved drug for treatment of **hyperreninemic hypertension**. It inhibits renin activity and consequently the RAAS.
- The efficacy and side effects of aliskiren are comparable to ACEIs and ARBs.

Calcium channel blockers (CCBs)

These are drugs that block **voltage-gated Ca^{2+} channels.**

Classification of CCBs according to tissue selectivity

- CCB with mainly **cardiac** effects: **verapamil, diltiazem.**
- CCB with mainly **vascular** effects (dihydropyridines): **nifedipine, amlodipine, nimodipine, nicardipine**
- CCB with main effect on **other tissue**: **flunarizine, cinnarizine**

Types of Ca^{2+} channels

Voltage-dependent Ca^{2+} channels

They open in response to cell membrane depolarization

L-type channels (Long lasting):
- It is the dominant type in cardiac and vascular smooth ms.
- CCBs block this type of channels.

T-type channels (Transient).
N-type channels (Neuronal).

Receptor operated Ca^{2+} channels

- These are Ca^{2+} channels linked to G-protein receptors.
- They open in response to increase intracellular IP3.
- Examples: Ca^{2+} channels coupled to α1 receptors.

Pharmacological effects

CVS	Nifedipine	Diltiazem	Verapamil
Heart:			
– Negative inotropic effect	—	++	+++
– A-V conduction	—	↓↓	↓↓↓
– HR	↑ (reflex)	↓	↓↓
Blood vessels:			
– Coronary VD	+++	++	++
– Peripheral VD	+++	++	++
– Blood pressure	↓↓↓	↓	↓

Other effects

- They **relax all smooth muscles** (vascular, bronchial, GIT, **uterine**, etc.).
- They ↓ Ca^{2+}- mediated **cell necrosis** and **apoptosis**.
- Verapamil ↓ **insulin release** from pancreatic beta cells but of little clinical significance.

Therapeutic uses

Cardio-selective CCBs (verapamil & diltiazem):

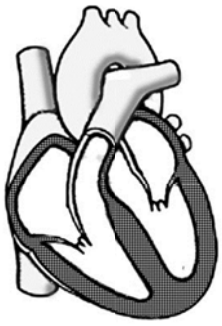
- **Ischemic heart disease (IHD):**
  - They ↓↓ myocardial contractility and myocardial O_2 demand.
  - They produce coronary VD and ↑ coronary blood flow.
  - They ↓ Ca^{2+}- mediated myocyte cell necrosis.

N.B. vasculoselective CCBs (dihydropyridines) e.g nifedipine are also beneficial in IHD but they cause considerable peripheral VD, so the dose should be adjusted to avoid hypotension and reflex tachycardia.

- **Cardiac arrhythmias: supraventricular tachycardia (SVT):**
  - SVT include atrial flutter, fibrillation, paroxysmal atrial tachycardia, etc.
  - Verapamil ↓ AV conduction, so it **protects** the ventricles from the rapid atrial rate (also β-blockers have the same effect).

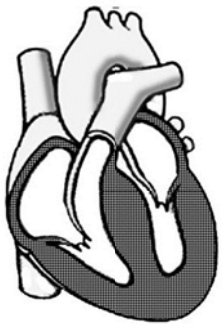
N.B. Nifedipine is contraindicated as it causes hypotension and reflex tachycardia.

- **Hypertrophic obstructive cardiomyopathy (HOCM):**
  - In hypertrophic obstructive cardiomyopathy, the wall of the left ventricle and interventricular septum is much thickened leading to narrowing of the aortic outlet and obstruction of blood flow.
  - Increasing contractility worsens the obstruction while decreasing contractility reduces resistance to blood flow through the aortic outlet and improve exercise tolerance.



Normal

N.B. Nifedipine is contraindicated because it produces reflex tachycardia → worsening of the outflow obstruction.



Hypertrophic cardiomyopathy

- **Arterial hypertension:**
  - They ↓ myocardial contractility and COP.
  - They cause peripheral VD due to ↓ Ca^{2+} influx in the vascular smooth ms.

Vasculo-selective CCBs (Nifedipine and amlodipine):

- Arterial hypertension.
- Peripheral vascular disease (e.g. Raynaud's disease and intermittent claudication): to improve peripheral microcirculation.
- **Nifedipine** is sometimes used to relax the uterus and delay preterm labor.
- **Nimodipine** has high affinity for cerebral BV. It is used for prevention of cerebral vasospasm and ischemia complicating subarachnoid hemorrhage.

Adverse effects

Verapamil & diltiazem:

- Bradycardia and heart block.
- Worsening of CHF (due to their –ve inotropic effect).
- Constipation due to ↓ GIT motility.

Nifedipine:

- Hypotension and reflex tachycardia.
- Gingival (gum) hyperplasia.
- Salt & water retention (=ankle edema; more common than with verapamil due to significant VD and hypotension).

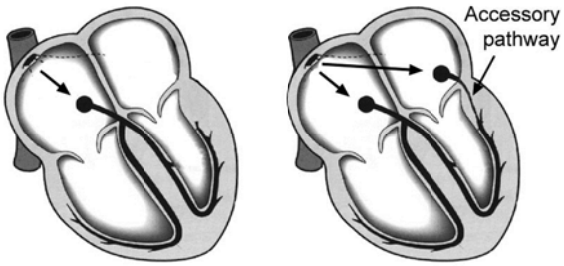
How to treat ankle edema due to CCBs?

- Minimize salt intake.
- Avoid prolonged standing.
- ACEIs.

Contraindications & precautions

Verapamil & diltiazem:

- Congestive heart failure.
- Bradycardia and heart block.
- Wolff-Pakinson-White syndrome:
  - In WPW syndrome, there is accessory conducting pathway between atria and ventricles other than the normal AV system causing a unique type of atrioventricular re-entry tachycardia.



  - As a rule, most drugs that ↓ AV nodal conduction (**A**denosine; **B**eta-blockers; **C**CBs; **D**igoxin) can paradoxically ↑ the conduction in the **abnormal** pathway leading to worsening of the tachycardia.
  - WPW syndrome can be managed by **amiodarone** but definitive treatment includes laser ablation of the accessory pathway (see later).
- Verapamil **should not** be combined with **digitalis** or **β-blockers** as it may aggravate bradycardia caused by these drugs *(nifedipine is the drug of choice to be used with β-blockers because it doesn't cause bradycardia).*

Nifedipine:

- Hypotension.
- Hypertrophic obstructive cardiomyopathy (HOCM) Why?
- Unstable angina (risk of reflex tachycardia).
- Supraventricular tachycardia (SVT) Why?

Vasodilators

Classification

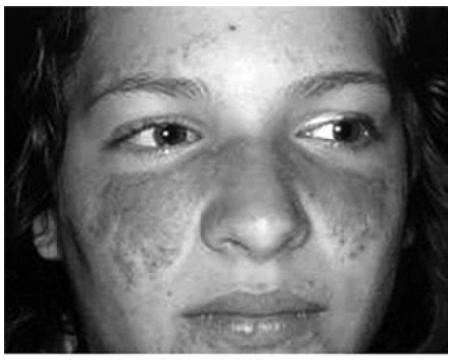
- **Arterio-dilators: Nifedipine – Hydralazine – Minoxidil – Diazoxide**
  - They dilate arteries and ↓↓ BP (→ ↓ afterload)
  - They are used in severe systemic hypertension.
- **Venodilators: Nitrates**
  - They dilate mainly veins →↓ venous return (→ ↓ preload)
  - They are used in acute pulmonary edema.
- **Mixed dilators: Sodium nitroprusside – Prazosin – ACEIs – Trimetaphan**
  - They ↓ preload & afterload so they are used in CHF.

General considerations

- Vasodilators relax vascular smooth ms and ↓ peripheral resistance.
- They usually cause **reflex sympathetic stimulation** (e.g. reflex tachycardia) so they can be combined with **beta-blockers**.
- They usually cause **salt and water retention** (due to reflex stimulation of aldosterone release) so they should be combined with **diuretics**.
- The use of vasodilators is **declining** as a result of newer modalities, such as ACEIs and CCBs, which are more effective with fewer adverse effects.

Hydralazine

- It is a direct **arteriolodilator** by unclear mechanism.
- It is used in **severe hypertension** and hypertension in **pregnancy** (3rd choice after α-methyldopa and nifedipine).
- It is usually combined with **diuretics** to counteract salt and water retention, and **β-blockers** to counteract reflex tachycardia.
- It may cause **systemic lupus erythematosis** (SLE)-like syndrome especially in slow acetylators. The patient develops mild form of arthritis, renal impairment, and skin rash that usually disappear upon stopping of the drug.



SLE-like rash caused by hydralazine

Minoxidil

- It is a direct **arteriolodilator** by **opening K^+ channels** → hyperpolarization → relaxation of the vascular smooth ms.

- It is given orally for **chronic hypertension** but its use as antihypertensive is declining; however, it should be combined with diuretics and β-blockers.
- It was found to stimulate **hair growth** (hypertrichosis) (by unclear mechanism), so it is now used **topically** to prevent hair loss in both males and females.

Diazoxide

- Structurally related to **thiazides** but it is not diuretic
- It is a direct **arteriolodilator** by **opening K^+ channels** → hyperpolarization → relaxation of the vascular smooth ms.
- It is given parenterally in **hypertensive emergencies** but its use is declining.

Sodium nitroprusside

- It liberates **nitric oxide (NO)** → ↑ cGMP → dilatation of both **arteries** and **veins** → ↓ both preload and afterload.
- It is given by **i.v. infusion** in **hypertensive emergencies** and **acute heart failure** because it has **rapid** action
- It can be converted to **cyanide** and **thiocyanate**. The accumulation of cyanide and risk of toxicity are minimized by concomitant administration of **sodium thiosulfate** (see angina) or **hydroxocobalamin** (vitamin B12).
- Sodium nitroprusside in aqueous solution is **sensitive to light** and must be made up **fresh** before each administration and covered with opaque foil.

Fenoldopam

- It stimulates peripheral dopamine (**D1)** receptors in renal and mesenteric arteries, leading to VD and decrease peripheral resistance.
- It is used parenterally as a **rapid-acting vasodilator** to treat **emergency hypertension** in hospitalized patients.

Endothelin-1 receptor antagonists

- **Endothelin-1** is 21 amino acid peptide. It is the predominant endothelin secreted by the vascular endothelium. It is elevated in patients with **pulmonary hypertension** and **coronary artery disease**.
- It acts on two types of receptors, **ET_A** and **ET_B**. ET_A receptors is the main subtype in smooth ms and mediates **VC** and vascular smooth ms hypertrophy.
- **Bosentan** is orally active nonselective blocker of **ET_A** and **ET_B** receptors, while **ambrisentan** is a selective **ET_A** blocker.
- Both drugs are approved for treatment of **primary pulmonary hypertension**.

Specialized vasodilators

Drugs used for erectile dysfunction: Sildenafil, tadalafil

- These drugs inhibit **phosphodiesterase (PDE) type 5** the enzyme responsible for breakdown of **cGMP** in erectile tissue (and lung) → ↑ cGMP → VD of the corpus cavernosum.
- They are very effective for treatment of **erectile dysfunction** in men. The effect of the drug appears after 30 min of oral administration and lasts for 4-5 hours.
- Sildenafil is also approved for treatment of **pulmonary hypertension**.
- **Side effects** include blue discloration of vision, headache, and optic neuropathy.
- These drugs are **contraindicated** in patients taking **nitrates** or **nicorandil** for treatment of angina because nitrates also act by ↑ cGMP leading to severe VD, hypotension, and reflex tachycardia → aggravation of angina and development of **arrhythmia**.

Choice of the antihypertensive drugs:

Clinical condition	Best choice
Starting therapy for non-complicated essential hypertension	Patient <55 years old: ACE inhibitors Patient >55 years old: CCBs If not adequate, add thiazide or beta blockers.
Hypertension of pregnancy	α-methyldopa Labetalol – Nifedipine - Hydralazine
Hypertension in a diabetic patient with diabetic nephropathy (proteinuria)	ACE inhibitors
Hypertension with chronic kidney disease	S. creatinine <3 mg/dl: ACEIs S. creatinine >3 mg/dl: CCBs
Hypertension with CHF	ACE inhibitors - diuretics
Hypertension with bronchial asthma	CCBs
Hypertension with angina	CCBs - beta-blockers
Hypertension with thyrotoxicosis, sympathetic overactivity, arrhythmia, or, HOCM	Beta-blockers
Hypertension with BPH	α1 blockers
Primary pulmonary hypertension	Endothelin receptor antagonists

Management of hypertensive emergencies:

Hypertensive emergencies are clinical situations associated with one or more of the following:

- BP > 180/120mmHg.
- Target organ damage e.g. cerebral stroke, encephalopathy, heart failure, aortic dissection, edema of the optic disc (papilledema).

Hypertensive encephalopathy

Is a clinical presentation consists of severe headache, mental confusion, blurred vision, and focal neurologic signs. If untreated it may progress over a period of 12–48 hours to convulsions, coma, and even death.

Management:

- Hospitalization and start parenteral therapy to lower BP rapidly (within a few hours not minutes).
- Chronic hypertension is associated with autoregulatory changes in cerebral, myocardial, and renal blood flow; so if sudden lowering of BP is done, cerebral, renal, and myocardial ischemic events can develop.
- The initial target in the first 1-2 hrs is to lower systolic BP by no more than **25%,** maintaining diastolic BP at no less than 100 mmHg.
- Drugs commonly used: **sodium nitroprusside**, **labetalol, fenoldopam,** all are given by slow **i.v.** infusion.
- Recent guidelines state that the following drugs are **not recommended**:
  - **Nifedipine**, **nitroglycerin**, and **hydralazine**: because these agents can cause sudden, uncontrolled, and severe reductions in BP that may precipitate cerebral, renal, and myocardial ischemic events with fatal outcomes.
  - **Furosemide** can lead to significant volume depletion and should be used only if there is associated volume overload as in case of pulmonary edema and acute heart failure.

Part 2: Therapy of peripheral vascular disease (PVD)

It is a narrowing of the **arteries** other than coronary and cerebral vessels. It commonly affects arteries of lower limbs, but also renal and mesenteric arteries.

Risk factors

- Diabetes and smoking are the most important risk factors.
- Age > 65 years, hypercholesterolemia, hypertension and obesity.

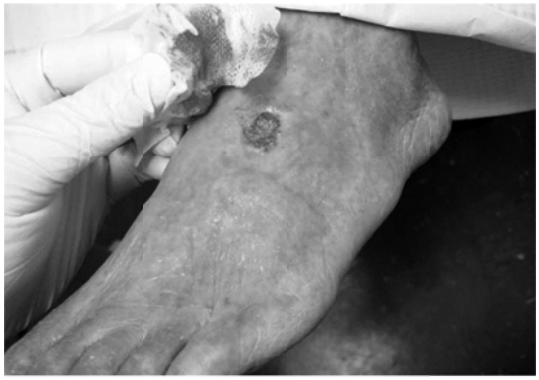
Manifestations

- Intermittent claudication: pain in muscles when walking
- Rest pain in the soles of the feet, particularly when the feet are elevated.
- Skin: cool, bluish, ischemic ulcers.

Management

Life-style:

- Stop smoking: the most important factor
- Control of risk factors:
  - **Statins** for hypercholesterolemia.
  - Treatment of hypertension and DM.



An ischemic ulcer in a person with severe peripheral artery disease.

Drug therapy:

Pentoxifylline

- It increases RBC deformability by **inhibition of PDE enzyme**; this effect reduces blood viscosity and facilitates passage of RBCs through narrowed capillaries and ischemic sites.
- It is the 1st drug approved to improve microvascular circulation in patients with **intermittent claudication**, diabetic angiopathy, and chronic leg ulcers. Typical dose is 400 mg twice a day.

Cilostazol

- It is the 2nd drug recently approved for treatment of **intermittent claudication.**
- It inhibits **PDE enzyme (type 3)** leading to VD and ↓ platelet aggregation.
- **Headache** is the most common side effect.
- Cliostazol is **contraindicated** in patients with CHF because recent evidence showed that inhibitors of PDE enzyme type 3 increase mortality in those patients.

Clopidogrel

Antiplatelet agents such clopidogrel (75 mg/d) have additional benefits when compared with aspirin in diabetic patients with PVD.

Part 3: Ischemic heart disease and antianginal drugs

Basic information

Ischemic heart disease includes:

- **Chronic stable angina (Classic; exertional angina):**
  - It is due to atheromatous narrowing of the coronary artery.
  - Pain is induced by effort and disappears with rest.

- **Acute coronary syndromes (ACS):**
  - ***Unstable angina:*** It is due to rupture of atheromatous plaque and formation of thrombus. The patient experiences acceleration in the frequency or severity of chest pain, or new-onset angina pain.
  - ***Myocardial infarction:*** An intraluminal thrombus completely occludes the epicardial coronary artery at the site of plaque rupture leading to irreversible coagulative necrosis.

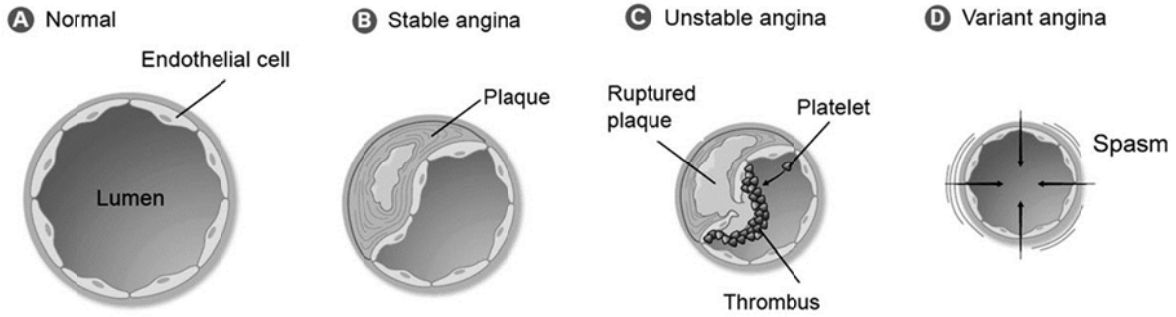
Afterload: it is the resistance that the ventricles must overcome to eject blood during systole. It is mainly determined by the resistance of the arterial side.

Preload: the stress (stretch) of the ventricular wall caused by venous filling just before contraction (also known as end-diastolic pressure). It is mainly determined by the amount of venous return (VR).

N.B. veins are capacitance vessels; venodilatation leads to decrease VR and preload.

- **Prinzmetal's angina (Variant angina; angina of rest; α-mediated angina):**

  The coronary artery undergoes severe spasm due to overactivity of α_1 receptors. The patient develops pain at rest.



Chronic stable angina

Definition: retrosternal pain due to ischemia of the myocardium as a result of imbalance between heart work *(O_2 demand)* and coronary blood flow *(O_2 supply)*.

Clinical picture:

Central chest pain is the cardinal symptom:

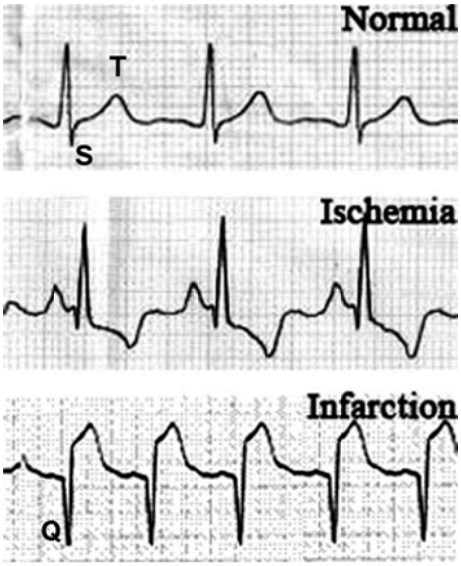
- Site and radiation: retrosternal, radiating to the left shoulder and the left arm.
- Character: any character *(usually sense of chest tightness)*.
- Precipitated by 3E: **e**xertion, **e**motion, **e**ating, and relieved by rest and nitrates.
- Duration: usually < 10-15 min. If longer than 15 min → suspect ACS.

Diagnosis:

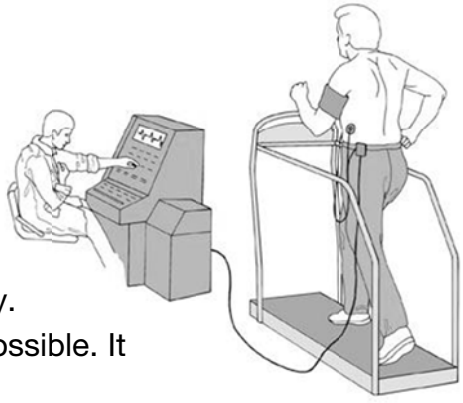
- **ECG:**
  - Resting 12-lead ECG: this is often normal *and does not exclude ischemic heart disease.*
  - During attack: there is ST segment depression and T-wave inversion.
  - In myocardial infarction: ST elevation and deep Q-wave.
- **Exercise ECG:** recording ECG under controlled physical effort to record ischemic changes.
- **Nuclear isotope stress imaging.**
- **Coronary angiography.**

Guidlines

- Do not use people's response to glyceryl trinitrate (GTN) to make a diagnosis.
- Refer people to hospital as an emergency if an ACS is suspected.
- Do not exclude an ACS when people have a normal resting 12-lead ECG.
- Do not routinely administer oxygen. Only offer oxygen to:
  - People with arterial oxygen saturation (SaO2) < 92%.
  - People with COPD.



Management of stable angina



- **Non-drug therapy = life style modification:**
  - The same as hypertension (see before).
- **Pharmacological therapy:**
  - **Immediate treatment of acute chest pain:**
    - Glyceryl trinitrate (GTN): sublingual or spray.
    - Aspirin 300 mg loading dose as soon as possible. It reduces the risk of progression to MI.
    - Refer the patient to hospital if an ACS is suspected.
  - **Long-term therapy:**

- Beta-blockers: the first-line agents for chronic stable (exertional) angina.
- CCBs: the second-line agents for chronic stable angina
- Long and intermediate acting nitrates.
- pFOX inhibitors: trimetazidine
- Newer antianginal drugs: ranolazine and nicorandil
- Lipid lowering drugs: statins (see chapter 6).
- Antiplatelet drugs: e.g. aspirin, clopidogrel (see pharmacology of blood).

- **Surgical treatment (myocardial revascularization).**

Organic nitrates and nitrites

Classification

	Dose	Onset	Duration
Short-acting nitrates:			
Amyl nitrite crushable ampoules	0.3 ml inhalation	1-2 min	5-10 min
Glyceryl trinitrate tablets or spray	0.5 mg SL	1-5 min	10-20 min
Isosorbide dinitrate	5 mg SL	3-5 min	60 min
Glyceryl trinitrate (Tridil®)	5 µg/min i.v.i.		
Intermediate-acting nitrates:			
Isosorbide dinitrate	10 mg oral	15 min	3-6 hrs
	40 mg oral SR	30 min	6-10 hrs
Long-acting nitrates:			
Isosorbide mononitrate	20 mg oral	30 min	6-8 hrs
	60 mg oral SR	30 min	6-10 hrs
Transdermal patches		30 min	12-18 hrs

Pharmacokinetics

Absorption: nitrates are rapidly absorbed from all sites of administration.
Metabolism: in the liver:

- If given oral → **extensive first-pass** metabolism (oral bioavailability <10%)
- If given sublingual → **no first-pass** metabolism → high bioavailability.
- Mononitrate: has **no hepatic metabolism** → long duration of action.

Excretion: via the kidney.

Mechanism of action

- Nitrates cause formation of the free radical **nitric oxide (NO)** which is identical to the endothelial derived relaxing factor **(EDRF)** → ↑ cGMP → VD (more on veins than arteries).
- They also ↑ formation of vasodilator PGE2 and PGI_2.

Pharmacological effects

CVS: Blood vessels:

- VD of the venous (and to lesser extent the arterial) side leading to ↓ preload and ↓ afterload → ↓ cardiac work.
- VD of coronary arteries leading to increased coronary blood flow.
- VD of arteries in the face and neck leading to *flushing of the face.*
- VD of meningeal arteries leading to *throbbing headache*.

Heart: Reflex tachycardia (in high dose) 2ry to ↓ BP.
BP: High doses cause ↓↓ in both systolic and diastolic BP.

Smooth ms: Relaxation of all smooth ms (bronchial, GIT, uterine, and biliary).

Respiration: Reflex tachypnea due to hypotension in **high** doses.

Blood: Methemoglobinemia in **high** doses due to oxidation of Hb into met-Hb.

Therapeutic uses

- **Angina pectoris**

  Nitrates are used for treatment of all types of angina both for relieving the **acute** attack and for prophylaxis. The **mechanism** is due to:

  - Nitrates cause formation of the free radical **nitric oxide (NO)** which is identical to the endothelial derived relaxing factor **(EDRF)** → ↑ cGMP → VD (more on veins).
  - They also ↑ formation of vasodilator PGE_2 and PGI_2.

  These effects lead to:

  - Decrease cardiac work & myocardial O_2 demand through:
    - Venodilatation → ↓ venous return (preload = ↓ end-diastolic pressure).
    - Arteriolodilatation → ↓ peripheral resistance (afterload).
  - Enhancement of coronary blood flow (perfusion) through:
    - Coronary VD.
    - Redistribution of blood from large epicordial vessels to ischemic subendocardial vessels.

- **Myocardial infarction:** to ↓ the area of myocardial damage.
- **Acute heart failure:** to ↓ preload and afterload.
- **Treatment of cyanide poisoning:** see box

Adverse effects

- **Hypotension** and **reflex tachycardia:** may aggravate angina.
- **Throbbing headache:** due to VD of meningeal arteries.
- **Flushing** of the face.
- **Nitrate tolerance:** means diminished response to nitrates with continuous administration which cannot be corrected by increasing the dose. The exact mechanism is unclear but there are 2 theories to explain this:
  - Recent studies showed that continuous administration of nitrates leads to formation of **free radicals** of the reactive oxygen species (ROS) leading to oxidation and inhibition of the enzyme MALDH2 responsible for bioactivation of nitrites into the vasoactive NO.
  - Prolonged VD by nitrates leads to reflex sympathetic stimulation and activation of renin-angiotensin system → VC and salt & water retention.
  - Prevention of nitrate tolerance: make a daily **nitrate-free interval** (10–12 h) to give chance for bioactivating enzymes to regenerate. During this period, give another anti-anginal drug e.g. beta-blocker or CCBs.
- **Methemoglobinemia:** rare and require high doses.

Treatment of cyanide poisoning

Principle: cyanide has high affinity for metHb more than normal Hb.

- **Sodium nitrite** (300 mg i.v.) is given to convert part of Hb to metHb to attract cyanide ions and form cyan-metHb.
- **Sodium thiosulphate** (25 gm i.v.) is given to convert cyan-metHb to thiocyanate (non-toxic) → renal excretion.

Precautions during nitrate therapy

- Use the **smallest effective dose** to avoid hypotension and reflex tachycardia.
- The patient should **consult his doctor** if anginal pain does not improve after taking 3 SL tablets of GTN during 15 min (the pain may be due to MI).
- Nitroglycerine tablets should not be put in **direct sunlight** (light sensitive) or with **cotton** (to avoid formation of the explosive *nitrocellulose*).
- The **expiry date** should be checked (active tablets have **burning** taste).
- Nitrates should not be used with **sildenafil.** Why?

Beta-blockers

- Beta-blockers are considered first-line in **chronic exertional** (classic) angina *(note that short acting nitrates are the first line during the **acute** attack)*.
- Treatment objectives include lowering the resting HR to 50-60 beats/min and limiting maximal exercise HR to ~ 100 beats/min or less.

- There is little evidence to suggest superiority of any particular β-blocker, but β-blockers with ISA should be avoided because the reduction in HR and O2 consumption would be minimal.
- They are contraindicated in **Prinzmetal's (variant) angina** because they block the β_2-mediated coronary dilatation leaving the α_1 receptors unopposed → ↑ coronary spasm.

Mechanism of β-blockers in exertional angina

- They ↓ contractility, HR, and systolic BP → ↓ myocardial work and O_2 demand.
- They ↑ diastolic (coronary) filling time.
- Cause redistribution of blood from normal to ischemic (subendocardial) regions
- Cytoprotective effect: they produce metabolic switch from myocardial *fat* utilization to *carbohydrates* utilization (i.e. improves myocardial metabolism).

Combination of BBs and nitrates ↑ their efficiency & ↓ their side effects**:**

	β-blockers	Nitrates	Combination
– **HR**	↓	↑ (Reflex)	↓ or no effect
– **Contractility**	↓	↑ (Reflex)	↓ or no effect
– **Diastolic filling time**	↑	↓	↑ or no effect
– **Blood pressure**	↓	↓	↓↓

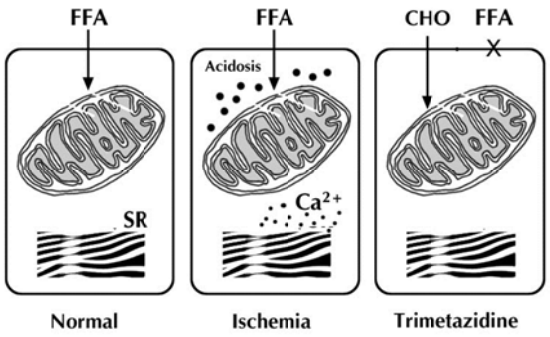
Calcium channel blockers (CCBs)

- They are considered first-line treatment for **Prinzmetal's** (variant) angina.
- They are considered second-line alternative after beta-blockers in chronic stable angina in whom beta-blockers are contraindicated.
- Short acting dihydropyridines are associated with increased risk of ACS and should be avoided. Long acting dihydropyridines (e.g. amlodipine) and non-dihydropyridines (verapamil and diltiazem) are more preferred.
- **Amlodipine** is the CCB of best choice for symptomatic treatment of angina and/or hypertension in patients with chronic heart failure.

Newer options for treatment of chronic angina

- **pFOX inhibitors, potassium channel openers,** and **ranolazine** are examples of new anti-anginal drugs. These drugs alter the balance between myocardial work and O2 supply by novel mechanism(s) of action.
- Their efficacy in treatment of angina is controversial; however they are approved for treatment of chronic stable angina **in combination** with β-blockers, CCBs, and nitrates.

pFOX inhibitors (metabolic modifiers): Trimetazidine



- They are termed pFOX inhibitors because they partially **inhibit fatty acid oxidation** in the myocardium.
- This "metabolic switch" from fats to carbohydrate utilization requires less O_2 consumption.
- By inhibition of fatty acid oxidation, they ↓ intracellular lactic acidosis leading to ↓ intracellular Ca^{2+} & Na^{+} accumulation and ion disturbance, so they prevent cell necrosis and preserve contractile function.
- It does not affect HR, blood pressure or coronary blood flow.

Potassium channel openers: Nicorandil

- Nicorandil is a new antianginal drug with 2 proposed mechanisms of action:
  - It opens ATP-dependent K^{+} channels in the vascular wall leading to VD of peripheral and coronary arteries.
  - Nitrate-like activity: it has a nitrate component and ↑ cGMP like nitrates but tolerance to its effects is less marked.
- Like nitrates, it should **not** be used with **sildenafil**.

Ranolazine

- It ↓ intracellular Ca^{2+} indirectly by reducing the late Na^{+} current that facilitates Ca^{2+} entry into myocardial cells. The reduction in intracellular Na^{+} and Ca^{2+} load reduces cardiac contractility and work.
- It does not affect HR, blood pressure or coronary blood flow.

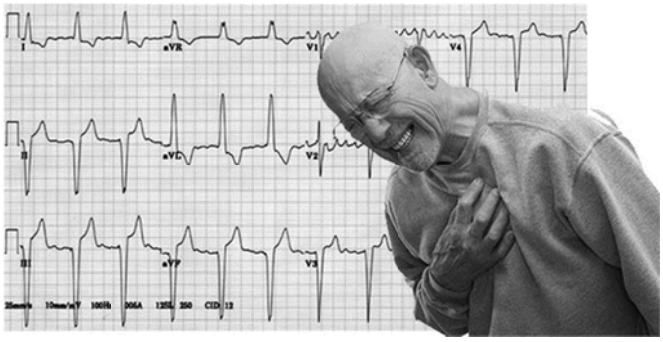
Antiplatelets and cholesterol lowering drugs: see pharmacology of blood.

Choice of antianginal drugs in patients with another disease:

Angina with….	Most preferred	Least preferred
Bronchial asthma	Nitrates, CCBs	Beta-blockers
Heart failure	Amlodipine	Beta-blockers, Verapamil
Hypertension	Beta-blockers, CCBs	Nitrates
Diabetes mellitus	Nitrates, Nifedipine	Beta-blockers, Verapamil

MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION (AMI)

Manifestations: persistent central crushing chest pain + ST segment elevation or depression + pathological Q wave + raised biochemical markers of myocardial cell death (troponin enzyme).
All cases must be **hospitalized** in a specialized coronary care unit.



■ Non-pharmacologic therapy:

Patients presenting within 12 hours of symptom onset, the treatment of choice is percutaneous coronary intervention (PCI, or coronary angioplasty). A balloon catheter, guided by x-ray imaging, is introduced into the occluded artery to open it.

■ Pharmacologic therapy:

- **Morphine sulfate (5 mg i.v.):**
  - To produce analgesia and ↓ stress of the patient → ↓ sympathetic discharge and heart work.
  - Morphine causes venodilatation → ↓ venous return and cardiac work.
- **Oxygen:** recent evidence suggests that routine O2 administration has doubtful significance and did not reduce mortality.
- **Nitroglycerine** and **beta-blockers:** to limit the infarct size.
- **Anticoagulant drugs: heparin** 10,000 IU i.v. then 5000 IU/8h s.c. especially when the patient is obese or if there is history of previous MI.
- **Thrombolytic (fibrinolytic) therapy:** streptokinase, urokinase, or t-PA as early as possible (see blood).
- **Sedatives:** diazepam 5 mg i.v.
- **Treatment of Complications:**
  - Cardiogenic shock → dobutamine i.v.i - Arrhythmia → lidocaine i.v.

Morphine and AMI

Morphine is usually given s.c. but in AMI it is given **5 mg i.v.**

Morphine is contraindicated in cases of MI involving the inferior wall of the heart **(inferior MI)** because in this case, the patient has bradycardia and morphine causes **vagal stimulation** and aggravates bradycardia.

Meperidine is a good alternat-ive in cases of inferior MI because it has **atropine-like action** and counteract bradycardia.

What other opioid analgesics are contraindicated in AMI?

Pentazocin and **butorphanol** because they *increase pulmonary and systemic vascular resistance with more strain on the heart* (see CNS).

Part 4: Therapy of congestive heart failure (CHF)

Basic information

Definition: Heart failure (HF) is a progressive **clinical syndrome** in which either structural or functional abnormalities impair the ability of the heart to meet the metabolic demands of the body. .

Classification, clinical picture, and therapeutic aim:

- **Anatomical classification**

Left-sided heart failure (LSHF):
- Usually due to systemic hypertension.
- The cardinal manifestations are those of **pulmonary congestion** e.g. tachypnea, dyspnea (difficulty in breathing), orthopnea (dyspnea on lying back), paroxysmal nocturnal dyspnea, cough with expectorations, bilateral basal lung crepitation, etc.

Right-sided heart failure (RSHF):
- Usually due to pulmonary hypertension or lung disease.
- The cardinal manifestations are those of **systemic congestion** e.g. congested neck veins, congested liver, bilateral leg edema, right ventricular hypertrophy, etc.

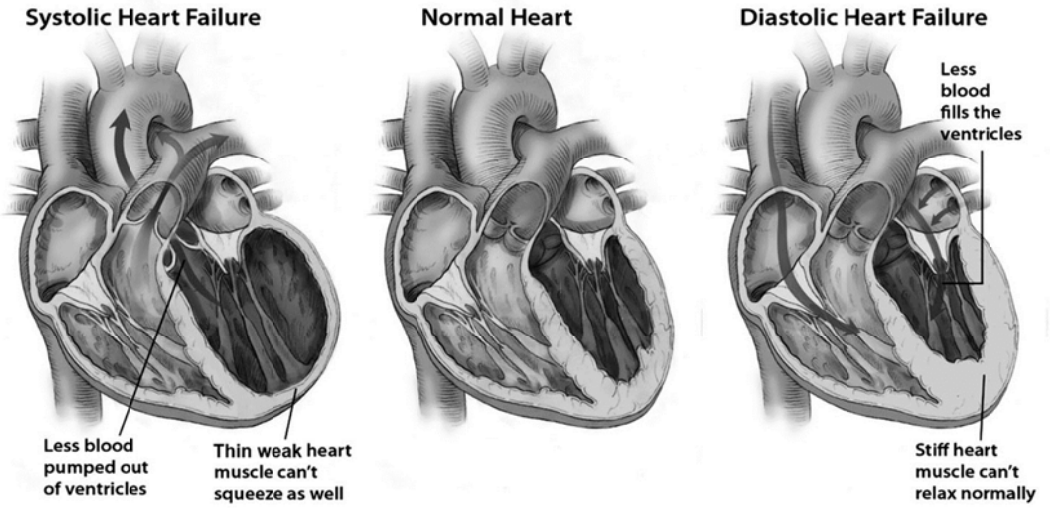
Total or congestive heart failure (CHF): combination between the two.

- **Pathological classification**

Systolic dysfunction (decreased contractility) is caused by reduced muscle power e.g, MI, cardiomyopathies, and ventricular hypertrophy (strain). Ventricular hypertrophy can be caused by *pressure overload* (e.g, systemic or pulmonary hypertension and aortic or pulmonic valve stenosis) or *volume overload* (e.g, valvular regurgitation, high-output states e.g. thyrotoxicosis and arteriovenous fistula).

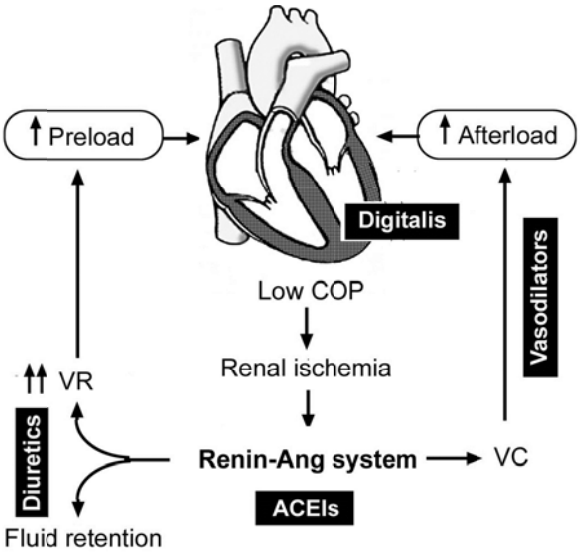
Diastolic dysfunction (restriction in ventricular filling) is caused by increased ventricular stiffness e.g. ventricular hypertrophy, infiltrative myocardial diseases

(e.g. amyloidosis), myocardial ischemia and MI, and pericardial disease (e.g, pericarditis and fibrosis).



The decreased COP leads to the following compensatory mechanisms:

- Sympathetic overactivity leading to tachycardia.
- Renal ischemia → ++ of RAAS → VC (Ang-II) and fluid retention (aldosterone) → ↑ afterload and preload → more HF and edema (vicious circle).



■ Clinical classification

HF is classified by the New York Heart Association (NYHA) into the following classes:

NYHA Class	Symptom
I (mild)	No symptoms while performing ordinary physical activity (walking, climbing stairs, etc.).
II (mild)	Mild symptoms (mild shortness of breath, palpitations, fatigue, and/or angina) and slight limitation during ordinary physical activity.
III (moderate)	Marked limitation in activity due to symptoms, even during less than ordinary activity. Comfortable only at rest.
IV (severe)	Severe limitations with symptoms even while at rest. Mostly bedbound patients.

Therapy of heart failure

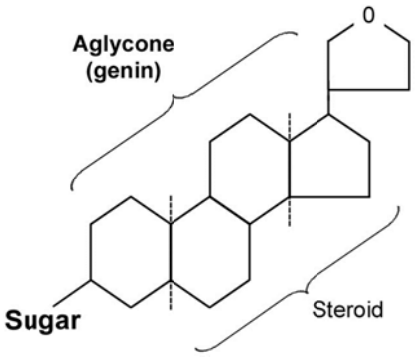
- **Non-drug therapy = life style modification:**
  - Rest.
  - Dietary **s**odium (salt) and fat restriction.
  - Avoid **s**tress, **s**moking and alcohol.
  - Weight reduction.
  - Control of risk factors e.g. surgical correction of valvu**l**ar diseases and treatment of hyperthyroidism, hypertension, etc.
  - Avoid drugs that ↑ BP: e.g. sympathomimetics, sodium containing drugs, etc.

- **Drug therapy:**
  - Positive inotropic drugs:
    - Cardiac glycosides (Digitalis).
    - Dopamine & dobutamine (used for **short term** only).
    - Phosphodiesterase inhibitors: inamrinone & milrinone.
  - Diuretics.
  - ACEIs.
  - Vasodilators: nitrates and hydralazine
  - Other drugs: e.g. beta-blockers and spironolactone.

Cardiac glycosides:

Digoxin, Digitoxin, Ouabain

Source and chemistry



- Natural plant derivatives (Foxglove plant).
- Cardiac glycosides contain a lactone ring and a steroid (aglycone) moiety attached to sugar molecules.
- Digoxin is the most widely used.

Pharmacokinetics of digoxin

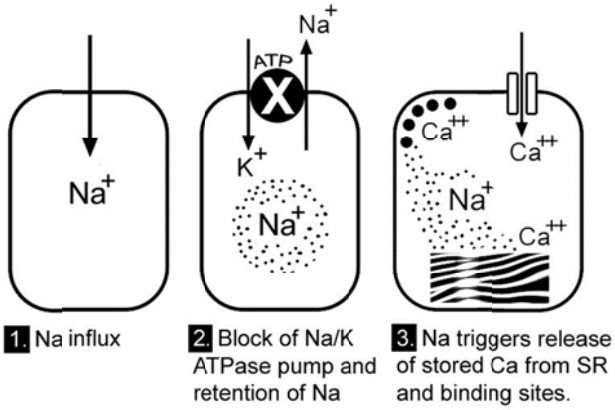
- Digoxin distributes to most body tissues and **accumulates in cardiac tissue**. The concentration of the drug in the heart is twice that in skeletal muscle and at least 15 times that in plasma.
- Elimination is **renal**. Dose adjustment should be done according to **creatinine clearance**.

Mechanism of action

- **Positive inotropic effect:**

Digitalis ↑ cardiac contractility by increasing free intracellular Ca^{2+} through **inhibition of membrane-bound Na^+/K^+ ATPase enzyme**. This result in inhibition of Na^+/K^+ pump with subsequent accumulation of intracellular Na^+ and Ca^{2+} via:

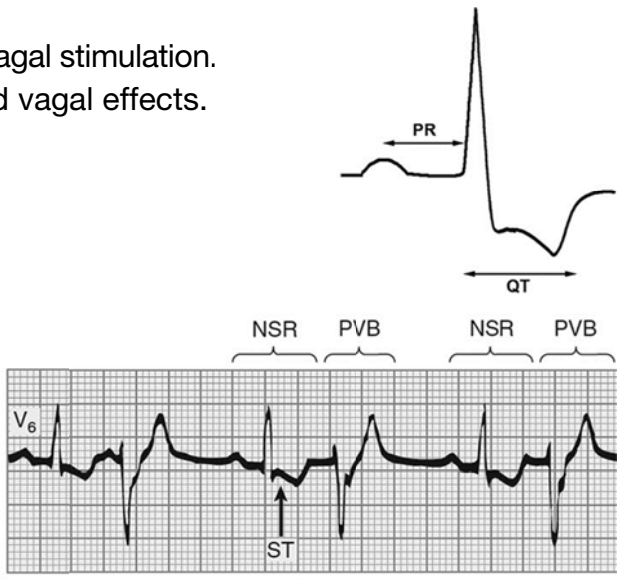
- Increase Ca^{2+} release from the sarcoplasmic reticulum.
- Displacement of intracellular Ca^{2+} from its binding sites.
- Increased intracellular Na^+ prevents Ca^{2+} expulsion from the cell by the Na^+/Ca^{2+} exchanger.



- **Autonomic effects:**
  - ↑ vagal activity: By direct and indirect mechanisms.
  - ↓ sympathetic activity due to relieve of hypoxia & improved tissue oxygenation.

Pharmacological effects

- ↑ **Contractility and COP:** due to +ve inotropic effect. This leads to:
  - Improvement of RBF → **diuresis** and ↓ RAAS (i.e. ↓ fluid retention).
  - Relief of lung congestion.
- ↓ **HR: (B r a d y c a r d i a)** due to:
  - ↑ vagal tone and ↓ sympathetic activity on the heart.
  - Direct inhibition of the AV conducting system.
- **Conduction velocity:**
  - Intra atrial conduction: ↑ due to vagal stimulation.
  - A-V conduction: ↓↓ by direct and vagal effects.
- ↑ **Excitability and automaticity:** leading to ectopic foci and arrhythmia of any type (bigeminy, trigeminy, etc.).
- **ECG changes:**
  - Prolonged PR interval.
  - Short QT interval.
  - ST segment depression & T-wave inversion.
- **Normalization of arterial and venous pressures** due to improved hemodynamics.



ECG record showing digitalis- induced bigeminy. The complexes marked NSR are normal sinus rhythm beats; an inverted T wave and depressed ST segment are present. The complexes marked PVB are premature ventricular beats

Therapeutic indications

- The use of digoxin is now limited to cases of **chronic CHF associated with atrial flutter or fibrillation (AF)** because digoxin is the only drug that ↑ contractility and ↓ AV conduction in the same time.
- In cases of AF alone, other drugs like verapamil or beta-blockers are preferred.
- In cases of CHF without AF, other drugs like diuretics and ACEIs are preferred.

Contraindications

- **Absolute contraindications:**
  - **Heart block:** because digitalis worsens AV conduction by direct and vagal effects.
  - **Hypertrophic obstructive cardiomyopathy (HOCM):** because increasing cardiac contractility will ↑ the outflow tract resistance and accelerates heart failure (see before).
  - **Wolff-Parkinson-White (WPW) syndrome:** although digitalis (and verapamil) ↓ conduction in the normal pathway, they can ↑ conduction in the **abnormal** pathway leading to ↑ arrhythmia (see before).
  - **Paroxysmal ventricular tachycardia:** digitalis ↑ excitability and automaticity.
- **Relative contraindications:**
  - All causes of **bradycardia** (e.g. sick sinus syndrome, hypersensitive carotid sinus, with beta-blockers or verapamil) because addition of digoxin can lead to severe bradyvardia or even heart block.
  - **Systemic hypertension:** digitalis will ↑ the strain of the LV (you must correct hypertension first by giving VDs or diuretics).
  - **Pulmonary hypertension** due to **chronic lung disease:** digitalis will ↑ the strain of the RV (you must correct pulmonary hypertension first by giving VDs).
  - **Cardiac diseases:**
    - Acute MI: digitalis ↑ the infarct size and aggravates arrhythmia.
    - Cardiomyopathy…. digitalis is useless.
  - **Renal or hepatic diseases:** digoxin must be avoided in renal patients while digi**T**oxin must be avoided in hepa**T**ic patients.
  - In patients likely to require **cardioversion:** because digitalis may lead to fatal arrhythmia if given with cardioversion.

Drug interactions

Drug	Mechanism/effect
Antacids - Kaolin Cholestyramine	Bind digoxin in the gut and decrease bioavailability (absorption)
Metoclopramide	Increase gut motility leads to decrease digoxin absorption.
Atropine	Decrease gut motility leads to increase digoxin absorption
Quinidine	Decrease renal clearance of digoxin and displace digoxin from plasma proteins. Serum digoxin is increased.
Loop diuretics and thiazides	Thiazides or loop diuretics may cause **hypokalemia** and hypomagnesemia which can ↑ the risk of digitalis **toxicity**

Dosage and administration

- **Initial digitalization:**
  - It is done by giving **one tablet** 0.25 mg /day (5 days/week) from the start.
  - The Cpss will be achieved after **5 t½** (i.e. after one week for digoxin).
  - **Rapid (loading) method** is done in emergency conditions to achieve rapid Cpss. It is given as **2 tablets** (0.5 mg) **twice** daily for **2 days (2x2x2).**
- **Maintenance dose:** one tablet (0.25 mg)/day, 5 days/week.

N.B.

- The optimum therapeutic plasma level is **1–2 ng/ml.**
- Arrhythmia occurs when the level exceeds **2 ng/ml.**

Assessment of response to digitalis

- Relief of dyspnea and orthopnea.
- Relief of tachycardia and tachypnea.
- Relief of edema, lung congestion, and fatigue.
- Increase urine volume. Improvement of physical performance.

Precautions during digitalis therapy

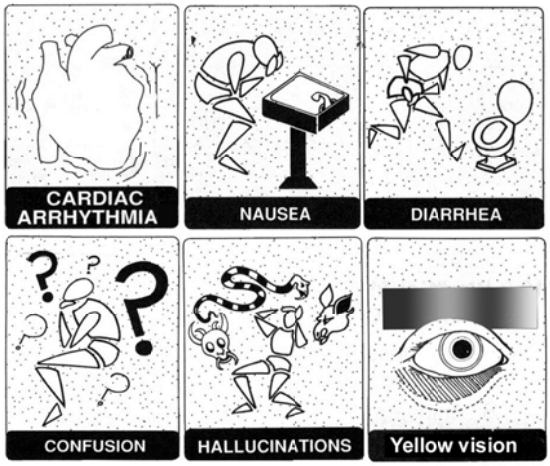
- Never give digitalis i.v. before being sure that the patient has not received digitalis during the last 14 days to avoid digitalis toxicity.
- Continuous monitoring of plasma K^+ level.
- Mention all the **relative contraindications.**

Digitalis toxicity

Predisposing factors

- **Hypokalemia:** increases digoxin binding and effect.
- **Hypercalcemia** (N.B. Hypocalcemia renders digitalis less effective).
- Presence of renal impairment.

Manifestations



- **Cardiac:**
  - Bradycardia and variable degree of heart block.
  - Paroxysmal atrial tachycardia
  - Any type of arrhythmia (premature beats, bigemeny, trigemeny, etc.)

- **Extracardiac:**
  - The **first** manifestation is **fatigue** and **anorexia**, followed by GIT symptoms e.g. diarrhea, nausea & vomiting due to stimulation of CTZ.
  - CNS: headache, delirium, hallucination, and convulsions.
  - Vision: **yellow vision** (chromatopsia), diplopia, amblyopia, scotoma, etc. due to retrobulbar neuritis.
  - Others: skin rash, gynecomastia, galactorrhea.

Management

- Stop digitalis administration.
- Correct hypokalemia by giving K^+ either i.v. or oral (2 gm/4 h).
- Antiarrhythmic drugs:
  - Lidocaine (in ventricular arrhythmia): 1-2 mg/kg i.v. bolus then 1-2 mg /min i.v.i.
  - Phenytoin (in ventricular arrhythmia with heart block): 250 mg i.v. over 10 min.
  - Atropine: if there is bradycardia or heart block.
- Specific digitalis antibodies **(Fab fragments; Digibind)** to bind digitalis and promote its renal clearance (the most **specific** therapy).

Other positive inotropic drugs

Phosphodiesterase (PDE) inhibitors: Inamrinone – Milrinone

- They inhibit PDE enzyme (type **3**) → ↑ cAMP → ↑ Ca^{2+} influx in myocardial cells → ↑ myocardial contractility.
- They have VD properties.
- They are used only **i.v.** for **short term** treatment of **CHF** in patients not responding to digitalis. They are not safe for long term use.
- **Adverse effects include:** thrombocytopenia, cardiac arrhythmia, increase liver enzymes (hepatotoxicity).
- Milrinone is less toxic than inamrinone

Diuretics

Mechanism in heart failure

- They ↓ fluid retention and pulmonary congestion leading to improvement of tissue oxygenation
- They ↓ preload & afterload so improve myocardial function.
- **Spironolactone** antagonizes the effect of aldosterone that is increased in CHF due to secondary stimulation of RAS. Recent evidence showed that it reduces mortality rates in patients with advanced heart failure (NYHA class III and IV).

Disadvantages of diuretics

- Excessive use of diuretics will ↓ ECF volume → ↓ COP.
- Diuretic-induced acid-base imbalance may impair cardiac function.
- Diuretic-induced hypokalemia can ↑ digitalis toxicity and cardiac arrhythmia.

These adverse effects could be minimized by **diuretic combination** (loop diuretics plus K^+ sparing diuretics) to minimize hypokalemia and acid-base imbalance.

Vasodilators (nitrates and hydralazine)

- **Nitrates** and **hydralazine** have complementary hemodynamic actions:
  - Nitrates are primarily venodilators, →↓ preload.
  - Hydralazine is a direct arterial dilator →↓ systemic vascular resistance and afterload.
- Recent evidence showed that combination of nitrates and hydralazine reduces mortality and hospitalizations for patients with HF.
- A fixed-dose combination product is available (USA and Europe) that contains isosorbide dintrate 20 mg and hydralazine 37.5 mg.
- Guidelines recommend addition of hydralazine and nitrates to moderate to severe HF despite therapy with ACE inhibitors, diuretics, and β-blockers.
- The combination is also appropriate as first-line therapy in patients unable to tolerate ACE inhibitors or ARBs due to any contraindication.

ACEIs and ARBs

Beneficial effects in heart failure:

- They ↓ arterial BP → ↓ afterload.
- They ↓ aldosterone → ↓ Na & H_2O retention → ↓ preload.
- They prevent myocardial wall thickening and cardiac remodeling.

Beta-blockers

High doses of β-blockers are generally not recommended in heart failure because they produce –ve inotropic effect and may precipitate cardiac decompensation, but **small doses** have some benefits in heart failure:

According to recent evidence, a number of drugs have been shown to reduce mortality in patients with chronic HF. These are:

- **ACE inhibitors**
- **Spironolactone**
- **Beta-blockers**
- **Hydralazine with nitrates**

Beneficial effects in heart failure:

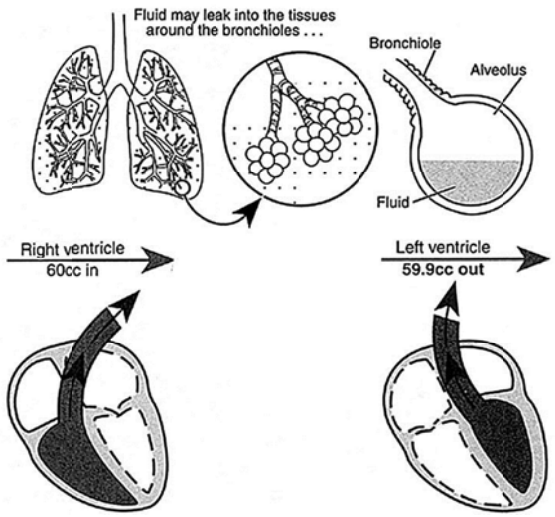
- β-blockers reduce tachycardia and sympathetic overactivity.
- β-blockers reduce BP → ↓ ventricular strain associated with HF.
- β-blockers inhibit renin release → ↓ cardiac remodeling caused by RAAS.
- **Carvedilol** is a new beta-blocker with additional VD and antioxidant properties.

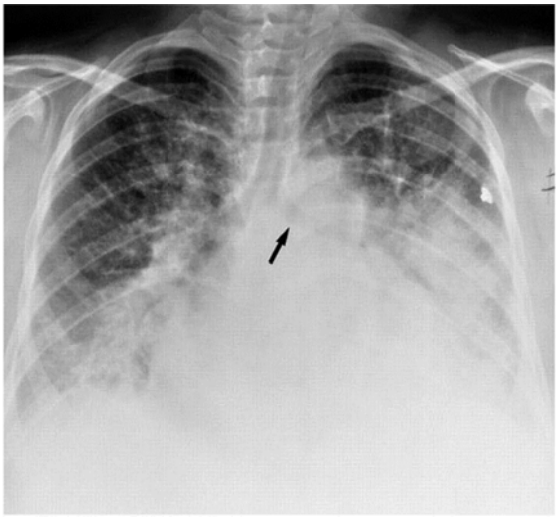
According to currently available evidence, **bisoprolol, metoprolol,** and **carvedilol** have shown the most useful effects in patients with chronic HF.

MANAGEMENT OF ACUTE CARDIOGENIC PULMONARY EDEMA

Pathophysiology of APE

Acute cardiogenic pulmonary edema (APE) is accumulation of fluid (transudate) in the lung interstitium and alveoli as a result of increased capillary hydrostatic pressure secondary to LV dysfunction.





Manifestations

– Dyspnea, orthopnea and wheezes.
– **Chest x-ray**: patchy or diffuse alveolar filling (haziness).

Management

- Hospitalization and **sitting** or semi-sitting position.
- High-flow **oxygen** *(hypoxia causes pulmonary VC and increased cardiac load).*
- **Furosemide** (20-80 mg IV): to ↓ venous return and pulmonary congestion. It is the most important treatment.
- **Morphine** (2-4 mg IV):
  - To ↓ stress and anxiety.
  - Venodilatation → ↓ VR → ↓ lung congestion.
  - It ↓ pulmonary stretch reflex → ↓ tachypnea & work of breathing.
- **Nitroglycerine** (sublingual or i.v.).
- Hemodynamic support according to systolic BP:
  - Maintain systolic BP >100 mmHg.
  - If the SBP is <100 mmHg, start IV **dopamine** or **dobutamine** at 5-15 µg/min.

N.B.
Digoxin is indicated only if rapid AF is present.

Part 5: Management of shock

Shock is a circulatory disorder. It is complex state of hypotension and impaired tissues perfusion of vital organs (acute circulatory failure).

Diagnosis

- Systolic BP **< 90** mmHg OR mean arterial BP (MAP) **< 60** mmHg.
- Tachycardia and tachypnea
- Oliguria (urine < 20 ml/h), or anuria.
- Cool pale extremities with slow capillary refilling.
- Confusion and restlessness.

Anaphylactic shock

It is a medical emergency that requires immediate recognition and intervention.

Causes, manifestations, and time course

Acute hypersensitivity reaction in response to allergic substance (food, drugs or venom) → massive release of histamine from mast cells:

  - Skin changes (the first feature): erythema, urticaria, or angioedema.
  - Hypotension (fainting).
  - Bronchoconstriction (wheeze or hoarse voice).
- Fatal food reactions typically occur after **30–35** minutes.
- Insect stings cause shock after **10–15** minutes.
- Intravenous drug reactions occur within **5** minutes.

Treatment

- Apply tourniquet proximal to the site of injection if possible.
- Epinephrine **0.5 ml i.m.** (s.c. injection is slow).
  - It is the drug of choice and potentially lifesaving.
  - i.m. injection in the thigh (vastus lateralis) gives more rapid effect.
  - Repeat after 5 min if no response.
- Antihistamine (e.g. chlorpheniramine 10 mg **i.v.**).
- Hydrocortisone 200 mg **i.v** to ↓ antigen/antibody reaction.
- Intravenous fluids (0.5-1 L) and monitor BP.

Neurogenic Shock

- Neurogenic shock is caused by **loss of sympathetic tone** of blood vessels resulting in the massive dilatation of arterioles and venules.
- It can be caused by spinal anesthesia, spinal cord injury, pain, and anxiety.

Treatment

- Recumbent position with head down.
- Vasopressor sympathomimetics and sedatives.

Hypovolemic shock

Causes

Blood loss (hemorrhage); Plasma loss (severe burn); Water loss (vomiting, diarrhea).

Grades of hypovolemic shock

	Blood loss	Response
Class I	Up to 15% (750 ml)	Compensatory mechanisms maintain BP.
Class II	15-30% (750-1500 ml)	Hypoxia, hypotension, ↓ urine output
Class III	30-40% (1500-2000 ml)	Profound shock with severe acidosis
Class IV	> 40% (> 2000 ml)	Coma …….. death

Treatment

- I.v. fluids (Ringer solution is more superior to normal saline for use in massive hemorrhage).
- Blood transfusion
- Dopamine: to ↑ COP.

Cardiogenic shock

Causes

- Acute MI
- Blunt cardiac trauma
- Myocardial depression due to any cause (drugs, infection, etc.).

Treatment

- All measures of treatment of acute MI (see before).
- Dobutamine i.v.i. (usually at 5 - 20 µg/kg/min).
- Lidocaine i.v. for control of ventricular arrhythmia.

Septic shock

Cause: severe infection → release of inflammatory cytokines from the inflammatory cells → venodilatation (↓ venous return) and progressive tissue hypoxia.

Treatment

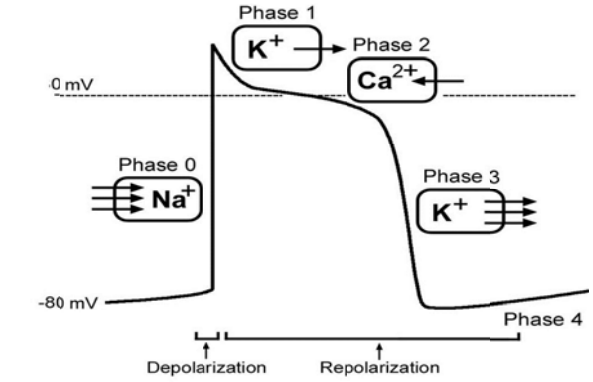
- Antibiotics according to the type of pathogen.
- Dopamine or dobutamine to ↑ COP.
- Low dose steroids to minimize toxemia.
- Oxygen if O2 saturation is <94%.

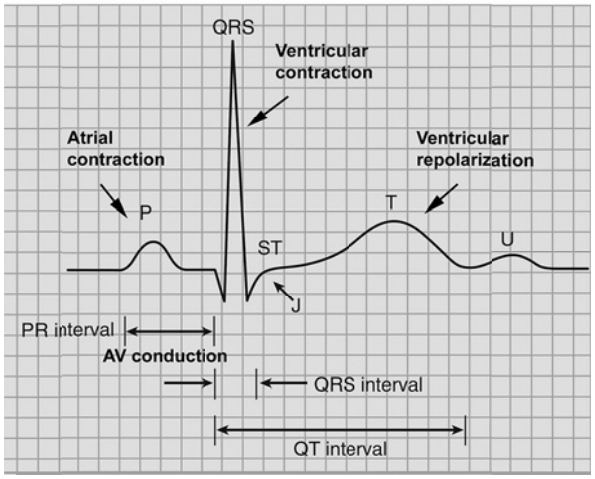
Part 6: Cardiac arrhythmia and antiarrhythmic drugs

Basic information

Cardiac action potential

- In the resting state, K^+ ions is found mainly intracellular, while Na^+ and Ca^{2+} are mainly extracellular making the interior of the cell electrically *negative*.
- Contraction and relaxation occur when rapid redistribution of ions across the cell membrane occurs during 4 phases known as **"action potential".**





Phases of action potential:

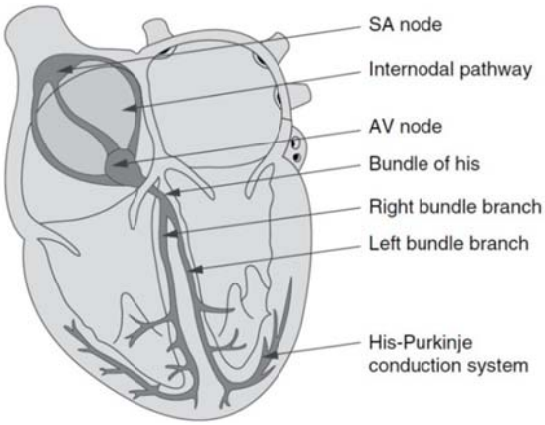
- **Phase 0:** rapid depolarization of the cell due to rapid influx of Na^+.
- **Phase 1:** short period of rapid re-polarization due to outflow of K^+.
- **Phase 2:** "plateau": delay in re-polarization due to slow influx of Ca^{++}.
- **Phase 3:** second period of rapid repolarization due to rapid out-flow of K^+.
- **Phase 4:** the resting state is restored. Na^+ ions are extruded out the cell and K^+ ions returns back by the Na^+/K^+ pump and so on.
- The slope of phase 4 determines when the 2nd action potential starts. When the slope is increased, the distance between 2 cardiac cycles shortens (i.e. tachycardia) and vice versa.

Impulse formation (automaticity)

- Cardiac **automaticity** refers to the ability of certain cells to self-generate electrical impulses that spread throughout the heart.
- Under normal conditions, the **SA node** is the dominant pacemaker (i.e. has the highest automaticity).
- Normal myocardial cells don't have automaticity i.e. cannot generate impulses.
- Under certain pathologic conditions, some myocardial cells may acquire spontaneous repetitive firing, this is called **abnormal automaticity** or **ectopy**. These **ectopic** pacemakers compete with the SA node for control of the heart.

Impulse conduction

- Electrical activity spreads from the **SA node** to the ventricles via the **AV node** and the **bundle of His**, and then down through the right and left **bundles**.
- In the **ECG**, the **P wave** represents the spread of depolarization wave through the atria (atrial contraction). The **QRS complex** represents the spread of depolarization wave through the ventricles (ventricular contraction). The **ST segment** and **T wave** represent ventricular repolarization (relaxation).



Cardiac arrhythmia

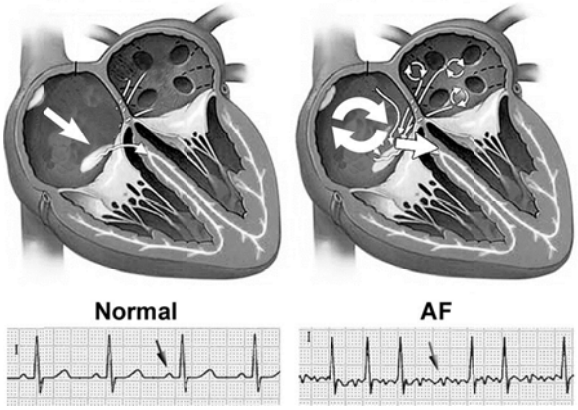
Arrhythmia means disturbance in the normal heart rhythm. It results from:

- Abnormal impulse generation;
- Abnormal impulse conduction;
- Both.

Abnormal impulse formation:

- **Nodal abnormality:** e.g. sinus tachycardia and sinus bradycardia.
- **Extranodal abnormality:** e.g. premature atrial or ventricular contractions (ectopic beats).

Abnormal impulse conduction



- **Re-entry:**

- This is a circus movement of an impulse that circulates around certain area in a unidirectional fashion and excites the conducting system more than once.
- It is the most common cause of **atrial flutter** and **fibrillation** (AF).
- Wolff–Parkinson–White syndrome (WPW) is an example of anatomically defined re-entry. WPW syndrome is an atrioventricular re-entrant tachycardia, secondary to an accessory AV conducting pathway (see before).

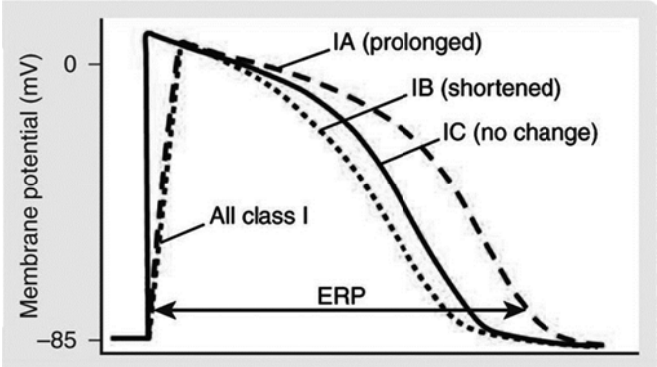
- **Heart block:**

– AV conduction is **delayed** (first degree), **intermittent** (second degree), or **completely blocked** (third degree).

ANTIARRHYTHMIC DRUGS

- Antiarrhythmic drugs produce effects by altering one or more of the following factors: 1) Automaticity; 2) Conduction velocity; 3) Refractory period; 4) Membrane responsiveness.
- Almost all antiarrhythmic drugs have more than one mechanism of action. The simplified **Vaughan Williams classification system** assumes that each drug has **one main** mechanism of action:

Class I: Na⁺ channel blockers:



- **Class IA: e.g. quinidine, procainamide, disopyramide**: moderately block **Na⁺** channels and ↑ ERP (effective refractory period) and APD (action potential duration)
- **Class IB: e.g. lidocaine, mexiletine:** weakly block **Na⁺** channels and ↓ ERP and APD.
- **Class IC: e.g. flecainide, propafenone:** strongly block **Na⁺** and **K⁺** channels with no effect on ERP or APD.

Class II: Beta-blockers: e.g. propranolol, bisoprolol, metoprolol

They ↓ AV conduction and inhibit phase 4 depolarization.

Class III: K⁺ channel blockers: e.g. amiodarone, dronedarone, ibutilide, sotalol

They inhibit mainly **K⁺** channels and ↑ ERP.

Class IV: Ca⁺ channel blockers: e.g. verapamil and diltiazem

They inhibit mainly **Ca^{2+}** channels and ↑ ERP.

Other unclassified drugs: digoxin, adenosine, Mg sulphate

Quinidine (subclass 1A)

Mechanism and pharmacological effects

- It blocks **activated Na^+** channels leading to decrease the rate of phase-0 depolarization, decrease excitability, and ↑ APD and ERP.
- It blocks **muscarinic** and **α** receptors leading to atropine-like action (vagolytic) and hypotension.
- Quinidine has complex effect on **AV conduction** due to direct and vagolytic actions:
  - At low doses: its vagolytic action predominates → ↑ AV conduction.
  - At therapeutic doses: its direct action predominates → ↓ AV conduction
- It has –ve inotropic effect and antimalarial effect (against *P. falciparum*).

Therapeutic uses

- Quinidine was used for many years to treat **supraventricular** and **ventricular** arrhythmias, and to **maintain** sinus rhythm after conversion from atrial flutter and fibrillation; however, it is **rarely** used today because of availability of more effective and less toxic drugs.

Adverse effects and precautions

- **Cinchonism:** tinnitus (i.e. hearing of ringing or hiss), headache, blurred vision, vomiting, and diarrhea.
- **Hypotension:** after rapid i.v. infusion due to α-receptors blockade.
- **Paradoxical tachycardia:** quinidine has atropine-like action and, it may ↑ AV conduction and cause "*paradoxical tachycardia*". Digitalis or verapamil should be given before quinidine to offer rate control by ↓ AV conduction.
- **Quinidine syncope:** quinidine ↑ QT interval and may predispose the patient to a serious type of arrhythmia *(torsade de pointes).* Quinidine therefore should not be given to patients with long QT syndrome or with other drugs that ↑ QT interval.

Procainamide (subclass 1A)

- This drug is equivalent to quinidine as an antiarrhythmic agent and has similar cardiac and toxic effects. Like quinidine, its use now is very **limited.**
- **Additional adverse effect:** procainamide is metabolized by hepatic acetylation; 30% of patients (slow acetylators) develop drug-induced systemic lupus erythematosus (SLE) after long term therapy.

Drug-induced SLE like syndrome

Hydralazine (+++)
Procainamide (++)
Isoniazid (+)
Quinidine (+)
Phenytoin (+)

Lidocaine (subclass 1B)

- Lidocaine (lignocaine) is exclusively **Na^+ channel blocker**; it is highly selective for damaged tissues.
- It undergoes extensive first-pass metabolism so, it is **not given orally**.
- It is given only **i.v.** for acute suppression of ventricular arrhythmia associated with **acute MI** (not for long-term treatment). The usual dose is 50-100 mg i.v. half of this dose may be repeated after 5-10 min if necessary.
- It has **no effect** on AV conduction, so it is **not used** for supraventricular arrhythmia.
- Most adverse effects are **neurologic**.

N.B.

- **Mexiletine** is very similar to lidocaine but can be given **orally**. It is used primarily for long-term treatment of ventricular arrhythmias associated with **previous MI**.
- **Phenytoin** is antiepileptic drug with class 1B activity. It is used primarily in the treatment of **digitalis-induced tachyarrhythmia**. It has a limited role in the treatment of other ventricular arrhythmias. The IV loading dose is 250 mg given over 10 minutes.

Flecainide (subclass 1C)

- It blocks both **Na^+** and **K^+** channels leading to decrease the rate of phase-0 depolarization and **slows AV conduction**. Due to its complex effects on cardiac tissue, the APD is **not altered**.
- It is used for atrial and ventricular arrhythmia and for maintenance sinus rhythm after conversion from atrial flutter and fibrillation.
- Flecainide increases the incidence of ventricular fibrillation and sudden death after MI (proarrhythmic effect), so it is **contraindicated** for patients with ischemic heart disease or structural heart disease (e.g. LV hypertrophy).

Class II: Beta blockers

Mechanism of action

They ↓ sympathetic stimulation, inhibit phase 4 depolarization, depress automaticity, prolong AV conduction, ↑ heart rate and ↓ contractility.

Therapeutic uses

- All arrhythmia induced by sympathetic overactivity.
- Arrhythmia due to thyrotoxicosis.

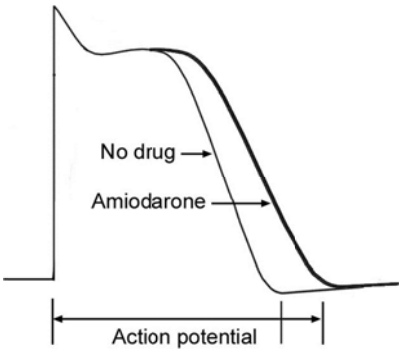
- Arrhythmia associated with HOCM.
- Supraventricular arrhythmia (AF).
- Arrhythmia due to mitral valve prolapse.

Class III: Amiodarone

- It is structurally related to thyroxine. It contains ~ 40% iodine. **Dronedarone** is chemically similar to amiodarone but does not contain iodine.
- Amiodarone has **long t½** and **large Vd** so, it can accumulate in many tissues leading to wide range of adverse effects.

Mechanism of action

- Blocks mainly **K^+** channels → slowing of phase 3 → ↑ ERP.
- Blocks **Na^+** channels → ↓ excitability.
- Blocks **Ca^{2+}** channels → – ve inotropic and chronotropic effects.

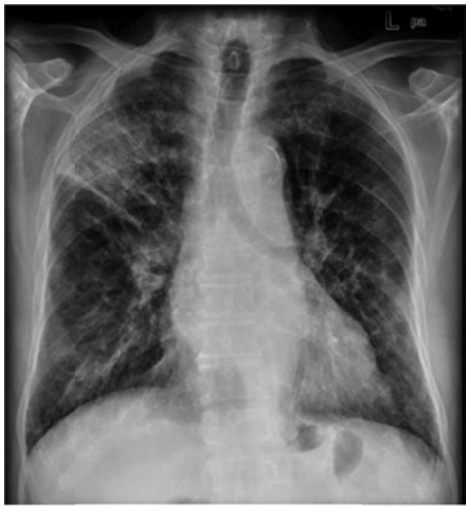


Therapeutic uses: (most types of arrhythmia)

- Supraventricular and ventricular arrhythmia.
- WPW syndrome.
- Arrhythmia resistant to other drugs.

Adverse effects

- Dose-related **pulmonary toxicity** (fibrosis) is the most important adverse effect.
- **Hepatic** toxicity.
- **Thyroid dysfunction**: hypo- or hyperthyroidism because of its iodine content.
- **Corneal microdeposits:** reversible, does not affect vision.
- **Bradycardia** and heart block.
- **Photosensitivity** leading to gray-blue skin discoloration in sun-exposed areas.



Chest x-ray in an elderly patient on amiocarone demonstrates numerous reticular opacities most marked in the right upper zone

Class IV: CCBs (verapamil and diltiazem)

Mechanism of action: They ↓ SAN activity and AV conduction

Therapeutic uses

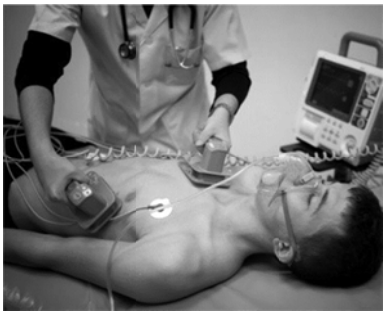
- Non-dihydropyridines (verapamil and diltiazem) are primarily used to reduce HR in **supraventricular tachycardia** (SVT) and arrhythmia associated with HOCM.
- CCBs have **no role** in the chronic management of **ventricular tachycardia** (VT). IV verapamil should **never be used** in the acute management of VT, as it may cause hemodynamic collapse.

Other antiarrhythmic agents: Adenosine

- It is a purinergic **A1 receptor agonist**; this leads to opening of K^+ channels and inhibition of Ca^{2+} channels (i.e. hyperpolarization) in the AV conducting system and directly **inhibits AV nodal conduction**.
- It has very short half-life of 8-10 seconds.
- It is the drug of choice for immediate termination of paroxysmal supraventricular tachycardia (including WPW syndrome). It is given as a bolus dose of 6 mg i.v. followed, if necessary, by a dose of 12 mg.
- The drug is less effective in the presence of adenosine receptor blockers such as **theophylline** or caffeine.
- It is contraindicated in patients with **asthma** because it can cause **bronchospasm**.

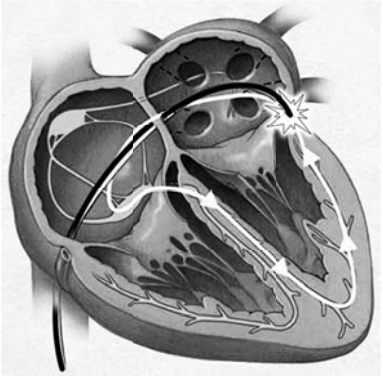
Non-pharmacological methods

DC cardioversion



- It is application of direct current (electric shock) to the chest wall for **emergency** control of any type of arrhythmia especially **rapid AF** in an unstable patient (i.e. hypotensive).
- The patient should be **heparinized** before the procedure.
- Following electrical cardioversion, patients should be anticoagulated for at least 4 weeks.

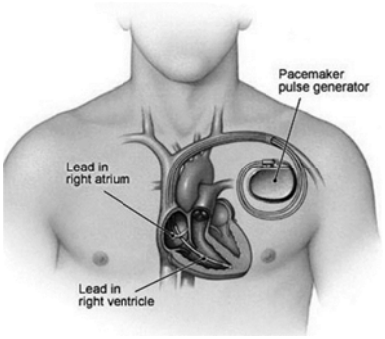
Laser ablation



- It is used for many types of arrhythmias.
- A catheter is inserted into a specific area of the heart. A special machine directs energy through the catheter to small areas of the heart muscle that causes the abnormal heart rhythm. This energy "disconnects" the pathway of the abnormal rhythm.
- Laser radiofrequency ablation is the definite treatment of **WPW syndrome**.

Artificial pacemakers and implantable cardioverter defibrillators

- They are battery-powered electronic devices that are implanted under the skin or in the chest cavity to monitor and pace the heart.



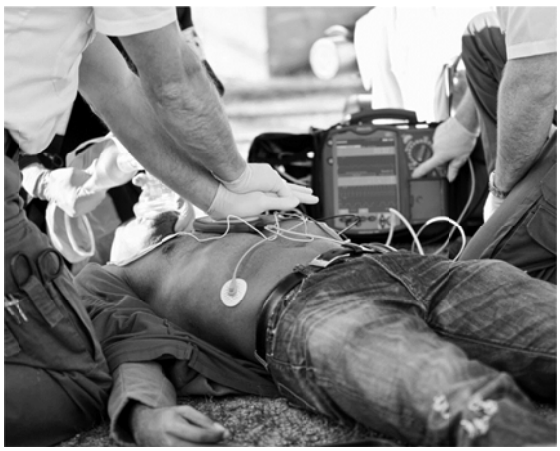
Management of cardiac arrest

Cardiac arrest involves cessation of cardiac **mechanical** activity as confirmed by absence of signs of circulation (absent pulse and apnea).

Causes

- Coronary heart disease (~80%).
- Cardiac disease: e.g. HOCM, Brugada syndrome.
- Cardiac arrhythmia especially ventricular.
- Others: trauma, electrolyte imbalance, electrical shock, drugs, etc.

Patterns of arrest



- Complete asystole: the ECG is flat line.
- Ventricular fibrillation: ECG shows fibrillation waves.
- Pulseless electrical activity (PEA): There is some electrical activity (other than VF) without detectable pulse.

Management

- The ultimate goal of treatment is to preserve life by early CPR 30:2 i.e. cycles of 30 chest compressions followed by 2 rescue breaths.
- Administer electrical defibrillation at 360J then repeat CPR for 2 min.
  → No response → **Epinephrine** 1 mg i.v. /3-5 min with CPR.
  → No response → DC shock with CPR for 2 min.
  → No response → **Amiodarone** 300 mg i.v. with CPR.
  → No response → DC shock with CPR.

  Shock – Drug **– Shock –** Drug **– Shock**

Notes

Review Questions

Mention the pharmacodynamic principles underlying the use of:

- Verapamil in angina pectoris
- Verapamil in hypertrophic obstructive cardiomyopathy
- Nifedipine in arterial hypertension
- Lisinopril in arterial hypertension
- Captopril in diabetic nephropathy
- Nitroglycerine in angina pectoris
- Digoxin in congestive heart failure

Mention the pharmacodynamic principles underlying the contraindication of:

- Nifedipine in supraventricular tachycardia
- Verapamil in Wolff-Parkinson-White syndrome
- Captopril in hypertension associated with severe chronic renal failure
- Digoxin in heart failure associated with heart block
- Beta-blockers in Prinzmetal's (variant) angina

Mention the precautions underlying the use of:

- Nitrates in angina pectoris
- ACEIs in hypertension
- Quinidine in atrial arrhythmia

Mention the essential lines of treatment of the following emergency conditions:

- Acute severe arterial hypertension
- Acute pulmonary edema
- Acute myocardial infarction
- Acute anaphylactic shock

Mention 3 side effects of each of the following drugs:

- Verapamil
- Captopril
- Isosorbide dinitrate
- Amiodarone

Mention the rational of the following combinations:

- Nitrates with beta-blockers in angina pectoris
- Hydralazine with diuretics in systemic hypertension
- Captopril with furosemide in arterial hypertension

Mention the main differences between:

- Verapamil and nifedipine
- Digitalis and quinidine
- Captopril and lisinopril

Of each of the following questions, select THE BEST SINGLE answer:

1. The followings drugs given alone are useful for treatment of hypertension EXCEPT:
A. Amiodarone.
B. Propranolol.
C. Captopril
D. Furosemide
E. Verapamil

2. Significant relaxation of arteriolar and venular smooth muscles can be pro-duced by which of the following drugs:
A. Hydralazine
B. Minoxidil
C. Diazoxide
D. Sodium nitroprusside
E. Nifedipine

3. One of the following drugs is effective in treatment of ischemic episodes in patients with variant angina:
A. Propranolol
B. Nitroglycerine
C. Sodium nitroprusside
D. Diltiazem
E. Hydralazine

4. The following is true about calcium channel blockers:
A. Verapamil has a positive inotropic effect
B. Verapamil dilates coronary arteries more than nifedipine
C. Verapamil effectively relieves A-V block
D. Diltiazem may cause ankle edema
E. Nifedipine is contraindicated in Raynaud's disease

5. Negative inotropy and chronotropy are most prominent with the use of the following drug:
A. Nifedipine
B. Nicardipine
C. Nimodipine
D. Diltiazem
E. Verapamil

6. Which of the following mechanisms best explains the antihypertensive actions of clonidine:
A. Blockade of β1 adrenergic receptors
B. Blockade of α1 adrenergic receptors
C. Blockade of central α2 receptors
D. Stimulation of presynaptic α2 receptors
E. Stimulation of presynaptic β2 receptors

7. When glyceryl trinitrate (nitroglycerine) tablets are prescribed for angina pectoris, the patient should be told:
A. To take it to prevent pain
B. To take it at the onset of pain
C. That if throbbing headache and palpita-tion occur the patient should take another
D. That if he feels faint he should stand up perfectly
E. To keep the tablet in a warm humid place e.g. a shelf over the bath

8. Which of the following antihypertensive drugs may cause fetal pulmonary hypoplasia and growth retardation if used during pregnancy:
A. Hydralazine
B. Alpha-methyldopa
C. Atenolol
D. Clonidine
E. Captopril

9. All the following statements are true for nitroglycerine EXCEPT:
A. Can cause adverse reactions of headache and tachycardia
B. Undergoes significant first-pass biotransformation
C. Can be used i.v. for the treatment of acute heart failure
D. Has duration of action of several hours after sublingual administration
E. Can increase exercise tolerance if taken immediately before exercise

10. A 57-year-old man is being treated for an atrial arrhythmia. He complains

of headache, dizziness, and tinnitus. Which one of the following antiarrhythmic drugs is the most likely cause?

A. Quinidine.
B. Amiodarone.
C. Procainamide.
D. Propranolol.
E. Verapamil

11. A 58-year-old woman is being treated for chronic suppression of a ventricular arrhythmia. After 2 months of therapy, she complains about feeling tired all the time. Examination reveals a resting heart rate of 10 beats per minute lower than her previous rate. Her skin is cool and clammy. Laboratory test results indicate low thyroxin and elevated thyroid-stimulating hormone levels. Which of the following antiarrhythmic drugs is the likely cause of these signs and symptoms?

A. Amiodarone.
B. Procainamide.
C. Propranolol.
D. Quinidine.
E. Verapamil.

12. A 56-year-old patient complains of chest pain following any sustained exercise. He is diagnosed with atherosclerotic angina. He is prescribed sublingual nitroglycerin for treatment of acute chest pain. Which of the following adverse effects is likely to be experienced by this patient?

A. Hypertension.
B. Throbbing headache.
C. Bradycardia.
D. Sexual dysfunction.
E. Anemia.

13. A 68-year-old man has been successfully treated for exercise-induced angina for several years. He recently has been complaining about being awakened at night with chest pain. Which of the following drugs would be useful in preventing this patient's nocturnal angina?

A. Amyl nitrite.
B. Nitroglycerin (sublingual).
C. Nitroglycerin (transdermal).
D. Esmolol.
E. Hydralazine.

14. Compensatory increases in heart rate and renin release that occur in heart failure may be alleviated by which of the following drugs?

A. Milrinone.
B. Digoxin.
C. Dobutamine.
D. Enalapril.
E. Metoprolol.

15. A 58-year-old man is admitted to the hospital with acute heart failure and pulmonary edema. Which one of the following drugs would be most useful in treating the pulmonary edema?

A. Digoxin.
B. Dobutamine.
C. Furosemide.
D. Minoxidil.
E. Spironolactone.

16. A 45-year-old man has recently been diagnosed with hypertension and started on monotherapy designed to reduce peripheral resistance and prevent NaCl and water retention. He has developed a persistent cough. Which of the following drugs would have the same benefits but would not cause cough?

A. Losartan.
B. Nifedipine.
C. Prazosin.
D. Propranolol.
E. Verapamil.

17. Which one of the following drugs may cause a precipitous fall in blood pressure and fainting on initial administration?

A. Atenolol.
B. Hydrochlorothiazide.
C. Nifedipine.
D. Prazosin.
E. Verapamil.

18. Which one of the following antihypertensive drugs can precipitate a hypertensive crisis following abrupt cessation of therapy?

A. Clonidine.
B. Diltiazem.
C. Enalapril.
D. Losartan.
E. Hydrochlorothiazide.

19. Which of the following statements is most correct regarding the use of drugs in hypertension?

A. beta-blockers are contraindicated if hypertension is associated with heart failure
B. calcium channel blockers are contraindicated if the patient also has obstructive pulmonary disease
C. diuretics are contraindicated in hypertension associated with diabetes
D. vasodilators are contraindicated in a patient taking a diuretic
E. ACE inhibitors are contraindicated if the patient is pregnant

20. β-Blockers have been effective in the treatment of heart failure. They primarily exert their effect by:

A. Binding to the receptor that binds norepinephrine
B. Inducing a prominent diuretic effect
C. Increasing contractility
D. Improving asthma control
E. Increasing heart rate to meet the additional demands placed upon the heart in CHF

21. A patient has periodic episodes of paroxysmal supraventricular tachycardia (PSVT). Which of the following drugs would be most suitable for outpatient prophylaxis of these worrisome electrophysiologic events?

A. Adenosine
B. Lidocaine
C. Nifedipine
D. Nitroglycerin
E. Verapamil

22. We prescribe a beta-adrenergic blocker for a patient with chronic-stable ("effort-induced") angina, and the incidence and severity of anginal attacks are reduced. Which of the following best explains the pharmacologic action by which the beta blocker does this?

A. Decreases myocardial oxygen demand
B. Dilates the coronary vasculature
C. Exerts antiplatelet/antithrombotic effects
D. Reduces total peripheral resistance
E. Slows AV nodal conduction velocity

23. Your patient is a 50-year-old man with essential hypertension and no other complications. Which of the following drugs would be the most rational first choice for starting his antihypertensive therapy?

A. Angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker
B. Beta-adrenergic blocker
C. Nifedipine
D. Thiazide diuretic
E. Verapamil or diltiazem

24. We have a 50-year-old man with asymptomatic hyperuricemia, and we are about to start therapy for newly diagnosed essential hypertension (BP 136/90 mm Hg, based on repeated measurements with the patient supine and at rest). Which of the following antihypertensive drugs is most likely to increase his serum uric acid levels further, and possibly precipitate a gout attack?

A. Captopril
B. Hydrochlorothiazide
C. Labetalol
D. Losartan
E. Verapamil

25. We've just diagnosed essential hypertension in a 58-year-old female patient. She tends to be tachycardic. Notes written by her ophthalmologist indicate that she has chronic open-angle glaucoma. Which of the following drugs would be the most rational

choice for this woman, given only the information presented in this question?

A. Captopril
B. Diltiazem
C. Hydrochlorothiazide
D. Timolol
E. Verapamil

26. Our newly diagnosed hypertensive patient has a history of vasospastic angina. Which of the following drugs or drug classes would be the most rational for starting antihypertensive therapy because it exerts antihypertensive effects, directly lowers myocardial oxygen demand and consumption, and also tends to inhibit cellular processes that otherwise favor coronary vasospasm?

A. Angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker
B. Beta-Adrenergic blocker
C. Nifedipine
D. Thiazide diuretic
E. Verapamil (or diltiazem)

27. Quinidine is ordered for a patient with recurrent atrial fibrillation and who refuses any interventions other than drugs in an attempt to terminate and control the arrhythmia. Which of the following is the most likely effect of quinidine?

A. Is likely to increase blood pressure via a direct vasoconstrictor effect
B. Is contraindicated if the patient also requires anticoagulant therapy
C. Slows spontaneous SA nodal depolarization as its predominant effect
D. Tends to slow electrical impulse conduction velocity through the AV node
E. Will increase cardiac contractility (positive inotropic effect) independent of its antiarrhythmic effects

28. A patient who has been taking an oral antihypertensive drug for about a year develops a positive Coombs' test. Which of the following drugs is the most likely cause?

A. Captopril
B. Clonidine
C. Labetalol
D. Methyldopa
E. Prazosin

29. A patient has Stage III essential hypertension. After evaluating the responses to several other antihypertensive drugs, alone and in combination, the physician places the patient on oral hydralazine. Which of the following adjunct(s) is/are likely to be needed to manage the expected and unwanted cardiovascular side effects of the hydralazine?

A. Captopril plus nifedipine
B. Digoxin plus spironolactone
C. Digoxin plus vitamin K
D. Hydrochlorothiazide and a beta blocker
E. Triamterene plus amiloride

30. At high (but not necessarily toxic) blood levels, a cardiovascular drug causes lightheadedness, tinnitus, and visual disturbances such as diplopia. What is the most likely drug that caused these responses?

A. Atropine
B. Captopril
C. Dobutamine
D. Propranolol
E. Quinidine

31. We have a patient who is diagnosed with variant (vasospastic) angina. Which of the following drugs would be most appropriate, and generally regarded as most effective, for long-term therapy aimed at reducing the incidence or severity of the coronary vasospasm?

A. Aspirin
B. Atorvastatin
C. Diltiazem
D. Nitroglycerin
E. Propranolol

32. The following treatments can be applied for rapid relief of acute anginal pain EXCEPT:
A. Sublingual nitroglycerine
B. Sublingual isosorbide dinitrate
C. Oral aspirin
D. Inhaled amylnitrite
E. Intravenous nitroglycerine

33. Which of the following statements is true concerning the action of enalapril:
A. It is prodrug for an angiotensin II blocker
B. Stimulates angiotensin II receptors
C. Increases endogenous bradykinin levels
D. Does not lower blood pressure in "normal renin" hypertension
E. Best indicated to patients with hypertension associated with liver disease

34. Beta-blockers are considered the first choice in the control hypertension in the following cases EXCEPT:
A. Hypertension with thyrotoxicosis
B. Hypertension with ventricular premature beats
C. Hypertension with variant angina
D. Hypertension with high plasma renin
E. Young patient with increased sympathetic activity

35. Severe myocardial pain due to acute inferior MI with excessive vagal stimulation can be best managed by:
A. Morphine
B. Meperidine
C. Butorphanol
D. Diclofenac
E. Indomethacin

36. The enhancement of myocardial contractility after digitalis is due to:
A. Increased cyclic AMP
B. Stimulation of calmodulin
C. Beta-adrenergic stimulation
D. Increased production of adenosine
E. Inhibition of the sodium pump

37. An ideal drug for treatment of ventricular arrhythmia due to acute myocardial infarction is:
A. Propranolol
B. Lidocaine
C. Quinidine
D. Procainamide
E. Verapamil

38. Digoxin is not indicated to treat heart failure as long systemic hypertension is present because:
A. The heart may develop more strain and failure
B. Absorption of digoxin will be reduced
C. Excretion of digoxin will be reduced
D. Liability for digoxin toxicity is high with hypertension
E. Systemic hypertension will be reduced suddenly

39. Wolff-Parkinson-White syndrome can be successfully treated by:
A. Quinidine
B. Verapamil
C. Atenolol
D. Digoxin
E. Amiodarone

40. All the following are positive inotropic drugs EXCEPT:
A. Digitalis
B. Adrenaline
C. Aminophylline
D. Dopamine
E. Amiodarone

41. All the following are class I antiarrhythmic drugs EXCEPT:
A. Lidocaine
B. Quinidine
C. Propranolol
D. Phenytoin
E. Procainamide

42. Which of the following cardiac glycosides has the clearly higher therapeutic index:
A. Ouabain.
B. Digoxin.
C. Digitoxin.

D. Deslanoside
E. None of the above

43. The ECG of a patient who is receiving digitalis in the therapeutic range would be most likely to show:
A. Prolongation of the QT interval.
B. Prolongation of the PR interval.
C. Symmetrical peaking of the T-wave
D. Widening of the QRS complex
E. Deep Q wave

44. If both quinidine and digoxin are administered concurrently, which of the following effects does quinidine have on digoxin?
A. The absorption of digoxin from the GIT is decreased
B. The metabolism of digoxin is prevented
C. The concentration of digoxin in the plasma is increased
D. The excretion of digoxin is increased
E. The ability of digoxin to inhibit N^+/K^+ ATPase is reduced

45. All of the following are considered mechanisms of antiarrhythmic drugs EXCEPT:
A. Calcium channel blockade
B. Inhibition of catecholamine action on the heart
C. Sodium channel blockade
D. Increasing the slope of phase 4 depolarization
E. Prolongation of effective refractory period (action potential duration)

46. All the following are side effects of amiodarone EXCEPT:
A. Corneal microdeposits
B. Tachycardia
C. Thyroid dysfunction
D. Pulmonary infiltration
E. Hepatotoxicity

47. Digitalis toxicity is enhanced by which one of the following:
A. Decreased extracellular Ca++
B. Decreased stimulation rate
C. Increased extracellular Mg++
D. Decreased extracellular K+
E. Decreased extracellular Na^+

48. The most specific line for treatment of digitalis toxicity is:
A. Stop digitalis administration
B. Administration of potassium
C. Administration of Fab fragments
D. Administration of phenytoin
E. Administration of calcium

49. The usefulness of digitalis in management of atrial fibrillation depends on its ability to:
A. Decrease atrial impulse formation
B. Decrease vagal control over the heart
C. Decrease conduction time through the A-V node
D. Increase the effective refractory period of the A-V node
E. Increase conduction time in the atria

50. Quinidine is either contraindicated or should be used with caution in all of the following EXCEPT:
A. Complete atrioventricular block.
B. Digitalis intoxication
C. Severe congestive heart failure
D. Atrial fibrillation of recent origin
E. History of idiosyncrasy due to quinidine

51. A 45-year-old man asks his physician for a prescription for sildenafil to improve his sexual performance. Because of risks from a serious drug interaction, this drug should not be prescribed, and the patient should be urged not to try to obtain it from other sources, if he is also taking which of the following drugs?
A. An angiotensin-converting enzyme inhibitor
B. A beta-adrenergic blocker
C. A nitrovasodilator (e.g., nitroglycerin)
D. A statin-type antihypercholesterolemic drug
E. A thiazide or loop diuretic

52. A 70-year-old woman is treated with sublingual nitroglycerin for occasional bouts of effort-induced angina. Which of the following best describes the mechanism by which nitroglycerin causes its desired antianginal effects, or a mediator involved in it?

A. Blocks beta adrenergic receptors
B. Forms cyanide, much like the metabolism of nitroprusside does
C. Increases local synthesis and release of adenosine
D. Raises intracellular cGMP levels
E. Stimulates phosphodiesterase

53. All of the following are recommended at the initial stages of treating patients with heart failure EXCEPT:

A. Reduced salt intake
B. Verapamil
C. ACE inhibitors
D. Diuretics
E. Vasodilators

54. Which one of the following drugs increases digoxin plasma concentration by a pharmacokinetic mechanism?

A. Captopril
B. Hydrochorothiazide
C. Lidocaine
D. Quinidine
E. Sulfasalazine

55. Regarding verapamil, which one of the following statements is false?

A. Angina pectoris is an important indication for the use of verapamil
B. Contraindicated in the asthmatic patient
C. Relaxes vascular smooth muscle
D. Slows the depolarization phase of the action potential in AV nodal cells
E. Used in management of supraventricular tachycardias

56. Exertion–induced angina, which is relieved by rest, nitroglycerin, or both, is referred to as:

A. Prinzmetal's angina
B. Unstable angina
C. Classic angina
D. Variant angina
E. Preinfarction angina

57. Which of the following drugs is a class IV antiarrhythmic that is primarily indicated for the treatment of supraventricular tachyarrhythmias?

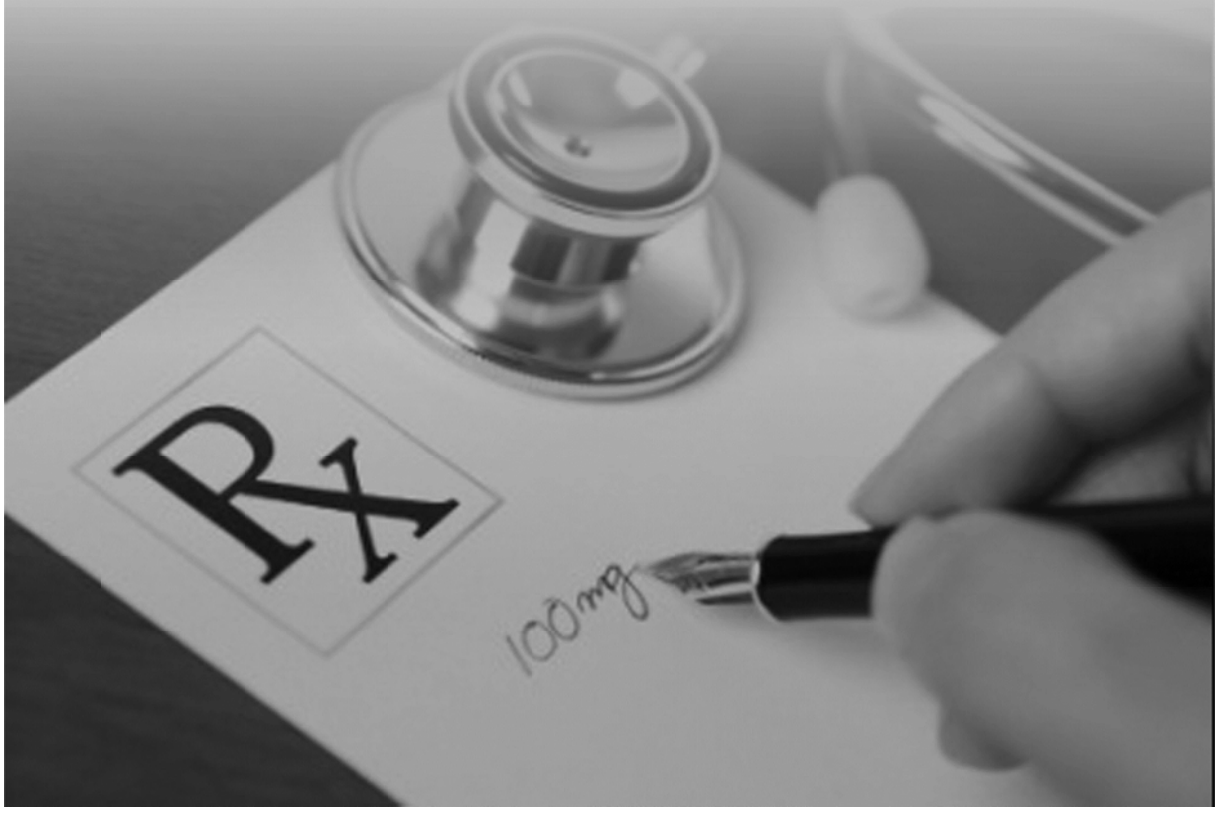
A. Diltiazem
B. Digoxin
C. Mexiletine
D. Quinidine
E. Propranolol

Answers

1 A	13 C	25 D	37 B	49 D
2 D	14 E	26 E	38 A	50 D
3 D	15 C	27 C	39 E	51 C
4 D	16 A	28 D	40 E	52 D
5 E	17 D	29 D	41 C	53 B
6 D	18 A	30 E	42 E	54 D
7 B	19 E	31 C	43 B	55 B
8 E	20 A	32 C	44 C	56 C
9 D	21 E	33 C	45 D	57 A
10 A	22 A	34 C	46 B	
11 A	23 D	35 B	47 D	
12 B	24 B	36 E	48 C	

Chapter 6

Pharmacology Of The Blood



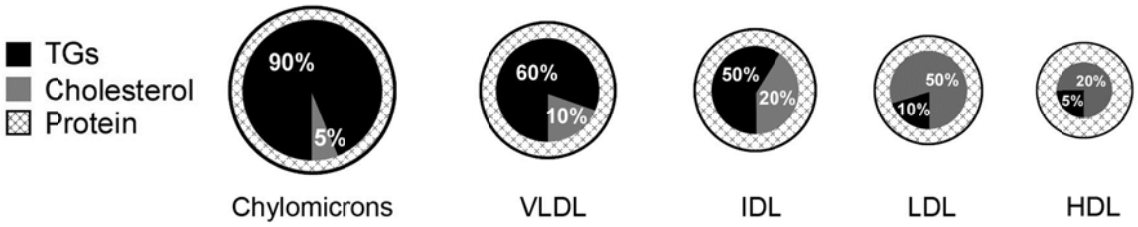
Chapter 6

Pharmacology Of The Blood

Part 1: Hyperlipidemia and drugs that lower plasma lipids

Basic information

- **Lipoproteins** consist of a hydrophobic lipid core (TGs or cholesterol) surrounded by a hydrophilic coat of phospholipids and proteins (apoproteins), which render them miscible in aqueous plasma.
- There are **5** classes of lipoproteins depending on their relative proportion of the core lipids, type of apoprotein, size, and density:



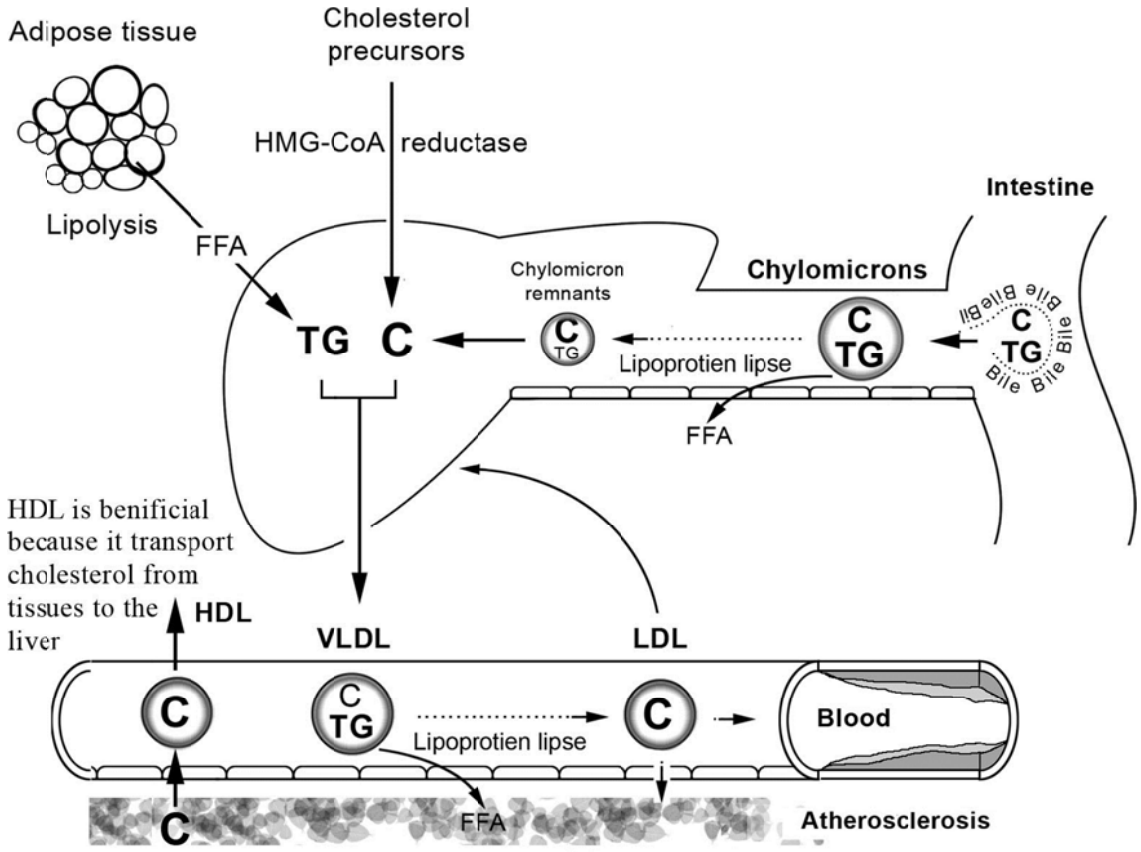
- The **intestine** is the main *source* of lipid precursors. The **liver** is the main site of *synthesis* of lipoproteins. The **adipose tissue** is the main site of *storage* of TGs. Fat cells don't synthesize any lipoproteins.

Lipoprotein metabolism

- **In the exogenous pathway**, absorbed cholesterol and TGs are transported in plasma as **chylomicrons**. On the vascular endothelium, the core TGs is hydrolyzed by a surface-bound *lipoprotein lipase* into FFA which enter the tissue and utilized. The chylomicrons **remnants** (containing mainly cholesterol) pass to the liver where cholesterol is stored, oxidized to bile acids, or secreted in the bile. Alternatively, it may enter the synthesis of **VLDL**.
- **In the endogenous pathway**, cholesterol and newly synthesized TGs are assembled as **VLDL** and delivered to the blood where TGs core is hydrolyzed by

lipoprotein lipase into FFA as described above. The smaller VLDL particles having less TGs and more cholesterol are now termed **LDL**. Cholesterol in the LDL may be: (1) utilized by the tissues; (2) returns again to the liver; (3) deposited subintimal in blood vessels and cause **atherosclerosis**.

- When cells **die**, cholesterol in their plasma membranes is returned to the liver as plasma **HDL** particles. HDL functions as scavenger lipoproteins.



Classification of hyperlipidemia

- **Primary (familial; hereditary) hyperlipidemia:** is genetically determined.

Class	Increased lipoprotein	Synonym
Type I	↑ chylomicrons	Familial chylomicronemia
Type IIa	↑ LDL	Familial hypercholesterolemia
IIb	↑ LDL and VLDL	Familial combined hyperlipidemia
Type III	↑ IDL	Familial dysbetalipoproteinemia
Type IV	↑ VLDL	Familial hypertriglyceridemia
Type V	↑ VLDL and chylomicrons	Familial mixed hyperlipedemia

- **Secondary (acquired) hyperlipidemia:**
  - Hypercholesterolemia: hypothyroidism, nephrotic syndrome, and drugs.
  - Hypertriglyceridemia: DM, alcohol, gout, chronic renal failure.

LIPID LOWERING DRUGS

Classification of drugs

- **Inhibitors of intestinal cholesterol absorption:**
  - Bile acid binding resins: cholestyramine, colestipol
  - Ezetimibe
- **Activators of plasma lipoprotein lipase:** fibric acid derivatives
- **HMG-CoA reductase inhibitors:** statins.
- **Inhibitors of hepatic lipid production:** nicotinic acid, acipimox
- **Other drugs:** d-thyroxin, neomycin, and probucol

Drug therapy is indicated in:

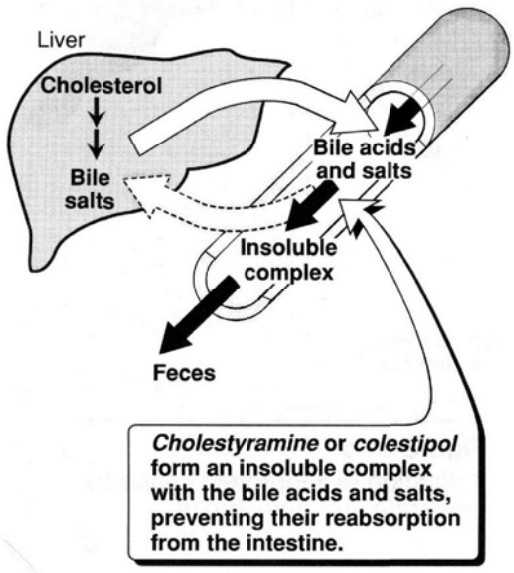
Failure of non-drug therapy.

Primary (hereditary) hyperlipidemia.

Cholestyramine and colestipol

Mechanism of action

They form **complexes** with bile acids in the intestine and ↓ enterohepatic absorption of bile salts and ↓ absorption of cholesterol.



Therapeutic uses

- Hypercholesterolemia **(type IIa):** Bile acid sequestrants are effective in reducing plasma cholesterol (10%–20%) in patients with some normal LDL receptors.
- Diarrhea due to bile acid malabsorption.
- Pruritus due to obstructive jaundice.

Adverse effects

- GIT upset (the most common): nausea, vomiting and **steatorrhea** (due to ↓ fat absorption).
- ↓ absorption of fat-soluble vitamins.
- ↓ absorption of anionic drugs e.g. digitalis and warfarin.

Ezetimibe

Mechansism of action

Ezetimibe is a selective inhibitor of intestinal cholesterol absorption. It is effective even in the absence of dietary cholesterol because it inhibits reabsorption of cholesterol excreted in the bile.

Therapeutic uses

Hypercholesterolemia: ezetimibe is synergistic with HMG-CoA reductase inhibitors, producing decrease of 25% in LDL cholesterol.

Adverse effects

Reversible hepatic dysfunction: liver function tests should be done at regular intervals.

HMG-CoA reductase inhibitors (Statins)

(Lovastatin, Pravastatin, Mevastatin, Atorvastatin)

Mechanism of action

Competitive **inhibition of hydroxy-methyl-glutaryl coenzyme-A** (HMG-CoA) **reductase** → ↓ **cholesterol synthesis** and ↑ hepatic uptake of LDL.

N.B.

Statins should be taken at night as this is when the majority of cholesterol synthesis takes place. This is especially true for simvastatin which has a shorter half-life.

Therapeutic uses

- Hypercholesterolemia **(type II).**
- With other drugs for combined hyperlipidemia**.**

Adverse effects

H : **Hepatic dysfunction** leading to elevation of serum transaminases. Therapy should be stopped if liver enzymes rise > 3-folds the upper normal value.

M : **Myopathy, myositis** and **rhabdomyolysis** in both **skeletal** and **cardiac** muscle leading to ↑ of *creatine phosphokinase (CPK)* enzyme.

G : **GIT upsets:** nausea, vomiting, anorexia (the most common).

Co-A : **Cataract** (lenticular **O**pacity) in middle-**A**ged individuals.

Reductase : **R**enal dysfunction (especially with lovastatin).

Fibric acid derivatives (Fibrates)

(Clofibrate, Fenofibrate, Bezafibrate, Gemfibrozil)

Mechanism of action

Fibrates act on **nuclear receptors** called *peroxisome proliferator activated receptors-α (PPAR-α)* leading to ↑ synthesis of **lipoprotein lipase** → ↑ peripheral catabolism of **VLDL** and **chylomicrons (TGs).**

Therapeutic uses:

- Hypertriglyceridemia **(types IIb, III, IV and V).**
- Fenofibrate has **antidiuretic action** in individuals with mild to moderate diabetes insipidus.

Adverse effects

- **GIT upsets:** nausea, vomiting (the most common).
- Increase formation of **cholesterol gallstones**.
- **Hepatic dysfunction** and elevation of serum transaminases.
- Fibrates increase the **risk of myopathy** if used in combination with **statins**.
- Skin **rash** and dermatologic reactions.

Nicotinic acid (Niacin; vitamin B3)

Mechanism of action

- Niacin (but not nicotinamide) **inhibits lipolysis** in adipose tissue and inhibits **fatty acid synthesis** by the liver → ↓ hepatic **VLDL** and **LDL** synthesis.
- This is distinct from the role of niacin as a vitamin, in which it is converted to nicotinamide and is used for the biosynthesis of the cofactors NAD and NADP.

Therapeutic uses

In combination with other drugs for **all types** of hyperlipidemia (**except type I** which is mainly treated by diet control).

Adverse effects

- **Skin flushing** and **burning** sensation (the most common). It is harmless effect mediated by PGs and histamine release and can be diminished by taking aspirin 30 minutes before taking nicotinic acid.
- Gastric irritation (the drug should be avoided in peptic ulcer).
- Hyperglycemia, hyperuricemia, and reversible increase in serum transaminases.

Summary

	Effect on LDL	Effect on HDL	Effect on TGs
Bile acid-binding resins	↓↓↓	↑	----
Reductase inhibitors	↓↓↓	↑	↓
Fibrates	↓	↑	↓↓↓
Niacin	↓	↑↑↑	↓↓

Treatment with drug combinations

Hypercholesterolemia	Cholestyramine + Reductase inhibitors
Hypertriglyceridemia	Niacin + Fibrates
Familial combined hyperlipidemia	Cholestyramine + Fibrates. Cholestyramine + Niacin. Statins + Fibrates *(this combination may ↑ risk of myopathy).*

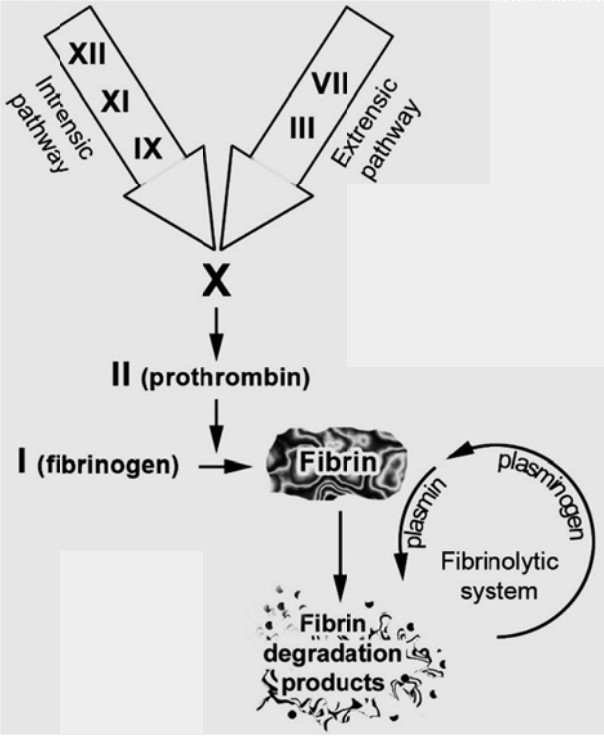
Part 2: Drugs affecting hemostasis

Basic information

Hemostasis is the spontaneous arrest of bleeding from damaged blood vessel.

The coagulation system:

It consists of a number of plasma proteins (factors). Each factor activates another till activation of fibrinogen to form fibrin.
Activation cascade is done through 2 systems: the **intrinsic system** (can be monitored by the activated partial throboplastin time "APTT") and the **extrinsic system** (can be monitored by prothrombin time).



Prevention of clotting:

- Plasma contains a number of proteins that normally prevent clotting through inhibition of clotting factors (e.g. **antithrombin III).**
- **Heparin** activates antithrombin III thus inhibits activation of factors IX, **X**, XI, and XII.
- **Oral anticoagulants** inhibit synthesis of clotting factors by the liver.

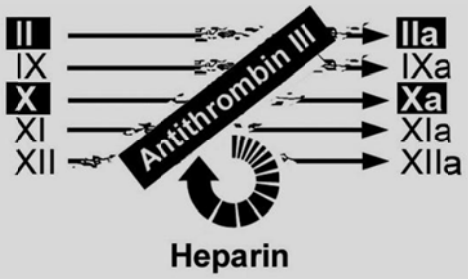
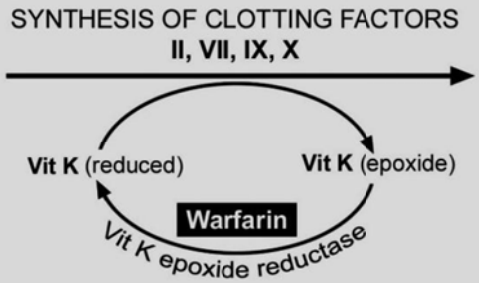
Dissolution of blood clots:

- There are other plasma proteins that can dissolve blood clots (i.e. *fibrinolytic system* e.g. **plasmin)**.
- There are some drugs that activate plasminogen to form the active plasmin and thus enhance fibrinolysis (e.g. **streptokinase, urokinase, etc.).**
- **Aminocaproic acid** is an inhibitor of fibrinolysis.

Drugs can affect hemostasis and thrombosis through:

- By modifying the integrity of the **vessel wall.**
- By modifying **blood coagulation** (clot formation).
- By modifying **platelet** adhesion and activation.
- By modifying **fibrinolysis.**

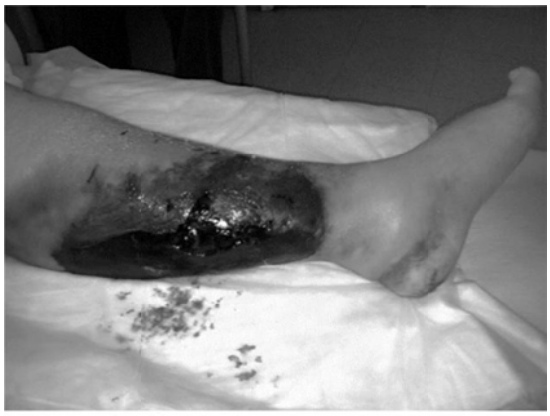
DRUGS THAT PREVENT COAGULATION (ANTICOAGULANTS)

	Heparin	Warfarin (Oral anticoagulant)
Source & chemistry	Natural sulfated polysaccharide present in mast cells & carries **–ve** charge Commercial preparations are derived from bovine lung or porcine intestinal extracts	Synthetic cuomarin compound
Absorption **Distribtion**	▪ **No** because it precipitates by gastric HCl. ▪ Can**not** cross BBB or placenta.	▪ **Good** (bioavailability is 100%). ▪ Can cross BBB and placenta.
Mechanism of action	▪ Its action depends on the presence of a natural clotting inhibitor called heparin cofactor **(antithrombin III)** in plasma. ▪ Small quantities of heparin can activate antithrombin III leading to inhibition of several clotting factors especially factor X & thrombin (factor II). 	▪ Warfarin inhibits **vitamin K epoxide reductase enzyme** in the **liver** leading to inhibition of formation of the active form of vitamin K → ↓ synthesis of vitamin K-dependent clotting factors **(II, VII, IX,** and **X)**. ▪ The action of warfarin could be antagonized by vitamin K. 
Onset and duration	**Immediate** and **short** (2-4 hrs).	**Delayed** for 8-12 hrs *(time needed for depletion of clotting factors & vit K)* and **long** (3-7 d)
Pharmacol effects	▪ Anticoagulant **in vivo** & **in vitro** ▪ Stimulates *lipoprotein lipase* → ↓↓ serum triglycerides (TGs).	Anticoagulant **in vivo** only.
Therapeutic uses	▪ **Treatment of established thrombosis:** heparin is given parenteral 5000-10,000 U **i.v.** then 5000 U **s.c.**/8h to maintain blood coagulation 2-3 times as normal and prevent further	Warfarin is given oral 2-10 mg/day for **prevention and treatment of:** – Deep vein thrombosis **(DVT)** – Postoperative thrombosis. – Cerebral venous thrombosis.

	extension of the thrombus. ▪ **Prevention of thrombosis:** 5000 U **s.c.**/8-12 hrs.	– Coronary thrombosis: treatment continued for several years. – Acute arterial & pulmonary **embolism**: anticoagulation is initiated by heparin and maintained by warfarin. – **AF** and **artificial** heart valves
Monitoring of therapy	By **activated partial thromboplastin time (APTT).** It must be kept 2-3 times as the normal value.	By **prothrombin time (PT) or International Normalized Ratio (INR). I**t is the ratio of the PT in the patient to that of normal person. It must be kept 2-3 times as the normal value.
Adverse effects	▪ **Bleeding is the most common and dangerous SE** (e.g. hematuria & major organ bleeding). It could be treated by the following: (a) Immediate stopping of the drug. (b) Fresh frozen plasma (FFP): to provide fresh clotting factors. **(c) Protamine sulfate (Protam):** – Protamine carries **+ve** charge that combines with heparin (carries **-ve** charge) to form stable complex. – **1 mg** of protamine can bind to **100 U** of heparin.	**(c) Vitamin K_1:** 10 mg slowly i.v. or i.m. to enhance synthesis of clotting factors.
	▪ **Hematoma** if given **IM** (so, contraindicated to give it IM). ▪ **Thrombocytopenia:** immune-mediated reaction due to formation of antibodies that can bind to platelets. Platelet count should be performed regularly ▪ **Osteoporosis** and spontaneous fractures on long-term therapy ▪ **Alopecia and dermatitis:** rare and transient.	▪ **Hemorrhagic skin necrosis**: when starting warfarin, biosynthesis of protein C is reduced leading to temporary procoagulant state. This can lead to hemorrhagic infarction of skin, breast, intestine and fatty tissue. normally avoided by concurent heparin administration. ▪ **Teratogenicity:** abnormal bone formation in early pregnancy *(fetal warfarin syndrome).* ▪ **CNS Hemorrhage** in the fetus if given in late pregnancy. ▪ **Sudden withdrawal** may lead to thrombotic catastrophes.

Low-molecular-weight heparins (LMWH) (Enoxaparin – Dalteparin)

- **Standard (unfractionated) heparin** is a mixture of different molecular weight fractions (MW 3000-30,000 Da) that can affect more than one coagulation factor and produce thrombocytopenia (↑ risk of bleeding).
- **LMWH** has a MW less than 8000 Da that makes it **specific for factor X** with minimal effects on platelets and other clotting factors.



Hemorrhagic skin necrosis caused by warfarin

	Unfractionated heparin	LMWH
Molecular weight range	Wide (ranges from 3000 to 30,000 Da)	Less than 8000 Da
Anti-factor Xa activity	Less specific	More specific
Non-specific binding to vascular endothelium and plasma proteins	High	Low
Bioavailability after s.c. injection	Low *(due to binding to s.c. tissue)*	High
Half-life	Short (given 3 times/d)	Long (given once/d)
Thrombocytopenia	Common (10%)	Less common (<2%)
Risk of bleeding	High	Low
Lab monitoring	APTT (Essential)	Anti-factor Xa levels (May be unnecessary)

Synthetic factor Xa inhibitors

Fondaparinux
- Synthetic polysaccharide that have the same mechanism like LMWH (i.e. selective inhibitor of factor Xa).
- It is given by **s.c.** injection **once daily** (has long t½).

Direct thrombin inhibitors (DTIs)

Bivalirudin
- It is a synthetic **hirudin analogue** (hirudin is a direct thrombin inhibitor peptide present in the saliva of medicinal **leech)**.
- Bivalirudin is a reversible and short-acting DTI. It is given **i.v.**

	– It is approved as alternative to heparin to treat patients with heparin-induced thrombocytopenia. – **Bleeding** is the major side effect.
Argatroban	– Synthetic compound that binds reversibly to **thrombin**. – It can be used as alternative to heparin to treat patients with heparin-induced thrombocytopenia. – It is given **i.v.** and has immediate onset of action.
Dabigatran	– It is the first **oral** DTI approved by the FDA in 2010. – It was found superior to warfarin in preventing the risk of stroke and systemic embolism in susceptible patients.

Use of anticoagulants during pregnancy

- Pregnancy is a hypercoagulable state due to increase levels of coagulation factors and venous stasis. Pegnancy increases the risk of venous thrombosis and pulmonary embolism.
- The use of warfarin in the first trimester is associated with birth defects (5%), while its use near fullterm increases the risk of fetal hemorrhage.
- Neither UFH nor LMWH cross the placenta; therefore, do not cause fetal bleeding or teratogenicity, but they can reduce bone mass density and cause **osteoporosis** if used throught pregnancy.
- Anticoagulation is recommended in most pregnant patients with a mechanical heart valve. The American College of Chest Physicians (ACCP) recommends the use LMWH until 13 weeks' gestation, THEN change to warfarin until the patient is close to delivery (34 weeks), and THEN restart LMWH. Long-term anticoagulants should be resumed postpartum.

Contraindications of anticoagulant therapy

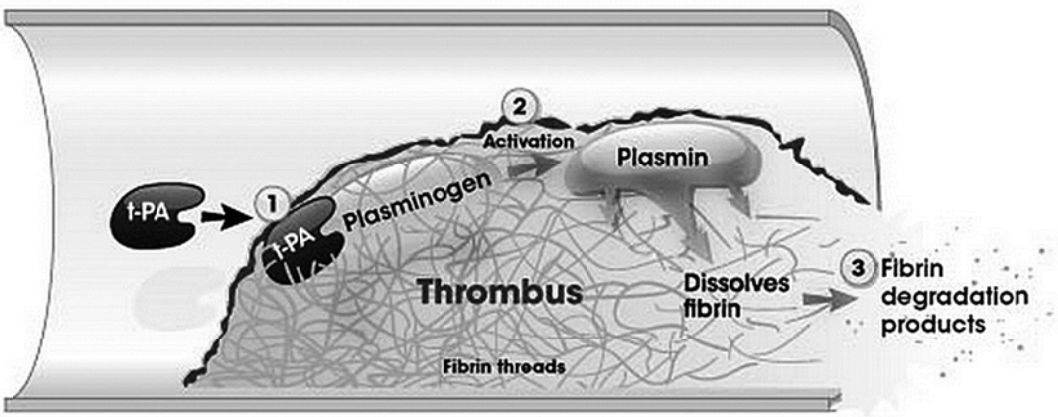
Hematological:	– Hemorrhagic blood diseases e.g. hemophilia & thrombocytopenia.
Neurological:	– **R**ecent hemorrhagic stroke within 3 weeks. – **R**ecent brain or eye surgery.
CVS:	– **S**ubacute bacterial endocarditis (SBE). – Uncontrolled hypertension (→ risk of cerebral bleeding).
GIT:	– **A**ctive PU, esophageal varices, and hemorrhagic pancreatitis – **A**ctive inflammatory bowel disease (ulcerative colitis).
Liver:	– Liver failure (this patient has bleeding tendency)
Renal:	– Renal failure.
Gynecological:	– Threatened abortion. – Warfarin is not given in the first timester.

Drug interactions of oral anticoagulants (warfarin)

Drugs that potentiate warfarin	Drugs that inhibit warfarin
▪ **Microsomal enzyme inhibitors** (e.g. cimetidine, chloramphenicol) ↓ metabolism of warfarin. ▪ **Oral antibiotics:** ↓ vit K synthesis by killing the gut flora ▪ **Liquid paraffin:** ↓ vit K absorption ▪ **NSAIDs:** displace warfarin from pp.	▪ **Microsomal enzyme inducers** (e.g. phenobarbital, rifampin) ↑ metabolism of warfarin. ▪ **Oral contraceptives** and **vit K**. ↑ synthesis of clotting factors ▪ **Aluminum hydroxide:** ↓ warfarin absorption

FIBRINOLYTIC (THROMBOLYTIC) DRUGS

- Normally, when a fibrin clot is formed, **plasminogen** gets in contact with this clot and becomes activated into **plasmin** by the help of naturally occurring **tissue plasminogen activators (t-PAs)**. Plasmin causes lysis of the clot.
- These endogenous activators preferentially activate plasminogen that is bound to fibrin, which (in theory) confines fibrinolysis to the formed thrombus and avoids systemic activation.
- Fibrinolytic drugs cause rapid activation of plasminogen to form plasmin, but unfortunately, they may activate **both** fibrin-bound plasminogen and circulating plasminogen thus, both protective hemostatic thrombi and pathogenic thromboemboli are broken down (→ risk of bleeding).



(1) Recombinant t-PA (alteplase) binds to fibrin in thrombus (2) converts entrapped plasminogen to plasmin that (3) initiates local fibrinolysis.

Streptokinase

- Streptokinase is a protein (not an enzyme) that is isolated from streptococci; it activates plasminogen into plasmin non-enzymatically.
- It may be antigenic (causes allergy) in some people.

Urokinase

- Urokinase is a protease originally isolated from urine; the drug is now prepared in recombinant form from cultured kidney cells.
- It is less antigenic than streptokinase.

Streptokinase and urokinase act on both circulating plasminogen and fibrin-bound plasminogen causing a generalized fibrinolytic state (bleeding).

Recombinant tissue plasminogen activators (t-PAs): (Alteplase, reteplase, and tenecteplase)

- They are recombinant human proteins produced in cultured cells.
- They are **most specific** to fibrin-bound plasminogen; local activation of plasmin at the thrombus site reduces the incidence of systemic bleeding.
- **Reteplase** and **tenecteplase** have long half-life. The long half-life permits administration as a bolus i.v. injection rather than by continuous infusion. (two injections i.v. separated by 30 minutes for **reteplase**, one single i.v. injection for **tenecteplase**).

Therapeutic uses of thrombolytic drugs

- They are given by **i.v. route** in cases of acute **myocardial infarction**, ischemic stroke, pulmonary embolism, and arterial thrombosis.
- In cases of acute MI, they should be given within **12 h** of onset. The maximum benefit is obtained if treatment is given within **90** minutes of the onset of pain.
- Before thrombolysis, care should be taken to ensure there is no liability for bleeding in a critical site e.g. retina, CNS, etc.

Adverse effects of thrombolytic drugs

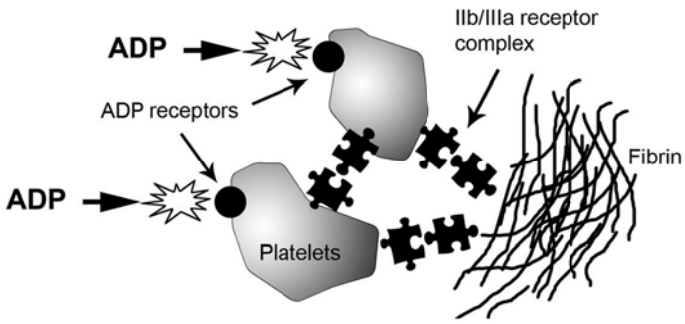
- **Systemic bleeding** is the major adverse effect. The risk is high with streptokinase and low with the recent recombinant tissue plasminogen activators.
- Streptokinase can cause **allergy, fever**, and **hypotension** during i.v. infusion.

ANTIPLATELET (ANTITHROMBOTIC) DRUGS

Aspirin

- Aspirin inhibit platelet aggregation by:
  - Irreversible inhibition of COX enzyme → ↓ TXA_2 → ↓ platelet *aggregation.*
  - Irreversible acetylation of platelet cell membranes → ↓ platelet *adhesions.*
  - Decrease platelet ADP synthesis → decrease platelet *accumulation.*
- At higher doses (> 325 mg/day), aspirin may decrease endothelial synthesis of PGI2, which inhibits platelet activity. Low doses (75-150 mg/day) ↓ synthesis of platelet TXA2 more than PGI2 in endothelial cells and avoid this effect.
- Other NSAIDs **do not have** comparable antithrombotic activity.

Blockers of platelet ADP receptors:
(Ticlopedine, clopidogrel, prasugrel)



- These drugs **irreversibly** inhibit the binding of **ADP** to its receptors on platelets and, thereby, inhibit the activation of the **glycoprotein IIb/IIIa** receptors required for platelets to bind to fibrinogen and to each other.
- **Clopidogrel** is approved for prophylaxis of thrombosis in both cerebrovascular and cardiovascular disease (e.g. coronary artery disease, coronary angioplasty, peripheral vascular disease, etc.). The maintenance dose is 75 mg/d orally.
- Clopidogrel is a **prodrug**, and its therapeutic efficacy relies entirely on its active metabolite. Some people have genetic deficiency in the enzymes that metabolize clopidogrel; they are called "**poor metabolizers**", and cannot benefit from this drug.
- Ticlopedine has been largely replaced by clopedogrel because of serious adverse effects (neutropenia and **bleeding**). Clopidogrel has **fewer** incidence of these effects.

Blockers of platelet glycoprotein IIb/IIIa receptors:
(Abciximab, eptifibatide, tirofiban)

- Activation of this receptor complex is the "final common pathway" for platelet aggregation and binding with fibrinogen. Persons lacking this receptor have a bleeding disorder called Glanzmann's thrombasthenia.
- **Abciximab** is the Fab fragment of a monoclonal antibody that binds to gpIIb/IIIa and blocks binding of platelets to fibrinogen.
- **Eptifibatide** is a small synthetic peptide that competitively blocks gpIIb/IIIa receptor.
- **Tirofiban** is a peptide of low MW that binds to the gpIIb/IIIa receptor.
- These drugs have been approved for use in patients undergoing percutaneous coronary intervention, for unstable angina, and for post-MI.

Dipyridamole

- Dipyridamole **inhibits phosphodiesterase (PDE) enzyme** → ↑ cGMP → VD and inhibition of platelet activity. It also **inhibits uptake of adenosine** into platelets and RBCs leading to extracellular accumulation and prolongation of its action.
- The use of dipyridamole as an antithrombotic agent is limited to prophylaxis (combined with warfarin) in patients with **prosthetic** (mechanical) **heart valves.**

DRUGS USED IN BLEEDING DISORDERS (HEMOSTATIC AGENTS)

Systemic agents

- **Vitamin K:** essential for synthesis of factors II, VII, IX, X by the liver.
- **Vitamin C** and **rutin:** preserve the integrity of the vascular wall.
- **Fresh blood or plasma transfusion:** as sources of coagulation factors.
- **Plasma fractions:**
  - Thromboplastin (factor III): prepared from mammalian tissues.
  - Antihemophilic globulin (factor VIII): given in hemophilia A.
- **Calcium (factor IV):** as a coagulation factor.
- **Aminocaproic acid** and **tranexamic acid:** inhibitors of fibrinolytic system.
- **Ethamsylate (Dicynone):** given i.m. to reduce capillary bleeding.

Local agents

- **Physical methods:** application of pressure, cooling or heat coagulation.
- **Vasoconstrictor drugs:** e.g. adrenaline nasal pack in epistaxis.
- **Astringents:** drugs which precipitate surface proteins e.g. alum sulphate.
- **Thrombin** and **thromboplastin:** applied on the bleeding surface as powders.
- **Fibrin and fibrinogen:** available as dried sheets and used in surgery.
- **Oxidized cellulose:** it forms an adhesive mass on the bleeding surface.
- **Sclerosing agents:** chemicals that cause thrombosis in veins and permanent obliteration, e.g. ethanolamine oleate (given i.v. for varicose veins).

Vitamin K

- **Vitamin K1 (phytomenadione)** is a naturally occurring **fat-soluble** vitamin present in green vegetables. It is available clinically in oral and parenteral forms.
- **Vitamin K2** is synthesized by intestinal bacteria.
- Both vitamins K1 and K2 require **bile** salts for absorption from the intestine.

Mechanism of action: Vitamin K is required for posttranslational modification of clotting factors II, VII, IX, and X by liver cells.

Therapeutic uses

- To reverse bleeding episodes caused by **overdose of warfarin, salicylates**, and oral hypoglycemic drugs.
- To correct **vitamin deficiency** caused by dietary deficiency, or in patients receiving oral antibiotics.
- To prevent **hypothrombinemia of the newborn**: all newborns should routinely receive 1–2 mg of vitamin K directly after birth (especially in premature infants).

Adverse effects: parenteral vitamin K1 is dissolved in **oil**; rapid i.v. administration can cause dyspnea, chest pain, or even death.

N.B. severe hepatic failure is associated with bleeding tendency (due to reduced synthesis of clotting factors) that **does not** respond to vitamin K.

Plasma fractions

- Deficiencies in plasma coagulation factors can cause bleeding. Spontaneous bleeding occurs when factor activity is **less than 5–10% of normal**. Factor VIII deficiency (classic hemophilia, or hemophilia A) and factor IX deficiency (Christmas disease, or hemophilia B) account for the most common heritable coagulation defects.
- Plasma protein preparations are available for treatment of these disorders. They are administered **i.v.**
- Plasma fractions are frequently prepared from **blood** or **plasma** pooled from multiple individuals; thus, they are associated with high risk of exposure to **infection** (hepatitis and HIV). For this reason, recombinant preparations are recommended whenever possible.

Hemophilia

Genetic deficiency of factor VIII (hemophilia A) or IX (hemophilia B).

Manifestations: bleeding on minor trauma.

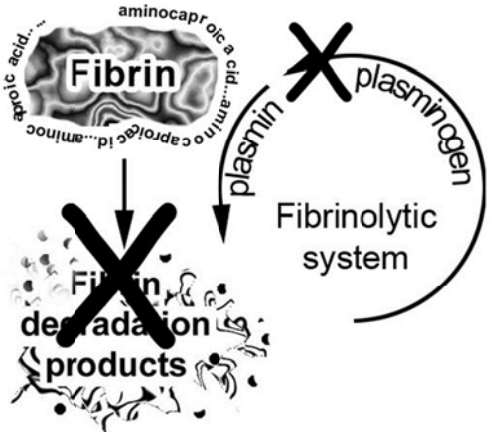
Treatment:
1. **Plasma fractions:** antihemophilic globulin (factor VIII) in hemophilia A and Christmas factor (factor IX) in hemophilia B.
2. **Desmopressin** (intranasal): can ↑ factor VIII activity (but not factor IX).
3. **Tranexamic acid:** help to stabilize blood clots in both diseases.

Inhibitors of fibrinolysis:
(Aminocaproic acid and tranexamic acid)

Aminocaproic acid is a synthetic agent that competitively inhibits plasminogen activation. **Tranexamic acid** is more potent analogue of aminocaproic acid.

Therapeutic uses

- To prevent **bleeding** from tissues rich in plasminogen activators e.g. lung, prostatic surgery, menorrhagia, and ocular trauma.
- Prophylaxis for rebleeding from **intracranial aneurysm**.
- As adjunctive therapy in **hemophilia**.
- To stop bleeding caused by **toxicity of fibrinolytic drugs**.



DRUGS AFFECTING BLOOD VISCOSITY

Pentoxifylline

- **Pentoxifylline** is a synthetic methylxanthine structurally similar to caffeine.
- Pentoxifylline appears to inhibit RBCs **phosphodiesterase (PDE)** → ↑ **RBC** membrane **flexibility** and ↓ blood viscosity (rheologic modifier).
- It is approved for use to improve microvascular circulation in patients with **intermittent claudication**, diabetic angiopathy, chronic leg ulcers, and peripheral vascular disease.

Part 3: Drugs used in the treatment of anemias

Anemia is defined as a low hemoglobin (Hb) concentration due to **reduced production** or **increased loss** of RBC. The WHO defines anemia as Hb <13 g/dL in men or <12 g/dL in women.

Iron deficiency anemia (hypochromic microcytic anemia)

- Iron deficiency is the most common cause of anemia.
- The total amount of transferrin determines the **total iron-binding capacity** (TIBC) of plasma.
- **Transferrin saturation** (i.e. plasma iron/TIBC) is normally 20–50% and provides a useful index of iron status.
- In iron-deficiency states, there is ↓ in plasma iron and ↑ in TIBC, so transferrin saturation is **< 20%.** The opposite occurs in hemochromatosis.

Iron

- **Absorption:**
  - Iron is absorbed from upper small intestine in the ferrous state (Fe2+) more than in the ferric state (Fe3+). About 10% of dietary iron is absorbed.
  - Factors that ↑ absorption: pregnancy & growing infants, gastric HCl and vit C.
  - Factors that ↓ absorption:
    - Malabsorption syndromes: e.g. celiac disease.
    - *Antacids:* form insoluble complexes with iron.
    - *Tannic acid* (strong tea): precipitates iron
    - *Tetracyclines:* chelate iron.
- **Transport:** in plasma via **transferrin** and stored in the reticulo-endothelial system and bone marrow as **ferritin**.

N.B.

Hepcidin is a protein synthesized by the liver. It **decreases** iron absorption by the intestine, and it may contribute to the anemia of chronic diseases.

- **Excretion:** There is no active mechanism for excretion of iron. Small amounts are excreted through stool, urine, and sweat. The main regulation of iron level in the body is done at the level of absorption.

Causes of iron deficiency anemia (= Indications of iron therapy)

- **Deficient intake:** e.g. poor diet or malabsorption syndrome.
- **Increased demand:** e.g. in **p**regnancy and **p**remature babies (iron & folic acid should be given to pregnant women from the 4th month).
- **Excessive blood loss**.

Preparations of iron

- **Oral iron:**
  - Many oral iron preparations are available (*Ferrous sulfate*, *ferrous gluconate, & ferrous fumarate)* which are are **effective** and recommended for most patients. Vitamin C may be given with iron to improve absorption.
  - The Hb usually reaches normal levels within **1-2 months** but treatment should be continued for **3-6 months** to replenish iron stores.

- **Parenteral iron:**

  Indications:
  - Inability to tolerate or absorb oral iron.
  - Severe anemia or extensive blood loss cannot be corrected by oral iron.

  Administration:
  - *Iron dextran or iron carboxymaltose* **is** given by slow i.v. infusion as a 1000 mg diluted in 500 ml saline over 1-2 hours. The initial 25 ml should be infused slowly (as a test dose) and the patient should be observed for allergic reactions.
  - Other parenteral preparations should be administered according to product labeling information.

Adverse effects of iron

- **Oral iron: GIT upset** (most common)**:** nausea, epigastric pain, abdominal cramps, constipation or diarrhea. These effects can be minimized by taking iron after meals.

- **Parenteral iron:**
  - Local pain and tissue staining with i.m. injection.
  - Anaphylactoid (allergic) reaction in 3% of patients. True anaphylaxis is very rare.
  - Lymphadenopathy.

Iron toxicity

- **Acute iron toxicity:**

  Causes: more frequent in children due to accidental ingestion of iron tablets.

  Manifestations:
  - Vomiting, hematemesis and bloody diarrhea.
  - Metabolic acidosis, shock, coma & death.

  Treatment:
  - Gastric lavage by phosphate or carbonate solutions to form insoluble complexes.
  - **Desferrioxamine** (**Desferal**; iron chelating compound): 1-2 gm i.m. to chelate systemically absorbed iron. It can cause hypersensitivity reaction.
  - Supportive treatment for GIT bleeding, metabolic acidosis, and shock.

- **Chronic iron toxicity:**

  Causes:
  - Excessive iron absorption: e.g. in **hemochromatosis** (autosomal recessive disorder characterized by ↑ iron absorption; transferrin saturation is >50%)
  - Excessive blood transfusion: e.g. in thalassemia major.

  Manifestations: excess iron is deposited in the liver, pancreas and skin.

  Treatment:
  - Intermittent phlebotomy is the treatment of choice: one unit of blood is removed every one week until the excess iron is removed.
  - Periodic desferrioxamine i.m. when phlebotomy cannot be performed e.g. in patients with thalassemia major.

Red cell deficiency anemia (Anemia of chronic renal failure)

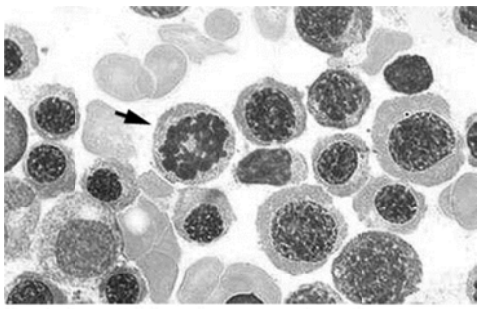
- **Erythropoietin (EPO)** is a glycoprotein secreted by interstitial cells of the renal cortex (90%) and 10% by the liver. It is essential for normal reticulocyte production. Patients with chronic renal failure develop **red cell deficiency anemia** due to deficiency of EPO.
- Recombinant human EPO is available **(epoetin alfa,** and **darbepoetin)** for treatment of the following anemias:
  - Anemia of chronic renal failure.
  - Anemia due to bone marrow suppression e.g. cancer chemotherapy or zidoviodin (AZT) therapy.
  - Anemia of multiple myeloma and rheumatoid arthritis.
- EPO is given s.c. injection once weekly to target Hb level between **10-12 gm/dl**.

Adverse effects

- **Hypertension** and increased blood viscosity (due to ↑ RBC mass) leading to thrombotic complications especially when **Hb is > 12 gm/dl**.
- **Seizures** and headache probably caused by rapid expansion of blood volume.
- **Iron deficiency** due to rapid ↑ in RBC mass, so **parenteral iron** should be given with EPO (**N.B.** in renal failure, oral iron is not effective due to poor absorption in such case).

Vitamin deficiency (megaloblastic) anemias

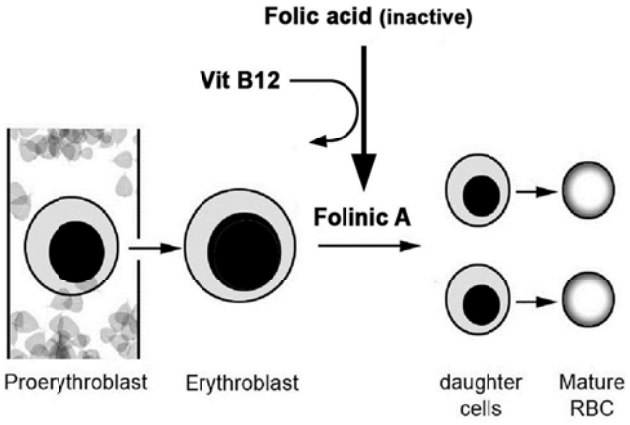
- Megaloblastic (macrocytic) anemia results from failure of DNA synthesis during RBCs development. Failure of DNA synthesis leads to continuing cell growth without division, which presents as nonfunctioning macrocytosis.
- The defect in red cell DNA synthesis is most often due to deficiency of vitamin B12 and /or folic acid. Vitamin B12 is needed as a co-factor for conversion of dihydrofolic acid into the **active form** (folinic acid) which is important for DNA synthesis.



Peripheral blood smear showing hypersegmented neutrophils, characteristic of megaloblastic anemia.

Vitamin B_{12} (cyanocobolamine)

- **Vitamin B12** is essential for normal **DNA** synthesis, which is most apparent in tissues that are actively dividing, such as the GI tract and erythroid precursors.
- Vitamin B12 is absorbed from the distal ileum after binding to the intrinsic factor.



Deficiency of vitamin B_{12}

- **Blood:** megaloblastic anemia.
- **GIT:** sore tongue and abnormal GIT epithelium.
- **CNS (Subacute Combined Degeneration):** degeneration of the brain, spinal cord and demyelination of nerve sheath.

Pernicious anemia

Atrophy of the gastric mucosa that becomes unable to secrete intrinsic factor or HCl → chronic vit B12 deficiency.

Therapeutic uses

- **Megaloblastic and pernicious anemia:**
  - If there is no neurological manifestations, it is given as 1 mg i.m. 3 times/week for 2 weeks, then once every 3 months.
  - Improvement in Hb concentration is apparent in 7 days and normalizes in 1–2 months.
  - Pernicious anemia requires life-long treatment.
- Peripheral neuropathy especially **diabetic neuropathy**.
- Hydroxocobalamin (variant of vit B_{12}) can be used in **cyanide poisoning**. It acquires the CN ions and is converted into cyanocobolamine.

Folic acid (vitamin B9; leucovorin)

Folic acid is composed of three subunits: pteridine, para-aminobenzoic acid (PABA), and one to five glutamic acid residues. Absorbed folic acid from diet requires reduction by *dihydrofolate reductase* to the active form **tetrahydrofolate**.

Deficiency of folic acid

- **Megaloblastic anemia** is more common with folic acid deficiency than vitamin B12 deficiecncy. It occurs after 4 months of folic acid deficiency.
- Folic acid deficiency during pregnancy leads to **neural tube defect**.

Therapeutic uses

- **Megaloblastic anemia:**

  In megaloblastic anemia there is deficiency of **vit B_{12}** or **folic acid.** If the patient has combined deficiency of both agents, it is necessary to treat vitamin B12 deficiency first because administration of folic acid alone leads to utilization of all vitamin B12 stored in tissues for developing red cells; so, anemia would be partially corrected but neurogenic symptoms are aggravated *(subacute combined degeneration)*

- **Pregnancy:** folate requirement is increased from 400μg to 800μg/day to prevent **fetal neural tube defect (spina bifida).**
- To prevent toxicity of **antifolate drugs:** see box.
- Malabsorption syndrome.

Antifolate drugs

Trimethoprim Pyrimethamine Methotrexate	↓ Folinic acid synthesis
Oral contraceptives	↓ Folic acid absorption
Phenytoin Phenobarbital	↑ Folic acid metabolism

Hemopoietic growth factors

- **Erythropoietin (EPO):** see before.

- **Granulocyte/macrophage colony stimulating factor (GM-CSF)**

– GM-CSF is a recombinant protein expressed in yeasts. Ilts principal action is to stimulate myelopoiesis in granulocyte–macrophage pathways as well as megakaryocytic and erythroid progenitor cells.

– **Uses:**
  – It is given **i.v.** in cases of neutropenia and aplastic anemia.
  – To stimulate stem cells after bone marrow transplantation.

– **Adverse effects:**
  – **F**ever & **F**atigue
  – Arthralgia *(bone pain)* & myalgia *(muscle pain)*.
  – **Capillary leak syndrome:** edema, pleural and pericardial effusion.

- **Granulocyte colony stimulating factor (G-CSF; Filgrastim)**

– G-CSF stimulates maturation of immature **neutrophils**.
– **Uses:** Neutropenia due to cancer chemotherapy.
– **Adverse effects:** similar to GM-CSF

- **Megakaryocyte (platelet) growth factor**

– **Interleukin-11 (IL-11)** is a protein produced by fibroblasts and stromal cells in the bone marrow. It acts on specific cell receptors to stimulate growth of primitive **megakaryocytes** to form mature **platelets**.
– **Oprelvekin** is a recombinant IL-11 approved for treatment of thrombocytopenia.

Drug-induced aplastic anemia (bone marrow depression)

- It is considered the most serious **drug-induced** hematologic effect because of the **high** mortality rate, (> 50% of cases). It is diagnosed by presence of **two** of the following criteria:
  – WBC count ≤ 3500/mm^3,
  – Platelet count ≤ 55,000/mm^3
  – Hb ≤ 10 g/dL

- There is fever and pharyngitis not responding to antibiotics, pallor, petechiae, and bleeding appear on the average about **5-6** weeks after the initiation of the offending agent.

Mechanism of drug toxicity

Damage to the hematopoietic stem cells due to:

- Direct, dose-dependent drug toxicity (the most common mechanism)
- Formation of toxic metabolites (idiosyncrasy).
- Immune reaction.

Management

- Stop the offending drug.
- Give fresh blood transfusion.
- Corticosteroids to inhibit the immune reaction.
- C-CSF or GM-CSF.
- Penicillin to combat infection.
- Stem cell transplantation in severe or resistant cases.

Drugs associated with drug-induced aplastic anemia

- Chloramphenicol
- Anti-cancer drugs
- Anti-thyroid drugs
- Carbamazepine
- Sulfonamides
- Interferone-alfa

Notes

Review Questions

Classify hypolipidemic drugs. Mention the mechanism of action of each class.

Mention the mechanism of action and adverse effects of each of the following:

- HMG CoA reductase inhibitors (statins).
- Clopidogrel
- Erythropoietin
- Niacin

Mention the mechanism of action and therapeutic uses of:

- Vitamin K1
- Tranexamic acid
- Warfarin

Mention the essential lines of the treatment of:

- Iron toxicity
- Heparin toxicity
- Warfarin toxicity

Give the reason:

- vit B12 must be combined with folic acid during treatment of megaloblastic anemia.
- Parenteral iron should be given during erythropoietin therapy.

Mention 3 differences between:

- Streptokinase and alteplase (t-PA).
- Standard heparin and low molecular weight heparin.

Mention the mechanism and management of **drug-induced bone marrow depression.**

Mention the **drug-drug interactions of warfarin.**

Of each of the following questions, select ONE BEST answer:

1. All of the following lipid-lowering drugs are correctly matched with their mechanism of action EXCEPT:
A. Cholestyramine – bile acid binding resin
B. Niacin – inhibits lipolysis
C. Clofibrate – HMG-CoA reductase inhibitor
D. Gemfibrozil –activation of lipoprotein lipase
E. Lovastatin – inhibits cholesterol biosynthesis

2. Niacin or nicotinic acid:
A. Inhibits HMG-CoA reductase
B. Increases plasma levels of VLDL
C. Lowers triglycerides due to its action as a vitamin.
D. Should not be combined with a bile acid-binding resin
E. Inhibits the production of VLDL in the liver.

3. Simvastatin, an HMG-CoA reductase inhibitor- All are true EXCEPT:
A. Lowers low density lipoprotein (LDL) cholesterol
B. Is particularly useful in heterozygous familial hypercholesterolemia
C. Acts locally on HMG-CoA reductase in the intestine
D. May be associated with rhabdomyolysis
E. Is effective if prescribed with a bile acid binding resin.

4. Absorption of iron:
A. Is greater in anemic man than in normal one
B. Is decreased by ascorbic acid.
C. Is more efficient when it is in ferric form
D. Takes place mostly in the ileum.
E. Is enhanced by co-administration of desferroxamine

5. In the treatment of iron deficiency anemia:
A. Therapy with iron should last for 6 months to replenish iron stores
B. Parentral iron is usually preferred than oral iron
C. The patient is advised to take oral iron on an empty stomach.
D. Black stool is a strong indication for discontinuation of oral iron.
E. Metabolic alkalosis is the major feature of acute iron toxicity

6. Vitamin B12:
A. Is normally absorbed in the upper small intestine
B. Therapy by mouth is the first choice in pernicious anemia
C. Is good trial therapy in undiagnosed anemias
D. Its deficiency can lead to anemia and neurological symptoms
E. Is the first choice for the treatment of aplastic anemia.

7. Recombinant human erythropoietin has been used for the treatment of:
A. Aplastic anemia
B. Anemia associated with renal failure
C. Megaloblastic anemia
D. Sickle cell anemia
E. Thalassemias

8. All of the following anticoagualnt drugs are correctly matched with their mechanism of action EXCEPT:
A. Warfaine – inhibits synthesis of vitamin K-dependent clotting factors in the liver
B. Heparin – increases the activity of antithrombin III in plasma
C. Bivalirudin – selectively inhibits thrombin action
D. LMWH – selectively inhibit factor IX.
E. Fondaparinux – selectively inhibits factor X.

9. The anticoagulant action of heparin can be effectively antagonized by:
A. Vitamin C
B. Vitamin K
C. EDTA
D. Thromboplastin
E. Protamine

10. All the following statements about vitamin K are correct EXCEPT:
A. Is widely distributed in plants.
B. Requires bile for its absorption
C. Is necessary for the formation of factor IX in the liver.
D. Increases synthesis of prothrombin in patients with severe liver disease.
E. Deficiency may occur as a result of oral antibiotics.

11. In thrombolytic therapy, one statement is NOT true:
A. Streptokinase should be given within 6 hrs of coronary thrombosis.
B. Recombinant tissue plasminogen activator is superior to streptokinase
C. Streptokinase is easier to use than urokinase since it is non-antigenic
D. Bleeding remains the major side effects of all fibrinolytic drugs.
E. The complication of bleeding should be treated by tranexamic acid.

12. The following statements about platelet activity are correct EXCEPT:
A. Intact vascular endothelium does not attract platelets because it synthesizes PGI2.
B. TXA2 is synthesized mainly by platelets.
C. Dipyridamole reduces platelet activity by increasing cAMP concentration.
D. Clopidogrel blocks platelet ADP receptors.
E. Aspirin is a reversible inhibitor of TXA2.

13. Which of the following pharmacological agents activates plasminogen after binding to fibrin?
A. Streptokinase
B. Urokinase
C. Alteplase (tPA)
D. Antiplasmin
E. Aminocaproic acid

14. The major untoward effect of heparin is:
A. Bleeding
B. Crossing the placenta
C. Elevation of hepatic transaminases
D. Allergic reactions
E. Inhibition of aldosterone synthesis

15. The lowering of plasma lipids by lovastatin occurs because it:
A. inhibits HMG coenzyme A (CoA) reductase
B. binds bile acids
C. it inhibits VLDL secretion
D. stimulates HMG CoA excretion
E. increases the activity of lipoprotein lipase

16. All of the following statements are true EXCEPT:
A. Heparin acts both in vitro and in vivo
B. Coumarin (warfarin) acts in vivo only
C. Heparin can enter the placenta causing fetal bleeding
D. Coumarin (warfarin) is considered a vitamin K antagonist
E. Heparin must be administered parenterally

17. Which of the following statements is true concerning cholestyramine?
A. It inhibits free fatty-acid release from adipose tissue
B. It releases lipoprotein lipase
C. It is an anion-exchange resin that binds bile add in the intestinal lumen
D. It blocks the final step in the formation of cholesterol in the body
E. When used in large doses, it decreases serum cholesterol, triglycerides, and phospholipids, possibly via an effect on synthesis.

18. Which statement regarding heparin is NOT true:
A. It inhibits the action of thrombin.
B. Is less effective in-patients with inherited or acquired deficiency of antithrombin III.
C. Is monitored in the laboratory by measurement of activated partial thromboplastin time (APTT).
D. It inhibits antithrombin III.
E. Is reversed by protamine sulfate.

19. All of the following are recognized adverse effects of heparin EXCEPT:
A. Osteoporosis.
B. Alopecia.

C. Thrombocytopenia.
D. Allergy
E. Fetal cleft palate.

20. All of the following inhibit platelet activation and/or aggregation EXCEPT:
A. Warfarin
B. Eptifibatide
C. Ticlopedine
D. Prostacyclin (PGI2).
E. Dipyridamole.

21. A 22-year-old woman with deep vein thrombosis in her second trimester of pregnancy, was treated for 7 days with intravenous unfractionated heparin. Which one of the following drugs would be most appropriate outpatient follow-up therapy for this patient?
A. Warfarin.
B. Aspirin.
C. Alteplase.
D. Unfractionated heparin.
E. Low-molecular-weight heparin (LMWH).

22. Protamine sulfate administered intravenously to stop heparin-induced bleeding. The mechanism of protamine is:
A. Degrades the heparin.
B. Inactivates antithrombin.
C. Activates the coagulation cascade.
D. Activates tissue-plasminogen activator.
E. Ionically combines with heparin.

23. The most important complication of streptokinase therapy is:
A. Hypotension
B. Bleeding
C. Fever
D. Anaphylaxis
E. Thrombosis

24. Severe cases of bleeding due to fibrinolytic agents are treated with:
A. Aspirin
B. Heparin
C. Aminocaproic acid
D. Vitamin K
E. Thromboplastin

25. Select the most appropriate hypolipidemic drug for a patient with raised LDLcholesterol level but normal triglyceride level:
A. Simvastatin
B. Clofibrate
C. Probucol
D. Nicotinic acid
E. Thyroxin

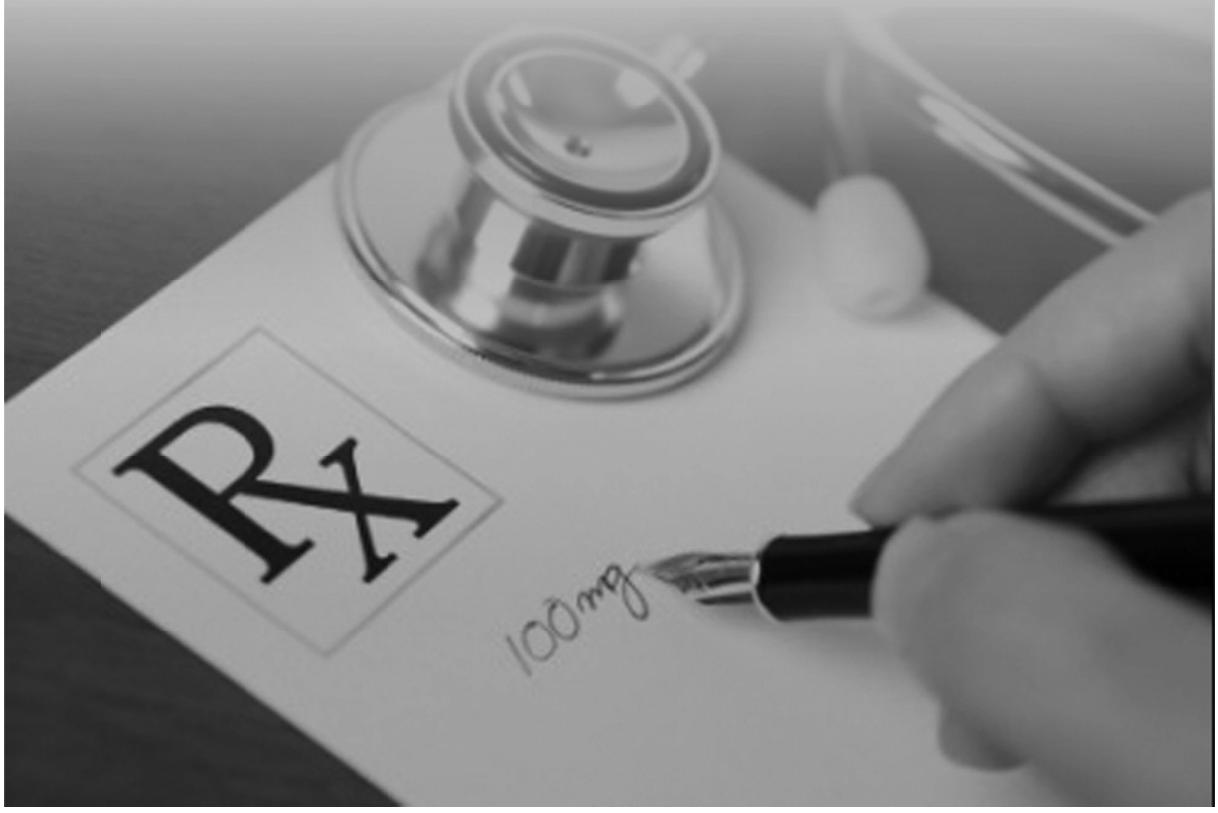
26. Combined therapy with dipyridamole and warfarin is recommended in subjects with the following:
A. Risk factors for coronary artery disease
B. Prosthetic heart valves
C. Chronic arteriovenous shunts for repeated haemodialysis
D. Pulmonary embolism
E. Deep vein thrombosis

Answers

1 C	7 B	13 C	19 E	25 A
2 E	8 D	14 A	20 A	26 B
3 C	9 E	15 A	21 E	
4 A	10 D	16 C	22 E	
5 A	11 C	17 C	23 B	
6 D	12 E	18 D	24 C	

Chapter 7

Respiratory Pharmacology



Chapter 7

Pharmacology of the Respiratory System

Part 1: Agents used to treat cough

Basic information

- Cough is one of the most common symptoms seen in clinical practice.
- The initial stimulus arises in the bronchial mucosa, where irritation results in stimulation of "Cough" receptors, which are specialized stretch receptors. Afferent impulses reach the cough center in the medulla via the vagus nerve and trigger a cough reflex.
- Cough may be acute (<3 weeks), subacute (3-8 weeks) or chronic (>8 weeks).

Causes of cough:

- **Acute cough:** respiratory infection is the most common cause.
- **Chronic cough:**
  - Upper airway cough syndrome (post-nasal drip): due to allergic rhinitis, chronic sinusitis or tonsillitis. It is the most common cause of chronic cough.
  - Bronchial asthma: the 2nd most common cause.
  - Gastoesophageal reflux disease (GERD).
  - Other causes: ACEIs, lung tumors, CHF.

MANAGEMENT OF COUGH

- **Specific treatment:** directed to the cause of cough e.g. antibiotics for respiratory infections.
- **Non-specific treatment:**
  - **Antitussives:** are used to stop dry cough.
  - **Mucolytics and expectorants:** are used in productive cough to liquefy bronchial secretions and facilitate their removal.

COUGH SUPPRESSANTS (ANTITUSSIVES)

Definition: they are drugs that reduce the frequency or intensity of coughing.

Peripheral antitussives: they ↓ afferent impulses of the cough reflex.

- **Steam inhalation with menthol or tincture benzoin compound**

– It is one of the best and easy ways to relieve acute cough. Inhaling water steam with or without medications (e.g. menthol) helps flush out mucus and moisturizes dry, irritated air passages. The efficacy of added medication is not proved.

- **Benzonatate**

– It is a glycerol derivative chemically related to the local anesthetic **procaine**. It depresses peripheral cough receptors at the lung by local anesthetic effect.

Central antitussives: they inhibit cough center in the medulla.

- **Opioids: Codeine and hydrocodone**

– They are *natural* derivatives of morphine. They directly inhibit the cough center in the medulla at doses that are lower than those needed for analgesia.
– They are generally not recommended because of adverse effects.

Adverse effects

– **D**rowsiness and constipation.
– Drug **d**ependence if used for long duration.
– Respiratory **d**epression in large doses. Children less than 5 years old are more sensitive to respiratory depression so, codeine is not recommended to children < 5 years.

N.B.
Some antihistamines (diphenhydramine) have antitussive activity, the mechanism is unknown. It has undesirable **atropine-like effect** → drying of mucosal secretions.

- **Opioid isomers: Dextromethorphan**

– It is *synthetic* L-isomer of opioids.
– It has selective central antitussive action with **very few** opioid effects (i.e. **less** addiction liability, analgesic action, respiratory depression, or constipation).
– High doses can cause neuropsychiatric effects e.g. sedation and hallucinations.

MUCOLYTICS

Definition: they are agents that reduce viscosity of respiratory secretions without increasing their amount.

■ Bromhexine

– Bromhexine acts on the mucus at the formative stages within the mucus-secreting cells. It disrupts the structure of acid mucopolysaccharide fibers in mucoid sputum and produces a less viscous mucus, which is easy to expel.
– Because bromhexine can disrupt the gastric mucosal barrier, it should be avoided in patients with peptic ulcer.

■ Ambroxol

– It stimulates synthesis and release of surfactant by type II pneumocytes. Surfactant acts as an anti-glue factor by reducing the adhesion of mucus to the bronchial wall.

■ *N*-Acetylcysteine and carbocyseine

– Acetylcysteine has free sulfhydryl (-SH) groups that break disulfide bonds in mucus and reduces its viscosity.
– Unlike acetylcysteine, carbocysteine does not act directly on mucus but rather, it affects the structural components of mucus.

Therapeutic uses of mucolytics

- Chronic respiratory diseases: chronic bronchitis, emphysema, bronchiectasis and cystic fibrosis.
- Post-operative and post-traumatic pulmonary complications.
- Chronic sinusitis and chronic otitis media.
- **N.B.** Intravenous *N*-acetylcysteine is used as an antidote for acetaminophen (paracetamol) toxicity (quite apart from its mucolytic activity).

EXPECTORANTS

Definition: drugs that increase water content and amount of the respiratory secretions. This action facilitates the removal of respiratory secretions.

Adequate hydration is the single most important measure to encourage expectoration. Using an expectorant in addition may produce the desired result.

■ Potassium iodide

– Iodides accumulates in the bronchial glands and stimulate secretion of low viscosity watery mucous.
– The use of iodides is accompanied by wide range of **side effects** including unpleasant (metallic) taste, increase lacrimal and salivary secretions, painful salivary swelling, hypothyroidism, and skin eruptions (rash).

- **Guaifenesin**

– It is one of the most widely used over-the-counter (OTC) expectorants. It increases bronchial fluid secretions by unclear mechanism.

- **Other expectorants**

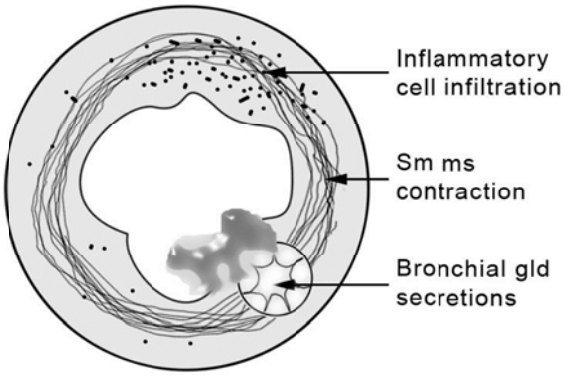
– Many other traditional expectorants (e.g., ammonium chloride, tincture ipecacuanha, herbal remedies) are found in numerous OTC cough mixtures. Their efficacy is doubtful, particularly in the dosages of most preparations.

Part 2: Therapy of bronchial asthma

Definition: *Asthma* is a chronic inflammatory disorder of the airways causing airflow obstruction and recurrent episodes of wheezing, breathlessness**,** chest tightness, and coughing.

Pathogenesis

Frequent exposure to allergic stimuli causes infiltration of the bronchial wall by acute and chronic **inflammatory cells.** These cells release many **inflammatory cytokines** e.g. histamine, adenosine, PGs, LTs, PAF, etc. leading to:



- Hypertrophy of airway smooth ms
- Increased mucus secretion that is difficult to expel.
- Congestion and edema of the respiratory mucosa.

Predisposing factors

- **Recurrent respiratory infection:** the most important factor.
- **Genetic factors:** asthma occurs in families with positive history of allergy.
- **Psychological factors:** are present in 40 % of asthmatics.

Drugs that cause bronchoconstriction in asthmatic patients

- Cholinomimetic drugs.
- Non-selective β- blockers.
- Histamine releasers e.g. morphine, trimetaphan, curare, penicillins.
- Adenosine
- NSAIDs

Clinical presentation

- **Chronic asthma**

– There is dyspnea, chest tightness, coughing (particularly at night), and expiratory wheezing.

– Patients can present with mild intermittent symptoms that require no medications or only occasional short-acting inhaled β2-agonists to severe symptoms despite multiple medications.

■ **Acute severe asthma**

– Uncontrolled asthma can progress to an acute state in which inflammation, airway edema, mucus accumulation, and severe bronchospasm that is poorly responsive to bronchodilator therapy.
– There are severe dyspnea, inspiratory wheezing, cyanosis; the patient may be able to say only a few words with each breath.

MANAGEMENT OF ASTHMA

BRONCHODILATORS

3 groups of bronchodilator drugs:

- **β-adrenergic agonists.**
- **Muscarinic receptor blockers: ipratropium.**
- **Xanthines**: **theophylline.**

β-adrenergic agonists

Classification

- **Non-selective β-receptor agonists:** e.g. adrenaline, isoprenaline and ephedrine. They are rarely used as bronchodilators.
- **Selective β2 agonists:**
  Short acting: salbutamol, terbutaline, fenoterol (duration 3-4 hrs).
  Long acting: salmeterol and formoterol (duration 12 hrs).

Mechanism of action

- Stimulation of bronchial β_2 receptors → ↑ cAMP → bronchodilatation.
- Stimulation of β_2 receptors in the mast cells → ↓ histamine release
- They ↓ bronchial inflammation and wall edema.

Administration

- In acute asthma: short acting β_2 agonists are given by inhalation or i.v infusion.
- In chronic asthma: long acting β_2 agonists are given orally or by inhalation.

Adverse effects

– **T**achycardia and arrhythmia due to:
  – *Reflex from hypotension (caused by VD of sk ms BV).*

  - *Direct activation of cardiac β_1 (due to loss of selectivity in high doses).*
- **T**remors of skeletal ms and nervousness.
- **T**olerance with prolonged use *(requiring temporary cessation of the drug).*
- **H**ypokalemia *(due to shift of K^+ from blood to cells).*

Muscarinic antagonists: Ipratropium bromide

- **Atropine** blocks M_3 receptors in airway ms leading to bronchodilatation through unopposed β_2 action, but it is **not used for treatment of asthma** because:
  - It is non-selective M_3 blocker leading to many side effects e.g. dry mouth and urine retention.
  - It can cross BBB and causes CNS side effects e.g. sedation.
  - It causes excessive dryness of bronchial secretions making it difficult to expel
- **Ipratropium is more preferred than atropine because:**
  - It is more selective muscarinic blocker than atropine.
  - It is quaternary ammonium compound that can't cross BBB.
  - Does not cause excessive dryness of bronchial secretions.
- **Ipratropium is not sufficient alone for bronchodilatation.** It is usually combined with **β_2 agonists** to get synergistic effect.

Methylxanthines

Classification

- **Natural:** e.g. caffeine, theophylline, and theobromine.
- **Semisynthetic:** e.g. aminophylline (salt of theophylline).

For asthma, the most commonly used xanthine is **theophylline.**

Mechanism and pharmacological effects

- Xanthines are adenosine **A receptor antagonists** leading to:
  - Bronchodilatation (block bronchoconstrictor effect of adenosine).
  - CNS stimulation (block the inhibitory effect of adenosine on **t**he CNS)
  - ↓ mediator release from mast cells.
  - ↑ AV conduction.
- They inhibit **phosphodiestrase** enzyme (PDE3 and PDE4) → ↑ cAMP leading to:
  - Bronchodilatation (PDE4).
  - ↑ cardiac contractility and arrhythmogenic action (PDE3).
  - VC of cerebral and VD of peripheral vessels.
  - Relaxation of most smooth muscles (GIT, biliary, ureteric, etc).
  - Diuresis.

Therapeutic uses

■ **Respiratory uses:**

– Acute severe asthma: aminophylline may be given by **slow i.v. infusion** 250 mg i.v. (at least over 15 minutes to avoid syncope or cardiac arrest), followed by maintenance i.v infusion of 0.7 mg/kg/h.
– Chronic bronchial asthma: sustained release tablets of theophylline 100-300 mg/day or rectal suppository of aminophylline can be given.

Evidence

In acute asthma, IV aminophylline is not likely to result in any additional bronchodilation compared to standard care with inhaled bronchodilators and steroids.

■ **CNS uses:**

– To reverse CNS depression.
– To delay physical and mental fatigue (caffeine).
– Treatment of migraine (caffeine + ergotamine): to increase VC of cerebral blood vessels and increase absorption of ergotamine from GIT.
– Neonatal apnea syndrome: caffeine is the agent of choice.

■ **CVS uses:**

– Acute pulmonary edema due to acute left sided HF.

Adverse effects

– **CNS:** irritability, headache, insomnia, nervousness and convulsions.
– **CVS:** palpitations, tachycardia, and arrhythmias. **Rapid i.v. injection** can cause hypotension, syncope and **cardiac arrest.**
– **GIT:** nausea, anorexia, **hyperacidity** and reactivation of peptic ulcer.

Precautions

- Aminophylline must be given by slow i.v.i. (at least over 15 minutes to avoid sudden syncope or cardiac arrest).
- Used with caution in severe cardiac disease, severe hypoxemia, and renal and hepatic disease and in elderly and neonates.
- They should not be given to patients with peptic ulcer.

Drug interactions

- **Enzyme inhibitors** (cimetidine and erythromycin) → ↑ serum levels of methylxanthines and ↑ their toxicity (arrhythmia).
- **Enzyme inducers** (smoking, rifampin) → ↓ their serum levels and reduce their effect.

Evidence

There is increased risk of arrhythmia when using both β2 agonist and xanthines in the same time because both drugs are arrhythmogenic.

REDUCTION OF BRONCHIAL INFLAMMATION

Corticosteroids

Q

Why NSAIDs can not be given in bronchial asthma?

Because NSAIDs inhibit *Cox* enzyme but NOT *lipooxygenase* enzyme leading to accumulation of LTs which are potent bronchoconstrictors.

Mechanism of action

Corticosteroids can effectively ↓ bronchial inflammation and **hyperreactivity** through:

- They inhibit B cell function → ↓ antigen-antibody reaction.
- They inhibit T cell functions → ↓ mediators and cytokine release.
- They inhibit macrophage activity and stabilize lysosomal membranes.
- They inhibit mast cells → ↓ histamine release and capillary permeability.
- They inhibit phospholipase A2 enzyme →↓ synthesis of PGs & LTs.
- Corticosteroids cause up-regulation of β2 receptors.

Use in asthma

- Acute severe asthma: **hydrocortisone** 200 mg given by i.v. injection**.** It may be repeated every 4 h if necessary.
- Chronic bronchial asthma: oral **prednisolone** 20 mg/d or **dexamethazone** 4-8 mg/d, or by inhalation (**beclomethasone**).
- **Inhaled corticosteroids (e.g. beclomethazone):** should be considered the 1st choice in newly diagnosed asthma. They have the following advantages:
  - Their efficacy is equal to inhaled β_2 agonists.
  - Minimal systemic side effects.

Adverse effects

- **If used systemically:** …..see endocrine chapter.
- **If used by inhalation:** → **oropharyngeal candidiasis.** It could be avoided by:
  - Mouth wash and gargle after each inhalation.
  - Candida infection can be treated by **nystatin mouthwash** or **amphotricin-B lozenges.**

Precautions

- They must be **withdrawn gradually** to avoid acute Addisonian crisis.
- **Diet** should be rich in K^+ and proteins and low in NaCl and carbohydrates.
- **Continuous check** for any increase in weight, edema, sugar in urine or BP.
- If the patient develops **acute infection**, he must be treated by adequate antibiotics with decreased dose of steroid.

PROPHYLACTIC TREATMENT

The following classes of drugs are not bronchodilators but are used to reduce frequency of asthma exacerbations.

Leukotriene inhibitors:

Zafirlukast and montelukast

- They **block leukotriene (LTD4) receptors.**
- Zafirlukast is given twice daily but montelukast is given once daily.

Zileuton

- It inhibits 5-lipooxygenase enzyme →↓ leukotriene synthesis.
- Zileuton is microsomal P450 inhibitor and can inhibit the metabolism of many drugs e.g. warfarin and theophylline.

- In clinical trials, leukotriene inhibitors reduced frequency of asthma exacerbations as equal to corticosteroids.
- Montelukast is approved to control asthma in children.

Mast cell stabilizers:

Cromolyn and nedocromil

- Cromolyn sodium (disodium cromoglycate) and nedocromil are poorly soluble drugs and should be given as micronized powder through spinhaler.
- They inhibit mast cell degranulation by unclear mechanism probably by altering the function of **chloride channels** in the mast cell membrane.
- They were used to reduce frequency of attacks **(i.e. prophylactic treatment)** in some allergic conditions e.g. bronchial asthma, allergic rhinitis, and allergic conjunctivitis.
- Their use now becomes **very limited** and has been largely replaced by leukotriene inhibitors.
- **Adverse effects** occur at site of administration e.g. local irritation of the throat, chest tightness, and bronchospasm.

N.B.

Mast cell stabilizers are not given during the acute attack. If given during the acute attacks, they may aggravate bronchospasm.

Ketotifen

- It is a 2nd generation antihistamine and a mast cell stabilizer.
- It is used as eye drops to treat **allergic conjunctivitis**, and orally as a prophylactic treatment in bronchial asthma and other seasonal allergies.

OTHER DRUGS USED IN TREATMENT OF BRONCHIAL ASTHMA

- **Expectorants and mucolytics:** to reduce mucus viscosity.

- **Mixture of oxygen (20%) and helium (80%): Heliox**
  - Helium is an inert gas. Its low density facilitates O_2 diffusion through obstructed airways → ↓ work of breathing.

- **Anti-IgE monoclonal antibodies: Omalizumab**
  - Omalizumab is a new drug that inhibits the binding of IgE to mast cells and prevents mast cell degranulation. It may also inhibit IgE synthesis by B cells.
  - It reduces frequency and severity of asthma even when the dose of corticosteroids is reduced.

Stepwise approach for treatment of chronic asthma

The management of stable asthma is now well established with a stepwise approach:

Step 1:	Inhaled short-acting B2 agonist (SABA) as required
Step 2:	Add inhaled steroid at 400 mcg/day
Step 3:	▪ Add inhaled long-acting B2 agonist (LABA) ▪ Still inadequate: continue LABA and increase inhaled steroid dose to 800 mcg/day
Step 4:	▪ increase inhaled steroid up to 2000 mcg/day ▪ Add a 4th drug e.g. Leukotriene antagonist, SR theophylline, oral B2 agonist tablets.
Step 5:	▪ Use oral steroid tablet in lowest dose in addition to the high dose inhaled steroid (2000 mcg/day). ▪ Refer the patient for specialist care.

Treatment of acute severe asthma (status asthmatics)

Definition: acute severe asthma (status asthmatics) is a condition in which bronchodilators are poorly effective in relieving the attack.

Management

- Hospital admission.
- **Oxygen:** to maintain peripheral capillary O2 saturation (SpO2) between 94-98%.

- **β2 agonists:** use high dose by inhalation.
- Add **ipratropium bromide** by inhalation to the β2 agonists.
- **Hydrocortisone:** 200 mg i.v. / 6hs.
- Consider a single dose of **IV magnesium sulphate** (1.2-2 g over 20 min) to patients who failed to respond to initial inhaled bronchodilator therapy.
- Correction of acidosis and dehydration by i.v. fluids.

In acute severe asthma, IV **aminophylline** is not likely to result in any additional bronchodilation compared to standard care with inhaled bronchodilators and steroids.

Routine prescription of **antibiotics** is not indicated for patients with acute asthma.

Part 3: Oxygen therapy

Basic information

Arterial blood gases (ABG): normal values and interpretation

Parameter	Normal range	Interpretation
pH	7.34 – 7.44	– Acidosis ↓ binding of O2 to Hb (tissue hypoxia) – Alkalosis ↑ binding of O2 to Hb.
Arterial O2 saturation at ambient air **SaO2**	94 –100 %	– At open air, SaO2 must be > 94% and PaO2 >80 mm Hg (or 10.6 kPa). – **Hypoxemia** means SaO2 < 90% and/or PaO2 <60 mm Hg (or 8 kPa). At this level, supplemental oxygen should be administered. – At a PaO2 < 30 mmHg, the patient is at risk of death and must be oxygenated immediately.
Arterial O2 partial pressure **PaO2**	80 – 100 mmHg (10.6 –13 kPa)	
Arterial CO2 partial pressure **PaCO2**	35 – 45 mmHg (4.5 – 6 kPa)	– High value (**respiratory acidosis**) denotes hypoventilation problem (e.g. COPD). – Low value (**respiratory alkalosis**) denotes hyperventilation problem.
$HCO3^-$	22 – 26 mmol/L	– Low value denotes **metabolic acidosis**. – High value denotes **metabolic alkalosis**.

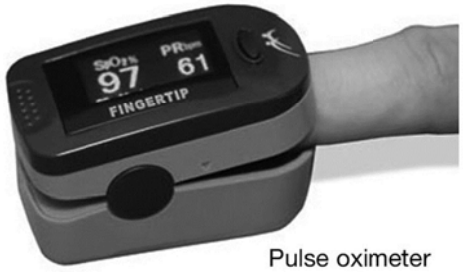
N.B.

- **Hypoxia:** low oxygen level at the tissues.
- **Hypoxemia:** low oxygen level in the arterial blood.

OXYGEN THERAPY

Key points

- Oxygen is stored either in liquid or gaseous form in metal cylinders (green tanks). Oxygen concentrators are also available for long term home use; they extract oxygen from air using electric current.
- Oxygen is commonly delivered to the patient through nasal cannula or face mask.
- Diagnosis of hypoxemia is done either by pulse oximeter (easy) or by arterial blood gas analysis (see table for reference ranges).
- Dyspnea does not necessarily indicate hypoxemia. Severe hypoxemia can be present without dyspnea and vice versa.



Pulse oximeter

Indications of oxygen therapy

Oxygen should not be used routinely unless there is evidence of hypoxia.

- **Acute hypoxic conditions:** acute MI, acute pulmonary edema, carbon monoxide poisoning, cardiac and respiratory arrest, low COP and metabolic acidosis (bicarbonate <18mmol/L).
- **Chronic hypoxic conditions** (long-term oxygen therapy): e.g. COPD and CHF.

Monitoring and stopping

- ABG or oximetry should be done within 2 hours of starting oxygen therapy and oxygen delivery is adjusted accordingly.
- Oxygen should be stopped when SaO2 > 92% while the patient is breathing at room air.
- For patients with COPD, the oxygen saturation target should not exceed 92% to avoid CO2 retention (see below).

Dangers, adverse effects and precautions

- Fire and explosions: (safety measures are required).
- Irritation of nose, pharynx and trachea.
- Inhibition of mucociliary function → ↓ tracheal outflow of mucous.
- CO2 toxicity:

- In patients with COPD who receive supplementary O2, CO2 retention can occur through 2 mechanisms:
  - Increase O2 saturation of blood reduces deoxygenated Hb which carries CO2 in blood (in the form of bicarbonate).
  - In patients with COPD, hypoxia is the main stimulant of respiration (hypoxic drive). If 100% O2 was administered, hypoxia is corrected and the hypoxic drive is lost leading to CO2 retention.
- CO2 retention can lead to headache, drowsiness (narcosis) or even death.
- Prevention: In people with COPD, CO2 toxicity can be prevented by careful control of the supplemental oxygen. Just enough oxygen is given to maintain an oxygen saturation of 88 - 92%.

- Retrolental fibroplasias: high concentration of O_2 in neonates (<32 weeks) stimulates fibrous tissue formation posterior to the eye lens and permanent blindness. So, O_2 should be used only when needed and its concentration must not exceed 35-40% in premature infants.
- Pulmonary oxygen toxicity: high O2 concentrations (> 60%) given for >48 hours can damage alveolar membrane and cause alveolar edema.

Notes

Review Questions

- Discuss different drugs used in the treatment of **cough.**
- Discuss the different lines of treatment of **bronchial asthma.**
- Discuss pharmacology of **xanthenes:** classification, mechanism of action, pharmacologic effects, therapeutic uses, and side effects.
- Mention uses of mucolytics.
- Mention precautions during the use of methylxanthines.
- Mention precautions during the use of corticosteroids in BA.
- Mention the main side effects of oxygen therapy.
- Mention the main side effects of selective beta-2 agonists.
- Mention the main lines of treatment of status asthmaticus.
- Mention 3 drugs causing bronchoconstriction and mention the mechanisms.

Mention the pharmacodynamic principles underlying the use of:

– Beta-2 agonists in bronchial asthma.
– Methylxanthines in bronchial asthma.
– Montelukast for prophylaxis of bronchial asthma.
– Acetylcystiene in chronic bronchitis.

Mention the rationale of the following combinations:

– Oxygen with helium in chronic obstructive lung disease.
– Corticosteroids with beta-2 agonists in bronchial asthma.

Of each of the following questions, select ONE BEST answer:

1. Which of the following mucolytics act by breaking disulfide bonds of proteoglycans, which causes depolymerization and reduction of viscosity of sputum?
A. Acetylcysteine
B. Iodides
C. Trypsin
D. Water vapor
E. Licorice

2. Which of the following drugs is a methylxanthine used in the treatment of bronchial asthma?
A. Salbutamol
B. Ipratropium
C. Theophylline
D. Pentoxifylline
E. Dipyridamole

3. The mechanism of methylxanthines action in bronchial asthma is:
A. Inhibition of the enzyme phosphodiesterase
B. Beta2 -adrenoreceptor stimulation
C. Inhibition of the production of inflammatory cytokines
D. Inhibition of M-cholinoreceptors
E. Inhibition of leukotriene receptors

4. Which of the following drugs can decrease the effect of leukotrienes in the inflamed tissue?
A. Zileuton
B. Montelukast
C. Theophylline
D. Loratidine
E. Cromoglycate

5. Which of the following drugs can decrease the concentration of leukotrienes in the inflamed tissue?
A. Zileuton
B. Montelukast
C. Theophylline
D. Loratidine
E. Cromoglycate

6. Indicate the expectorant which increase lung surfactant:
A. Sodium benzoate
B. Trypsin
C. Ambroxol
D. Tincture Ipecacucnha
E. Iodides

7. Which one is considered the major side effect of Theophylline:
A. Bradycardia
B. Arrhythmia
C. Depression of respiratory center
D. Elevation of the arterial blood pressure
E. Depression of mood

8. Choose the drug belonging to class mast cell stabilizers:
A. Zileuton
B. Zafirlucast
C. Epinephrine
D. Salbutamol
E. Sodium cromoglycate

9. Which of the following drugs can disrupt mucus synthesis within bronchial glandular cells?
A. Potassium iodide
B. Acetylcystiene
C. Bromhexine
D. Trypsin
E. Ambroxol

10. Which of the following is not a recognized action of terbutaline?
A. Diuretic effect.
B. Cardiac arrhythmia.
C. Skeletal muscle tremors.
D. Smooth muscle relaxation.
E. Tachycardia.

11. Disodium cromoglycate has as its major action:
A. Smooth muscle relaxation in the bronchi.
B. Stimulation of cortisol release by the adrenals.
C. Block of calcium channels in the lymphocytes.
D. Block of mediator release from mast cells.
E. Block of cAMP synthesis in the basophils.

12. The following may induce bronchospasm EXCEPT:
A. Propranolol.
B. Morphine.
C. Aspirin
D. Captopril
E. Theophylline.

13. Which of the following drugs given for cardiovascular indications might complicate the management of asthma in the same patient?
A. Hydralazine.
B. Verapamil.
C. Nitroglycerine
D. Quinidine.
E. Propranolol.

14. Methylxanthines:
A. Cause decreased gastric acid secretion.
B. Are potent diuretics in most patients.
C. Cause increase in mental alertness and even insomnia in some patients.
D. Are potent vasoconstrictors.
E. Cause fatigue of respiratory muscles

15. Theophylline is therapeutically useful in asthma because:
A. It has no significant effects on the heart.
B. It stimulates the respiratory center.
C. It increases mediator release from mast cells.
D. It is a potent stimulant of beta-receptors.
E. It increases cAMP without desensitizing receptors in bronchioles

16. In status asthmaticus, all are true EXCEPT:
A. Salbutamol and ipratropium may be given by nebulized aerosol
B. IV aminophylline is useful.
C. Hydrocortisone is preferred to prednisolone for initial therapy.
D. Humidified oxygen should be given.
E. Morphine provides useful sedation

17. All of the following drugs are central antitussives EXCEPT:
A. Codeine
B. Pholcodeine
C. Noscapine
D. Dextromethrphane
E. Ticture benzoin Co.

18. In designing a dosage regimen for aminophylline all are true EXCEPT:
A. Children (ages 3-12 y) have faster clearance of this drug than adults or infants
B. Patients with history of cardiac disease should be carefully monitored, because aminophylline may induce ventricular extrasystoles and other arrhythmias
C. Excessive doses result in skeletal muscle tremors and CNS excitation.
D. The use of tobacco by the patient inhibits the metabolism of aminophylline.
E. Erythromycin increases the serum levels of theophylline.

19. Ipratropium bromide is:
A. Derivative of phenylephrine.
B. Less effect on sputum viscosity.
C. Tertiary amine
D. Given by inhalation, oral and parenteral routes
E. More effective bronchodilator than B2 agonist

20. Disodium cromoglycate, all are true EXCEPT:
A. Is well absorbed from the GIT.
B. Stabilizes mast cells and prevent their degranulation.
C. Is inhaled as a powder for prophylaxis of bronchial asthma.
D. Can cause bronchconstriction during administration.
E. Can be used in the treatment of allergic rhinitis.

21. All of the following drugs are mucolytics EXCEPT:
A. Bromhexine
B. Iodides
C. Acetylcysteine
D. Ambroxol
E. Ketotifen

22. Oropharyngeal candidiasis is a common side effect of which of the following:
A. Inhaled beta-2 agonists
B. Inhaled ipratropium
C. Inhaled corticosteroids
D. Inhaled disodium cromoglycate
E. Oxygen

23. Oropharyngeal candidiasis could be treated by:
A. Liquorice lozenge
B. Amphotericin-B lozenge
C. Ampicillin
D. Aminoglycosides
E. Steam inhalation

24. Which of the following statements is NOT true:
A. Antitussives decrease the amount and liquefy bronchial secretions.
B. Peripheral antitussives are used when the cough arises above the larynx
C. Mucolytics used in the treatment of productive cough to liquefy copious bronchial secretion.
D. Iodides can be used as expectorant and mucolytic
E. Inhalation of water vapor or adequate intake of water is an excellent mucolytic & expectorant.

25. Combination of B2 agonists and ipratropium can lead to:
A. Antagonistic effect.
B. Additive effect.
C. Potentiating effect.
D. Synergistic effect.
E. No effect

26. The Symptoms of allergen-mediated asthma result from which of the following?
A. Increased release of mediators from mast cells
B. Increased adrenergic responsiveness of the airways
C. Increased vascular permeability of bronchial Tissue
D. Decreased calcium influx into the mast cells
E. Decreased prostaglandin production

27. Drugs that can dilate bronchi during an acute asthmatic attack include all of the following except
A. Epinephrine
B. Terbutaline
C. Nedocromil
D. Theophyline
E. Ipratropium

28. Which of the following is a prophylactic agent that appears to stabilize mast cells?
A. Aminophyline
B. Cromolyn
C. Epinephrine
D. Ipratropium
E. Metaproterenol

29. Which of the following has overdose toxicity that includes insomnia, arrhythmias, and convulsions?
A. Aminophylline
B. Cromolyn
C. Epinephrine
D. Ipratropium
E. Metaproterenol

30. Which of the following is a very long acting β2 – selective agonist that is used for asthma prophylaxis?
A. Aminophyline
B. Cromolyn
C. Epinephrine
D. Ipratropium
E. Salmeterol

31. In the emergency department, the preferred first-line therapy for asthma exacerbation is
A. Theophyline
B. A beta2-agonist
C. A corticosteroid
D. Cromolyn sodium
E. An antihistamine

32. A drug administered by inhalation of powder as a prophylactic for asthma
A. Ephedrine
B. Disodium cromolyn
C. Isoproterenol
D. Ocytriphylline
E. Epinephrine

33. When administering oxygen to a hypoxemic patient with COPD, the target oxygen saturation level would be:

A. 94 – 98%
B. 92 – 94%
C. 88 – 92%
D. 60%
E. 100%

34. Regarding oxygen therapy, one statement is true:

A. Severe dyspnea does not necessarily indicate hypoxia.
B. Oxygen should be started immediately to all acutely ill patients.
C. Oxygen should be stopped as soon as oxygen saturation reaches 88% in room air.
D. Acidosis increases binding of oxygen to hemoglobin.
E. Oxygen therapy reduces mortality in acute myocardial infarction.

35. Which of the following drugs given for cardiovascular indications might precipitate bronchospasm in asthmatic patients?

A. Hydralazine.
B. Verapamil.
C. Nitroglycerine
D. Quinidine.
E. Adenosine.

Answers

1 A	7 B	13 E	19 B	25 D	31 B
2 C	8 E	14 C	20 A	26 A	32 B
3 A	9 C	15 E	21 E	27 C	33 C
4 B	10 A	16 E	22 C	28 B	34 A
5 A	11 D	17 E	23 B	29 A	35 E
6 C	12 E	18 D	24 A	30 E	

Simplified approach

Mansoura Clinical Pharmacology

For Medical students

Edited by

Staff members of
Clinical Pharmacology Department
Faculty of Medicine
Mansoura University

Volume 3

رقم الإيداع بدار الكتب: 1456 لسنة 2000
بتاريخ 2000/9/6

Preface

Clinical training for undergraduate students often focuses on diagnostic rather than therapeutic skills. Sometimes students are only expected to copy the prescribing behavior of their clinical teachers, or existing standard treatment guidelines, without explanation as to why certain treatment is chosen. Books may not be much help either. Pharmacology reference works and formularies are drug-centered, and although clinical textbooks and treatment guidelines are disease-centered and provide treatment recommendations, they rarely discuss why these therapies are chosen. Different sources may give contradictory advice.

This book in primarily intended for under graduate medical students who are about to enter the clinical phase of their studies. It will provide step by step guidance to the process of rational prescribing together with many illustrative examples. It teaches also skills that are necessary throughout a clinical career. Postgraduate students and practicing doctors may also find it a source of straightforward information.

I wish to acknowledge the ongoing efforts of my contributing authors, and we are deeply grateful to all those who have with such good grace given us their time and energy to supply valuable facts and opinions, they principally include:

- **Prof. Hussein El-Beltagi** who took over the preparation of all books since the 1st edition in 1995 including the revision process, printing control, distribution and selling control.
- **Assist. Prof. Mohamed-Hesham Daba** who took over the revision process and amendments of the last two editions.
- **Assist. Prof. Abdel-Motaal Fouda** who prepared the last two editions in a readable up-to-date text to provide essential information necessary throughout the clinical career.
- **Dr. Sameh Abdel-Ghany** who assisted in the revision process.

Much of any merit this book may have is due to the generosity of those named above.

Gamal M. Dahab (MD, PhD)

Professor Emeritus in Clinical Pharmacology
Mansoura Faculty of Medicine

Mission and Vision

Our mission

The Clinical Pharmacology Department is seeking excellence and leadership in four major core activities: education, research, community service, and faculty and staff development. We are connecting basic medical sciences with clinical care through innovative and disciplined teaching of clinical pharmacology in an integrative manner

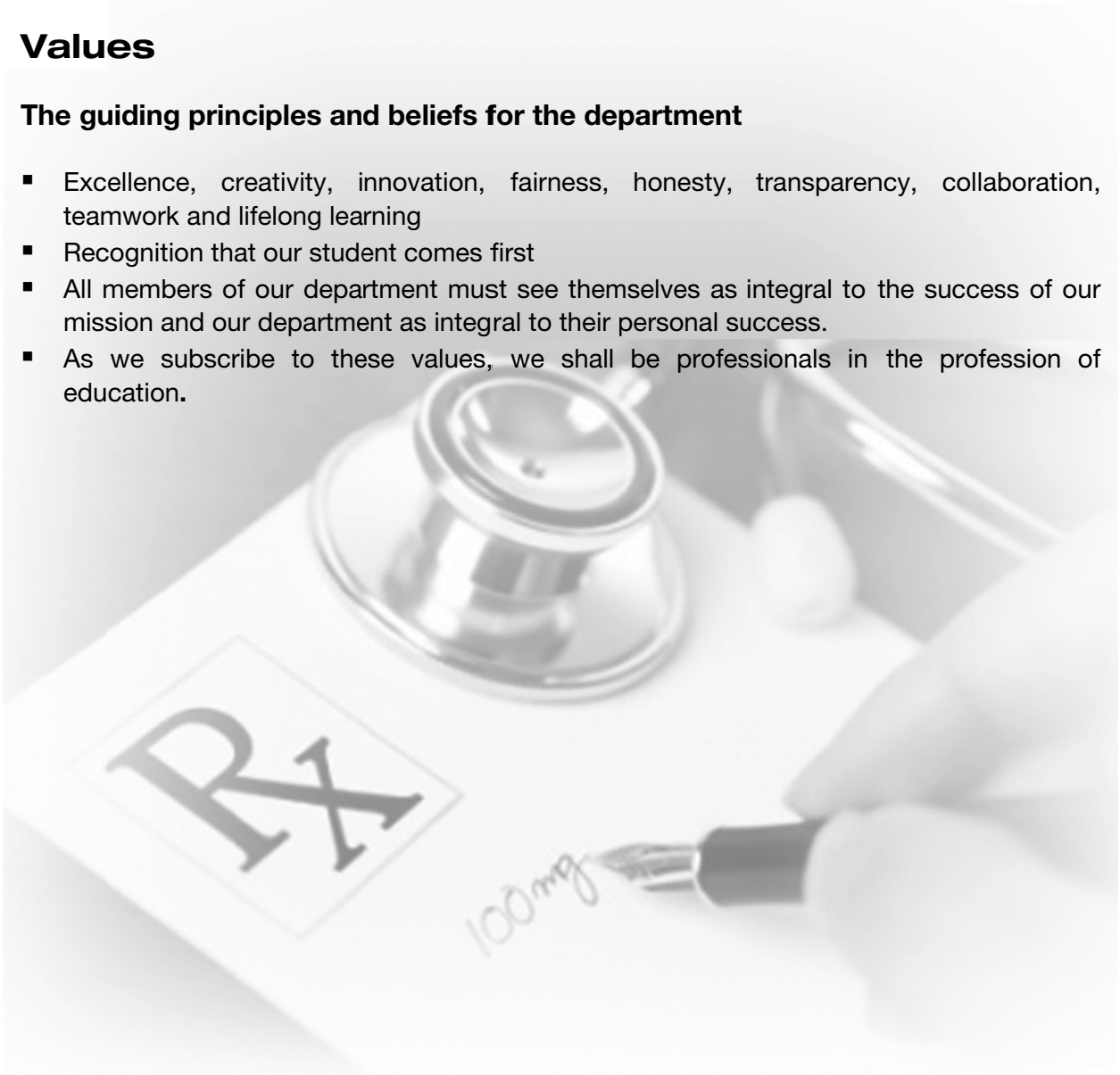
Our vision

The department of Clinical Pharmacology is aiming to be a premier academic model in the field of pharmacology and therapeutics in Egypt and Middle East through promoting use of the best therapeutics and developing newer experimental and clinical research projects.

Values

The guiding principles and beliefs for the department

- Excellence, creativity, innovation, fairness, honesty, transparency, collaboration, teamwork and lifelong learning
- Recognition that our student comes first
- All members of our department must see themselves as integral to the success of our mission and our department as integral to their personal success.
- As we subscribe to these values, we shall be professionals in the profession of education.



Contributers

Effat A. Haroun MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Elhamy M. El-Kholy MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Gamal M. Dahab MD, PhD, MSc (Int.Med)
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Farida M. El-Banna MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Aly M. Gaballah MD, PhD, MSc (int.Med**)**
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Layla T. Hanna MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Mohamed Kheriza MD, PhD, MSc (Int.Med)
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Abdel-Rahman A. Yassin MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Mohmmad A. Attia MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Mohamed Abdel-Ghani MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Hussien M. El-Beltagi MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Karawan M. Abdel-Rahman MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Somaya A. Mokbel MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Amany A. Shalaby MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Amal Abdel-Hamid MD, PhD
Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Essam A. Ghyati MD, PhD
Assist. Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Mohamed-Hesham Y. Daba MD, PhD
Assist. Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Abdel-Motaal M. Fouda MD, PhD
Assist. Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Vivian Boshra MD, PhD
Assist. Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Hala A. Al-Ashri MD, PhD
Assist. Prof. of Clin Pharmacology
Mansoura Faculty of Medicine

Nageh Rizk MD, PhD
Lecturer in pharmacology
Mansoura Faculty of Medicine

Elsayed A. Hassan MD, PhD
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

Mohamed Abdel-Monem MD, PhD
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

Mahmoud A. Naga MD, PhD
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

Ahmad Hassan MD, PhD
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

Ahlam El-masry MD, PhD
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

Rehab Hamdy MD, PhD
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

Mohamed Abou El-khair MD, PhD
Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

Sameh A. Abdel-Ghani MSc.
Assist. Lecturer in Clin Pharmacology
Mansoura Faculty of Medicine

Table of Contents

CHAPTER 8: GASTROINTESTINAL PHARMACOLOGY

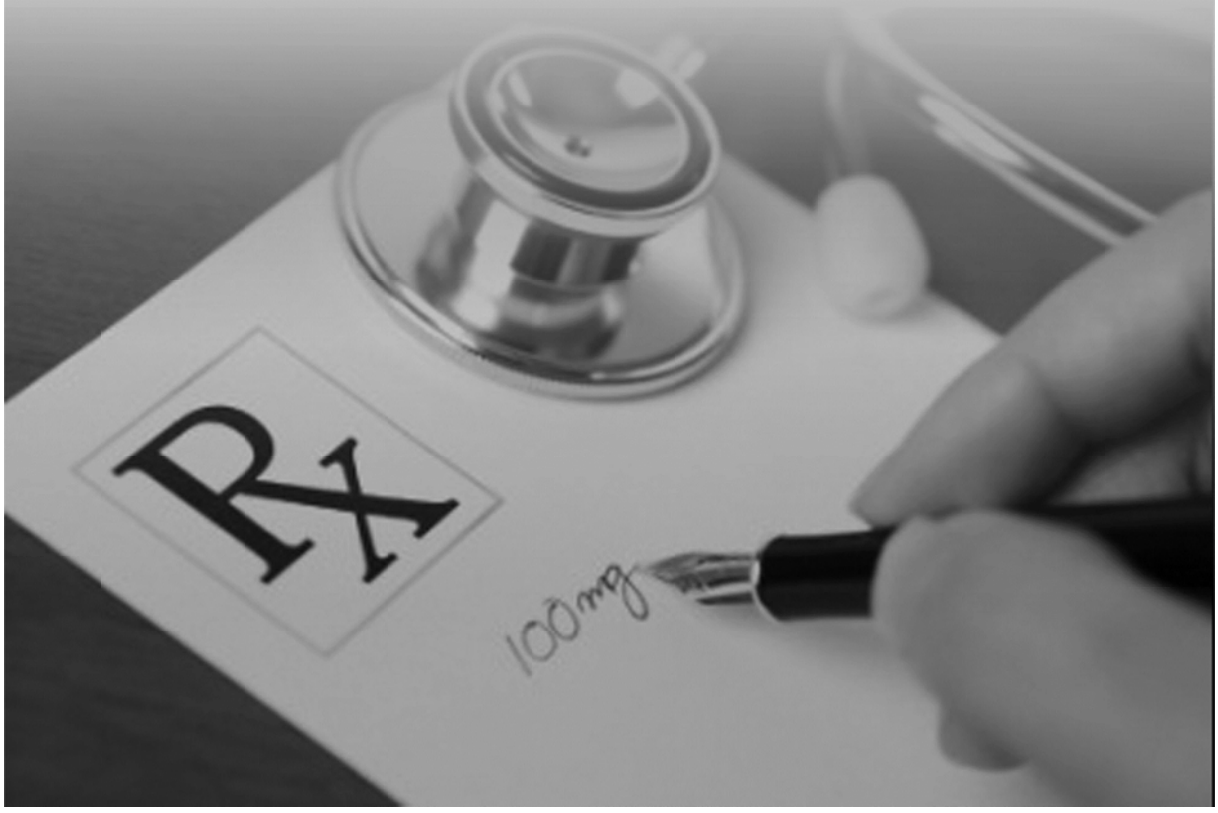
CHAPTER 9: ENDOCRINE PHARMACOLOGY

CHAPTER 10: CNS PHARMACOLOGY

CHAPTER 11: ANTIMICROBIAL DRUGS

Chapter 8

Gastrointestinal Pharmacology



Chapter 8
Gastrointestinal Pharmacology

Part 1: Peptic Ulcer Disease and Reflux Esophagitis

PEPTIC ULCER

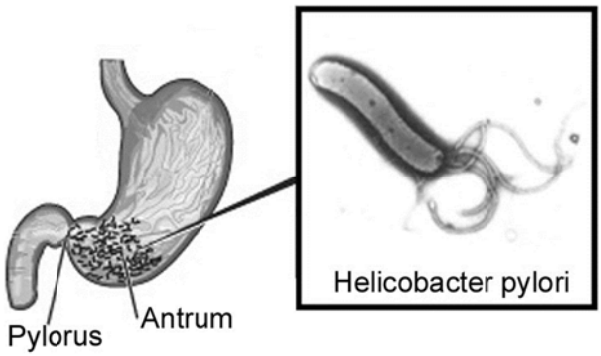
Definition: ulceration of the duodenum or stomach due to imbalance between local invasive force (e.g. HCl and pepsin) and protective mechanisms.

Invasive factors:

- Stress: ↑ HCl and pepsin secretion by parietal cells.
- Diet: coffee, alcohol and spices.
- **Drugs:** NSAIDs, corticosteroids, morphine, methylxanthines, etc.
- **Infection** with ***Helicobacter pylori.***
  H. pylori is spiral gram –ve flagellates found in the antrum of human stomach. Certain enzymes and toxins produced by the bacteria cause tissue damage. Infection with *H. pylori* can be diagnosed by endoscopic biopsy or serological markers.

Defensive mechanisms:

- Mucus production by gastric mucosa.
- Pancreatic bicarbonate secretion.
- Good mucosal blood flow.
- Local PGE_2 and PGI_2 production.

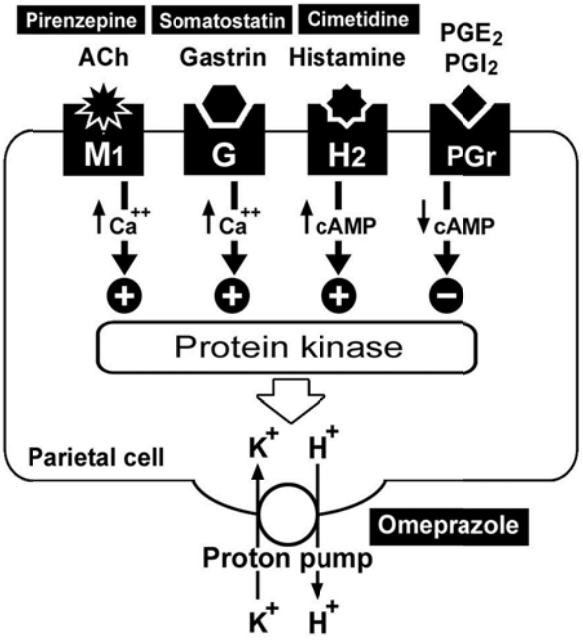


Regulation of HCl secretion

- **Ach:** ↑ HCl secretion through $\mathbf{M_1}$ receptors → ↑ intracellular Ca^{2+}.
- **Gastrin:** ↑ HCl secretion through **G** receptors → ↑ intracellular Ca^{2+}.
- **Histamine:** ↑ HCl secretion through $\mathbf{H_2}$ receptors → ↑ intracellular cAMP.

Both Ca^{2+} and cAMP activate H^+/K^+ *ATPase* at the membrane of the parietal cell to secrete H^+ into the gastric lumen **"proton pump"**.

- **PGE_2** and **PGI_2:** act on PG receptors → ↓ cAMP → ↓ HCl secretion.

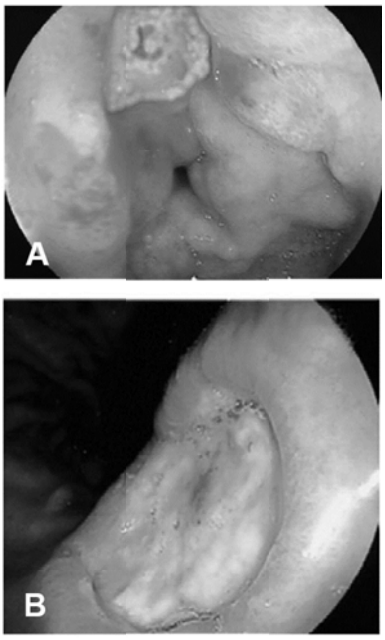


Clinical picture

- Epigastric pain: characterized by:
  - Diffuse and worsens by food in **GU.**
  - Localized (point tenderness) and relieved by food in **DU.**
- Signs of complications e.g. bleeding, anemia, etc.

Diagnosis

- Endoscopy: visualization of the ulcer.
- Radiologic: by barium meal.



Endoscopic views. (a) Duodenal ulcer with inflamed duodenal .folds. (b) Benign gastric ulcer

Therapy of peptic ulcer

Non-drug therapy = life style modification

- Rest and **S**edation: they improve healing and relief pain of DU.
- Stop **S**moking, **S**pices, alcohol, coffee, and tea: because they ↑ HCl.
- Avoid **S**tress: because stress ↑ HCl.
- Avoid ulcerogenic drugs: e.g. NSAIDs.
- Diet:
  - Frequent small meals in DU in order to buffer high acidity.
  - Encourage milk and fats.
  - Avoid **S**pices and fried food

Pharmacological therapy

- **Drugs that neutralize HCl:** antacids

- **Drugs that ↓ HCl secretion:**

- Selective M_1 blockers: pirenzepine, telenzepine.
- H_2 blockers: cimetidine, ranitidine, famotidine.
- Proton pump inhibitors: omeprazole, lanzoprazole, etc.

- **Drugs that ↑ mucosal defense mechanisms:**
  - Sucralfate
  - Colloid bismuth compounds: e.g. bismuth subcitrate.
  - Carbenoxolone
  - PGE_1 analogues: misoprostol.

- **Antimicrobial drugs** for *H. pylori*: see later.

- **Adjuvant therapy:** Sedatives and multivitamins to ↓ stress to enhance healing.

ANTACIDS

- Antacids are weak bases that are taken orally and partially neutralize gastric acid and reduce pepsin activity.
- They are used as **symptomatic relief** of hyperacidity and should **not** be used as long-term treatment.

Sodium bicarbonate	Calcium carbonate	Magnesium and aluminum salts (Mg hydroxide and Aluminium hydroxide)
▪ It can be **absorbed** systemically leading to salt & water retention, and metabolic alkalosis. ▪ It is contraindicated in hypertension and heart failure. ▪ It has **rapid** onset and short duration.	▪ **Partially** absorbed antacid. ▪ Ca^{2+} may act directly to stimulate gastrin secretion leading to acid rebound. ▪ It is contraindicated in hypercalcemia and renal stones.	▪ They are **poorly** absorbed from GIT and have no systemic effects. ▪ The unabsorbed Mg salts cause osmotic **diarrhea**; the unabsorbed Al salts cause **constipation**. ▪ They have **slow** onset.

Adverse effects

- **Change in bowel habits:** Al^{3+} hydroxide causes *constipation*, while Mg^{2+} hydroxide cause *diarrhea*. For this reason, both salts are combined together to manage this problem.

- **Rebound hyperacidity:** with Ca^{2+} and $NaHCO_3$ containing antacids.
- **Cation overload:**
  - Na^+ salts → hypertension and systemic alkalosis.
  - Ca^{2+} salts → hypercalcemia, renal stones and **milk-alkali syndrome.**

Milk-alkali syndrome

Patients with PU usually administer large amounts of milk and antacids to relieve symptoms of hyperacidity.

- Excess milk ⟶ hypercalcemia.
- Excess antacids ⟶ alkalosis (due to continuous wash of HCl).

- **Decrease absorption of other drugs:** the metal ion in some preparations can chelate other drugs especially tetracycline, digitalis and iron.

N.B. when **iron** or **tetracycline** is prescribed with antacids, we should make **30 min** interval between both drugs to avoid **chelation** with the antacid.

DECREASE HCL SECRETION

1. Selective M_1 blockers:

(Pirenzepine - Telenzepine)

Mechanism of action: selectively block gastric M_1 receptors → ↓ **basal** HCl secretion.

Uses: The selective M_1 blockers are **weak** inhibitors of HCl secretion and are now replaced by more effective drugs. They are sometimes used as adjuvant therapy with H_2 blockers.

Adverse effects: high doses produce atropine-like effects: dry mouth, blurred vision, tachycardia, urine retention.

N.B. Atropine itself is not used in the treatment of PU because it is non-selective M blocker and **may aggravate esophageal reflux.**

2. H2 blockers:

(Cimetidine – Ranitidine – Famotidine - Nizatidine)

Mechanism and pharmacological effects

- They act as competitive inhibitors of histamine H2-receptors on the parietal cell. This results in a marked ↓ in histamine-stimulated HCl secretion.
- Although other agents such as gastrin and ACh may induce acid secretion, histamine is the predominant final mediator that stimulates HCl secretion.

Therapeutic uses

- Duodenal and gastric ulcers.
- Prophylaxis & treatment of stress ulcers (e.g. after burn or major trauma).
- Prophylaxis against bleeding of esophageal varices.
- Reflux esophagitis.
- Zollinger-Ellison syndrome (gastrin-secreting tumor of the pancreas which ↑ HCl secretion): usually larger doses are required.
- With ulcerogenic drugs (e.g. NSAIDs) to protect the gastric mucosa from injury.

Adverse effects (mostly with cimetidine):

- **Cimetidine** has **anti-androgenic effects** (due to block of androgen receptors) leading to ↓ sperm count, impotence and gynecomastia.
- **Cimetidine** inhibits **hepatic microsomal enzymes (P450)** leading to ↓ metabolism of other drugs e.g. theophylline, warfarin, sulphonylureas, etc.
- **R**eversible hepatotoxicity and **R**eversible anemia.
- **CNS** symptoms: headache, slurred speech, delirium, coma, etc. occurs mainly in **elderly people** with **i.v.** administration.

Precautions of H2 blockers

- Avoid sudden withdrawal to prevent rebound ulceration.
- Avoid their use in pregnancy and lactation (they cross the placental barrier and secreted in breast milk).
- Avoid combination of cimetidine with drugs having narrow therapeutic index (because cimetidine inhibits microsomal P450 and ↑ their toxicity).

	Cimetidine	Ranitidine	Famotidine
H_2 Blocking effect:	Weak	Potent	More potent
Anti-anderogenic effect:	Strong	Minimal	No
Liver enzyme inhibition	Strong	Minimal	No
Adverse CNS effects:	Frequent	Less frequent	Less frequent
Duration of action:	8 h	12 h	24 h
Dose:	**800** mg/day for 6-8 weeks then **400** mg/day for 6-8 months	**300** mg/day for 6-8 weeks then **150** mg/day for 6-8 months	**20** mg/day for 6-8 weeks then **10** mg/day for 6-8 months

3. Proton pump inhibitors (PPIs):

(Omeprazole – Lansoprazole – Pantoprazole)

Chemistry: all are imidazole derivatives.

▶ **Imidazole derivatives:**

1. **Nasal decongestants:** Nafazoline
2. **Antimicrobials:** Metronidazole
3. **Antifungal:** Ketoconazole
4. **Antiparasitic:** Mebendazole
5. **Proton pump inhibitors:** Omeprazole

Mechanism of action

- They are **prodrugs**. They are converted into the active form in the gastric mucosa and produce **irreversible inhibition** of gastric H^+/K^+ *ATPase* enzyme leading to ↓ both **basal** and **stimulated** HCl secretion to around the **zero** level for 1-2 days.
- Full restoration of acid secretion after stopping the PPI takes about 3-5 days (time of re-synthesis of H^+/K^+ *ATPase*).
- Their bioavailability is decreased significantly by food and, ideally, should be administered 1 hour before a meal.

Therapeutic uses: The same as H_2 blockers **(dose of omeprazole: 20-40** mg/day orally for 4-6 weeks then **10-20** mg/day for 4-6 months to prevent recurrence).

Adverse effects

- Low incidence of diarrhea, abdominal colic, dizziness, skin rash, **leucopenia**, and transient increase of liver enzymes.
- **Decrease vit B_{12} absorption** after > 12 weeks of therapy due to interference with intrinsic factor secretion by the stomach.
- Inhibition of gastric acidity leads to **alteration of bioavialability of some drugs** e.g. ketoconazole, digoxin, and iron.
- Omeprazole **inhibits microsomal P450 enzymes** and decreases metabolism of phenytoin, warfarin, and cyclosporin. Newer PPIs do **not** affect liver enzymes.
- Omeprazole in high dose induced gastric **carcinoid tumor** in rats.

ENHANCING MUCOSAL DEFENSE MECHANISMS

1. Sucralfate

- It is an aluminum salt of sulfated sucrose.
- Slightly (3%) absorbed from the GIT. The aluminum metal may accumulate in cases of renal failure, so it should be avoided in **renal failure**.

Mechanism of action

- It **needs acidic medium** to be activated. In the presence of acidic medium, it

forms a complex with protein debris at the ulcer base and forms a physical barrier (so **not** taken with antacids, H_2 blockers, or PPIs).
- It ↓ pepsin secretion and ↑ secretion of endogenous PGs.

Adverse effects

– Constipation (due to presence of aluminum).
– ↓↓ absorption of tetracycline, digoxin and phenytoin.

N.B. Both sucralfate and bismuth compound are **not given** simultaneously with antacids or H_2 blockers (at least **30** min must be elapsed in-between). **Why?**

2. Bismuth compounds:
Bismuth subsalicylate and subcitrate

Mechanism of action

- In acidic pH, it forms a complex with protein debris at the ulcer base and forms a physical barrier.
- It ↓ pepsin secretion and ↑ secretion of endogenous PGs.
- It has **additional antimicrobial activity** against *H. pylori.*

Adverse effects

– Stool and teeth discoloration.
– **Encephalopathy** in presence of **renal failure**

Contraindications: Chronic renal failure and CNS diseases.

3. Carbenoxolone

It is a *liquorice* derivative having **steroid** structure.

Mechanism of action

- It ↑ production and viscosity of gastric mucus and ↑ mucosal resistance.
- It ↓ pepsin secretion and ↑ secretion of endogenous PGs.

Adverse effects

Salt & water retention (aldosterone-like effects) → edema and hypertension especially in cardiac and renal patients. This edema can be treated by thiazide diuretics (**not by spironolactone)** because both spironolactone and carbenoxolone have steroid structure and can compete with each other.

Contraindications: Hypertension and/or renal failure

4. Synthetic PGE1 analogue: Misoprostol

Mechanism of action

- It acts on specific receptors on gastric parietal cells to ↓ histamine-stimulated HCl secretion.
- ↑ mucus and bicarbonate secretion (cytoprotective action).
- ↑ mucosal blood flow and stimulates mucosal cellular regeneration.

Therapeutic uses

Prevention of peptic ulcer in high risk patients e.g. those on long term use of NSAIDs for chronic inflammatory diseases. [**misoprostol** 200 μg is combined with **naproxen** or **diclofenac** in single tablet].

Adverse effects

- Diarrhea and cramping pain: due to ↑ GIT motility and water secretion.
- Uterine contractions during pregnancy → **abortion**.

Contraindications: pregnancy.

ERADICATION THERAPY FOR *H. pylori*

- Infection with *H. pylori* is a **main cause of recurrence** of PU.
- The following 10 days ***"sequential protocol"*** is highly effective for eradication of *H. pylori*:

PPIs
Amoxicillin 1 g] twice daily for 5 days (days 1-5).

PPIs
Clarithromycin 500 mg
Tinidazole 500 mg] twice daily for 5 days (days 6-10).

THERAPY OF BLEEDING PEPTIC ULCER

- **Hospitalization** and **Fresh blood transfusion**.
- **Acid suppression with high dose PPIs** by continuous i.v. infusion is the standard of care e.g. omeprazole 80 mg i.v. bolus followed by 8 mg/h for 72h.
- **Vitamin K_1:** 10 mg i.m or s.c.
- **Endoscopic therapy:** several types of endoscopic treatments are available.

TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Definition: reflux of gastric contents into the esophagus due to incompetent lower esophageal sphincter (LES). **Heartburn** and chest pain are the major complain which may be misdiagnosed of angina pectoris.

Non-drug therapy = life style modification

- **Head of bed elevation:** because most damage to the esophagus occurs at night when HCl can remain in contact with the mucosa for long period.
- **Weight reduction.**
- **Avoid:**
  - **S**tress, **S**moking, **S**pices, alcohol.
  - Ulcerogenic **drugs** e.g. NSAIDs.

Drugs ↑ LES pressure:

- Metoclopramide
- Domperidone
- Bethanechol
- Erythromycin

Drugs ↓ LES pressure:

- Anticholinergic drugs
- Nitrates

Drug therapy

- Decreasing HCl secretion: H_2 blockers and proton pump inhibitors.
- Prokinetic drugs.
- Antacids and antacid combinations: (Gaviscon).

Surgical treatment: if medical therapy failed.

PROKINETIC DRUGS

Definition: they are drugs that increase **upper GIT motility** and enhance gastric emptying. They include:

- **Dopamine antagonists:** e.g. Metoclopramide and Domperidone.
- **Serotonin (5-HT4)** agonists: e.g. Mosapride
- **Cholinomimetic agents:** e.g. Bethanechol.
- **Macrolide antibiotics:** e.g. Erythromycin

1. Metoclopramide

Mechanism and pharmacological effects

- Metoclopramide ↑ LES tone and enhances gastric emptying and **upper** GIT motility through:
  - Blocking of dopamine (D) receptors (central & peripheral) leading to decrease the inhibitory action of dopamine on the GIT motility.
  - Enhances cholinergic transmission in the upper GIT.

- **N.B.** Metoclopramide has **no effect** on small intestinal or colonic motility.

- **Antiemetic action:** due to blockade of D2 receptors in the chemoreceptor trigger zone of the medulla (**CTZ).**

Therapeutic uses

- **Gastroesophageal reflux:** to enhance gastric emptying and ↑ LES pressure.
- **Disorders of gastric emptying**: e.g. diabetic gastroparesis and postoperative gastric retention.
- **Before small bowel endoscopy** (20 mg given by slow i.v.i.): to enhance gastric evacuation and peristaltic movement. Also to prevent vomiting.
- **Before emergency surgery** and labor to evacuate the stomach and prevent aspiration of gastric contents during anesthesia.
- **Treatment of nausea and vomiting** of various causes.

Adverse effects

- Sedation (the most common adverse effect).
- **Extrapyramidal effects** (e.g. *dystonia* and *dyskinesia*): (especially in **old age**) due to blockade of D_2 in the *basal ganglia*.
- **Hyperprolactinemia** due to blockade of D_2 in the *pituitary gland*.

Drug interactions

- **Anticholinergic drugs (e.g. atropine)** antagonize its prokinetic action.
- **Other dopamine blockers** (e.g. antipsychotic drugs) administered with metoclopramide may precipitate acute extrapyramidal effects.

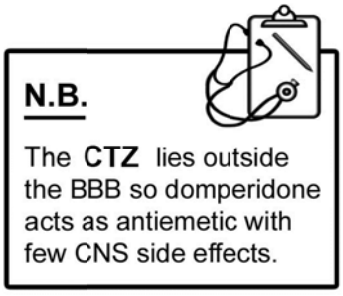
2. Domperidone

Mechanism and pharmacological effects

- **It blocks peripheral D_2 receptors leading to** ↓ the inhibitory action of dopamine on GIT motility. It does **NOT** cross BBB so it has no CNS side effects.
- **Antiemetic effect** less than metoclopramide.

Therapeutic uses

- The same uses as metoclopramide.
- To counteract nausea and vomiting caused by **levodopa** and **bromocriptine** during treatment of **Parkinson's disease** because it blocks D2 receptors in the CTZ responsible for vomiting but does **not** block D2 receptors in the basal ganglia responsible for parkinsonism.



Adverse effects: there is growing evidence that domperidone may ↑ QT interval and predispose to serious arrhythmia and sudden death.

	Metoclopramide	Domperidone
Dopamine receptor blockade	Central and peripheral	Peripheral only
Cholinergic transmission	Increase	No effect
Antiemetic effect	Strong	Weaker
Extra-pyramidal side effects	Present	No
Hyperprolactinemia	Significant	Minimal

3. Bethanechol

Bethanechol stimulates muscarinic M3 in the smooth ms of the GIT and myenteric plexus. It was used in the past for the treatment of GERD and gastroparesis, but now, it is rarely used for this indication due to multiple cholinergic side effects.

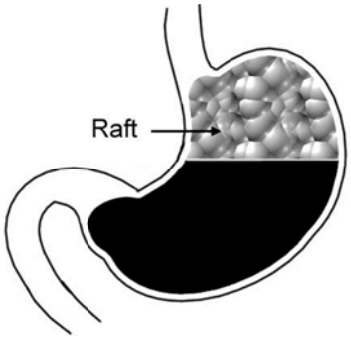
4. Macrolide antibiotics: erythromycin

Macrolide antibiotics such as erythromycin directly stimulate **motilin receptors** on GIT smooth muscle and promote the onset of a migrating motor complex. Intravenous erythromycin (3 mg/kg) is beneficial in some patients with gastroparesis; however, tolerance rapidly develops. It may be used in patients with acute upper GIT hemorrhage to promote gastric emptying of blood before endoscopy.

ANTACIDS AND ANTACID-ALGINIC ACID PRODUCTS

Gaviscon: (alginic acid + Mg-trisilicate + Al-hydroxide + $NaHCO_3$):

Alginic acid in presence of saliva and $NaHCO_3$ forms a highly viscous foamy solution of Na-alginate that floats on the gastric contents as a **raft** and prevents gastric reflux.



H2 BLOCKERS AND PPIS

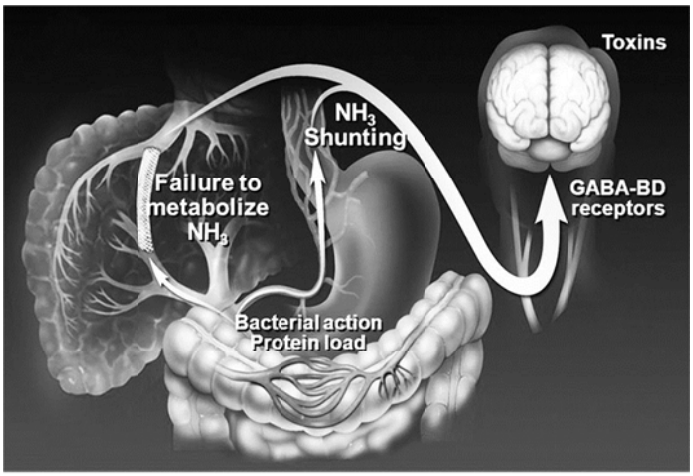
- PPIs are **more effective** than H2 blockers for the treatment of GERD.
- Once-daily dosing of PPIs provides effective symptom relief and tissue healing in 85–90% of patients; up to 15% of patients require twice-daily dosing.

Part 2: Management of Liver Disease Complications

MANAGEMENT OF HEPATIC ENCEPHALOPATHY

Definition and pathogenesis

Hepatic encephalopathy is the syndrome of disordered consciousness and neuromuscular activity seen in patients with acute or chronic liver failure.



Pathogenesis of portosystemic encephalopathy

The failing liver cannot metabolize **ammonia** and **benzodiazepines-like mediators (GABA-like transmitters)** generated by the intestinal bacteria. These toxins are shunted directly to the CNS causing encephalopathy.

Management: Treatment is aimed at **reduction of hyperammonemia:**

- **Diet:**
  - **Protein restriction** to decrease formation of ammonia by intestinal bacteria.
  - **Vegetable** protein is better tolerated than animal protein.
  - The rationale and benefit of dietary protein restriction is **controversial**.

- **Enemas**: cleansing of the colon is a rapid and effective method to remove ammoniagenic substrates. It can be done with lactulose or tape water.

- **Lactulose:**
  - It is synthetic non-absorbable disaccharide. In the colon, it is transformed by bacteria into **lactic** and **acetic** acids → ↓ pH of the colonic medium **leading to:**
    - Inhibition of intestinal bacteria → ↓ production of ammonia.
    - ↑ transport of ammonia from blood to intestinal lumen where it is converted to the poorly absorbed ammonium ion.
    - Osmotic laxation → ↑ excretion of ammonium ion.
  - It is administered orally or as enema (for patients in coma).
  - **Adverse effects:** relatively safe drug.

- **Oral antibiotics:**

  Neomycin:
  - It is non-absorbable aminoglycoside antibiotic.

- It ↓ blood ammonia by killing intestinal bacteria that generate ammonia.
- It is used in a dose of 1-2 g 4 times daily orally or as retention enema.
- Small amounts of neomycin may be absorbed (~1%) and result in ototoxicity and nephrotoxicity especially in patients with renal impairment.

Other antibiotics:

- **Metronidazole** acts on anaerobic bacteria. It is the preferred option if there is fear from adverse effects of neomycin (but given for short term).
- **Rifaximin:** is non-absorbable and better tolerated antibiotic.

MANAGEMENT OF VARICEAL BLEEDING DUE TO PORTAL HYPERTENSION

Management of acute bleeding

- **Fresh blood transfusion.**
- **Acid suppression** with **omeprazole** (80 mg) to minimize HCl irritation.
- **i.v. vasopressin or its analogues:**
  - **Vasopressin:**
    - It produces mesenteric VC leading to ↓ portal venous flow and pressure.
    - It can produce systemic VC (coronary, cerebral, limb, etc), so it is better combined with i.v. **nitroglycerine** to reduce systemic and coronary VC.
    - The vasopressin/nitroglycerine combination is **rarely** used now.
  - **Terlipressin:**
    - It is synthetic analog of vasopressin that is released in a slow and sustained manner allowing more sustained hemodynamic effects with fewer systemic side effects than vasopressin.
- **Prophylactic antibiotics:** to prevent infectious complications after GI hemorrhage. The preferred antibiotic is **i.v. ceftriaxone** 1 gm/day for 7 days.
- **Endoscopic sclerotherapy:** injection of the varices with a sclerosing agent to induce fibrosis and obliteration.

Prevention of re-bleeding (prophylaxis):

- **Beta-blockers (propranolol** 40 mg twice daily). It ↓ portal BP through:
  - They ↓ COP → ↓ portal blood flow.
  - They cause unopposed α- action → VC of the splanchnic vascular bed.
- **H_2 blockers or PPIs:** to prevent gastroduodenal erosions.
- **Metoclopramide:** to enhance gastric evacuation and ↑ LES pressure.

Part 3: Antiemetic Drugs

Several classes of antiemetic drugs are available that antagonize the neurotransmitter receptors known to be involved in the physiology of nausea and vomiting. The antiemetic drugs are classified according to their primary action; some agents affect multiple receptors.

Drug	Antiemetic mechanism	Uses as antiemetic	Adverse effects
1. Muscarinic blockers: ▪ Atropine ▪ Hyoscine	They block **M_1** receptors in the vestibulocerebellar pathway, solitary tract nucleus, and chemoreceptor trigger zone (CTZ).	Prevention and treatment of vomiting due to **motion sickness** (0.3-0.6 mg/8 hrs orally).	– Blurred vision – Dry mouth – Urine retention – Glaucoma – Tachycardia
2. H1-blockers: ▪ Diphenhydramine ▪ Cyproheptadine ▪ Cyclizine ▪ Meclizine	– They block H_1 (also M_1) receptors in the vestibulo-cerebellar pathway and CTZ. – They have sedative action.	– Vomiting due to **motion sickness** (diphenhydramine) – Vomiting of **pregnancy** (cyclizine and meclizine) – **True vertigo**: combined with VDs to improve labyrinthine blood flow.	– Sedation (excitation may occur in children). – Atropine-like actions (dry mouth, blurred vision, urine retention). – Hypotension
3. 5-HT3 blockers: ▪ Ondansetron ▪ Granisetron ▪ Tropisetron	They block $5HT_3$ receptors in the GIT, solitary tract nucleus and CTZ.	– Vomiting due to **cancer chemotherapy** or **radio-therapy.** – **Postoperative** nausea and vomiting.	– Dizziness, headache, and constipation.
4. Dopamine blockers ▪ Metoclopramide	– They block D2 receptors in the CTZ.	– Vomiting due to **drugs** or fevers.	– Sedation – Extrapyramidal effects e.g.

▪ Domperidone ▪ Phenothiazines e.g. chlorpromazine	– They inhibit peripheral transmission to VC.	– Vomiting due to **cancer chemotherapy**. – **Postoperative** nausea and vomiting.	dystonia and dyskinesia. – Hyperprolactinemia – Postural hypotension
5. Cannabinoid derivatives: ▪ Nabilone and Dronabinol	– It is a partial agonist at central and peripheral cannabinoid receptors (CB1). The exact mechanism is unclear.	– Vomiting due to **cancer chemotherapy** – Patients refractory to other antiemetics.	– Sedation – Hallucinations – Psychotropic effects – Postural hypotension – Drug abuse.
6. Vitamin B6 (pyridoxin)	May be related to the balance between GABA (CNS *inhibitory* transmitter) and glutamate (CNS *excitatory* transmitter).	– Vomiting in **pregnancy** (50 mg at bedtime). – Vomiting in **children**	-
7. Corticosteroids ▪ Dexamethasone ▪ Prednisolone	The exact mechanism is unclear.	– Combined with Vit B6 to treat vomiting in **pregnancy**. – Vomiting due to **cancer chemotherapy**.	– See endocrine chapter
8. Benzodiazepines ▪ Lorazepam ▪ Diazepam	Allosteric facilitation of central GABA inhibitory transmission	– **Stress-related** vomiting – To controls symptoms in **Ménière disease**	– See CNS chapter
9. Neurokinin-1 receptor blockers: ▪ Aprepitant	Substance-P induces vomiting through stimulation of NK-1 receptors. Aprepitant blocks this receptor.	– In combination with 5-HT3 blockers to treat vomiting due to **cancer chemotherapy**	– Diarrhea and fatigue

Part 4: Antispasmodic Drugs (smooth ms relaxants)

Classification

- **Anticholinergic drugs:** atropine, hyoscine, propantheline, oxyphenonium.
- **Direct smooth muscle relaxants:** papaverine, mebeverine, alverine, drotaverine.
- **Mixtures:** Librax (clidinium + chlordiazepoxide), Donnatal (hyoscine + phenobarbital).

<table>
<tr><th></th><th>Papaverine</th><th>Mebeverine, Alverine, Drotaverine</th><th>Librax</th></tr>
<tr><td rowspan="2">Chemistry & mechanism of action</td><td>It is opium alkaloid but chemically different from morphine</td><td>They are synthetic drugs</td><td rowspan="2">It is a combination of:
▪ Chlordiazepoxide: benzodiazepine that has antianxiety effect.
▪ Clidinium: anticholinergic drug which ↓ GIT motility and spasm</td></tr>
<tr><td colspan="2">The exact mechanism is unclear but may be due to inhibition of PDE enzyme →↑ cAMP → smooth muscle relaxation.</td></tr>
<tr><td>Use</td><td colspan="3">▪ Spasms of the GIT, bile duct and genitourinary tract.
▪ Librax is used for treatment of irritable bowel syndrome (IBS).</td></tr>
<tr><td>Side effects</td><td colspan="2">– Cardiac arrhythmia.
– Abnormal liver functions in the form of elevated serum transaminases and alkaline phosphatase.
– Headache and dizziness</td><td>– Atropine-like actions e.g, dry mouth, urine retention, etc.
– Sedation, drowsiness, confusion, etc.</td></tr>
<tr><td>C/I</td><td colspan="3">– Paralytic ileus.
– Constipation for more than one week</td></tr>
</table>

Part 5: Therapy of Constipation

Non-drug therapy: It is the **first line** in all cases of constipation

- **Diet rich in fibers** e.g. fruits, vegetables, whole meal bread, etc. to be increased to 30 g/day.
- Increase **fluid intake**
- Minimize **tea** and coffee.
- Physical **exercise** to activate abdominal muscles and intestinal peristalsis. This help food move more efficiently through the gut.

Drug therapy: LAXATIVES:

Drug causes of constipation:

- **A**tropine and related drugs.
- **A**luminum containing antacids
- **A**dsorbents (kaolin & pectin).
- **CCBs:** e.g. **V**erapamil
- **Opioids:** morphine & loperamide

1. Bulk-forming agents:

[Dietary fibers – Methylcellulose – Bran]

Mechanism of action

They are non-digestible fibers; they retain water in the gut and distend the large intestine → activation of stretch receptors → stimulation of peristalsis.

Adverse effects: they are **safe** laxatives but may cause:

- Bloating and abdominal distension.
- ↓ absorption of some drugs e.g. digoxin.
- They may form masses in the gut leading to intestinal obstruction.

2. Osmotic laxatives:

[Mg sulfate & Na salts – Lactulose – Polyethylene glycol]

Mechanism of action

They are retained in the gut lumen and retain water by their osmotic effect → activation of stretch receptors → stimulation of peristalsis.

Adverse effects

- Mg & Na salts (saline laxatives) may be absorbed systemically and produce *hypermagnesemia* and *hypernatremia* especially in patients with renal failure.
- Lactulose may produce abdominal discomfort.
- Polyethylene glycol may produce electrolyte disturbance (hypokalemia).

3. Irritant (or stimulant) laxatives:

[Castor oil – Senna – Bisacodyl]

Mechanism of action

They produce inflammation (irritation) of the intestinal mucosa and inhibit Na^+/K^+ *ATPase enzyme* leading to:

- Accumulation of water and electrolytes in the gut lumen.
- Direct stimulation of peristalsis by their irritant effect.

Adverse effects

Castor oil
- Bad taste.
- Stimulation of uterine contraction and **abortion**

Senna
- It passes in urine and cause **urine discoloration**
- It passes in breast milk and cause **cathartic** effect in the baby.
- Prolonged use → degeneration of gut nervous plexus → **atonic** (cathartic) colon.
- Increase menstrual blood flow and **abortion** in pregnancy.
- **Laxative dependence:** Irritant laxatives cause complete evacuation of the colon. The colon requires 2-5 days before the normal fecal mass can be reestablished. The patient becomes worry regarding the lack of bowel movement during this period and may use the laxative again and a vicious cycle is established leading to partial or complete loss of normal bowel function.

Bisacodyl
- It is prepared as enteric coated tablets to avoid gastric irritation. If it is given with milk or with other drugs that change gastric pH, the enteric coating may dissolve in the stomach and cause gastric irritation and pain
- Prolonged use → degeneration of gut nervous plexus → **atonic** (cathartic) colon *(should not be used more than 10 days).*

4. Stool softeners: Docusate sodium

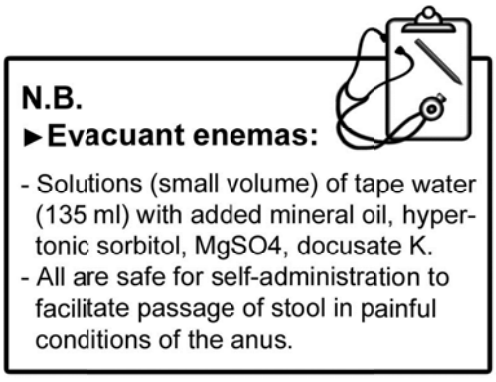
Mechanism: they are anionic surfactants that enable additional water and fats to be incorporated in the stool, making it easier to move through the GIT.

5. Lubricant laxatives:

[Liquid paraffin – Glycerin suppositories – Evacuant enema]

Mechanism of action

- **Paraffin oil** it coats the fecal matter and retards water absorption by the colon.
- **Glycerin** has hygroscopic effect. It draws water from rectal mucosa and lubricates the anal canal. It also stimulates reflex rectal contractions and promotes stool evacuation in 15-20 min.



Adverse effects: paraffin oil decreases absorption of fat-soluble vitamins

6. Chloride channel activators: Lubiprostone

Mechanism of action

It acts by activating chloride channels to increase fluid secretion in the intestinal lumen. This eases the passage of stool and causes little change in electrolyte balance.

General indications of laxatives

- **Constipation:** laxatives should not be used for prolonged duration to avoid laxative dependence.
- To fasten excretion of **toxic** substances from the GIT.
- To prepare the bowel before **X-ray** or colonoscopy.
- Hepatic encephalopathy (lactulose): to kill ammonia producing bacteria.
- Painful anal conditions e.g. anal fissure or piles.
- Postoperative: e.g. after hemorrhoids (piles) to avoid strain.

Contraindications of laxatives

- Laxatives are dangerous in cases of undiagnosed abdominal pain or inflammatory bowel disease. They may lead to intestinal perforation.
- Organic obstruction of the GIT.

Part 6: Therapy of Diarrhea

Causes of diarrhea

- **Infectious diarrhea:** bacterial, viral, fungal, protozoal, etc. Infectious diarrhea is the most common type.
- **Hormonal (secretory) diarrhea:** e.g. *serotonin* in carcinoid syndrome; *calcitonin* in medullary thyroid carcinoma, *histamine* in mastocytosis, *thyroxine* in hyperthyroidism. Diarrhea is caused by: (1) increased water secretions into the intestinal lumen and (2) increased intestinal motility.
- **Malabsorption syndromes:** e.g. bile acid malabsorption
- **Inflammatory (exudative) diarrhea:** caused by inflammatory bowel diseases e.g. *Crohn's disease* (transmural lesion in the small intestine) and *ulcerative colitis* (ulceration of the colon with bloody diarrhea).
- **Iatrogenic (drug induced) diarrhea:**
  - Overuse of laxatives.
  - Mg-containing antacids.

- Antibiotic-associated diarrhea (*pseudomembranous colitis*) see chemotherapy
- Cholinomimetic drugs.

Patterns of diarrhea

- **Acute self-limited diarrhea:** acute diarrhea disappears within 24 hrs.
- **Acute diarrhea (<2 weeks):** passage of watery stool more than 10 times/day associated with dehydration and electrolyte imbalance.
- **Chronic diarrhea: (>2 weeks):** persistent diarrhea for **3** weeks in adults or **4** weeks in infants. It causes weight loss and weakness.

Investigations of diarrhea

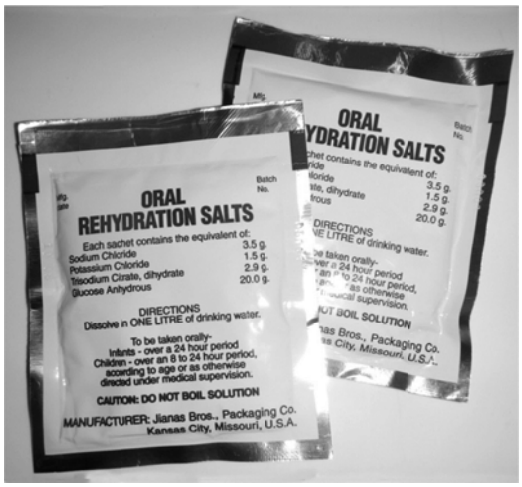
- **Stool examination:**
  - Macroscopic: consistency, color, blood, etc.
  - Microscopic: RBCs, WBCs, parasites, ova, etc.
  - Stool culture and sensitivity tests.
- **Endoscopy** and biopsy in chronic cases.
- **Radiologic** examination: by barium enema.

Treatment of diarrhea

Lines of therapy

- **Maintenance of fluid and electrolyte balance:** is the **first** priority.
- **Non-specific antidiarrheal agents:** should be applied after exclusion of other relevant causes of diarrhea.
- **Specific antidiarrheal agents:** treatment of the cause e.g.
  - Antimicrobials for infectious diarrhea.
  - Antiinflammatory drugs for inflammatory bowel diseases.
- **Antispasmodic drugs:** if there is colic or abdominal cramps.

I. MAINTENANCE OF FLUID AND ELECTROLYTE BALANCE

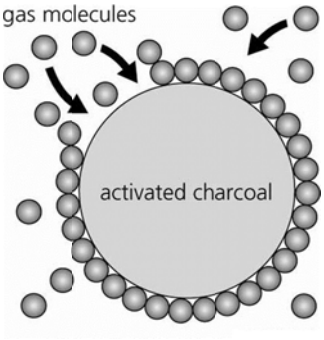


- **Oral Rehydration Therapy (ORT):**
  - Balanced salt solution containing electrolytes and glucose (glucose is important for sodium and consequently water absorption).
  - 90% of acute cases of childhood diarrhea can be corrected using ORT only.
- **Intravenous solutions:** if dehydration is severe.

N.B. in infants with dehydration, **blood pH, serum Na^+ and K^+** must be measured before giving any **i.v. solution** to avoid electrolyte and acid/base imbalance.

II. NON-SPECIFIC ANTIDIARRHEAL THERAPY

1. Adsorbents: Kaolin, pectin, activated charcoal



Mechanism

- They adsorb water, microoganisms and toxins.
- They coat the mucosa and protect it.

Adverse effects: they may ↓ absorption of other drugs.

2. Bismuth subsalicylate

Mechanism

- Bismuth: provides a **protective coat** for the mucosa and **binds toxins** produced by pathogenic bacteria.
- Subsalicylate: hydrolyzed by intestinal bacteria into **salicylic acid** →↓ intestinal inflammation, hypermotility and secretions.

3. Anti-cholinergic drugs: atropine, hyoscine and propantheline

Mechanism

- Antidiarrheal action: ↓ colonic peristalsis by blocking the response of intestinal smooth muscle to cholinergic stimulation.
- Antispasmodic action: relieve cramps associated with diarrhea.

4. Synthetic opioid preparations: diphenoxylate and loperamide

Mechanism

- They act on opioid **μ (mu)** and **δ (delta) receptors** in the enteric nervous system (both pre- and postsynaptic) leading to:
  - ↑ segmenting (non-propulsive) contractions of the small intestine.
  - ↑ water absorption and ↓ water secretion by intestinal mucosal cells.
  - ↓ Ach release by cholinergic neurons in the ENS.
- Loperamide **cannot cross BBB** while diphenoxylate can **cross BBB in very small amount** (no CNS effects in **usual** therapeutic doses) but it can cause addiction if used in large doses and for prolonged duration.
- They are commonly **combined with atropine** (e.g. **Lomotil®** is a combination of

diphenoxylate 2.5 mg + atropine 0.25 mg) to produce more ↓↓ in intestinal motility and decrease liability for abuse.

Adverse effects

- Anti-cholinergic side effects e.g. dry mouth.
- Addiction: if used for prolonged duration.
- Precipitation of **toxic megacolon** if used in ulcerative colitis.

5. Cholestyramine

Mechanism: it binds **bile acids** in the intestine preventing their absorption and decreasing their irritation.

Therapeutic uses: diarrhea due to **bile salt malabsorption.**

III. SPECIFIC ANTI-INFECTIVE AGENTS

- It is not necessary in simple gastroenteritis as most cases are viral in origin.
- Chemotherapy is necessary in specific types of enteritis e.g.

C. difficile colitis *Clostridium difficile*	**Metronidazole** 400 mg/8h orally for 10 days (1st choice). ***If no response to metronidazole:*** **vancomycin** 250 mg/6h**.**
Campylobacter jejuni	**Azithromycin** 500 mg/day orally for 3 days.
E. coli (enterotoxigenic and enteropathogenic)	**Ciprofloxacin** 500 mg/12h for 1-3 days
Non-typhoid Salmonella spp.	**Ciprofloxacin** 500 mg/12h for 5-7 days or **ceftriaxone** 1g IV/24h.
Shigella spp.	**Ciprofloxacin** 500 mg/12h for 3-5 days or **co-trimoxazole** 2 tab (80/400)/12h.
V. cholerae	**Doxycycline** 300 mg orally single dose or **ciprofloxacin** 500 mg/12h orally for 3 days.
V. parahemolyticus	**Ciprofloxacin** 500 mg/12h for 1-3 days

IV. ANTI-INFLAMMATORY DRUGS

1. Sulfasalazine (5-aminosalicylic acid "5-ASA" + sulfapyridine)

Mechanism: In the colon, the “azo” bond is broken by intestinal bacteria to release 5-ASA and sulfapyridine: 5-ASA has anti-inflammatory and immunosuppressive, while sulfapyridine is poorly absorbed sulfonamide with antibacterial action.

Therapeutic uses:

- Active ulcerative colitis (3-4 gm/day) and to maintain remission (2 gm/day).
- Rheumatoid arthritis.

Adverse effects: mainly due to sulfapyridine (sulfonamide) → drug allergy, bone marrow depression and **megaloblastic anemia** (avoided by giving **folic acid**).

Other aminosalicylates:

- **Mesalazine:** modified-release preparation.
- **Olsalazine** is a dimmer of 5-ASA. It is cleaved in the lower bowel to release 5-ASA.

2. Corticosteroids

Mechanism

- Stimulation of Na^+ absorption from the intestine.
- Anti-inflammatory action (see endocrine).

Therapeutic uses: they are given orally or as enema in severe cases.

- To control acute episodes of Inflammatory bowel diseases
- Refractory diarrhea unresponsive to other agents.

Travellers' diarrhea:

Diarrhea that occurs to travellers and tourists in high endemic areas. Transmission of infection is done through contaminated food or water.

Drug therapy:

- Prophylaxis: doxycycline (100 mg /day orally)
- Treatment: doxycycline + bismuth subsalicylate + fluids

3. Immunosuppressive agents

- **Cytotoxic drugs (azathioprine** and **6-mercaptopurine):** can be used in ulcerative colitis and Crohn's disease in small dose to avoid bone marrow depression.
- **Cyclosporine-A** use is limited for severe cases due to potential toxicity.

N.B.

- **Metronidazol** may be used in **Crohn's disease** to eradicate anaerobic bacteria.
- **Infliximab** (monoclonal antibodies): can be used in **Crohn's disease** to ↓ TNFα.
- **Aspirin** and **indomethacin** may of value in **acute diarrhea** because they ↓ PGs synthesis → ↑ absorption and ↓ secretions of intestinal fluids.
- **Clonidine** (α_2 stimulant) can be used in **diabetic diarrhea** to ↑ intestinal water absorption and ↓ electrolyte secretion.

Part 7: Drug Therapy of Gallstones (cholelithiasis)

Choleretics: are agents that increase bile production e.g. bile acids and bile salts.

Hydrocholeretics: are agents that increase volume of bile e.g. dehydrocholic acid.

Cholagogues: are agents that stimulate the evacuation of gall bladder e.g. olive oil.

The following drugs are used to dissolve non-calcified cholesterol stones:

Chenodeoxycholic acid (CDCA): It ↓ hepatic cholesterol synthesis and ↑ bile acid and phospholipid synthesis.

Ursodeoxycholic acid (UDCA)

- It is a metabolite of chemodeoxycholic acid.
- It is more potent in reduction of hepatic cholesterol synthesis without affecting the endogenous bile acid synthesis.
- Both CDCA and UDCA are given orally in a dose of 10-15 mg/kg/day for 6-12 month.
- Diarrhea is common side effect with CDCA but is unusual with UDCA.

Notes

Review Questions

1. Classify laxatives. Mention the mechanism of action of each class.
2. Mention the mechanism of action and adverse effects of each of the following:
   - Metoclopramide.
   - Cimetidine
   - Omeprazole
   - Senna
   - Lomotil
3. Mention the mechanism of action and therapeutic uses of:
   - Papaverine
   - Sulfasalazine
   - Terlipressin
4. Mention the drug-drug interactions of metoclopramide.
5. Mention 2 drugs used for the treatment of nausea and vomiting due to the following conditions. For each drug, mention the mechanism of action and the main adverse effects:
   - Vomiting due to cancer chemotherapy
   - Motion sickness
6. Give the reason for:
   - Atropine is combined with diphenoxylate in Lomotil preparation.
   - Domperidone, and not metoclopramide, is used for treatment of vomiting due to levodopa.
   - Irritant laxatives should not be given for long period.
   - Folic acid should be supplemented with sulfasalazine during treatment of ulcerative colitis and rheumatoid arthritis.
7. Mention 3 differences between:
   - Metoclopramide and domperidone.
   - Cimetidine and omeprazole.
8. Mention the mechanism and management of portosystemic encephalopathy.
9. Mention the essential lines of the treatment of bleeding esophageal varices.

Of each of the following questions, select ONE BEST answer:

1. Toxicities of cimetidine include which one of the following?
A. Blurred vision
B. Diarrhea
C. Orthostatic hypotension
D. P450 inhibition
E. Sleepiness

2. Which of the following will result from blockade of H2 receptors?
A. Decreased cAMP in cardiac muscle
B. Increased cAMP in cardiac muscle
C. Decreased IP3 in gastric mucosa
D. Increased IP3 in gastric mucosa
E. Increased IP3 in smooth muscle

3. Which of the following is most effective in the treatment of peptic ulcer disease?
A. Cimetidine
B. Lanzoprazole
C. Pirenzepine
D. Ondansetron
E. LSD

4. A 55-year-old woman with insulin dependent diabetes of 40 years' duration complains of severe bloating and abdominal distress, especially after meals. Evaluation is consistent with diabetic gastroparesis. The drug you would be most likely to recommend is:
A. Docusate
B. Dopamine
C. Loperamide
D. Metoclopramide
E. Sucralfate

5. The steatorrhea of pancreatic insufficiency can best be treated by:
A. Cimetidine
B. Misoprostol.
C. Bile salts.
D. Pancreatic lipase.
E. Secretin

6. A drug of choice in the therapy of inflammatory bowel disease is:
A. Sulfadiazine.
B. Sulfasalazine.
C. Sulfapyridine.
D. Sulfamethoxazole.
E. Salicylate sodium

7. An important drug in the therapy of portal systemic encephalopathy is:
A. Lactulose.
B. Lactate.
C. Loperamide.
D. Lorazepam.
E. Doxapine.

8. Bismuth salts are thought to be effective in peptic ulcer disease because they have bactericidal properties against:
A. Escherichia coli.
B. Bacteroides fragilis.
C. Clostridium difficile.
D. Helicobacter pylori.
E. Staphylococcus aureus.

9. Misoprostol has a cytoprotective action on the gastrointestinal mucosa because it:
A. Enhances secretion of mucus and bicarbonate ion.
B. Neutralizes acid secretion.
C. Antagonizes nonsteroidal anti-inflammatory drugs (NSAIDs)
D. Relieves ulcer symptoms.
E. Coats the mucosa.

10. The primary pharmacologic action of omeprazole is the reduction of:
A. Volume of gastric juice.
B. Gastric motility.
C. Secretion of pepsin.
D. Secretion of gastric acid.
E. Secretion of intrinsic factor.

11. Cimetidine slows the metabolism of many drugs because it inhibits the activity of:
A. Monoamine oxidase (MAO)
B. Tyrosine kinase.
C. Hydrogen - potassium - adenosine triphosphatase (H+, K+, ATPase).
D. Phase II glucuronidation reactions
E. Cytochrome P450.

12. The absorption of iron is reduced when large and prolonged doses of which of the following drugs are given?
A. Vitamin C
B. Alum hydroxide.
C. Aspirin.
D. Cimetidine.
E. Lactuolse.

13. Omeprazole, an agent for the promotion of healing of peptic ulcers, has a mechanism of action that is based on:
A. Prostaglandins.
B. Gastric secretion.
C. Pepsin secretion.
D. H+, K+, ATPase.
E. Anticholinergic.

14. An effective antidiarrheal agent that inhibits peristaltic movement is:
A. Clonidine.
B. Bismuth subsalicylate.
C. Oral electrolyte Solution.
D. Pectin.
E. Diphenoxylate.

15. The approved indication for misoprostol:
A. Reflux esophagitis.
B. Regional ileitis.
C. Ulcerative colitis.
D. Prevention of gastric ulceration in patients using large doses of aspirin like drugs.
E. Pathologic hypersecretory conditions such as Zolinger- Ellison syndrome.

16. Metoclopramide has antiemetic properties because it:
A. Lowers esophageal sphincter pressure.
B. Is a central dopamine- receptor antagonist.
C. Is a central opioid receptor agonist
D. Has cholinomimetic properties.
E. Has sedative properties.

17. Fomatidine has the following properties:
A. A potent proton pump inhibitor.
B. A potent antiemetic agent.
C. A potent inhibitory effect on cyt P450.
D. A potent anti-anderogenic action.
E. None of the above.

18. Radiation-induced vomiting can be treated by drugs that act on:
A. 5-HT3 receptors.
B. M1 receptors.
C. H1 receptors.
D. Alpha receptors
E. Beta receptors.

19. Cholesterol gallstones may be dissolved by oral treatment with:
A. Lovastatin.
B. Dehydrocholic acid.
C. Methyl teriary butyl ether.
D. Chenodeoxycholic acid.
E. Monoctanoin.

20. A patient who must take verapamil for hypertension and angina has become constipated. Which of the following drugs would be most suitable as a long term laxative?
A. Aluminum hydroxide
B. Diphenoxylate
C. lactulose
D. Metoclopramide
E. Mineral oil

21. Your cousin is planning a three-week trip overseas and asks your advice regarding medications for traveler's diarrhea. A drug suitable for non-infectious diarrhea is
A. Aluminum hydroxide
B. Bismuth subcitrate
C. Magnesium hydroxide
D. Metoclopramide
E. Mineral oil

22. Which of the following drugs or drug groups is not useful in the prevention of nausea and vomiting induced by cancer chemotherapy:
A. Dexamethasone
B. Dronabinol
C. Scopolamine
D. Ondansetron
E. Metoclopramide

23. A patient presents with Zollinger-Ellison syndrome due to a gastrinoma. He has two bleeding ulcers and diarrhea. A drug that irreversibly inhibits the H+/K + ATPase in gastric parietal cells is
A. Cimetidine
B. Cisapride
C. Glycopyrolate
D. Omeprazole
E. Ondansetron

24. A drug that is recently linked with some cases of cardiac arrhythmias and sudden death is:
A. Aluminum hydroxide
B. Lactulose
C. Loperamide
D. Ranitidine
E. Domperidone

25. One recognized advantage of domperidone over metoclopramide as a prokinetic agent is:
A. More prominent antiemetic action
B. More powerful stimulant of GIT motility
C. Less CNS adverse effects.
D. Less incidence of diarrhea
E. Less cardiac adverse effects

26. A cannabinoid receptors agonist that is useful for prevention of nausea and vomiting due to cancer chemotherapy is:
A. Dronabilone
B. Morphine
C. Diphenoxylate
D. Naloxone
E. Ondansetron

27. A pregnant woman with 28 weeks gestation complaining of distressing constipation. Which of the following drugs can be prescribed safely?
A. Ondansteron
B. Lactulose
C. Senna
D. Magnesium sulphate salt
E. Castor oil

28. Bisacodyl frequently can cause:
A. Abdominal cramps
B. Constipation
C. Skin rashes
D. Dizziness
E. Nauseas

29. Patients with acute bleeding due to ruptured esophageal varices could be managed by:
A. i.v. terlipressin
B. i.v. sodium bicarbonate
C. Oral lanzoprazole
D. i.v. hydrocortisone
E. Oral lactulose

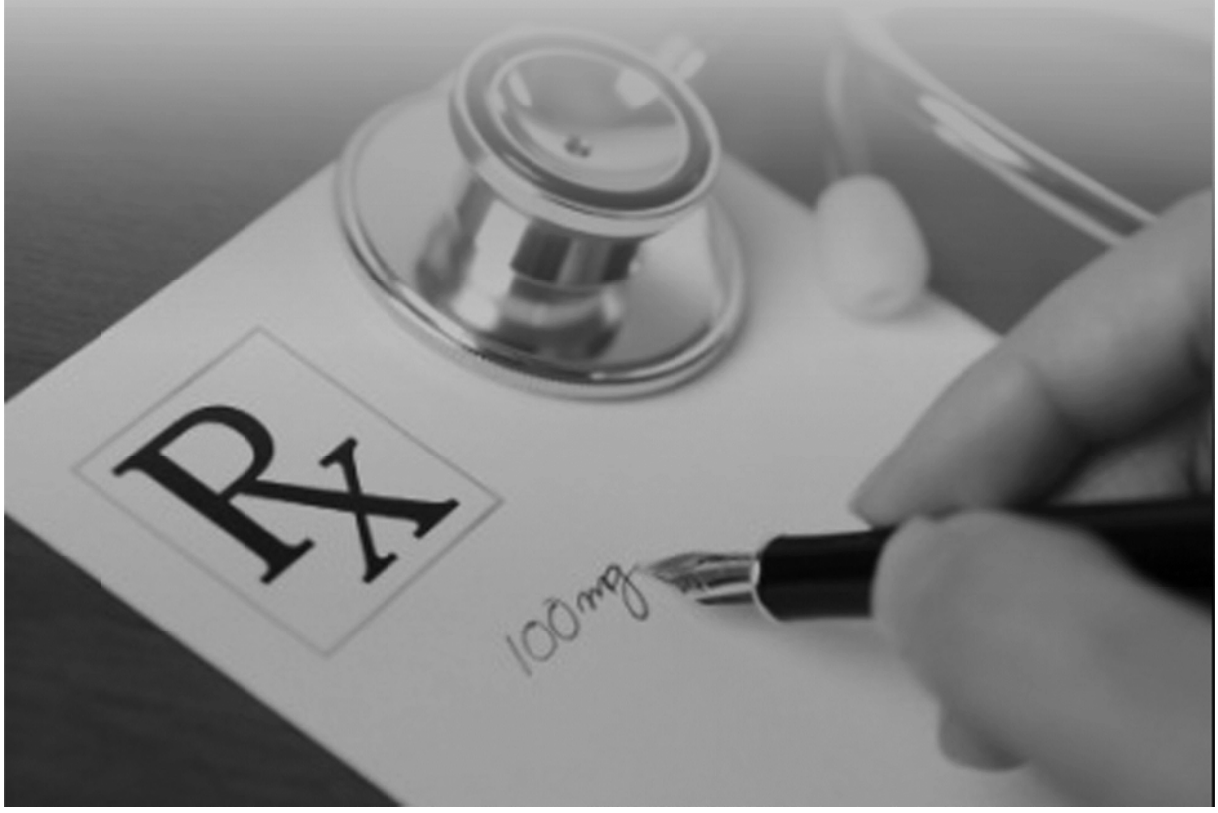
30. A patient being cared for by the gastroenterology service is being treated with sulfasalazine. Which of the following is the most likely purpose for which it is being given?
A. Antibiotic-associated pseudomembranous colitis
B. E. coli–induced diarrhea
C. Gastric H. pylori infections
D. Inflammatory bowel disease
E. NSAID-induced gastric ulcer prophylaxis

Answers

1 D	7 A	13 D	19 D	25 C
2 A	8 D	14 E	20 C	26 A
3 B	9 A	15 D	21 B	27 B
4 D	10 D	16 B	22 C	28 C
5 D	11 E	17 E	23 D	29 A
6 B	12 B	18 A	24 E	30 D

Chapter 9

Endocrine Pharmacology



Chapter 9
Endocrine Pharmacology

Part 1: Diabetes Mellitus and Antidiabetic Drugs

Definition of DM: It is a clinical syndrome characterized by disturbance in carbohydrates, fat, & proteins metabolism due to either *insulin deficiency* or *insulin resistance*.

Manifestations:

- Polyuria, polydipsia, polyphagia, and loss of weight.
- Complications of DM e.g. recurrent infections, angiopathy, retinopathy, nephropathy, DKA, etc.

Histology

There are **4** types of cells in the islets of Langerhans.

- **α cells** (20%) : secrete **glucagon**.
- **β cells** (75%) : secrete **insulin** and islet associated polypeptide (amylin).
- **δ cells** (3-5%) : secrete **somatostatin**.
- **F cells** < 2 %: secrete **pancreatic polypeptides** (facilitate digestive process).

Laboratory investigations:

- Urine analysis for glucosuria & ketonuria.
- Blood glucose: fasting and 2-hr after oral 75 g glucose.
- Glycated hemoglobin (HbA_1C): indicates average blood sugar level for the past 2-3 months

	Normal	IGT*	DM
Fasting BG	< 100 mg/dl	100-126	**> 126** mg/dl
2 hr after oral 75 g glucose	< 140 mg/dl	140-200	**> 200** mg/dl
HbA_1C	< 6%	6-6.5%	**> 6.5%** Elevated levels mean uncontrolled DM over the last **2-3** months.

*** IGT = Impaired glucose tolerance (prediabetes):** it can be controlled by **diet regime** alone.

Common types of DM:

- **Type 1 DM:** (old name: insulin dependent DM)
- **Type 2 DM:** (old name: non-insulin dependent DM)
- **Gestational DM:** appears during pregnancy and disappears after labor.

	Type 1 (IDDM)	Type 2 (NIDDM)
Pathophysiology:	Autoimmune condition against the pancreatic beta cells. The damaged pancreas **doesn't make** insulin.	The pancreas usually produces some insulin. But either the amount is **not sufficient**, or the body's cells are **resistant** to it.
Onset (age):	< 30 years	>30 years (adult-onset)
Body built:	Usually undernourished	Usually obese
Insulin therapy:	Essentially required.	Required in 20% of patients
Oral drugs:	Not required.	Essentially required.

Less common types of DM:

- **Latent autoimmune diabetes of adults (LADA):** is a condition in which type 1 DM develops in adults.
- **Maturity onset diabetes of the young (MODY):** is a condition in which type 2 DM develops in children or young adults who develop persistent, asymptomatic hyperglycemia without progression to diabetic ketoacidosis.

> **N.B.** *Adults with LADA or children with MODY are frequently misdiagnosed as having type 2 or type 1 DM, based on age rather than etiology.*

- **Secondary DM:** 2ry to drugs, infections, endocrine diseases, etc.

Lines of treatment:

- **Diet control**.
- **Diet + insulin (type 1).**
- **Diet + oral antidiabetic drugs (type 2).**
- **Exercise**: to enhance peripheral glucose utilization.

DIET REGIME

It is the **first line** of treatment in all types of DM.

✸ Glycemic Index (GI):

– It describes the capacity of a food to raise blood glucose in normal glucose

tolerant individuals.

– Foods with a high GI may be associated with ↑ risk of obesity and the postprandial hyperglycaemia, with such foods may also ↑ the risk of T2DM.

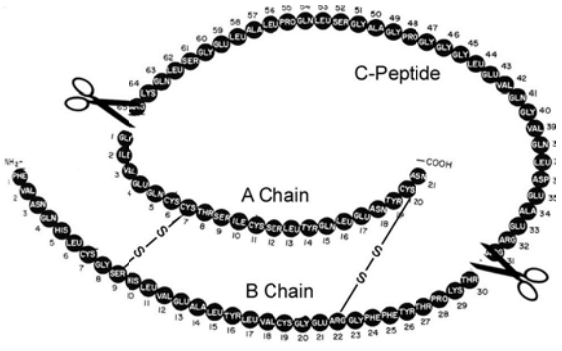
Caloric requirements of patients	
Average wt:	**30**-35 c/kg/d
Children or thin:	**40**-45 c/kg/d
Obese:	**20**-25 c/kg/d

Distribution of food elements
15 % from proteins
55 % from carbohydrates
30 % from fats

INSULIN

Chemistry

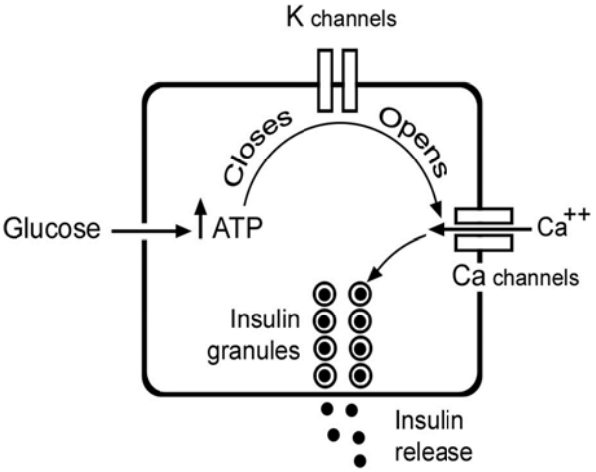
- 2 peptide chains: A (21 aa) and B (30 aa) linked by 2 disulfide bonds.
- Insulin is secreted as **proinsulin** then cleaved (within the storage granules in the β cells) into insulin and connecting peptide "C-peptide".



N.B. Measurable C-peptide levels indicate the presence of endogenously produced insulin and functioning β-cells.

Secretion

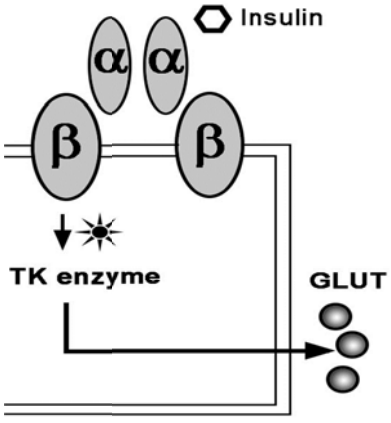
- Glucose enters β cells → ↑ ATP → closure of ATP-dependent K^+ channels → opening of voltage-gated Ca^{2+} channels → ↑ Ca^{2+} influx → insulin release.



Insulin receptors

– **A tyrosine kinase receptor** consists of 2 extracellular **α**-subunits and 2 transmembrane **β**-subunits.

– Binding of insulin to the α-subunits causes activation of the β-subunits → activation of **tyrosine kinase enzyme** which triggers a series of intracellular effects that ↑ number of **glucose transporters** (especially **GLUT4**) on the cell membrane → ↑ transport of glucose into the cell.



Up-regulation of insulin receptors:	Down-regulation of insulin receptors:
▪ **Insulin deficiency** (e.g. in fasting) ▪ **Drugs: INSULIN SENSITIZERS:** a) Thiazolidinediones: e.g. pioglitazone & rosiglitazone. b) Trace elements: e.g. selenium & chromium.	▪ **Insulin excess (Obesity)**. Obesity causes continuous stimulation of β-cells → hyperinsulinemia → down regulation of insulin receptors. ▪ **Drugs: e.g. corticosteroids**

Pharmacokinetics of insulin

- **Endogenous insulin:**
  - The pancreas releases insulin in the portal vein in small bouts at short intervals according to blood glucose levels. The liver clears ~ 50% of the secreted amount; the rest is distributed all over the body and cleared by receptor-mediated uptake and intracellular degradation.
  - The normal blood level of insulin is **5-15 μU/ml** (fasting) and **60-90 μU/ml** (postprandial).
- **Exogenous insulin:**
  - Insulin is not administered orally because it is rapidly destroyed by GIT enzymes. It is given **s.c.** (common) or **i.v.** (in emergencies).
  - The plasma **half-life** of insulin given **intravenous** is **10-12 min**.

Sources of commercial insulin

- **Traditional (animal) insulin:**

- Prepared from animals (beef and pork).
- P**O**rk insulin differs from human insulin in **O**ne aa (*alanine* in pork and *threonine* in human) while b**EE**f insulin differs from human in thr**EE** aa.
- Animal insulin may contain traces of animal proteins and proinsulin, so it is **more antigenic** and can cause insulin resistance.

- **Human insulin:**

- It is identical to human insulin and is prepared by recombinant DNA technology (genetic engineering) from yeasts or bacteria.
- Advantages: **Less antigenic** and rare development of insulin resistance.

- **Insulin analogs:**

- Recombinant insulin analogs are now available in which some amino acids in the "normal" insulin have been switched (e.g. insulin lispro) or replaced (e.g. insulin glargine), making a “different molecule” so as to get different pharmacokinetic properties.

Common examples of insulin preparations

Category	Generic name/Brand	Features	Onset	Peak	Duration
RAPID ACTING ANALOGS	**Insulin glulisine** **Insulin lispro** **Insulin aspart**	– They are human insulins that have been modified at 1–2 amino acids in the B chain to increase their solubility. – They are the fastest acting insulins. They must be injected just before meals.	5-15 min	1-2 h	3-5 h
SHORT ACTING INSULIN	**Regular; soluble; neutral** (Humulin R; Novolin R)	– It is identical to human insulin – It is the only type that can be given **i.v.** in diabetic emergencies e.g. diabetic ketoacidosis.	30 min	2-4 h	6-8 h
INTERMEDIATE ACTING	**NPH (isophane)*** (Humulin N; Novolin N)	– It is made by addition of the protein **P**rotamine to **N**eutral insulin to prolong its duration.	1-2 h	4-6 h	12-16 h
LONG ACTING INSULIN	**Insulin glargine** (Lantus) **Insulin detemir** **Insulin zinc suspension**	– They are insulin analogs with minor amino acid changes to make them long acting "peakless". – It is human insulin added to ↑↑ amount of zinc – They are usually administered once daily.	1-2 h	None	18-24 h
PREMIXED INSULIN (Biphasic)	**Humulin 70/30; Mixtard** (70% NPH – 30% regular) **Humalog Mix 75/25** (75% NPH – 25% lispro)	– They provide rapid onset and relatively prolonged duration – They are usually injected twice daily.	< 30 min		12-16 h

- NPH = Neutral Protamine Hagedorn
- Regular insulin can be mixed with NPH in the same syringe. The mixing order should be the clear regular drawn up *first* then the cloudy NPH (i.e. "clear-to-cloudy").
- NPH, insulin zinc and biphasic insulin are **cloudy** in appearance.

Insulin administration

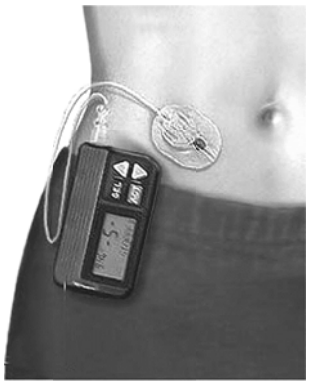
- All insulins are given by **s.c. injection.**
- **Regular insulin** is the only type that can be given **i.v.** in **diabetic emergencies**.
- The standard insulin concentration is 100 units/mL (U-100). It should be injected with a standard U-100 syringe.

Insulin requirement and long term regimens

- Generally, the total daily insulin requirement in units is equal to 0.55 times the person's weight in kilograms. A conservative total daily dose (TDD) of 0.4 units/kg/d is given initially to a newly diagnosed patient; the dose is then adjusted according to the blood glucose level.

- **Basal-bolus regimen:**
  - Give **long acting insulin** at bed time; plus three daily injection of **short acting insulin** before each meal. The long-acting insulin provides basal level of insulin that controls blood glucose during night and in-between meals, and the short acting insulin controls postprandial hyperglycemia.
  - It is commonly used for patients with Type-1 DM and in pregnant women with diabetes.

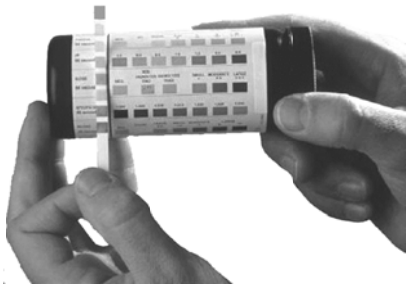
- **Twice-daily biphasic insulin regimen:**
  - Use biphasic insulin. The average daily requirement is 0.5 units/kg. Use the two-thirds rule:
  - Give the 2/3 of the TDD in the morning and the 1/3 at evening.
  - It is commonly used for patients with Type-2 DM



- **Insulin pump** (artificial pancreas): insulin is automatically released according to continuous measurement of blood glucose by electronic sensor.

Methods of administration

- S.c. injection (using insulin syringes).
- Portable pen injector (Novo® pen).



Follow up of insulin therapy

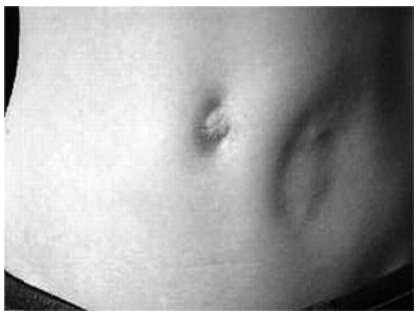
By estimation of glucose in **urine** using urine dipsticks or from **capillary** blood glucose level using portable glucometers.

Indications of insulin

- Type 1 DM.
- Type 2 DM in some conditions:
  - *After failure of oral drugs.*
  - *If the patient of type 2 got **"stress conditions"** e.g. infections, surgery, or pregnancy.*
- Diabetic ketoacidosis: **regular insulin** is the only type used **i.v.**
- Hyperkalemia (insulin + glucose i.v.): insulin ↑ shift of K^+ from blood to tissues.

Adverse effects of insulin

- **Hypoglycemia:** the most common and dangerous side effect.
- **Hypokalemia:** insulin causes shift of K^+ from extra- to intracellular fluid.
- **Hypersensitivity reactions:** urticaria, angioedema or anaphylactic shock.
- **Insulin resistance** (see below).
- **Local adverse effects:**
  - **Allergy:** at the site of injection, especially with animal insulin.
    Treatment:
    - Change the type of insulin.
    - Local corticosteroids.
  - **Lipodystrophy: (atrophy** or **hypertrophy)** of s.c. tissue after repeated injections.
    Treatment: rotating the injection site.
  - **Local infection**.



Insulin resistance (IR)

Definition: failure of the body cells to respond to either endogenous or exogenous insulin. As a result, larger doses of insulin are required to give the desired response.

Causes and mechanism of IR:

- Pre-receptors defect (Immunological): due to formation of antibodies against insulin.
- Receptor defect: due to **down-regulation** of insulin receptors e.g. in:
  - The metabolic syndrome: it is a combination of *central **obesity***, *hypercholesterolemia*, *heart disease, type2 DM* and *IR*.
  - Pregnancy.
  - Severe infection or stress.
  - Drugs: e.g. corticosteroids.

- Post-receptor defect (intracellular): abnormal signal transduction due to **genetic** defect.
- Local insulin resistance: due to degradation of insulin in s.c. tissue by proteolytic enzymes. It is **diagnosed by** changing the route of administration to i.v. injection. If there is good response, then the resistance is local.

Treatment of IR:

- **Life-style modification:**
  - Strict diet control.
  - Weight reduction.
  - Physical exercise.
- Correction of any **precipitating factor:** e.g. **infection** or **stress**.
- **Metformin:** to improve receptor sensitivity and ↓ intestinal glucose absorption (see later).
- **Thiazolidindiones (Insulin sensitizers):** e.g. pioglitazone to ↑ insulin sensitivity (see later).
- Change the site of injection regularly In cases of **local** insulin resistance

Hepatitis C makes people three to four times more likely to develop type 2 DM and insulin resistance.

ORAL ANTIDIABETIC DRUGS

1. Sulfonylureas

- Sulfonylureas are the most widely used medications for the treatment of T2DM.
- All of the sulfonylureas are well absorbed after oral administration and bind to plasma proteins.

Classification

- **First-generation compounds: chlorpropamide, tolbutamide, acetohexamide.**
- **Second-generation compounds: glibenclamide, glyclazide** and **glipizide**; they are up to 200 times more potent than first-generation agents.
- **Third-generation compounds:** e.g. **glimepiride**; these compounds may interact with different cellular proteins than other sulfonylureas.

Mechanism of action

- **Pancreatic action:**
  - Sulfonylureas ↑ **insulin secretion** by pancreatic β cells. They block K^+ channels in β cells, leading to depolarization, increased Ca^{2+} entry via voltage-dependent calcium channels, and increased insulin secretion.
  - They ↓ **serum glucagon**, which opposes the action of insulin.

- **Extrapancreatic action:**
  - They ↑ **insulin receptor sensitivity**, may be by increasing the number of insulin receptors. However, sulfonylureas do not decrease the insulin requirements of patients with type I diabetes.
  - They ↓ **hepatic output of glucose** (gluconeogenesis).

Therapeutic uses

- Type 2 DM (they are not effective in type 1 DM).
- **Chloropropamide** may be used in treatment of nephrogenic diabetes insipidus (it ↑ sensitivity of renal tubules to ADH).

Adverse effects

- **Hypoglycemia** especially with long acting drugs (chlorpropamide) or in elderly patients with hepatic or renal dysfunction .. *(contraindicated in renal failure).*
- Increased appetite and **weight gain.**
- **Pharmacologic failure** is common, initially affecting 15%–30% of patients (1ry failure) and 90% after 6–7 years of therapy (2ry failure). It is due to progressive decline in β cell function.
- **Hepatotoxicity** (cholestatic hepatitis) .. *(contraindicated in liver disease)*.
- **Allergic reactions**.

2. Meglitinides: repaglinide and nateglinide

- They **increase insulin secretion** by the same mechanism like sulfonylureas although the binding site on the β-cells is different.
- They have very **fast onset** and **short duration** so; they are taken **orally** just *before meals* to control **postprandial hyperglycemia**.
- They **don't contain sulfur**, so they can be used in patients allergic to sulfonylureas.
- **Hypoglycemia** is the major side effect.
- They should be used with caution in patients with **hepatic or renal impairment**.

3. Biguanides: metformin

Mechanism of action

- ↓ **intestinal glucose absorption** and ↓ hepatic gluconeogenesis. It does **not** increase insulin secretion (so it doesn't cause hypoglycemia).
- ↑ insulin receptors sensitivity.

Therapeutic uses

- Type 2 DM either alone (in mild cases) or in combination with other drugs.
- To enhance weight loss in **obese patients** (↓ glucose absorption).
- Recent studies showed that metformin is useful in the treatment of **polycystic ovary syndrome (POS)**; it lowers serum androgen levels and restores normal menstrual cycles and ovulation.

Adverse effects

- GIT upset (the most common): anorexia, vomiting, and diarrhea.
- ↓ absorption of vitamin B_{12}: rarely a clinical problem.
- Lactic acidosis: due to increased **anaerobic glycolysis** especially in patients with severe **renal** or **hepatic** diseases or if taken with **alcohol**.

4. Thiazolidinediones (insulin sensitizers): Pioglitazone – Rosiglitazone*

Mechanism of action

- They act on **nuclear genes** called peroxisome proliferator-activated receptor-gamma (PPAR- γ) present in muscles, adipose tissue, and liver cells **leading to:**
  - They ↑ insulin receptor **sensitivity** (by about 60%) and ↓ insulin resistance.
  - They ↑ number of glucose **transporters** →↑ glucose uptake.
  - They have beneficial effect on serum **lipoprotein** levels (↓TGs).
- They have **slow onset** and **prolonged duration** because their mechanism involves gene regulation.

Therapeutic uses: To improve **insulin resistance in type 2 DM.**

Adverse effects

- Hepatotoxicity
- Fluid retention leading to peripheral edema & **weight gain**. (They should be avoided in patients with CHF).

***N.B** pioglitazone is now the only thiazolidinedione on the market.

5. α-Glucosidase inhibitors (starch blockers): Acarbose – Miglitol

- They act by **competitive inhibition of intestinal *α-glucosidase enzyme*** → ↓ digestion & absorption of carbohydrates.
- **GIT side effects** are common: flatulence, diarrhea, abdominal pain.
- They should be avoided in patients with **inflammatory bowel disease.**

NEWER ANTIDIABETIC DRUGS

Incretins are group of metabolic peptides released by gastric and intestinal cells after eating to stimulate insulin secretion and lower plasma glucose. They are rapidly inactivated by the enzyme **dipeptidyl peptidase 4 (DPP-4).** The most important incretin peptide is **glucagon-like peptide-1 (GLP-1).**

1. Incretin (GLP-1) mimetics: Exenatide

Exenatide is a synthetic 39-amino acid GLP-1 analog; **liraglutide** is longer acting analog and more resistant to metabolism.

Mechanism of action

- They ↑ insulin secretion and ↓ glucagon secretion.
- They slow gastric emptying and ↓ appetite.

Therapeutic uses

- Type 2 DM either alone or in combination with **oral drugs**. (It should not be given with insulin).
- They are given **parenterally** (**s.c.**) 60 min **before** breakfast and dinner. (It should not be given **after** a meal).

Major adverse effects: nausea, vomiting, and **pancreatitis** (may be serious).

2. Dipeptidyl peptidase 4 inhibitors (Gliptins): Sitagliptin - Saxagliptin

Mechanism of action

- They **inhibit dipeptidyl peptidase 4 (DPP-4)**, the enzyme responsible for the proteolysis of the incretin GLP-1.
- DPP-4 inhibitors may also **improve β-cell function**.

Therapeutic uses

- Type 2 DM either alone or in combination with **metformin**.
- They are given **orally**; most common **side effects** are headache and nausea.

3. Amylin analogs: Pramlinitide

- **Pramlintide** is a synthetic amylin analog. Amylin is a polypeptide secreted by β-cells of the pancreas, and it acts in concert with insulin to reduce blood sugar.
- It is **injected s.c.,** typically with insulin.
- Common side effects are hypoglycemia and nausea.

Drug interactions with oral hypoglycemic drugs

Drugs potentiate the hypoglycemic effect:	Drugs antagonize the hypoglycemic effect:
▪ Microsomal enzyme inhibitors. ▪ **β-blockers:** ↓ hepatic glycogenolysis ▪ **Salicylates:** displacement of sulfonylureas from plasma proteins.	▪ Microsomal enzyme inducers. ▪ **β-agonists:** ↑ hepatic glycogenolysis. ▪ **Thiazides** and **diazoxide:** they open ATP sensitive K+ channels → ↓ insulin release and ↓ peripheral glucose utilization. ▪ Anti-insulin hormones: e.g. steroids and glucagon.

TREATMENT OF DIABETIC COMPLICATIONS

Hypoglycemic coma

Causes:
- Large dose of insulin or sulfonylurea.
- Missed meal while taking insulin or sulfonylureas.
- Vigorous muscular exercise without dietary adjustment.

Manifestations:
- Sympathetic overactivity: tremors, cold sweating, mydriasis, tachycardia, etc.
- Hunger pain, mental confusion, and coma.

Treatment:
- If the patient is conscious or semiconscious → give oral sugar solution.
- If the patient is in deep coma: (1) i.v. glucose 10%; (2) Glucagon 1 mg i.m.

Hyperglycemic coma (diabetic ketoacidosis; DKA):

Causes:
- Excess food intake.
- Inadequate insulin administration.
- Infection or stress condition.

Manifestations (DKA):
- **D**ehydration and dry shrunken tongue.
- **K**etosis: smell of acetone in breath and ketones in urine.
- **A**cidosis (pH < 7.3) → acidotic breathing (rapid and deep).
- Deep coma in late cases.

Treatment:

- **Fluid replacement:** fluid deficit = 4-5L.
  - Use normal (0.9%) saline. Ringer's lactate is also acceptable choice.
  - Start with 1–2 L/h for the first 2 hours, followed by 500 mL/h for 6 hours.
  - Potassium: is routinely added to the i.v. fluid as 20 mEq KCl/1L.
- **Regular insulin:**
  - Start with a bolus of dose of 0.1 units/kg i.v. followed by an infusion of 0.1 units/kg/hour.
  - Insulin infusion should continue until serum electrolytes, pH, and glucose level are normalized.
  - Glucose 5 % is given when blood glucose falls to ~250 mg/dl *to prevent cerebral edema.*
- **Bicarbonate (HCO_3):** is not routinely given unless there is severe acidosis (pH < 7.1).

Hyperosmolar hyperglycemic state (HHS):

- HHS was previously termed *hyperosmolar hyperglycemic nonketotic coma* (HHNC); however, the terminology was changed because coma is found in fewer than 20% of patients with HHS.
- It is a life-threatening medical emergency that is more common in old age.
- Pathogenesis: severe hyperglycemia causes ↑ water loss (osmotic diuresis) with little sodium loss → severe dehydration with hyperosmolarity. **Ketoacidosis is absent.**

	DKA	HHS
BG	> 250 mg/l	> 600 mg/l
pH	< 7.3	> 7.3
Ketonuria	++	--

Treatment: similar to DKA **except in**:

- **Fluid replacement:** fluid deficit >5L.
  - Rapid and aggressive i.v. isotonic saline is the principal treatment. The patient may require 5-8 L of saline.
  - Fluid replacement alone can reduce glucose levels.
- **Insulin** i.v.i similar to DKA. *Insulin used without concomitant vigorous fluid replacement increases the risk of shock.*
- Hypokalemia is usually less marked but **potassium** may be required early in the treatment.
- **LMWH** to prevent thrombotic complications.

Diabetic neuropathy

Diabetic neuropathy is the most common complication of diabetes mellitus (DM), affecting as many as 50% of patients with type 1 and type 2 DM. It may be cranial, sensory, sensory-motor or autonomic. DN is an irreversible process.

Pathogenesis

- **Advanced glycated end-products:** elevated intracellular levels of glucose cause a non-enzymatic covalent bonding with cellular proteins, causing microvascular damage, ischemia, hypoxia, and nerve damage.
- **Polyol pathway (sorbitol/aldose reductase pathway):** elevated intracellular glucose is converted into sorbitol via the enzyme *aldose reductase*. Sorbitol is toxic to tissues.

Treatment

- Tight, stable glycemic control is the most important factor for slowing progression of DN.
- **For neuropathic pain**, and tingling sensation: duloxetine (antidepressant drug) 30 mg/12h orally (first choice) or pregabalin (second choice).
- **For diabetic gastroparesis:** metoclopramide
- **For erectile dysfunction:** sildenafil

Part 2: Medical Treatment of Obesity

Basic information

Leptin

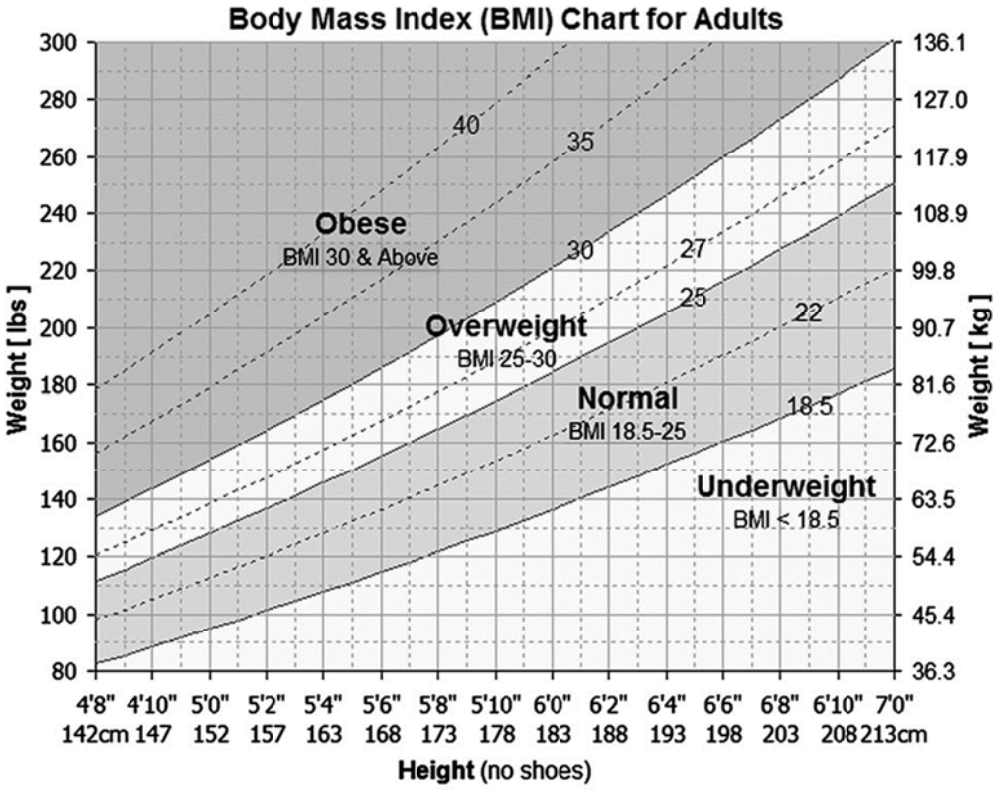
- It is thought to play a key role in the regulation of body weight.
- It is **produced (synthesized)** by **adipose tissue** and **acts on** satiety centers in the hypothalamus to ↓ appetite (i.e. **Leptin induces satiety**).
- As such when patients reach a certain peripheral fat mass, leptin acts as a **lipostat** to **reduce food intake**.

Ghrelin

- **Ghrelin stimulates hunger**.
- It is produced mainly by the fundus of the **stomach** and pancreas.
- Ghrelin levels ↑ before meals and ↓ after meals.

The body-mass index (BMI) – (Kg/m2)

- Normal: 18-25
- Overweight: 25-30
- Obese: >30
- Morbid obesity: >40



Medical treatment

1. Orlistat (Xenical®)

- Orlistat is a **pancreatic lipase inhibitor**. It inhibits digestion and absorption of dietary fats leading to weight loss.
- Orlistat is normally used for <1 year. Patients fail to lose at least 5% of their bodyweight within 3 months, orlistat should be discontinued.
- **Adverse effects** include steatorrhea and flatulence.

2. Lorcaserin (Belviq®)

- It is recently approved selective **5-HT_{2C}** receptor **agonist** in the hypothalamus leading to weight loss through **satiety.**
- It is used for long term control of obesity.
- **Adverse effects** are mild and include mainly **headache.**

3. Liraglutide (Saxenda®)

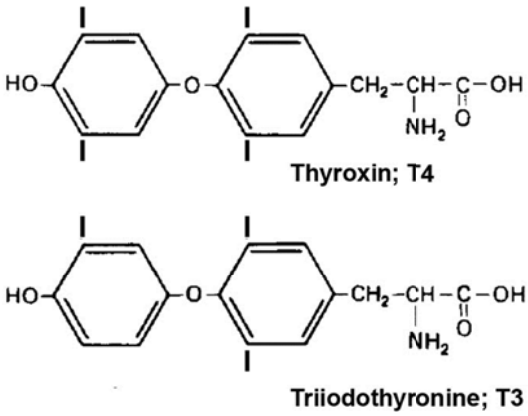
- It is an **injectable** long acting glucagon-like peptide-1 receptor agonist, binding to the same receptors as does the endogenous hormone GLP-1 that stimulates insulin secretion.
- It is developed principally for treatment of type 2 DM. In 2015, it was approved for treatment of morbid obesity in adults.

4. Sibutramine (Meridia®)

- **Centrally acting appetite suppressant** related to **amphetamine** (inhibits uptake of 5-HT and noradrenaline at hypothalamic sites that regulate food intake).
- **Adverse effects:** hypertension, arrhythmia, insomnia, and headache.
- It has been withdrawn in 2010 from the USA due to an increased risk of cardiovascular events, but still available in many countries including Egypt and Middle East.

Part 3: Thyroid Gland and Antithyroid Drugs

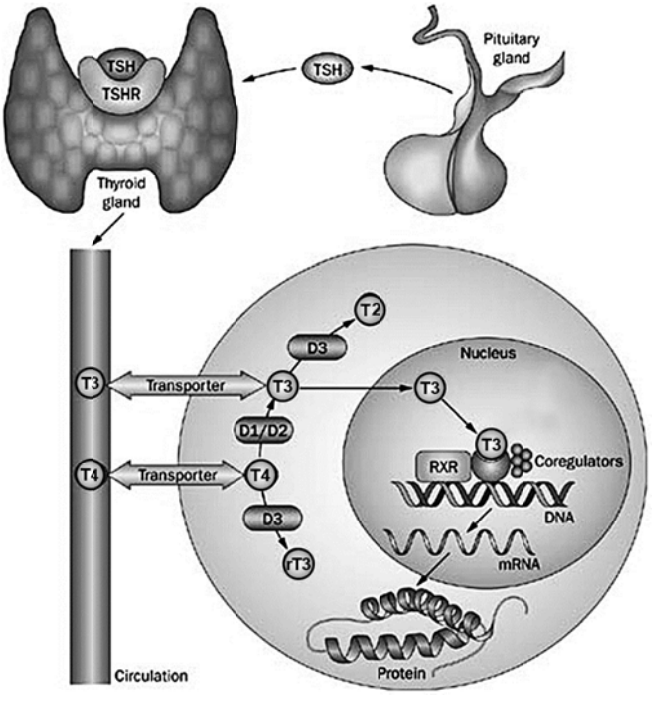
General principles



- The major hormone secreted by the thyroid is thyroxine (T_4), which is **deiodinated** in many tissues to the more potent triiodothyronine (T_3). Both are bound reversibly to thyroxine-binding globulin (TBG). Only the free (unbound) fraction enters cells and produces biological effects.
- The most important step in the process of thyroid hormone synthesis is **oxidation** (organification) of iodides by **peroxidase enzyme** to produce molecular iodine, which then attaches to tyrosine to form mono- and diiodotyrosine. T4 is formed by **coupling** of 2 diiodotyrosines, and T3 by coupling of diiodothyrosine with mono-iodotyrosine.
- T4 secretion is stimulated by thyroid-stimulating hormone (TSH). In turn, TSH secretion is inhibited by T4, forming a negative feedback loop.
- The gland synthesizes T4 > T3 (20:1) but T3 is 4-times more potent than T4.
- Most of the circulating T3 is derived from peripheral deiodination of T4.
- **B-blockers** and **corticosteroids** inhibit peripheral conversion of T4 into T3.

Preparations of thyroid hormones

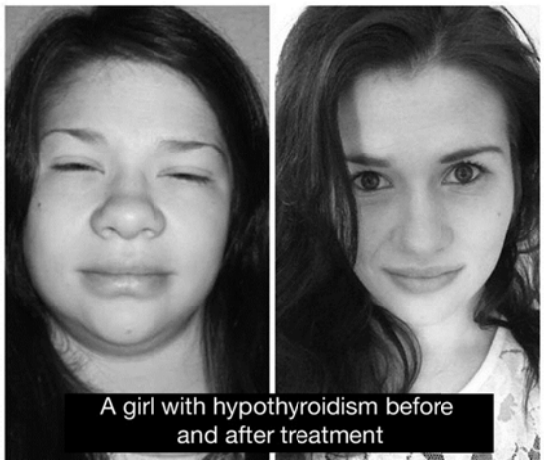
- **L-thyroxine:** a synthetic sodium salt of **T4** that maintains normal T4 and T3 levels (t ½ is 7 days).
- **Liothyronine:** a synthetic sodium salt of **T3** (t ½ is 1 day).



Mechanism of action

- T3 & T4 diffuse through the cell membranes and bind to cytoplasmic receptors then transported to the **nucleus and mitochondria**, where it interacts with many **DNA receptors (genes)** and affect their function.
- Most of T3 & T4 receptors are found in pituitary, liver, kidney, heart, sk ms.
- T3 & T4 are responsible for optimal growth and development.

Hypothyroidism (myxedema)

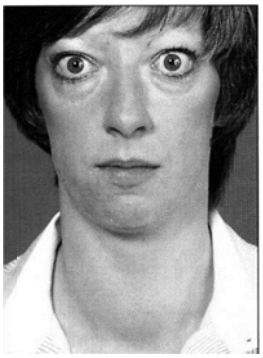


- Hypothyroidism in infants leads to **cretinism** (myxedema with physical and mental retardation).
- It is treated by replacement with **L-thyroxin** (T4). The therapeutic goal is 'normalization' of the TSH level.
- Children require more T4 than adults to maintain optimal physical and mental development.
- T3 (Liothyronine) is not used for replacement therapy because L-thyroxin (T4) can maintain normal T4 and T3 levels, and also because T3 has **shorter t½** .

Hyperthyroidism (thyrotoxicosis)

Definition: It is a clinical syndrome results from high levels of thyroid hormones.

Clinical types



- **Graves' disease:**
  - It is autoimmune disease in which there are abnormal antibodies *(thyroid stimulating immunoglobulins)* activates TSH receptors in the thyroid gland.
  - The gland is diffusely enlarged and soft.
  - The treatment is usually medical.
- **Toxic multinodular goiter:** treatment is usually surgical.
- **Less common types:** e.g. subacute (de Quervain's) thyroiditis. It is due to viral infection.

The term "goiter" means any thyroid swelling which is neither inflammatory nor neoplastic. Thyroid enlargement may occur with hypo- or hyperthyroidism.

Clinical picture

- Most manifestations of hyperthyroidism resemble sympathetic overactivity because thyroxin increases sensitivity of adrenergic β-receptors to circulating catecholamines.
- There are tachycardia, arrhythmia, sweating, lid lag, exophthalmos, etc.

Investigations

- Measuring serum T3, T4, and TSH **(the most important test):** T4 is ↑ and TSH is ↓.
- Assay for positive anti-thyroid antibodies: 90% +ve in Grave's disease.
- Thyroid scan for tumors.

Management

There are **2** main lines for treatment:

- **Medical treatment:** mainly for Grave's disease.
- **Surgical thyroidectomy:** mainly for multiple nodular goiter

MEDICAL TREATMENT (ANTITHYROID DRUGS)

1. Thiouracil drugs (thioamides)
(Carbimazole – Methimazole - Propylthiouracil)

Pharmacokinetics

- Methimazole is the active metabolite of carbimazole.
- The $t_{1/2}$ of propylthiouracil is 1.5 hr while the $t_{1/2}$ of methimazole is 6 hrs.
- The short t½ of these drugs has little effect on their effect because they are selectively accumulated in the thyroid.
- Propylthiouracil is preferable during **pregnancy** because it does not cross placental barrier (because it is strongly bound to plasma protein).

Mechanism of action

- They inhibit **oxidation** of iodides into iodine by inhibiting *peroxidase enzyme.* Consequently, they inhibit **iodination** of tyrosine and **coupling** of iodotyrosine to form iodothyronines.
- Propylthiouracil also inhibits the **peripheral conversion** of T4 into T3.
- Clinical response appears after 3-4 weeks till the stored hormones are depleted from the gland (but **propylthiouracil has faster effect,** so it is used in thyrotoxic crisis).

Doses and duration

- **Carbimazole (Neomercazole):** start with 30 mg/d till reach euthyroid state (after ~4-8 weeks) then maintain on 15 mg /d for **12-18 months** *(until the gland undergo spontaneous remission).*
- **Propylthiouracil:** start with 300 mg/d for 4-8 w then 150 mg/d for **12-18 months**.

Adverse effects

- **Agranulocytosis & bone marrow depression (<1%):** it is the most dangerous side effect but it is usually reversible (see chapter Blood).
- Hypothyroidism with **increased size and vascularity** of the gland due to ↑ TSH.
- Hypothyroidism of the infant (**fetal goiter**) if given during pregnancy *(less common with PTU)*.

- **Hepatotoxicity** that may be fatal *(more with propylthiouracil)*.
- **Hypersensitivity reactions:** may require stopping of the drugs.
- There is **50-68%** incidence of **relapse**.

Precautions during thiouracil treatment

- Therapy with thiouracil drugs should continue for **1-2 years** and should be **stopped gradually** (to prevent relapse).
- Agranulocytosis is prevented by **repeated WBC count** and by observing early manifestations of the disease (sore throat & fever).
- If used during **pregnancy,** propylthiouracil is the drug of choice.

2. Radioactive iodine

Radioactive iodine is an effective **oral** treatment for thyrotoxicosis caused by **toxic multinodular goiter**. It is relatively **'safe'** and has largely replaced surgery (unless there is huge gland causing pressure symptoms).

Mechanism of action

- The isotope usually employed is **^{131}I** with a t ½ of **8** days.
- Radioactive **^{131}I** is selectively accumulated in the thyroid tissue (normal or metastatic) and emits **β rays** that destroy the gland. After 6-12 weeks of administration, the gland will shrink in size and the patient becomes euthyroid.
- **Delayed hypothyroidism** is the main adverse effect (80%); the majority of patients will require thyroxin supplementation after 5 years.

Contraindications

- **Pregnancy and lactation**: ^{131}I crosses placental barrier and excreted in milk.
- **Age < 16 years** for fear of delayed malignant changes and gonadal damage.
- **Thyroid eye disease (exophthalmos; ophthalmopathy):** radioiodine may worsen the condition.

3. β-blockers (Propranolol)

- It controls sympathetic overactivity e.g. tachycardia and arrhythmia.
- It ↓ insomnia, and tremors (blocks central and peripheral β2 receptors).
- It inhibits peripheral conversion of T4 to T3.

N.B. If propranolol is contraindicated, give **diltiazem** to control tachycardia and arrhythmia (other CCBs are less effective).

SURGICAL TREATMENT: subtotal thyroidectomy

Indications

- Failure of the medical treatment.
- Multinodular goiter with tracheal compression.
- Presence of malignancy.

Preparation of patient before operation

- **Carbimazole:** 10 mg t.d.s. 6 weeks before the operation to reach euthyroid state.
- **Potassium iodide:** 10-14 days before operation to ↓ size and vascularity of the gland (see below).
- **Propranolol:** to control HR and cardiac arrhythmia.
- **Sedatives** (diazepam): to ↓ anxiety.

Iodides

- Potassium iodides or Lugol's iodine, 5 drops twice daily is given **10-14 days** before surgery in order to:
  - Iodides inhibit synthesis and **release of T4 & T3** from the gland by inhibiting the **proteolytic enzymes** that release T4 & T3 from thyroglobulin (the main mechanism).
  - They inhibit **release of TSH** leading to ↓ **size and vascularity of the gland**.
- Improvement in thyrotoxic symptoms occurs within 2–7 days, but if therapy with iodides is continued (>2-4 weeks), the beneficial effects disappear and manifestations of hyperthyroidism reappear **(iodine escape).**

Adverse effects

- Iodides are secreted in saliva, nasal, and lacrimal secretions causing **metallic taste** and **irritation** of the salivary glands, mucous membranes and gastric mucosa. They increase lacrimal and nasal secretions.
- **Iodine escape** if used > 2-4 weeks.
- Iodides increase intraglandular stores of iodine, which may **impair** uptake of thiouracil drugs or radioactive iodine by the gland. So, during preoperative preparation, they must be given **after thiouracil drugs** (or radioactive iodine), **not before them**.
- Allergic reactions: skin rash, drug fever, etc.

Thyrotoxic crisis (thyroid storm)

It is a sudden severe exacerbation of the manifestations of thyrotoxicosis due to sudden release of T3 & T4 (medical emergency). It is a common postoperative complication if the patient was not well-prepared.

Manifestations
- High fever with vomiting and sweating.
- Tachycardia, arrhythmia, acute heart failure, and shock.
- Convulsions, coma, and even death from heart failure.

Management

- **Intravenous fluids** and **Paracetamol** to control dehydration and fever.

  N.B. Aspirin must be avoided, because salicylate displaces bound T4 and T3, and also because of its uncoupling effect on oxidative phosphorylation renders the metabolic state even more severe.

- **Propranolol** (1-2 mg slowly i.v. or 40 mg oral /6 h) to control arrhythmia.
  - **Esmolol** is a short-acting β-blocker can be also given by i.v.i.
  - If β-blockers are contraindicated give **diltiazem** by i.v. infusion.
- **Potassium iodides:** 10 drops orally/day to block hormone release and peripheral conversion of T4 to T3.
- **Propylthiouracil:** 250 mg/6 hrs orally to block hormone synthesis. It acts more rapidly than other thiouracil drugs.
- **Hydrocortisone:** 100 mg i.v./6-8 h to elevates BP and reduces toxemia. It also blocks peripheral conversion of T4 to T3.
- **Plasmaphoresis** in severe cases to reduce circulating thyroxin.

Management of myxedema coma

Myxedema coma is an end state of untreated hypothyroidism. There is progressive weakness, hypothermia, hypoventilation, hypoglycemia, hyponatremia, water intoxication, shock, and death. It carries high mortality and is a medical emergency.

Management

- **Hospitalization** (**ICU):** artificial respiration may be required.
- **L-thyroxine (T4):** 400 µg i.v. initially, followed by 50 µg daily orally. **Intravenous T3** can be used.
- **Hydrocortisone:** 100 mg i.v./ 6-8 h because the patient usually has associated adrenal insufficiency.
- **Intravenous fluids** with caution to avoid excessive volume overload.

Part 4: Adrenocortical Steroids

Classification:
- **Glucocorticoids:** have mainly anti-inflammatory action.
- **Mineralocorticoids:** have mainly Na & water retaining action.
- **Sex hormones:** are mainly anabolic.

Glucocorticoids

	Anti-inflam potency	Na^+ retention potency	Duration of effect
Short-acting glucocorticoids:			
Hydrocortisone (cortisol)	**1**	**1**	8-12 h
Prednisone and Prednisolone	4	0.5	
Methylprednisolone	5	0.1	
Intermediate-acting glucocorticoids:			
Triamcinolone	5	0.1	12-36 h
Paramethasone	10	0.01	
Long-acting glucocorticoids:			
Dexamethasone	30	0.01	48 h
Betamethasone	30	0.01	
Aldosterone:	0.3	3000	

- Hydrocortisone (cortisol) is the natural (endogenous) glucocorticoid.
- Equivalent dose means 20 mg of hydrocortisone = 5 mg of prednisolone.
- Steroids with high anti-inflam action *(e.g. dexamethasone)* are better used for inflammatory conditions e.g. **rheumatic fever**, while those with high Na & H_2O retention *(hydrocortisone)* are better used for treatment of hypotension and **shock** states (they also have rapid action).

Pharmacokinetics

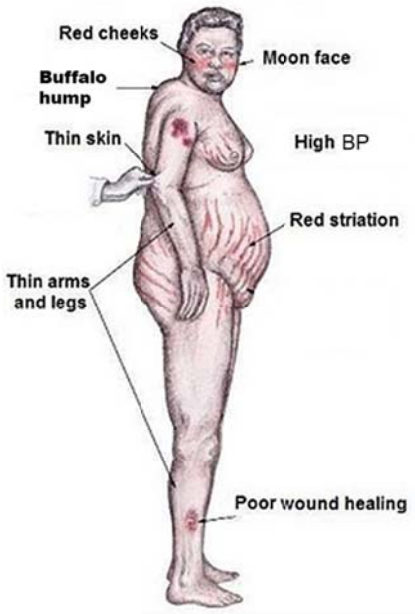
- All glucocorticoids are completely & rapidly absorbed by **all routes**.
- 80% of hydrocortisone is bound to plasma globulin, 10% to albumin.
- Plasma t ½ varies according to type (60-90 min for hydrocortisone). However, the effect of glucocorticoids is **prolonged** due to its effect on gene functions.
- Metabolism is by the liver and excretion is by the kidney.

Mechanism of action

Corticosteroids bind first to cell surface receptors then to cytoplasmic receptors

(carriers), then transported to the **nucleus**, where it interacts with many **DNA receptors** (steroid response elements) and affect their function.

Pharmacological effects:



- **On metabolism: (Cushing syndrome):**
  - Carbohydrate metabolism: hyperglycemia (↓ peripheral glucose utilization).
  - Protein metabolism: Catabolic effect → ↓ muscle mass and thin limbs.
  - Fat metabolism: ↑ lipolysis with redistribution of fat (moon face & buffalo hump).
  - On water and electrolyte balance: Na^+ & water retention and hypokalemia.
- **Anti-inflammatory and anti-immunological effects:**
  - They inhibit B cell function → ↓ antigen-antibody reaction.
  - They inhibit T cell functions → ↓ inflam mediators and cytokine release.
  - They inhibit macrophage activity and stabilize lysosomal membranes.
  - They inhibit mast cells → ↓ histamine release and capillary permeability.
  - They inhibit *phospholipase A2* enzyme → ↓ synthesis of PGs & LTs.
- **On CVS:** Hypertension due to:
  - Na^+ & water retention.
  - Increase sensitivity of BV and heart to circulating catecholamines.
- **Anti-shock effects:** due to:
  - Hypertensive and CVS effects (mention them).
  - Anti-inflammatory action (mention them).
- **Hematological effects:**
  - ↑ RBCs and neutrophils and ↓ lymphocytes and eosinophils.
  - ↑ coagulation factors and blood cholesterol.
- **On growth:** Growth retardation, which is not prevented by growth hormone.
- **On bone:** ↓ bone matrix and ↑ Ca^{2+} excretion (osteoporosis).

Administration

- Drug administration should follow the **circadian rhythm**: A double dose is given in the morning, and a single dose is given in the afternoon.

- **Alternate-day therapy** is clinically effective with minimal effect on the adrenal-hypothalamic-pituitary axis. In this therapy, double the dose of short- or intermediate-acting glucocorticoids is administered every other day.
- Glucocorticoids should be stopped **gradually** after long term administration.

Therapeutic uses

- **Inflammatory disorders:** e.g. iridocyclitis, neuritis, dermatitis, etc.
- **Autoimmune disorders:** e.g. vasculitis, rh fever, rh arthritis, hemolytic anemia, nephrotic syndrome, ulcerative colitis, etc.
- **Allergic disorders:** e.g. anaphylactic shock, urticaria, eczema, bronchial asthma, allergic conjunctivitis, etc.
- **Malignancy:** e.g. lymphoma, leukemias, multiple myeloma, etc.
- **Shock and hypotension…..Why?**
- **Organ transplantation:** as immunosuppressive to prevent graft rejection.
- **Cerebral edema:** dexamethasone is used after brain surgery to minimize inflammatory edema associated with tissue injury.
- **Acute hypercalcemia:** to enhance Ca^{2+} excretion.
- **As replacement therapy in acute and chronic adrenocortical insufficiency (Addison's disease).**

  N.B. Acute adrencortical insufficiency (acute Addisonian crisis):
  - Prolonged corticosteroid therapy produces feedback inhibition of ACTH and inhibition of endogenous cortisone secretion. When exogenous corticosteroids are suddenly stopped, severe hypotension and shock occurs.
  - Management:
    - i.v. fluids (saline).
    - Hydrocortisone 100 mg i.v./8h until the patient is stable.
    - ACTH: 0.5 mg i.m.

- **Stimulation of lung maturation in the fetus:**
  Lung maturation in the fetus is regulated by fetal secretion of cortisol. When delivery is anticipated before 34 weeks of gestation, **betamethasone** is given to reduce the incidence of respiratory distress syndrome in the infant. Betamethasone is chosen because its maternal protein binding is less than other steroids, allowing increased transfer across the placenta to the fetus.

Adverse effects

Most of these side effects occur after **long duration** of therapy:

- **Iatrogenic Cushing syndrome:** occurs if doses up to 100 mg hydrocortisone are used daily for > 2 weeks. It is characterized by moon face, buffalo hump, thin limbs, osteoporosis, hypertension, DM, edema, etc.
- **Immune suppression** leading to flaring of infections (especially viral and TB).
- **Hypertension** due to salt & water retention
- **Hyperglycemia.**
- **Peptic ulcer:** due to prolonged inhibition of gastroprotective PGs.
- ↑ **IOP (Glaucoma)**: due to ↓ aqueous humor drainage.
- **Osteoporosis.**
- **Growth retardation** in children.
- **Skin atrophy** & hypopigmentation after prolonged topical use.
- **Sudden withdrawal** after prolonged administration causes **acute addisonian crisis.**

Contraindications

- **Presence of infections:** especially viral infection and TB.
- **DM**.
- **Hypertension & heart failure:** they cause salt and water retention.
- **Peptic ulcer:** they ↓ synthesis of PGE_2 and I_2 that protect the stomach.
- **In early pregnancy:** may cause cleft palate.

N.B. Uses of corticosteroids in presence of T.B:
- TB meningitis: to prevent adhesions.
- TB of the suprarenal gland: to replace hypofunction.
- Miliary TB: to ↓ TB toxemia.

Mineralocorticoids

1. Natural mineralocorticoids: Aldosterone

Physiological actions: It binds to specific intracellular receptors in the DCT to inhibit Na^+ excretion (hypernatremia) and stimulates K^+ and H^+ excretion (hypokalemia).

2. Synthetic mineralocorticoids:

- **Deoxycorticosterone acetate (DOCA):** it has mainly mineralocorticoid effect.
- **Fluodrocortisone:** it has both gluco- and mineralocorticoid effects.

Part 5: Regulation of calcium metabolism (Bone mineral homeostasis)

1. Primary hormonal regulators of Ca^{2+} metabolism and bone mineral homeostasis:

Parathormone (PTH)	Calcitonin (CT)	Vitamin D
It is a single chain polypeptide secreted by the parathyroid glands. Its secretion is **not under pituitary control** but controlled by the level of serum Ca^{2+}.	It is a single chain polypeptide secreted by the C-cells of the thyroid. Its secretion is **not under pituitary control** but controlled by the level of serum Ca^{2+} and vitamin D.	It is fat-soluble vitamin found in **2** forms: ▪ **Vitamin D_2** (ergocalceferol): plants. ▪ **Vitamin D_3** (cholecalceferol): animals, and can be synthesized in human skin by the action of UV rays. The two forms must be activated by 2 OH at site **25** (liver) and **1** (kidney).
Mechanism and effects: PTH acts on specific receptors in bone and kidney leading to ↑ serum Ca^{2+} and ↓ PO_4 through: – **Bone:** ↑ bone resorption. – **Intestine:** ↑ Ca^{2+} absorption *(through activation of vit D).* – **Kidney:** ↑ Ca^{2+} reabsorption and PO_4 excretion.	**Mechanism and effects:** CT acts on specific receptors in bone and kidney leading to ↓ serum Ca^{2+} and PO_4 through: – **Bone:** ↓ bone resorption. – **Intestine:** ↓ Ca^{2+} absorption. – **Kidney:** ↓ reabsorption of Ca^{2+} and PO_4.	**Mechanism and effects:** Vit D acts on DNA receptors to synthesize proteins necessary for Ca^{2+} transport. – **Bone: the effect is complex:** when bone Ca^{2+} is deficient (rickets), vit D ↑ Ca^{2+} deposition (calcification) but excess vit D in normal subjects leads to bone resorption and hypercalcemia. – **Intestine:** ↑ Ca^{2+} absorption from the intestine. – **Kidney:** ↑ Ca^{2+} and PO_4 reabsorption.
Therapeutic uses:	**Therapeutic uses:**	**Therapeutic uses:**

Synthetic PTH **(teriparatide)** in low and intermittent doses may stimulate bone formation and can be used for **treatment of osteoporosis.**	Salmon CT (parenteral or intranasal) can be used for: ▪ Treatment of hypercalcemia and hyperphosphatemia. ▪ Treatment of osteoporosis. ▪ Treatment of Paget's disease of bone.	▪ Treatment of hypocalcemia and hypophosphatemia. ▪ Treatment of osteoporosis. ▪ Treatment of rickets (children) and osteomalacia (adults). **Drug interactions:** – Phenytion and phenobarbitone **(antiepileptic drugs)** stimulate hepatic microsomal enzymes → **↑ vitamin D metabolism**. So epileptic patients on long term therapy may develop osteomalacia or rickets. – Cholestyramine ↓ vitamin D absorption. – Thiazides ↑ the hypercalcemic effects of vitamin D.

2. Secondary hormonal regulators of Ca^{2+} metabolism and bone mineral homeostasis:

Glucocorticoids	Estrogen
▪ Prolonged administration of glucocorticoids can cause osteoporosis in adults and retarded growth in children due to **↑ renal Ca^{2+} excretion** and **↓ bone formation.** Also it antagonize intestinal vitD-stimulated Ca absorption ▪ Glucocorticoids can be used to **treat hypercalcemia** associated with lymphomas and sarcoidosis.	▪ Bone contains estrogen receptors. Estrogen administration ↑ blood levels of vitamin D and **↓ bone resorption**. ▪ Estrogen is used in the treatment of **postmenopausal osteoporosis,** but prolonged administration is not recommended because it may cause many side effects (e.g. breast cancer and endometrial carcinoma). ▪ **Selective Estrogen Receptor Modulators (e.g. Raloxifene)**, were developed to stimulate estrogen receptors in bones and block them in the breast and uterus (i.e. mixed agonist-antagonist).

3. Non-hormonal regulators of Ca^{2+} metabolism and bone mineral homeostasis:

Bisphosphonates (risedronate and zoldronic acid)	Thiazides	Fluoride
– They are analogs of pyrophosphate in which the P–O–P bond is replaced by the stable P–C–P bond. – After oral administration, all bisphosphonates have very poor (1–3%) oral absorption that is decreased by food. Recommendation is to administer on an empty stomach with a full glass of water and remain standing for 30 minutes. **Mechanism:** They inhibit many osteoclastic cell functions and induce cause **apoptosis** of osteoclasts. **Uses:** ▪ Treatment of hypercalcemia associated with malignancy and bone lesions associated with **bone metastasis.** ▪ Treatment of osteoporosis. ▪ Treatment of Paget's disease of bone and syndromes of ectopic calcification. **Side effects:** High doses can cause **renal impairment** and **osteonecrosis of the jaw.**	Thiazides are used to **decrease renal Ca^{2+} excretion** through ↑ the effect of PTH in stimulating renal Ca^{2+} reabsorption.	Fluoride is well-established for the prophylaxis of **dental caries** and is under investigation for the treatment of osteoporosis. Fluoride is accumulated in bones and teeth causing **stabilization of the hydroxyapatite crystal**.

Hypercalcemia

Causes: In over 90% of cases hypercalcemia is due to either **hyperparathyroidism** or **malignancy** (especially myeloma). Hypercalcemia normally suppresses PTH and so PTH is therefore the best first test to identity the cause of hypercalcemia.

Management of acute hypercalcemia

- Saline diuresis: 500-1000 ml/hour plus furosemide to increase urine flow and enhance Ca^{2+} excretion.
- Hydrocortisone: 100 mg i.v. to enhance Ca^{2+} excretion.
- Intravenous bisphosphonates.
- Hemodialysis especially when renal failure is present.

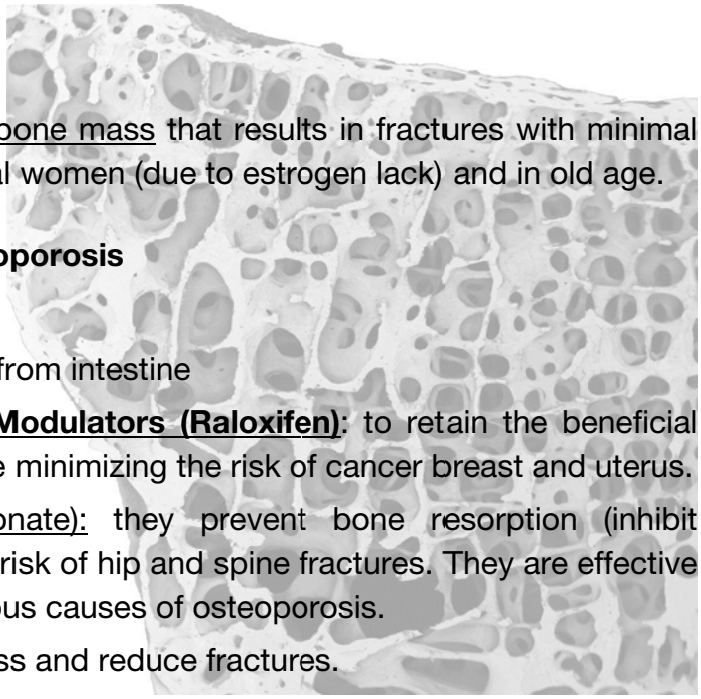
Hypocalcaemia

Causes: Hypoparathyroidism (N.B. tetany occurs when serum Ca^{2+} falls < 7mg/dl), chronic renal failure, vitamin D deficiency, etc.

Treatment

- Diet rich in calcium and low in phosphate
- Calcium gluconate: slowly i.v. (in acute conditions).
- Vitamin D: to ↑ Ca^{+2} absorption from intestine.
- Thiazide diuretics.

Osteoporosis



Definition: it is a condition of low bone mass that results in fractures with minimal trauma. It occurs in postmenopausal women (due to estrogen lack) and in old age.

Prevention and treatment of osteoporosis

- Diet rich in **calcium**.
- **Vitamin D**: to ↑ Ca^{+2} absorption from intestine
- **Selective Estrogen Receptor Modulators (Raloxifen)**: to retain the beneficial effects of estrogen on bone while minimizing the risk of cancer breast and uterus.
- **Bisphosphonates** (e.g. risedronate): they prevent bone resorption (inhibit osteoclastic activity) and reduce risk of hip and spine fractures. They are effective in both men and women for various causes of osteoporosis.
- **Calcitonin:** to increase bone mass and reduce fractures.
- **Teriparatide:** a recombinant form of PTH that has been recently approved for treatment of osteoporosis. It stimulates new bone formation and reduces risk of fractures.

- **Slow release fluoride preparation**: is a new treatment. It may reduce rates in postmenopausal osteoporosis.

Drug-induced osteoporosis

1. Corticosteroids.
2. Heparin.
3. Interferons.
4. Alum containing antacids.

Part 6: Sex Hormones

I. Estrogen

- **Natural estrogens:** estradiol, estrone and estriol
- **Semisynthetic estrogens:** Ethinyl estradiol and mestranol.
- **Synthetic estrogens:** diethyl stilbosterol.

Physiologic effects

- Normal development of genital tract and breast.
- Development of ♀ secondary sex characters.
- Metabolic effects:
  - Increase bone mass and prevent bone resorption.
  - Increase blood glucose and TGs.
  - Salt and water retention.
- Increase blood coagulation and platelet adhesiveness.

Therapeutic uses

- Contraceptive pills.
- Dysfunctional uterine bleeding.
- Replacement therapy in ovarian hypofunction.
- Postmenopausal symptoms e.g. atrophic vaginitis and osteoporosis.
- Cancer prostate.

Adverse effects and contraindications: see contraceptive pills.

II. Anti-estrogens:

1. Clomiphene citrate (Clomid)

- Clomiphene blocks estrogen receptors in hypothalamus and pituitary → ↑ FSH and LH → stimulate ovulation.
- It is used to **stimulate ovulation** in infertile women with normal pituitary function.
- **Adverse effects:** Ovarian enlargement and hot flushes.

2. Selective estrogen receptor modulators (SERMs):

- SERMs are ligands for the estrogen receptor that have agonist activity in one tissue but may have antagonist activity or no activity in another tissue.
- Currently, there are three SERMs: tamoxifen, raloxifene, and toremifene.

Tamoxifen

- It is an estrogen antagonist in the breast but is an agonist in the uterus and bone.
- It is used in the treatment of advanced, estrogen receptor positive **breast cancer** and for primary prevention of breast cancer in women at high risk.
- **Adverse effects:** tamoxifen increases the risk of endometrial cancer and thrombotic complications.

Raloxifene

- It is an agonist in bone but has no effect on the uterus or breast.
- It is used for the treatment and prevention of postmenopausal **osteoporosis**.
- **Adverse effects:** hot flashes and thrombotic complications.

3. Aromatase inhibitors:

- Aromatase is the enzyme that catalyzes the production of estrogens from androgenic precursors within the ovary and peripheral tissues.
- Aromatase inhibitors are a new class of oral estrogen synthesis inhibitors.
- **Anastrazole** and **letrozole (Femara)** are nonsteroidal competitive inhibitors of aromatase. **Exemestane** is a steroidal, irreversible aromatase inhibitor.
- These drugs are used for treatment of postmenopausal women with estrogen-receptor positive **breast cancer** who have received two to three years of tamoxifen and are switched to them for completion of a total of five years of adjuvant hormonal therapy.

II. Progesterone and progestins

- **Natural:** progesterone injection
- **Synthetic:** medroxy progesterone acetate.

Therapeutic uses

- Contraceptive pills.
- Dysfunctional uterine bleeding
- Dysmenorrhea and endometriosis.
- Threatened abortion.

Adverse effects

- Breakthrough bleeding.
- Increase risk of birth defects if given in early pregnancy.
- Liver dysfunction.

Antiprogesterone: Mifepristone

- It is a competitive blocker of progesterone receptors.
- It is used with $PGF_{2\alpha}$ to induce **medical abortion** in the first trimester.

III. Androgens and anabolic steroids

- **Natural androgens:** androsterone and testosterone
- **Synthetic androgens:** testosterone propionate.
- **Anabolic steroids:** nandrolone and stanazol.

Uses of androgens and anabolic steroids:

- Chronic debilitating diseases e.g renal failure.
- Chronic refractory anemia: e.g. sickle cell anemia, aplastic anemia.
- Illicit use by athletes: to increase muscle bulk and strength.

Adverse effects

- Reduction in spermatogenesis after stopping.
- Precocious puberty and premature closure of epiphysis in children.
- Cholestatic jaundice.
- Verilizing effects in females.

Contraindications

- Prostatic tumors (benign and malignant).
- Liver diseases
- Children.

Antiandrogens

1. 5 α-reductase inhibitors: Finasteride

- It inhibits ***5 α-reductase enzyme*** responsible for **conversion** of testosterone into the **active** form dihydrotestosterone (DHT).
- It is used in:

- Treatment of benign prostatic hyperplasia.
- Treatment of male baldness.
- Treatment of hirsutism in females.

2. Testosterone receptor blockers:

- **Cyproterone acetate:** is a competitive blocker of testosterone receptors. It is used in male hypersexuality, and hirsutism in females.
- **Flutamide:** used in cancer prostate.
- **Others: Spironolactone** is a competitive blocker of both aldosterone and testosterone receptors. It is used in hirsutism in females.

HORMONAL CONTRACEPTIVES

Types of hormonal contraceptives

- **Combined preparations** (the most effective type): contain both estrogen + progesterone given from the 5th day of menstruation for 21 days.
- **Single entity preparations:**
  - Progesterone alone (minipills): Don't affect lactation and don't carry risk of thrombosis but can cause uterine bleeding.
  - Estrogen alone (postcoital pills or morning-after pills): It is used within 72 hrs after sexual intercourse for 5 days.
  - Slow release progestins: Medroxyprogesterone acetate (Depo-Provera®) given i.m. every 3 months. It is suitable for unreliable women.
  - Implantable progestin preparation.

Mechanism of action

- They **inhibit ovulation** by exerting –ve feedback on LH (progesterone) and FSH (estrogen) secretion.
- Produce **endometrial changes** and interferes with **coordinated contraction** of the cervix, uterus, and fallopian tubes → ↓ sperm transport and fertilization.
- **Increase viscosity** of cervical mucus to inhibit sperm penetration.

Adverse effects

CVS: the most serious side effects especially in women above 35 years and in women who are smokers:

- Hypertension and increase risk of myocardial infarction.

- Thrombosis and thromboembolic catastrophes.
- Increase TGs levels.

CNS:
- Migraine headache.
- Cerebral hemorrhage (stroke) is 2-10 times higher.
- Mood changes and depression.

GIT:
- Nausea and vomiting.
- Cholecystitis and gall stones.
- Cholestatic hepatitis and hepatotoxicity.

Endocrinal:
- Hyperglycemia and DM.
- Weight gain and edema due to salt and water retention.
- Inhibition of lactation in lactating women.
- Menstrual irregularities: spotting bleeding, breakthrough bleeding, amenorrhea, and dysmenorrhoea.
- Loss of libido, acne, and hirsutism.

Cancer: increased risk of breast cancer.

Contraindications
- Hypertension or ischemic heart disease (IHD).
- History of embolism, thrombosis or cerebral hemorrhage.
- History of cancer breast or estrogen-dependent neoplasm.
- Migraine headache.
- Chronic liver disease and gall stones.
- Diabetes mellitus.
- Obese, smokers, or women over 35 years.
- Pregnancy.
- Depression.

N.B Causes of failure of contraceptive pills:
- If taken with **enzyme inducers** e.g. rifampin, phenytoin, etc.
- If woman taking **broad spectrum antibiotics** e.g tetracyclines *(see breakthrough pregnancy in general pharmacol).*
- **Paraffin oil** (laxative) ↓ intestinal absorption of contraceptive pills.

Part 7: Hypothalamic and Pituitary Hormones

ANTERIOR PITUITARY HORMONES

Growth hormone (GH)

GH promotes longitudinal bone growth and cartilage synthesis through stimulation of hepatic synthesis of **insulin-like growth factors** (somatomedins).

Therapeutic uses

- Replacement therapy in children with GH deficiency.
- Illicit use by athletes to increase body mass.

Adverse effects:

- Children may develop scoliosis during rapid growth.
- Peripheral edema and carpal tunnel syndrome.
- Hypothyroidism and gynecomastia.

Growth hormone antagonists: Octreotide

- It is a synthetic somatostatin analog.
- It is more potent and has longer duration than somatostatin.

Therapeutic uses

- Acromegaly.
- Hormone-secreting tumors (e.g. insulinoma, glucagonoma, gastrinoma, etc).
- Bleeding esophageal varices (given by i.v.i., it causes VC of splanchnic bl vessels and controls variceal bleeding with fewer side effects than vasopressin; see GIT).

Adverse effects: Bradycardia and conduction disturbances.

Adrenocorticotrophic hormone (ACTH)

ACTH is secreted by the pituitary to stimulate release of glucocorticoids, meniralocorticoids, and sex hormones. It also stimulates MSH → skin pigmentation.

Therapeutic uses

- To stimulate secretion of endogenous corticosteroids.
- Diagnostic: differentiation between 1^{ry} or 2^{ry} adrenal insufficiency.

Gonadotropin-releasing hormone (GnRH)

- GnRH is secreted by the hypothalamus to stimulate release of LH and FSH from anterior pituitary.
- **Pulsatile** injection of GnRH causes **stimulation** of LH & FSH but **continuous** infusion of GnRH causes **inhibition** of LH & FSH release.

Therapeutic uses

- Treatment of infertility caused by hypogonadism in both sexes by **pulsatile** injection of GnRH (to stimulate LH & FSH).
- Treatment of prostate cancer, endometriosis, and polycystic ovary syndrome by **continuous** administration of GnRH (to inhibit LH & FSH).
- In-vitro fertilization (IVF) programs.

Follicle-stimulating hormone (FSH)

Therapeutic uses

- Treatment of infertility caused by hypogonadism in both sexes.
- To stimulate ovulation as a part of in-vitro fertilization (IVF) programs.

Adverse effects

- Hyperstimulation syndrome (enlarged ovaries, ascites, fever, embolism, etc.)
- Gynecomastia in men.

Human chorionic gonadotropin (hCG)

It is glycoprotein produced by the placenta to stimulate ovarian corpus luteum to secrete progesterone (like LH). *h*CG can be used as LH substitute.

Therapeutic uses

- Treatment of infertility caused by hypogonadism in both sexes.
- To stimulate ovulation as a part of in-vitro fertilization (IVF) programs.
- Differentiation between undescended testes (cryptorchidism) and retracted testes (pseudo-cryptorchidism).

POSTERIOR PITUITARY HORMONES

Antidiuretic hormone (Vasopressin; ADH)

- It acts on 2 types of receptors: V1 and V2:
  - **V1:** present in **vascular** sm ms → VC and spasm.
  - **V2:** present in the **renal** collecting tubules → ↑ water reabsorption.

Therapeutic uses

- **Desmopressin:** synthetic long acting analog given by nasal administration in:
  - Diabetes insipidus (cranial type only): its action on renal V2 receptors is 3000 times more potent than on vascular V1 receptors.
  - Nocturnal enuresis: by reducing nighttime urine production.
  - Hemophilia: because it stimulates hepatic synthesis of factor VIII and endothelial cells to secrete von Willebrand factor.

- **Terlipressin** (Glypressin): used by i.v.i. to control acute variceal bleeding.
  Octreotide, vasopressin, and terlipressin have been shown to have efficacy in the control of acute variceal hemorrhage. **Terlipressin**, however, is the only medication that has been shown to improve patient survival.

Adverse effects

- Facial pallor and hypertension due to cutaneous VC.
- Coronary spasm.

Oxytocin

It causes **milk ejection** from the breast and **uterine contraction** at labor.

Therapeutic uses

- Induction and maintenance of labor (10-20 units by i.v.i).
- Control of postpartum hemorrhage.
- To stimulate milk secretion in nursing mothers (nasal spray)

Adverse effects and contraindications

- Rupture uterus in cephalopelvic disproportion (obstructed labor).
- Fetal asphyxia (from uterine spasm).
- Hypertension and cardiac arrhythmia

Notes

Review Questions

1. Classify types of **insulin**; mention its indications and side effects.
2. Classify types of **oral antidiabetic drugs**; mention their mechanism of action, indications and side effects.
3. Classify **antithyroid drugs;** mention their mechanism of action, side effects, and precautions of each group.
4. Classify **glucocorticoids**; mention their therapeutic uses, common side effects and contraindications.
5. Give full account on pharmacological regulation of **bone calcium homeostasis**.
6. Classify **oral contraceptives**; mention their mechanism of action, side effects and causes of failure.

Short questions:

1. Insulin resistance: definition, mechanism, and management.
2. Mention uses and side effects of sulfonylureas.
3. Mention drug interactions of oral hypoglycemic drugs.
4. Mention therapeutic uses and side effects of vasopressin.
5. Mention side effects (or contraindications) of oxytocin.
6. Mention drug interactions of vit D.
7. Mention treatment of osteoporosis.
8. Mention medical treatment of obesity.
9. Mention antiestrogens and their therapeutic uses.
10. Mention antiandrogens and their therapeutic uses.
11. Mention contraindications of anabolic steroids.
12. Mention side effects (or contraindications) of contraceptive pills.
13. Mention causes of failure of contraceptive pills.

Mention lines of treatment of the following emergency conditions:

1. Diabetic ketoacidosis.
2. Thyrotoxic crisis.
3. Myxedema coma.
4. Acute addisonian crisis.
5. Acute hypercalcemia.

Of each of the following questions, select ONE BEST answer:

1. Glucocorticoids are hormonal steroids:
A. Having an important effect on immune function
B. Having principally salt-retaining activity
C. Having androgenic or estrogenic activity
D. Having hypercalcemic activity
E. Having hyperkalemic activity

2. Correct statements about cortisol (hydrocortisone) include all of the following, EXCEPT:
A. Cortisol is synthesized from cholesterol
B. ACTH governs cortisol secretion
C. Most cortisol is inactivated in the liver
D. Cortisol has equal anti-inflammatory and salt-retaining activity
E. The half-life of cortisol in the circulations is normally about 60 hours.

3. Correct statements about glucocorticoids include all of the following, EXCEPT:
A. Effects of glucocorticoids are mediated by widely distributed glucocorticoid receptors that are members of the superfamily of nuclear receptors.
B. Glucocorticoids have high plasma protein binding
C. Glucocorticoids have dose-related metabolic effects on carbohydrate, protein, and fat metabolism.
D. Glucocorticoids have pro-inflammatory effects.
E. Glucocorticoids have catabolic effects in lymphoid and connective tissue, muscle, fat, and skin.

4. Which of the following glucocorticoids is relatively a short-acting drug?
A. Prednisolone
B. Dexamethasone
C. Triamcinolone
D. Paramethasone
E. Betamethasone

5. Which of the following glucocorticoids is an intermediate-acting drug?
A. Cortisone
B. Triamcinolone
C. Butamethasone
D. Prednisolone
E. Dexamethasone

6. Immunosupressive effect of glucocorticoids is caused by:
A. Reducing concentration of lymphocytes and inhibiting function of tissue macrophages and other antigen-presenting cells
B. Suppression of cyclooxygenase II expression which results in reducing amount of an enzyme available to produce prostoglandins
C. Activation of phospholipase A2 and reducing prostaglandin and leukotriene synthesis.
D. Activation of angiotensin-converting enzyme
E. Suppression of histamine release

7. Indication of glucocorticoids include of the following EXCEPT:
A. Chronic (Addison's disease) and acute adrenocortical insufficiency
B. Organ transplants (prevention and treatment of rejection – immunosuppression)
C. Inflammatory conditions of bones and joints (arthritis, bursitis, tenosynovitis).
D. Hypocalcemia
E. Gastrointestinal diseases (inflammatory bowel disease)

8. Indication for 1,25-dihydroxyvitamin D3 (calcitriol) administration is:
A. Vitamin D resistance
B. Elevated skeletal turnover
C. Hypercalcemia of malignancy
D. Hypophosphatemia
E. Primary hyperparathyroidism

9. Indication for risidronate administration is:
A. Failure of vitamin D formation in skin
B. Hypoparathyroidism
C. Elevated skeletal turnover
D. Hypophosphatemia

E. Metastatic bone disease

10. Correct statements about fluoride include all of the following, EXCEPT:
A. Fluoride is effective for the prophylaxis of dental caries
B. Fluoride is accumulated by bone and teeth, where it may stabilize the hydroxyapatite crystal
C. Subjects living in areas with naturally fluoridated water (1-2 ppm) had more dental caries and fewer vertebral compression fractures than subjects living in nonfluoridated water areas
D. Chronic exposure to very high level of fluoride results in thickening of the cortex of long bones and bony exostoses.

11. Which one of the following is most likely to be useful in the therapy of hypercalcemia?
A. Calcitonin
B. Glucocorticoids
C. 1-25 dihydroxy vitamin D3
D. Parenteral infusion of phosphate
E. Thiazide diuretics

12. Which of the following conditions is an indication for the use of calcitonin?
A. Chronic renal failure
B. Hypoparathyroidism
C. Intestinal osteodystrophy
D. Paget's disease of bone
E. Rickets

13. Which of the following drugs can cause rickets in children by increasing Vitamin D metabolism?
A. Tetracycline
B. Phenylbutazone
C. Phenytoin
D. Ciprofloxacin
E. Ibuprofen

14. Bone resorption is accelerated by:
A. Estrogens
B. Fluorides
C. Parathormone
D. Bisphosphonates
E. Calcitonin

15. Osteonecrosis of the jaw may be an adverse effect of:
A. Estrogens
B. Fluorides
C. Parathormone
D. Bisphosphonates
E. Calcitonin

16. Which of the following is an important effect of insulin?
A. Increased conversion of amino acids into glucose
B. Increased gluconeogenesis
C. Increased glucose transport into cells
D. Inhibition of lipoprotein lipase
E. Stimulation of glycogenolysis

17. Which of the following agents should be administered to achieve rapid control of the severe ketoacidosis in a diabetic boy?
A. Regular insulin
B. Glyburide
C. Insulin glargine
D. NPH insulin
E. Tolbutamide

18. Which of the following is the most likely complication of insulin therapy?
A. Dilutional hyponatremia
B. Hypoglycemia
C. Increased bleeding tendency
D. Pancreatitis
E. Severe hypertension

19. A 24-year-old woman with type 1 diabetes wishes to try tight control of her diabetes to improve her long-term prognosis. Which of the following regimens is *most* appropriate?
A. Morning injections of mixed insulin lispro and insulin aspart
B. Evening injections of mixed regular insulin and insulin glargine
C. Morning and evening injections of regular insulin, supplemented by small amounts of NPH insulin at mealtimes
D. Morning injections of insulin glargine, supplemented by small amounts of insulin lispro at mealtimes
E. Morning injection of NPH insulin and evening injection of regular insulin

20. Which one of the following drugs promotes the release of endogenous insulin?

A. Acarbose
B. Pioglitazone
C. Glipizide
D. Metformin
E. Miglitol

21. The combination of metformin and ethanol increases the risk of which of the following?
A. A disulfiram-like reaction
B. Excessive weight gain
C. Hypoglycemia
D. Lactic acidosis
E. Serious hepatotoxicity

22. Which of the following drugs is *most* likely to cause hypoglycemia when used as monotherapy in the treatment of type 2 diabetes?
A. Acarbose
B. Rosiglitazone
C. Glyclazide
D. Metformin
E. Miglitol

23. Which of the following drugs is taken during the first part of a meal for the purpose of delaying the absorption of dietary carbohydrates?
A. Acarbose
B. Exenatide
C. Glipizide
D. Pioglitazone
E. Repaglinide

24. The PPAR-γ receptor that is activated by thiazolidinediones increases tissue sensitivity to insulin by which of the following mechanisms?
A. Activating adenylyl cyclase and increasing the intracellular concentration of cAMP
B. Inactivating a cellular inhibitor of the GLUT2 glucose transporter
C. Inhibiting acid glucosidase, a key enzyme in glycogen breakdown pathways
D. Regulating transcription of genes involved in glucose utilization
E. Stimulating the activity of a tyrosine kinase that phosphorylates the insulin receptor

25. Which of the following patients is *most* likely to be treated with intravenous glucagon?
A. An 18-year-old woman who took an overdose of cocaine and now has a blood pressure of 190/110 mm Hg
B. A 27-year-old woman with severe diarrhea caused by a flare in her inflammatory bowel disease
C. A 57-year-old woman with type 2 diabetes who has not taken her glyburide for the last 3 d
D. A 62-year-old man with severe bradycardia and hypotension resulting from ingestion of an overdose of atenolol
E. A 74-year-old man with lactic acidosis as a complication of severe infection and shock

26. In Graves' disease, the cause of the hyperthyroidism is the production of an antibody that does which of the following?
A. Activates the pituitary thyrotropin-releasing hormone (TRH) receptor and stimulates TSH release
B. Activates the thyroid gland TSH receptor and stimulates thyroid hormone synthesis and release
C. Activates thyroid hormone receptors in peripheral tissues
D. Binds to thyroid gland thyroglobulin and accelerates its proteolysis and the release of its supply of T4 and T3
E. Binds to thyroid-binding globulin (TBG) and displaces bound T4 and T3

27. Methimazole reduces serum concentration of T3 primarily by which of the following mechanisms?
A. Accelerating the peripheral metabolism of T3
B. Inhibiting the proteolysis of thyroid-binding globulin
C. Inhibiting the secretion of TSH
D. Inhibiting the uptake of iodide by cells in the thyroid
E. Preventing the addition of iodine to tyrosine residues on Thyroglobulin

28. Though rare, a serious toxicity associated with the thioamides is which of the following?

A. Agranulocytosis
B. Lupus erythematosus-like syndrome
C. Myopathy
D. Torsades de pointes arrhythmia
E. Thrombotic thrombocytic purpura (TTP)

29. A 65-year-old man with multinodular goiter is scheduled for a near-total thyroidectomy. Which of the following drugs will be administered for 10–14 d before surgery to reduce the vascularity of his thyroid gland?
A. Levothyroxine
B. Liothyronine
C. Lugol's solution
D. Prednisone
E. Radioactive iodine

30. Which of the following is a sign or symptom that would be expected to occur in the event of chronic overdose with exogenous T4?
A. Bradycardia
B. Dry, puffy skin
C. Large tongue and drooping of the eyelids
D. Lethargy, sleepiness
E. Weight loss

31. When initiating T4 therapy for an elderly patient with longstanding hypothyroidism, it is important to begin with small doses to avoid which of the following?
A. A flare-up of exophthalmos
B. Acute renal failure
C. Hemolysis
D. Overstimulation of the heart
E. Seizures

32. A 27-year-old woman underwent near total thyroidectomy. She was started on levothyroxine. What hormone is produced in the peripheral tissues when levothyroxine is administered?
A. Methimazole
B. T3
C. T4
D. TSH
E. FSH

33. A 62-year-old woman presents with complaints of fatigue, sluggishness, and weight gain. She needs to sleep several times a day, which is unusual for her. She has been taking T4 for the past 15 yr without significant problems regarding her energy level. Her recent history is significant for diagnosis of arrhythmia, and she is currently taking an antiarrhythmic drug. What is the most likely cause of her current condition?
A. Amiodarone
B. Lidocaine
C. Procainamide
D. Sotalol
E. Verapamil

34. A 25-year-old woman presents with insomnia and fears she may have "something wrong with her heart." Lab tests confirm hyperthyroidism. Which of the following is a drug that produces a permanent reduction in thyroid activity?
A. ^{131}I
B. Methimazole
C. Propylthiouracil
D. Thiocyanate
E. Thyroglobulin

35. Glucocorticoids have proved useful in the treatment of which of the following medical conditions?
A. Chemotherapy-induced vomiting
B. Essential hypertension
C. Hyperprolactinemia
D. Parkinson's disease
E. Type II diabetes

36. A patient presents with pain and stiffness in his wrists and knees. The stiffness is worse first thing in the morning. A blood test confirms rheumatoid arthritis. You advise a short course of steroids. Which one of the following is the most potent anti-inflammatory steroid?
A. Cortisol
B. Dexamethasone
C. Fludrocortisone
D. Prednisone
E. Triamcinolone

37. A 34-year-old woman with ulcerative colitis has required long-term treatment with pharmacologic doses of a glucocorticoid agonist. Which of the following is a toxic effect associated with long-term glucocorticoid treatment?
A. A lupus-like syndrome
B. Adrenal gland neoplasm
C. Hepatotoxicity
D. Osteoporosis
E. Precocious puberty in children

38. Which of the following drugs is *most* useful for the treatment of hypercalcemia in Paget's disease?
A. Fluoride
B. Hydrochlorothiazide
C. Pamidronate
D. Raloxifene
E. Teriparatide

39. The active metabolites of vitamin D act through a nuclear receptor to produce which of the following effects?
A. Decrease the absorption of calcium from bone
B. Increase PTH formation
C. Increase renal production of erythropoietin
D. Increase the absorption of calcium from the GIT
E. Lower the serum phosphate concentration

40. Which of the following drugs is *most* likely to lower patient's serum PTH concentration?
A. Calcitriol
B. Cholecalciferol
C. Furosemide
D. Gallium nitrate
E. Risedronate

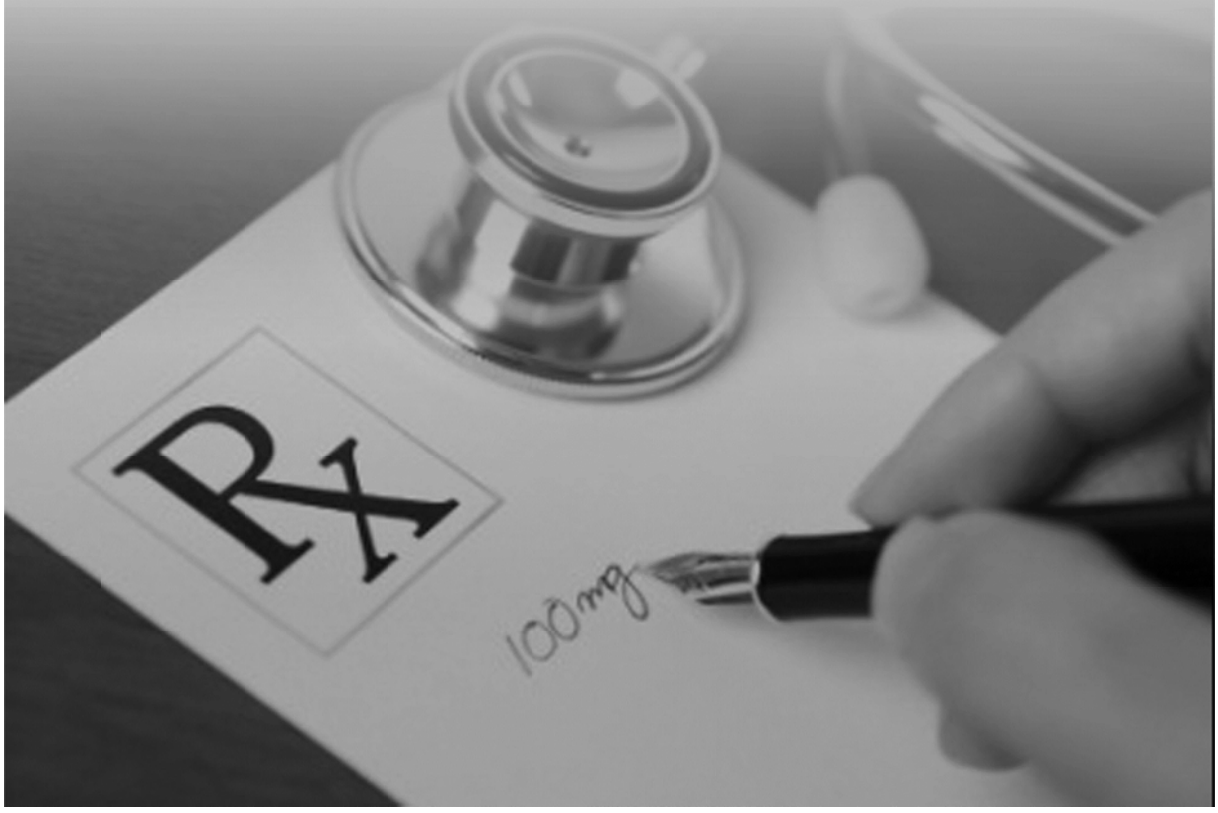
41. The patient began therapy with a nasal spray containing a protein that inhibits bone resorption. The drug contained in the nasal spray was which of the following?
A. Calcitonin
B. Calcitriol
C. Cinacalcet
D. Cortisol
E. Teriparatide

Answers

1 A	10 C	19 D	28 A	37 D
2 E	11 B	20 C	29 C	38 C
3 D	12 D	21 D	30 E	39 D
4 A	13 C	22 C	31 D	40 A
5 B	14 C	23 A	32 B	41 A
6 A	15 D	24 D	33 A	
7 D	16 C	25 D	34 A	
8 D	17 A	26 B	35 A	
9 E	18 B	27 E	36 B	

Chapter 10

CNS Pharmacology



Chapter 10

CNS Pharmacology

Part 1: CNS Stimulants

Classification:

1. **Respiratory stimulants** theophylline, nikethamide
2. **Psychomotor stimulants** amphetamines, antidepressants
3. **Psychotomimetic drugs** LSD, cannabis
4. **Spinal cord stimulants** strychnine

RESPIRATORY STIMULANTS (ANALEPTICS)

Definition: drugs that stimulate the depressed respiratory center (RC).

Classification:

- **Specific analeptics:**
  - Naloxon and nalorphine → used to treat opiates respiratory depression.
  - Flumazenil → used to treat benzodiazepines toxicity.
- **Non-specific analeptics:**
  - Direct RC stimulation: e.g. Xanthines (caffeine, theophylline) – Ethamivan - Heptaminol. They antagonize the GABA-mediated RC depression.
  - Indirect RC stimulation (reflex): e.g. Nicotine and lobeline. They stimulate RC indirectly through stimulation of the chemoreceptors in the carotid body.
  - Both (direct and indirect): Nikethamide - Doxapram

Therapeutic uses: all cases of RC depression (postanaesthetic, CNS depressants, COPD and some premature babies)

Adverse effects

- Tachypnea, tachycardia and hypertension.
- High doses can cause convulsions.

Contraindications

- Epilepsy (to avoid CNS stimulation).
- Severe hypertension, arrhythmia or IHD (to avoid cardiac arrhythmia).
- Thyrotoxicosis.
- Severe bronchial asthma.

PSYCHOMOTOR STIMULANTS

Definition: drugs that induce **euphoria** with **increased motor activity.**

Classification

- **Amphetamine and related drugs:** see ANS
- **Cocaine**
  - Cocaine inhibits tissue uptake of catecholamines.
  - Behavioral effects of cocaine are very similar to amphetamine.
  - Cocaine is used topically as a local anesthetic eye drops.
- **Xanthines:** see respiratory pharmacology.
- **Antidepressants:** see later.

PSYCHOTOMIMETIC DRUGS (HALLUCINOGENS)

Definition: drugs that affect **thought, perception** and **mood** with no effect on motor activity. They have **no clinical applications** but important for **drug abuse.**

Examples and Mechanisms

- **LSD (Lysergic acid diethylamide):** It stimulates central **5-HT** receptors and affects catecholamine action → severe hallucinations and delusions resembling acute **schizophrenia**.
- **Cannabis (hashish, marijuana):** It acts on cannabinoid receptors in the CNS (**CB_1**) causing loss of judgment of time & place and dream-like state. **I**t does not cause physical dependence but psychological dependence. **CB_2** receptors are found in peripheral tissue and immune system.
- **Phencyclidine:** It stimulates **δ-opioid** receptors and blocks the NMDA receptors and may interact with other neurotransmitter systems.

Part 2: Analgesics

Definition: drugs that relieve or decrease pain sensation.

Classification of analgesics:

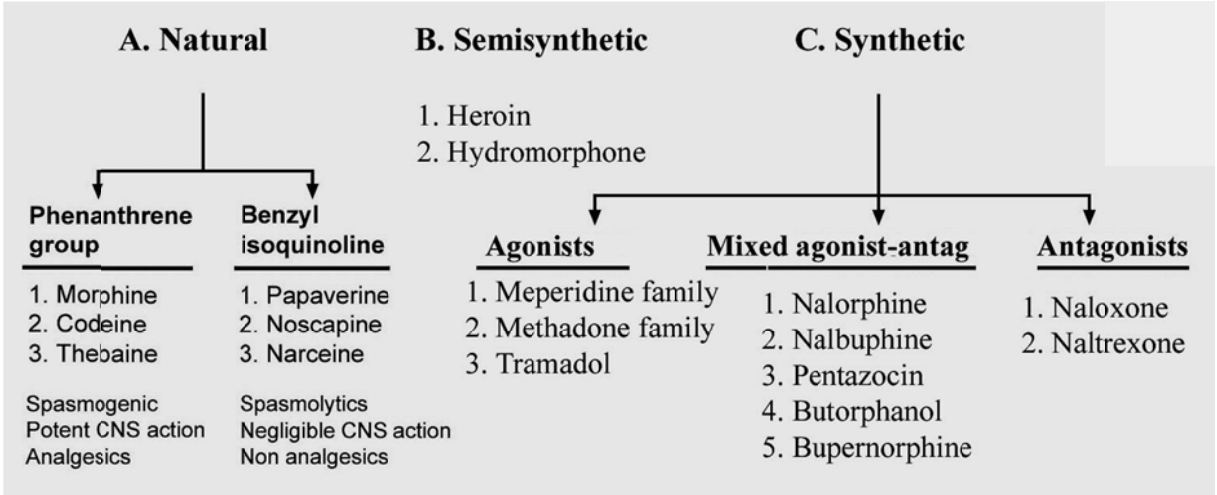
- **Opioid (narcotic) analgesics**
- **NSAIDs** (see chapter 4)**.**
- **Analgesic antipyretics:** e.g. paracetamol, Dipyron & Nefopam.
- **Drugs used for specific painful conditions** e.g. carbamazepine for trigeminal neuralgia, ergotamine for migraine.

OPIOID ANALGESICS

- They are drugs that decrease pain sensation without loss of consciousness and can induce physical dependence.
- **Opiates:** are drugs derived from opium plant (*Papaver sominiferum*). They include mainly morphine, codeine and papaverine.
- **Opioids:** are drugs with morphine-like activity.
- **Opiopeptins:** are endogenous peptides with opioid-like activity e.g. endorphins & enkephalins
- **Narcotics:** are drugs that produce narcosis i.e. drowsiness or stupor, with analgesia (stupor means marked impairment, but not complete loss of consciousness). These drugs are usually addictive. It is a **legal**, not a medical, term.

Papavar somniferum

Classification of opioid drugs



Mechanism of action

- Opioids such as morphine are believed to interact with three major receptors **(μ, δ, κ)**. Each opioid receptor has distinct subtypes (e.g., μ1, μ2). All three major receptors are present in high concentrations in the dorsal horn of the spinal cord.
- Interaction with **μ-receptors** contributes to supraspinal and spinal analgesia, respiratory depression, sedation, euphoria, decreased GI peristalsis, and physical dependence (addiction).
- The significance of interaction with **κ-receptors** is unclear, but it may contribute to analgesia (through inhibition of release of substance P at dorsal horn).

NATURAL OPIOID AGONISTS

1. Morphine

Pharmacokinetics

- **Oral absorption:** good (bioavailability is 25% due to significant first-pass effect). However, the analgesic effect is greater when the drug is administered parentrally
- **t½ :** 4-5 hrs.
- **Metabolism:** in the liver by conjugation leading to inactive metabolites.
- **Excretion:** renal (90%) – bile (10% as conjugated morphine).

Pharmacological effects

- **Analgesia**
  - **Dose-dependent analgesia (sensory & emotional):** consciousness is not lost and the patient can still locate the source of pain. Analgesia may be associated with **euphoria** and decreased anxiety.
  - Analgesia results from direct activation of **μ** and **δ** receptors in the spinal cord and possibly higher centers (thalamaus) leading to:
    - Activation of descending inhibitory pathways.
    - ↓ release of substance-P in pain transmission neurons in the spinal cord.
  - The psychic effect results from ↓ **NA release** in some CNS areas leading to decrease anxiety and reaction of the patient to pain.
  - Morphine and other exogenously administered opioids may also have some action on **peripheral** inflamed tissue.

N.B. Morphine can treat all types of pain **except itching. Why?**
a) Because morphine stimulates **histamine release** → ↑ itching.
b) Itching is different from pain sensation and has different receptors and centers.

- **Euphoria** (large doses produce dysphoria).
- **Miosis:** due to central stimulation of Edinger-Wistphal nucleus. **Severe miosis** is indicative of toxic doses.
- **Respiratory center depression**. This RC depression leads to CO_2 retention and cerebral VD → ↑↑ **intracranial tension.**
- **Cough suppression.**
- **Vagal stimulation.**
- **Nausea & vomiting:** due to stimulation of chemoreceptor trigger zone (CTZ).

CVS effects:

- **Orthostatic hypotension:** due to (a) Histamine release; (b) vagal stimulation.
- **Bradycardia:** due to vagal stimulation.

Smooth ms (Spasmogenic effects):

- **Bronchoconstriction:** due to: (a) Vagal stimulation. (b) Histamine release**.**
- **Constipation:** due to (a) spasmodic non-propulsive contractions of intestinal smoothms& decreased peristalsis; (b) ↑ intestinal water absorption.
- Spasm of the **sphincter of Oddi** → ↑ biliary pressure.
- **Feeling of urgency with difficult micturition** due to ↑ detrusor muscle tone with spasm of the internal urethral sphincter.
- **Uterus:** prolongation of labor by unclear mechanism.

Therapeutic uses

- **Analgesia:** for severe pain e.g. acute MI, cancer, surgery, etc.
- **Acute pulmonary edema (cardiac asthma).Why?**
  - ↓ stress & anxiety of the patient.
  - Venodilatation → ↓ VR & preload → ↓ pulmonary congestion.
  - Decrease tachypnea caused by the CNS response to hypoxic drive (due to its depressant effect on RC).
- **In anesthesia:**
  - As adjuvant to anesthetic agents (preanesthetic medication).
  - Regional anesthesia (epidural) to achieve long lasting analgesia by its effect on the spinal cord.
- **In severe colic:** (**morphine combined with atropine**). **Why?**
  - Because morphine is spasmogenic and atropine is spasmolytic.
  - To counteract muscarinic effects caused by excessive vagal stimulation (e.g. bronchoconstriction and bradycardia).

Preparations and doses

- Morphine sulphate: 10 mg s.c. or i.m. In acute MI it is given **5 mg i.v.**
- Intrathecal (epidural) injection: produce long lasting analgesia which is useful for critically ill patients at risk of RC depression.
- Sustained release preparations &transdermal patches are available.

Adverse effects:

CNS
- **Tolerance & physical dependence** (addiction) with prolonged use:
  - Physical dependence can occur within 24 h if given /4 h.
  - Tolerance may occur to analgesia and euphoria but not to respiratory depression.
- ↑↑ intracranial tension.
- **RC depression:** the most important effect and is dose-dependent.

Resp
- Bronchoconstriction.

CVS
- Postural hypotension

GIT
- Nausea, vomiting, and constipation.
- Increased biliary tract pressure and biliary colic.

Genito-Urinary
- Urine retention especially in patients with **enlarged prostate**.
- Prolongation of labor.

Eye
- Miosis is a consistent finding in morphine addiction.

Contraindications & precautions

- **Head injury & increased intracranial pressure**: Morphine causes respiratory depression & CO_2 retention. The ↑ CO_2 causes cerebral VD and ↑ intracranial tension.
- **Respiratory depression.**
- **Bronchial asthma:** Morphine causes bronchoconstriction due to (a) vagal stimulation; (b) histamine release. It also causes RC depression.
- **Biliary colic & gallstones:** due to spasm of the sphincter of Oddi → ↑ biliary pressure.
- **Senile enlarged prostate:** Morphine ↑ detrusor muscle tone with spasm of the internal urethral sphincter → feeling of urinary urgency with difficult micturition.
- **Hypotension and hypovolemia:** because morphine causes postural hypotension.
- **Hepatic damage:** Due to: (a) morphine is metabolized by the liver; (b) morphine increases the risk of hepatic encephalopathy due to marked CNS depression.
- **Hypothyroidism and adrenal insufficiency** (Addison's disease). **Why?**
  Because those patients have prolonged and exaggerated response to morphine.

- **Undiagnosed acute abdominal pain:** Morphine masks the pain (which may be dangerous e.g. appendicitis) and interferes with the correct diagnosis.
- **Infants and old patients:** are more susceptible to respiratory depression.

Chronic opioid toxicity (addiction)

- There are behavioral changes, constipation, itching &miosis.
- Sudden withdrawal (abstinence syndrome):
  - *Consists of:* irritability, nervousness, tremors, hypertension & ms cramps starts after 6-10 hrs from the last dose - peak effect at 48 hrs - gradually subsides over 5-10 days.
  - *Mechanism:* chronic administration of opioids ↓↓ endogenous production of endorphins and NA. Following sudden withdrawal, there is an immediate deficiency of endogenous opioids with rebound ↑ of NA release.

Treatment of chronic morphine addiction:

- Gradual withdrawal of morphine with substitution by **methadone,** then gradual withdrawal of methadone.
- **Clonidine:** to stimulate central α2 receptors and ↓ NA release.
- Sedatives: e.g. diazepam.

Acute opioid toxicity

Manifestations:

- Coma with depressed respiration, miosis, and shock.
- Death occurs from respiratory depression.

Treatment:

- Gastric lavage.
- Establish a patent airway and artificial respiration if needed.
- Opioid antagonists:
  - **Naloxone:** pure opioid antagonist and can reverse RC depression within minutes (0.4 - 0.8 mg i.v. for 2-3 doses).
  - **Nalorphine:** it is mixed agonist-antagonist (partial blocker).

N.B.
Opioid blockers are **indicated** in **acute** morphine toxicity but they are absolutely **contraindicated** in **chronic** morphine addiction because they precipitate severe withdrawal syndrome.

N.B.

- The duration of opioid antagonists is **shorter** than morphine. The patient should be watched carefully because he may go back into coma.
- Care should be taken to avoid **withdrawal** syndrome.

2. Codeine

Similar to morphine with the following differences:

- Has **greater oral bioavailability** (60%) due to **less first-pass effect**.
- The **analgesic** potency is **20%** of morphine, but more potent **cough** suppressant
- It has **little euphoric** effect.
- Most of the systemic effects of codeine are due to conversion in the liver into morphine by *demethylation* (codeine is *methylmorphine*).

Therapeutic uses

– Analgesic for mild to moderate pain (usually combined with paracetamol).
– As central antitussive (see chapter 7).

Adverse effects: (less than morphine)

– Constipation
– RC depression and addiction liability but it is fewer than morphine.

	Morphine	Codeine
Oral bioavailability:	25%	60%
Analgesic effects:	Strong	Weak (20%).
Antitussive effect:	Weak	Strong
Uses:	Mention its 4 uses	Analgesic and antitussive

SYNTHETIC AND SEMISYNTHETIC OPIOID AGONISTS

1. Heroin and hydromorphone

- They are semisynthetic opioids (heroin is diacetylmorphine).
- They are **more potent** than morphine but with rapid onset and shorter duration.
- They are **not used clinically** because they are **highly addictive.**

2. Meperidine (Pethidine)

Synthetic opioid similar to morphine with the following differences:

- **Better absorbed** orally and has **greater bioavailability** than morphine.
- The **analgesic** potency is **10%** of morphine.
- It is used as analgesic alternative to morphine in the following cases:
  - **Inferior MI** because in this case the patient usually has bradycardia.
  - It is preferred than morphine **during labor** because it has short duration and doesn't prolong labor (little or no spasmogenic action).

Adverse effects

- It causes **RC depression** and **addiction liability** but weaker than morphine.
- It causes **histamine release** and **bronchoconstriction**
- It has weak **atropine-like actions** → dry mouth, tachycardia, etc.
- It has **No** GIT, **No** antitussive, and **No** vagal stimulant effects.

	Morphine	Meperidine
Chemistry	Natural opioid	Synthetic opioid
Bioavailability	25%	Greater (50%)
Analgesic effect	Strong	Weak (10% of morphine)
Spasmogenic effects	Present	Absent
Autonomic effects	Vagal stimulation	Atropine-like action
Uses	Mention its 4 uses	Analgesic only

3. Fentanyl and alfentanil

- They are synthetic derivatives of meperidine**.** They are the **most potent** and the **shortest duration** opioid agonists.
- They are used as analgesic in **severe pain** (as long-acting transdermal **skin patch**). A transdermal fentanyl 12 microgram patch equates to approximately 30 mg oral morphine daily.

4. Methadone

Synthetic opioid similar to morphine with the following differences:

- The analgesic effect is **equal** to morphine**.**
- Has **longer duration** of action than morphine ($t_{1/2}$ is 24h)**.**

Uses:

- As analgesic.
- **Treatment of chronic opiate addiction and heroin users**:
  - It can satisfy the craving needs of the patient with less addictive features.
  - Methadone withdrawal symptoms are less severe than other opioids.

5. Tramadol

- It has two different mechanisms. First, it binds to the **μ**-opioid receptor. Second, it inhibits the reuptake of serotonin and NA.
- **Uses:** as **analgesic** for moderate to severe pain, especially musculoskeletal pain
- **Adverse effects:** It has relatively fewer side-effects than most opioids (but **addiction** can occur). It may induce **seizures** in epileptic patients.

6. Diphenoxylate and loperamide (see chapter 8)

SEMISYNTHETIC MIXED AGONISTS-ANTAGONISTS (partial agonists)

Nalorphine – Nalbuphine – Pentazocin – Butorphanol

- All these drugs have **agonist** activity on κ receptors and **antagonist** or **partial agonist** activity on μ receptors.
- They are used as **analgesics** alternative to morphine but their analgesic activity and respiratory depression are **less marked** than morphine.
- All these drugs (except nalbuphine) increase systemic and pulmonary vascular resistance leading to ↑ **cardiac load,** so they are, thus, **contraindicated to relieve pain of acute MI.**
- They can lead to **withdrawal symptoms** if given to opioid **addict** patients.

N.B.

For opioid analgesics, **potency** of the analgesic should be considered **more important** than efficacy because respiratory depression is dose-dependent.

SYNTHETIC FULL ANTAGONISTS

Naloxone and naltrexone

- They are competitive **blockers of all** opioid receptors.
- Naloxone is given **i.v.** and has short t½ (~1h) but naltrexone could be administered orally and has longer t½ (~48 h).
- They can precipitate **severe withdrawal** syndrome if administered to opioid-addict patient.

Therapeutic uses of naloxone

- **Acute opioid toxicity:** given i.v., the adverse respiratory and CVS effects of opioids are reversed within 1-2 min and lasts for 1-2 hrs.
- It is given during labor to mothers who received opioids **to prevent neonatal respiratory depression,** or it can be given to the neonate via the umbilical vein.

NON-OPIOID ANALGESICS

1. Acetaminophen (Paracetamol)

Pharmacokinetics

- Absorption is complete and rapid from GIT with peak levels after 30 min.
- Metabolism: liver by conjugation. At high doses, it is converted into **toxic metabolite** *(N-acetyl-benzoquinone)* that is responsible for hepatotoxicity.
- Excretion: mainly renal.

Mechanism & Pharmacological effects

- It is a **selective Cox III inhibitor** so it inhibits PGs synthesis in the brain only and has **analgesic & antipyretic** actions **without** effects on the enzymes that are responsible for synthesis of peripheral PGs and so it has **no anti-inflammatory action.**
- It has **little or No** effects on the CVS, GIT, respiratory or platelet functions.

Therapeutic uses

As analgesic and antipyretic **when aspirin is contraindicated** (e.g. patients with peptic ulcer, hemophilia, etc). Acetaminophen can be administered in **pregnancy** with greater safety than aspirin.

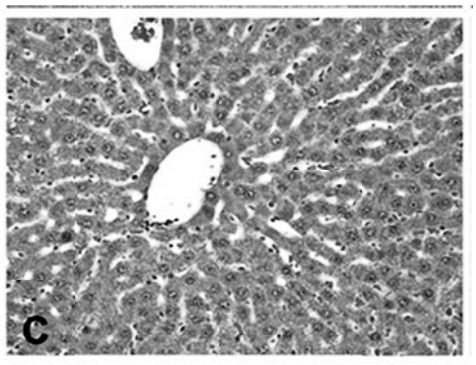
Adverse effects

- **At therapeutic doses:** acetaminophen is well-tolerated but may cause:
  - Skin rash& drug fever (as allergic reactions).
  - Long term use may lead to renal failure.

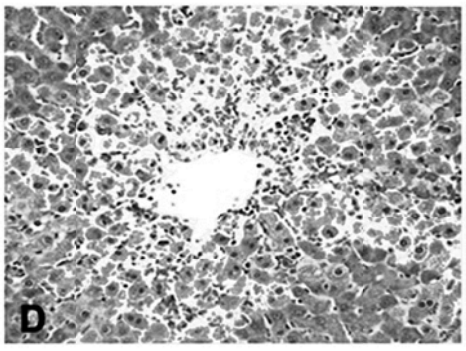
- **In toxic doses: dose-dependent hepato-toxicity** (centrilobular necrosis): It occurs with large doses (about **15 gm** in adults and **4 gm** in children)

  Mechanism of hepatotoxicity

  - Acetaminophen is converted to toxic metabolite *(N-acetyl-benzoquinone)* in the liver that needs detoxification by reduced **glutathione**.



Normal liver section



Hepatic cell necrosis
caused by acetaminphen toxicity

- When glutathione store is depleted, the toxic metabolite binds covalently to cellular proteins producing hepatocellular damage.
- Clinical symptoms of toxicity (e.g. vomiting) occur within 24 hrs but signs of hepatic damage (e.g. jaundice) occur after 2-6 days.

Treatment of toxicity

- **G**astric lavage with activated charcoal.
- **Sulfhydryl donors (acetylcysteine)** to restore hepatic glutathione. It must be started within **8** hours of toxicity.
- **Hemodialysis:** better within the first 12 hrs after ingestion.

The 20 hour IV protocol of acetylcysteine

- First, administer an initial loading dose of **150** mg/kg IV over 60 minutes.
- Next, administer **12.5** mg /kg per hour IV for 4 hours.
- Finally, administer **6.25** mg /kg per hour IV for 16 hours.

Nefopam (Acupan)

Mechanism and effects

- It is a **central analgesic** without antipyretic or anti-inflammatory activity. It is more potent than NSAIDs.
- The analgesic mechanism is **unclear** but may be related to inhibition of many transmitters reuptake or blocking central voltage-gated Na^+ channels.
- Nefopam is also used to combat severe **hiccups**.

Adverse effects

- Precipitation of epileptic convulsions in patients with epilepsy.
- Weak atropine-like actions: dry mouth, urine retention, etc.

Contraindications: history of epilepsy

Dipyrone (Novalgin)

Mechanism and effects

- **Analgesic antipyretic** that is more potent than aspirin. It has no anti-inflammatory action.
- Its use was restricted in many countries because of risk of **agranulocytosis** which is **not** dose-dependent.

Adverse effects

- **A**granulocytosis: reversible in 10 days after stoppage of the drug but lethal in 10% of cases.
- **A**llergic reactions and anaphylaxis.
- It can trigger bronchoconstriction in patients with **A**sthma.

Part 3: Sedative-Hypnotic Drugs

- These are drugs that cause sedation and relieve anxiety (anxiolytics), or can induce sleep. They are used primarily to treat anxiety and insomnia.
- Because there is considerable chemical variation within the group, these drugs are classified based on their clinical uses rather than on chemical structure.

Drugs with main use as sedatives:	Drugs with main use as hypnotics:
▪ Benzodiazepines ▪ Buspirone	▪ Barbiturates ▪ Ramelteon ▪ Chloral hydrate

1. Benzodiazepines

- Benzodiazepines (BDZ) have a **great margin of safety** over previously available sedative–hypnotic agents (e.g., barbiturates).
- Most benzodiazepines have qualitatively similar therapeutic actions but differ in their relative lipid solubility, metabolism, and elimination half-life.

Classification

- **Short acting (t½ < 5h):** midazolam – triazolam
- **Intermediate acting (t½ 5-24 h):** alprazolam – lorazepam - clonazepam
- **Long acting (t½ > 24 h):** diazepam – clorazepate - flurazepam

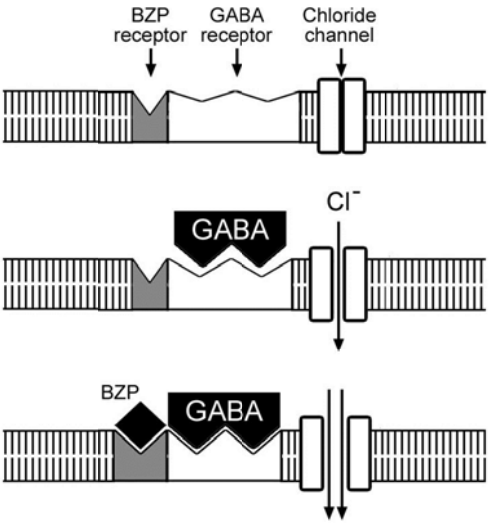
Pharmacokinetics

– Oral absorption is good and rapid. Highly lipid soluble drugs (e.g., midazolam, triazolam) have fast onset of action.
– Long acting drugs are metabolized by **oxidation** (CYP450) into **active** metabolites giving them long duration of action (e.g. diazepam).
– Short acting drugs are metabolized by **conjugation** into **inactive** metabolites followed by renal clearance.
– In a patient with liver dysfunction, **lorazepam** and **oxazepam**, which are metabolized **extrahepatically**, are less likely to cause excessive CNS depression.

Mechanism of action

- BDZ have special receptors in the CNS and peripheral tissue.
- By acting on these receptors, BDZ cause allosteric modulation of GABA action on $GABA_A$ receptors resulting in ↑ Cl- conductance and hyperpolarization.
- Six BDZ receptor subtypes have been discovered; **subtype 1** is the most widely expressed and mediates most of the effects of BDZ.

Pharmacological effects



- **Reduction of anxiety** (anxiolytic effect) in small dose producing calming effect in man & taming effect in animals
- **Hypnotic effect:** in higher doses.
- **Central skeletal muscle relaxation:** this is useful since increased ms tone is a common feature in anxiety and may lead to headache and ms pain.
- **Anticonvulsant effect.**
- **Acute amnesia:** after high doses.

Therapeutic uses

- **Anxiety disorders: e.g.**
  - Acute anxiety.
  - Generalized anxiety disorders (GAD).
  - Social phobia (social anxiety disorder).

  BDZ are effective for the **short-term** management (<6 weeks**)** of these anxiety disorders (*selective serotonin-reuptake inhibitors [SSRIs; see later] are now considered the first-line choices for the **long-term** management of anxiety disorders.*

- **Insomnia:** BDZ that have a rapid onset and sufficient duration are widely used (e.g., temazepam).

- **Anticonvulsants: Lorazepam** (and **diazepam**), given by i.v. may be used for initial treatment of status epilepticus and drug-induced seizures. The development of tolerance precludes their long-term use.

- **Short surgical procedures:** Shorter acting benzodiazepines (e.g., **midazolam**) are preferred before during surgery or endoscopy.

- **Preanesthetic medication.**

Adverse effects

- **Sedation, memory disturbance, dull attention** (interfere with learning ability).
- **Tolerance and physical dependence** (treated by gradual withdrawal).
- **Rebound insomnia** after discontinuation.
- **Hangover:** a state of psychomotor depression occurs in the following day after the use of long acting drugs (i.e. residual effect).
- **Apnea** after rapid i.v. injection *(flumazenil is the antidote)*

Flumazenil

Flumazenil is a **competitive antagonist** at benzodiazepine receptors. It is used to prevent or reverse the CNS effects from benzodiazepine overdose or to speed recovery from the effects of benzodiazepines used in anesthetic and diagnostic procedures.

Precautions: avoid BDZ use in the following conditions:

- Drivers and machine workers needing high attention.
- Pregnancy and lactation: fetal muscular hypotonia and impaired suckling may occur.
- Hepatic encephalopathy.
- Respiratory depression.
- Combination with other CNS depressants e.g. alcohol.

2. Buspirone

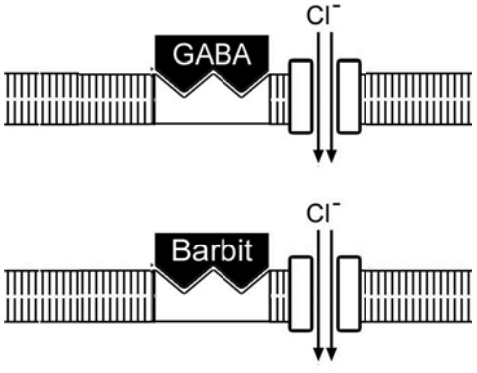
- It is partial agonist on **5-HT$_{1A}$** receptors in the midbrain.
- Selective anxiolytic without hypnotic or muscle relaxant effect.
- It suppresses anxiety after a long delay (2 or more weeks).
- It is the anxiolytic of choice in the elderly.
- No liability for drug dependence.
- **Adverse effects** include dizziness, headache, tachycardia and nervousness.

3. Barbiturates

- Barbiturates have been largely **replaced** by the more safe benzodiazepines and the SSRIs, for the treatment of anxiety and sleep disorders.
- **Phenobarbital** is a long acting barbiturate (~6-8h) used as an **anticonvulsant**; **thiopental** is ultrashort agent (~15-20 min) used as an i.v. **general anesthetic**.

Mechanism of action

- Barbiturates have either GABA-like action OR enhance the effects of GABA at GABA$_A$ receptors resulting in ↑ Cl- conductance and hyperpolarization.
- The action of barbiturates is non-selective i.e. increasing the dose of barbiturates → generalized CNS and **medullary depression**.

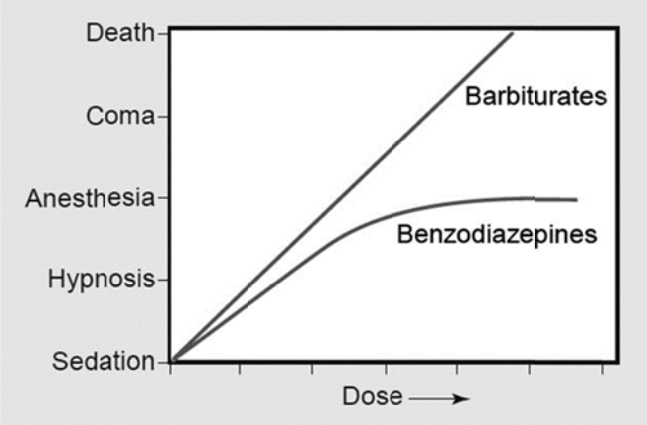


Therapeutic uses

- As sedative and hypnotics in the treatment of insomnia. They are largely replaced by benzodiazepines.
- **Phenobarbital** is used in the treatment of grand mal epilepsy.
- **Phenobarbital** is microsomal enzyme inducer. It is used in the treatment of hyperbilirubinaemia in neonates (physiological jaundice) to activate liver enzymes (glucuronyl transferase) and fasten metabolism of bilirubin.
- **Thiopental** is used as short i.v. anaesthetic in short procedures.

Adverse effects

- Physical dependence.
- **Respiratory** and **myocardial depression** (in acute toxicity)
- Phenobarbital is hepatic microsomal enzyme inducer.
- Phenobarbital may increase **porphyrin** synthesis. It can precipitate the symptoms of acute intermittent porphyria.



4. Ramelteon

- Ramelteon is prescribed for patients who have difficulty falling asleep. It is a selective agonist at **melatonin MT1** and **MT2** receptors that are involved in the promotion of sleep and that maintain the normal circadian rhythm.
- **Adverse effects** include dizziness and fatigue.

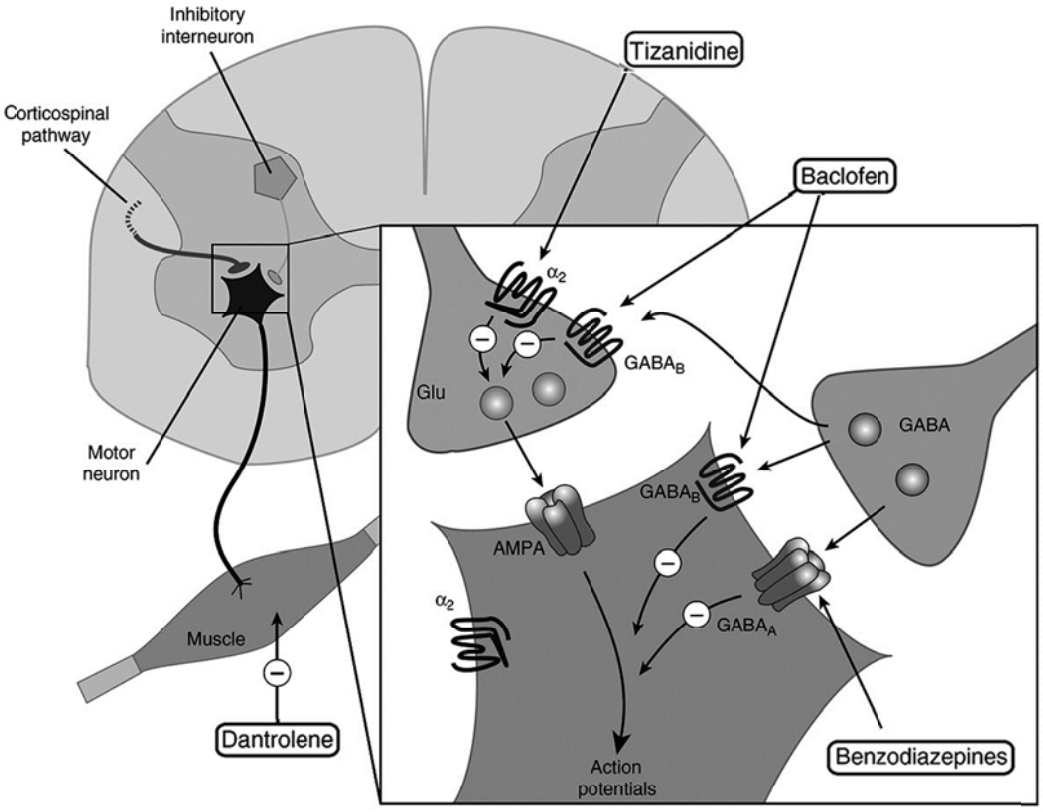
5. Chloral hydrate

- It is one of the oldest hypnotic drugs. It is an alcohol derivative.
- It produces hypnosis in 30 min and last for 6 hrs.
- It is used mainly as a hypnotic in children and elderly before short surgical or dental procedures but its use now is **very limited**.

Part 4: Skeletal Muscle Relaxants

Classification

- **Drugs act on brain higher centers:** e.g. carisoprodol, benzodiazepines, general anesthetics, anticonvulsant drugs, and antiparkinsonian drugs (see later).
- **Drugs act on neuronal transmission in the spinal cord:** e.g. tizanidine and baclofen.
- **Drugs act on the neuromuscular junction:** e.g. neuromuscular blockers and botolinum toxin.
- **Drugs act directly on the muscle contractile mechanisms:** e.g. dantrolene.



Sites of spasmolytic action of benzodiazepines (GABA-A), baclofen (GABA-B), tizanidine (α2) in the spinal cord and dantrolene (skeletal muscle). AMPA, amino-hydroxyl-methyl-isosoxaz-ole-proprionic acid, a ligand for a glutamate receptor subtype; Glu, glutamatergic neuron.

1. Carisoprodol

- Carisoprodol – (and its metabolite **mebrobamate**) – are centrally acting skeletal muscle relaxants. Their mechanism is unclear but seems to be similar to **barbiturates**. They bind to **$GABA_A$** receptors in the CNS leading to antianxiety, anticonvulsant, and skeletal muscle relaxation.
- The drug and its metabolite have **abuse** potential, so some countries limit its use.

2. Baclofen

- Baclofen is a GABA derivative that selectively stimulates **$GABA_B$** receptors in the spinal cord → ↓ release of excitatory transmitters.
- It is used as a skeletal muscle relaxant in neurological spastic conditions.

3. Tizanidine

- Tizanidine is a centrally acting **α2** agonist with greater effect on presynaptic α2 in the **spinal cord,** so it inhibits neurotransmission and reduces muscle spasm with minimal effect on blood pressure.

4. Dantrolene

- Dantrolene inhibits Ca^{2+} release from the sarcoplasmic reticulum of skeletal ms cells. It acts directly on the muscle contractile mechanisms.
- It is used for emergency management of **malignant hyperthermia** (1 mg/kg i.v.)

5. Botulinum toxin (Botox)

- Botulinum toxin is a neurotoxic protein produced by the bacterium *Clostridium botulinum*. It inhibits the release of ACh from motor nerve terminals leading to skeletal muscle paralysis.
- It is injected locally to treat local muscle spasm e.g. in cervical dystonia (spasmodic torticollis), and blepharospasm (uncontrolled muscle contraction or twitch of the eyelid). It is also used for cosmetic reduction of facial wrinkles.

6. Neuromuscular blockers: see ANS.

Therapeutic uses of skeletal muscle relaxants

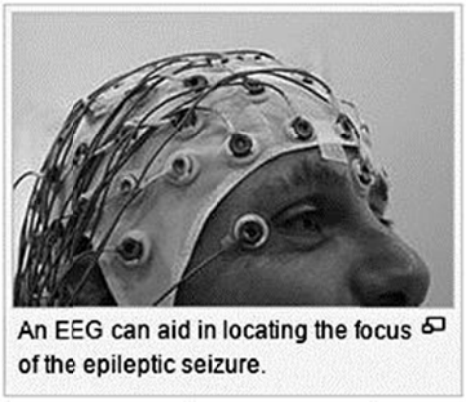
- Neurological spastic conditions such as multiple sclerosis, back pain, and spine injuries.
- Dantrolene is used for emergency management of malignant hyperthermia.
- Botolinum toxin is injected locally to relive blepharospasm, and for cosmetic reduction of facial wrinkles.
- Neuromuscular blockers are used to produce muscle relaxation during surgical procedures.

Mephensin

- Mephensin is a selective inhibitor of polysynaptic excitation of the spinal motor neurons through stimulation of **glycine receptors** in the spinal cord.
- It was historically used as antidote for treatment of **strychnine poisoning** but its clinical use now is **very limited** because of **serious side effects** including respiratory depression and hemolysis.

Part 5: Antiepileptic Drugs

Basic information


An EEG can aid in locating the focus of the epileptic seizure.

- **Epilepsy,** a chronic disease, occurs in approximately 1% of the population. The cause of most cases of epilepsy is unknown, although some people develop epilepsy as the result of brain injury, stroke, brain tumor, and drug toxicity. Genetic mutations are linked to a small proportion of the disease.
- Epileptic seizures result from excessive and abnormal cortical nerve cell activity in the brain.
- The diagnosis typically involves ruling out other conditions that cause similar neurological symptoms. This may be confirmed by brain imaging and electroencephalogram (EEG) but a normal test does not exclude the condition.
- Antiepileptic drugs (AEDs) are effective for about 80% of these patients. Lifelong treatment may be necessary.
- It may take weeks to establish adequate drug plasma levels and to determine the adequacy of therapeutic improvement. **Lack of compliance** is responsible for many treatment failures.
- AEDs are **most effective** and have the **least adverse effects** when they are used as **monotherapy.**
- Addition or withdrawal of any drug should be **gradual**, because seizures may occur on withdrawal.
- Some AEDs are **teratogenic;** this may call for the reduction or termination of therapy during pregnancy.

Classification of epilepsies:

Epilepsies are characterized by either focal or generalized abnormal neuronal discharges. Drug selection, based on seizure classification, is listed below in the order of general choice.

Partial seizures	**Simple partial**	Localized discharge; consciousness is not altered.	1. Carbamazepine 2. Lamotrigine 3. Valproic acid
	Complex partial	Localized discharge that becomes widespread; accompanied by loss of consciousness.	

Generalized seizures	**Tonic–clonic** (grand mal)	Dramatic convulsions with either jerking of the extremities or rigidity of the entire body; accompanied by loss of consciousness.	1. Valproic acid 2. Lamotrigine 3. Carbamazepine
	Absence (petit mal)	Sudden onset of altered consciousness that lasts 10–45 seconds, with up to hundreds of seizures per day; begins in **childhood** or adolescence.	1. Ethosuximide 2. Valproic acid 3. Clonazepam
	Myoclonic syndromes	Lightning-like jerks of one or more extremities occurring singly or in bursts of up to a hundred; accompanied by alteration of consciousness.	1. Valproic acid 2. Lamotrigine

- **Status epilepticus:**

  Prolonged seizure (>20 min) of any of the types previously described; the most common is life-threatening generalized tonic–clonic status epilepticus.

1. Diphenylhydantoin (Phenytoin)

Mechanism: it blocks Na^+, K^+ and Ca^{2+} channels in the **brain** (and **heart)** leading to decrease propagation of abnormal impulses. It produces some degree of drowsiness.

Any antiepileptic drug must have one or more of the **following mechanisms:**

1. **Decrease brain excitability** through blocking Na^+ or Ca^{2+} influx.
2. **Enhancement of GABA action.**
3. **Inhibition of excitatory transmitters** (aspartate and glutamate).

Therapeutic uses

- Partial and generalized seizures
- Status epilepticus: it should be given **i.v.** in the form of **fosphenytoin** (prodrug).
- Ventricular arrhythmia.

Adverse effects

– CNS: Nystagmus, diplopia, ataxia.
– Hepatotoxicity.
– Microsomal enzyme induction.
– Bone marrow depression & Megaloblastic anemia (due to ↓ folic acid).
– Teratogenicity: craniofacial abnormalities.
– Gingival hyperplasia: 2ry to increased expression of platelet derived growth factor (PDGF).
– Lymphadenopathy.

2. Carbmazepine (Tegretol)

Mechanism: it blocks Na^+ channels & ↓ excitability of cortical neurons.

Therapeutic uses

- Partial and generalized seizures (grand mal epilepsy).
- Trigeminal neuralgia.

Adverse effects

- CNS: diplopia & ataxia.
- Hepatotoxicity.
- Microsomal enzyme induction.
- Bone marrow depression.
- Congestive heart failure (CHF).

3. Valproic acid (Depakene)

Mechanism: it activates *glutamic acid decarboxylase* enzyme→ ↑ GABA synthesis.

Therapeutic uses: all types of epilepsy.

Adverse effects

- Sedation
- Microsomal enzyme inhibition
- Teratogenicity.
- Alopecia
- Pancreatitis

4. Ethosuximide (Zarontin)

Mechanism: blocks neuronal voltage-dependent Ca^{2+} and Na^+ channels.

Therapeutic uses: absence seizures (petit mal epilepsy) **(1st choice).**

Adverse effects

- Sedation
- Vomiting
- Leucopenia

5. Benzodiazepines: Clonazepam and diazepam

Mechanism: allosteric modulation of GABA action to facilitate its effects.

Therapeutic uses

- Clonazepam: petit mal epilepsy.
- Diazepam: status epilepticus.

Adverse effects: see before.

6. Barbiturates: Phenobarbitone

Mechanism: enhancement of GABA-mediated inhibition of glutamate excitation.

Therapeutic uses: grand mal epilepsy (contraindicated in petit mal epilepsy).

Adverse effects: see before.

NEWER ANTIEPILEPTIC DRUGS

1. Felbamate

Mechanism

- Block glycine site on the N-methyl-D-aspartate (NMDA) receptors.
- Block voltage-dependent Ca^{2+}& Na^{+} channels.

Therapeutic uses: wide variety of partial and generalized seizures.

Adverse effects

– Hepatotoxicity
– Microsomal enzyme induction.
– Bone marrow depression.

2. Lamotrigine

Mechanism

- Decreases glutamate and aspartate, which are excitatory neurotransmitters
- Blocks sodium channels and high voltage-dependent calcium channels leading to ↓ excitability.

Therapeutic uses: wide variety of partial and generalized seizures and typical absence seizures in children and adults.

3. Gabapentin

Mechanism: unknown but may interfere with voltage-dependent Ca^{2+} channels

Therapeutic uses: as adjuvant therapy in wide variety of partial and generalized seizures.

Adverse effects: headache, nystagmus, dizziness & ataxia.

4. Tiagabine

Potent and specific inhibitor of GABA uptake into glial and other neurons. Thus, it enhances the action of GABA by decreasing its removal from the synaptic space.

Precautions during antiepileptic therapy

- Proper **choice** of the antiepileptic drug according to type of epilepsy.
- Start with **single drug** and if fails, substitute it or add another drug.
- **Dose** of the drug is adjusted according to:
  - *Plasma concentration of the drug.*
  - *Patient's response.*
- Therapy is given for 2-3 years then withdrawn **gradually**.

Drugs used for treatment of Status epilepticus

Diazepam (drug of choice) 10 mg i.v. or 500 μg/kg **rectal** (in children) **OR:**

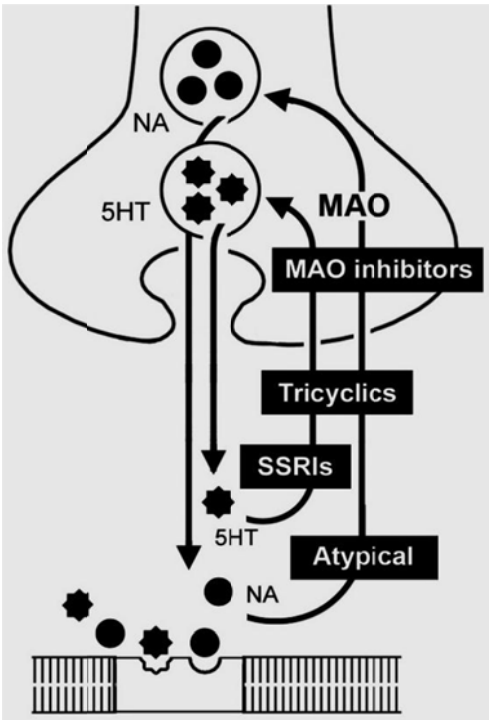
- Fosphenytoin: 100 mg i.v.
- Phenobarbitone: 200 mg i.v.
- In severe cases:
  a) Thiopental i.v.
  b) Artificial respiration.

Part 6: Antidepressant Drugs

Basic information

- Depression is a disorder of mood rather than disturbance of thought or cognition. It is postulated that depression is due to **deficiency** of **NA** and/or **5-HT** in the CNS while **mania** results from functional **excess**. Psychic depression is characterized by both ***emotional*** and ***biological*** symptoms.
- Recent studies suggest that overactivity of post-synaptic **5-HT$_2$A** receptors in some brain areas is involved in the pathogenesis of depression and psychosis.
- **Unipolar depression (major depressive disorder):** more common, may be ***reactive*** (70%) or ***endogenous*** (25%), characterized by low mood and loss of interest or pleasure in normally enjoyable activities.
- **Bipolar depression (manic-depressive disorder):** less common, characterized by oscillating periods of depression and mania. There is strong hereditary origin.
- The therapeutic effect occurs only after **2-3 weeks** of drug administration and is more closely associated with adaptive changes in neuronal receptors and brain neurotropic factors.

The sad woman by Edith Wilkinson



Classification of antidepressant drugs:

- **Tricyclic antidepressants (TCA)** e.g. imipramine, amitriptyline.
- **Selective serotonin reuptake inhibitors (SSRI):** e.g. fluoxetine, sertraline.
- **Atypical heterocyclic antidepressants:** e.g. maprotiline, trazodone.
- **Monoamine oxidase inhibitors (MAOI)** e.g. clorgyline, selegiline.

1. Tricyclic antidepressants (TCA)

Imipramine, Desipramine, Clomipramine, Amitriptyline, Nortriptyline

Pharmacokinetics

- They are well absorbed after oral administration. They have **large Vd**.
- Most TCA have **long $t_{1/2}$** because they are metabolized into active metabolites and undergo enterohepatic cycling.

Mechanism of action: *(inhibition of the amine pump)*

- TCA inhibit neuronal reuptake of both 5-HT & NA leading to their accumulation in synaptic spaces and the brain tissue.
- It has been suggested that improvement of the **emotional** symptoms is related to enhancement of **5-HT** transmission while improvement of **biological** symptoms is related to enhancement of **NA** transmission.
- Elevation of mood in depressed patients occurs after 2-3 weeks

Therapeutic uses

- Major depressive disorder.
- Nocturnal enuresis in children (**imipramine**).
- Chronic pain syndromes, neuropathic pain, and prophylaxis of migraine (unclear mechanism).

Adverse effects

- **Sedation** is common at the start of therapy but tolerance develops later. It may be due to antagonism with histamine H1 and/or muscarinic receptors.
- **CNS troubles:** memory dysfunction, agitation, seizures, and suicidal thoughts.
- **Atropine-like action:** very common - dry mouth, blurred vision, urine retention, etc.
- **Orthostatic (postural) hypotension**: due to peripheral **α1** receptor blockade.
- Cardiac **arrhythmias:** tachycardia, widening of QRS, and ↑ QT interval.
- **Hepatotoxicity:** cholestatic hepatitis.
- Weight gain.

Drug interactions

- Toxic synergism with **MAOIs** and **SSRIs** (irritability and convulsions).
- TCA antagonize the antihypertensive effect of **clonidine** and **methyldopa**.
- TCA have additive **anticholinergic effect** with other drugs having anticholinergic activity.

TCA overdose

- Metabolic acidosis
- Atropine-like effects
- Cardiac arrhythmia

Management

- IV NaHCO3 (1st step).
- IV lidocaine
- Dialysis is ineffective

2. Selective serotonin reuptake inhibitors (SSRIs)

Fluoxetine, Paroxetine, Sertraline, Citalopram, Escetalopram

- They are the most commonly prescribed antidepressants due to their limited toxicity. They are also used for some other psychiatric disorders.
- **Sertraline** is the preferred antidepressant following **myocardial infarction** as there is more evidence for its safe use in this situation than other antidepressants.
- When stopping an SSRI the dose should be **gradually** reduced over a 4 week period, this reduces the risk of relapse.

Mechanism of action

- They selectively block 5HT reuptake leading to accumulation of 5-HT in brain tissue.
- Their effect appears after 2-3 weeks like other antidepressants.

Therapeutic uses

- Major depressive disorder.
- Obsessive-compulsive disorder (OCD).
- Anxiety disorders (generalized anxiety disorder, social phobia, panic disorder).

Adverse effects

- **GIT irritation** is the most common side effect. A **proton pump inhibitor** should be prescribed if a patient is also taking a NSAID to avoid GIT bleeding.
- **Sedation** or **insomnia** at the start of therapy but tolerance develops later.
- **Muscle cramps** and twitches.
- **Sexual dysfunction** in up to 40% of patients – the main cause of noncompliance.
- Dangerous **"serotonin reaction"** may occur if given with **MAOIs** or **TCA** (hyperthermia, muscle rigidity, cardiovascular collapse).

3. Atypical antidepressants

The pharmacological properties of atypical heterocyclic antidepressant agents are similar to those of TCAs.

Mechanism of action

- **Trazodone:** blocks mainly **$5HT_2A$** receptors in addition to **H1**, and **α1** receptors. It is highly sedating and can cause postural hypotension.
- **Mertazapine:** blocks mainly **$5HT_2A$** receptors in addition to **H1**, and **α2** receptors. It causes weight gain.
- **Maprotiline:** selective blocker of **NA reuptake**. It is highly sedating and can cause seizures.

4. Monoamine oxidase inhibitors (MAOIs)

Clorgyline, Selegiline, Pargyline, Moclobemide

Mechanism of action

- They inhibit MAO enzyme leading to accumulation of active monoamines (NA, 5-HT, dopamine) in neuronal tissue.
- Most MAOIs are **irreversible inhibitors**. Recovery of MAO takes several weeks. **Moclobemide** is a **reversible** inhibitor.

N.B. There are 2 isotypes of MAO enzyme:

MAO-A enzyme
- Present in the cytoplasm of neurons (CNS) and peripheral tissues (e.g. liver).
- It acts non-specifically on NA, 5-HT, and dopamine.
- **Clorgyline** is a specific inhibitor.

MAO-B enzyme
- Present mainly in the CNS and acts more on dopamine.
- **Selegiline** is a specific inhibitor.

Therapeutic uses

- **Major depression:** they are **not** used as a first-line, but usually reserved as a last line after other classes of drugs have failed.
- **Selegiline** (selective MAO-B inhibitor) is used for treatment of **Parkinsonism** (see later).

Adverse effects

- **CNS stimulation:** irritability, insomnia, tremors, hyperthermia, convulsions
- **Hepatotoxicity**: occurs more with the old members.
- **Orthostatic (postural) hypotension** and **sexual dysfunction**.

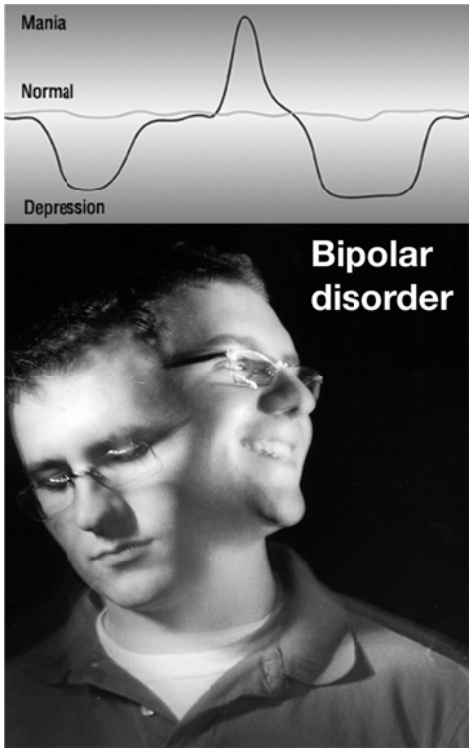
Interactions

- **Drug-drug interactions:**
  - Toxic synergism with **tricyclic antidepressants** and **SSRIs**.
  - Potentiation of **sympathomimetics** (including cold remedies & nasal decongestants).

- **Drug-food interactions: Hypertensive crisis (cheese reaction):**
  - **Tyramine** is an indirect sympathomimetic present in some food and normally metabolized by MAO-A in the liver.
  - When the patient takes MAO-A inhibitor or non-selective MAOIs, severe hypertension can occur after eating tyramine-rich food *e.g. fermented cheese, yogurt, beer, herrings*.
  - Treatment: by giving combined α + β blockers (prazosin + propranolol).

Part 7: Mood Stabilizing Drugs (treatment of mania and bipolar disorder)

- **Sodium valproate** is the only specific antimanic agent and is the treatment of choice in the **acute stages**.
- **Lithium** is the drug of choice for **long-term** treatment to prevent relapse.



Lithium carbonate

Mechanism of action

- It ↓ cAMP in neuronal cells and ↓ NA release → ↓ neuronal firing.
- It inhibits many metabolic processes in the nerve tissue.

Therapeutic uses

- Treatment of **mania** *(valproate is the 1st choice).*
- Treatment of **manic-depressive disorder** (bipolar depression)**.** It is given in the manic phase while TCA or SSRIs are given in the depressive phase.

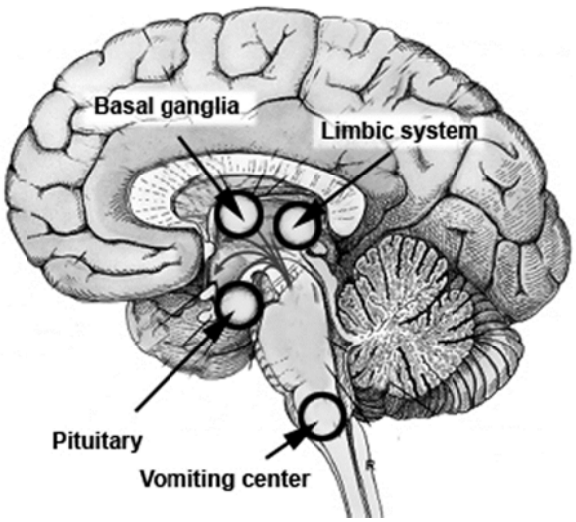
Adverse effects

- Lithium has a very narrow therapeutic index, monitoring of plasma levels is essential.
- It has long plasma half-life being excreted entirely by the kidneys.
- Toxicity may be precipitated by dehydration, renal failure, diuretics (especially thiazide) or ACE inhibitors.

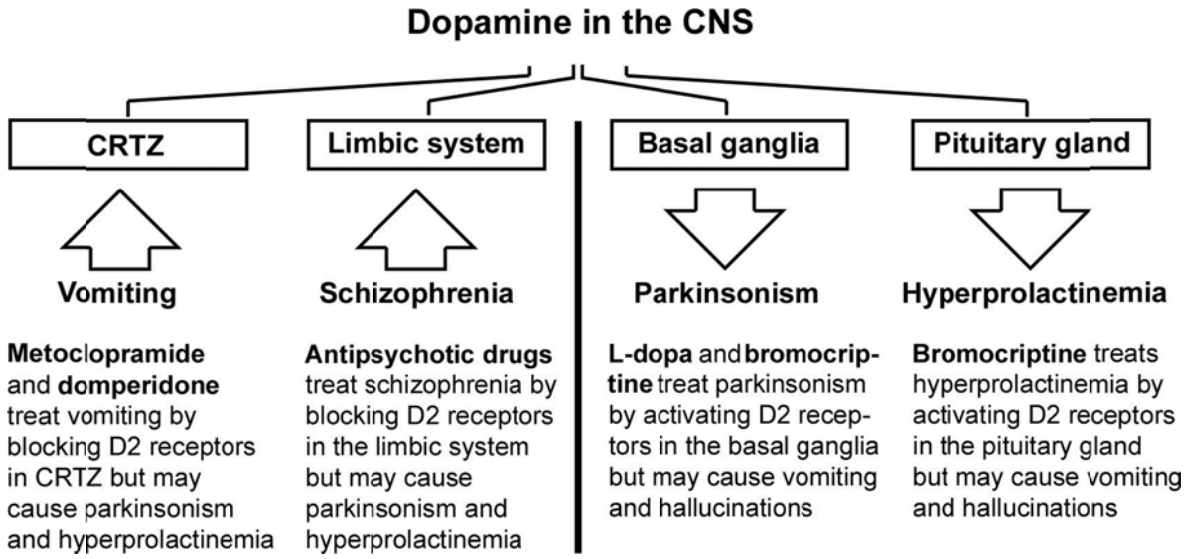
– Anorexia, nausea, vomiting and diarrhea.
– Nephrogenic **diabetes insipidus** leading to polyurea and thirst.
– Hypotension and cardiac **arrhythmia**.
– **Thyroid** dysfunction
– **Fine tremors** (coarse tremors are seen with toxic levels).
– Teratogenicity.

Part 8: Antipsychotic Drugs (Neuroleptics)

Basic information



Central dopaminergic pathways and drugs affecting them:



- The term "**psychosis**" denotes a variety of mental disorders. **Schizophrenia** is a particular kind of psychosis characterized by abnormal social behavior and failure to recognize what is real.
- Common **"positive"** symptoms include false beliefs (delusions), unclear or confused thinking, and auditory hallucinations. **"Negative"** symptoms include reduced social engagement, blunted emotions, and inactivity.
- It is suggested that **central dopamine overactivity and $5HT_2A$ receptors** play important role in the pathogenesis.

Self-portrait of a person with schizophrenia, representing that individual's perception of the distorted experience of reality in the disorder

Classification of drugs

- **Typical (classic; old) neuroleptics:**
  - **Phenothiazines:** chlorpromazine, promethazine.
  - **Butyrophenones:** haloperidol, droperidol.
  - **Thioxanthenes:** thiothixene, chlorprothixene.

- **Atypical (newer) neuroleptics:**
  - **Risperidone– Olanzapine – Clozapine**

Mechanism and therapeutic action

- The **typical antipsychotic** drugs primarily block central **D_2** receptors in the mesolimbic and mesocortical areas of the CNS leading to ↓ hallucinations and delusions but can lead to serious **extrapyramidal** adverse effects.
- The **atypical antipsychotic** drugs combine between blockade of **D_2** (to a lesser degree) and **5-HT_2A** receptors, so they have **fewer extrapyramidal** side effects.
- The **typical antipsychotic** drugs have greater effect on the control of **positive** symptoms (hallucinations and thought disturbances), while **atypical** drugs have greater effect on **negative** symptoms (social withdrawal).

Therapeutic uses

- **Schizophrenia & mania (typical and atypical antipsychotics):**

– Antipsychotic drugs produce an **immediate quieting action.** However, their antipsychotic effects typically take **longer** time to occur (a week or more).

- **Other therapeutic uses of typical antipsychotics:**

– **Chloropromazine** is sometimes used to relieve **intractable hiccough** and as anaesthetic adjuvant in certain operations to produce **hypothermia.**

– **Severe nausea or vomiting** associated with, e.g., radiation treatment and cancer chemotherapy. Typical antipsychotic agents have strong antiemetic activity due to D2-receptor blockade in the chemoreceptor trigger zone (CTZ) of the medulla. The most commonly used are the phenothiazines **chloropromazine** and **promethazine**

Adverse effects

- **CNS:**
  - **Extrapyramidal manifestations:**
    – These adverse effects are related to a **D2-receptor blockade** in the basal ganglia. They occur most likely with **old** generation drugs.

- They include:
  - Parkinsonian-like syndrome
  - Dystonia: sustained muscle contractions cause twisting movements or abnormal postures
  - Dyskinesia: involuntary repetitive facial, lip, and tongue movements occurs with chronic therapy. It may be irreversible.

Dystonia caused by antipsychotic drugs.

- **Neuroleptic malignant syndrome:**
  - It is a serious complication with mortality rate 20%, occurs more with old generation drugs.
  - It consists of autonomic disturbance, ms rigidity, hyperthermia, and sweating.
  - It needs immediate stopping of the antipsychotic therapy.

- **Autonomic side effects:**
  - **α-receptor blockade** leading to postural hypotension and sexual dysfunction
  - **Muscarinic blockade** → atropine-like actions

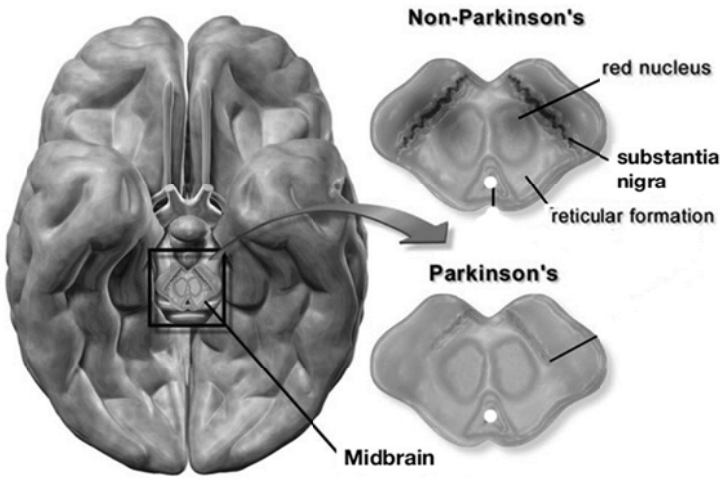
- **Endocrine disturbance (occurs more with atypical agents):**
  - Weight gain
  - Hyperglycemia and precipitation of DM.
  - Gynecomastia, amenorrhoea

- **Other adverse effects:**
  - Cardiac arrhythmia
  - Cholestatic jaundice
  - Agranulocytosis (particularly associated with **clozapine**)

	Typical drugs	Atypical drugs
Mechanism	Block mainly D2 receptors	Block D2 (less) and $5HT_2A$ (more)
Effect	More effect on +ve symptoms	More effect on – ve symptoms
Extrapyramidal side effects	Common	Less common
Neuroleptic malignant synd	Common	Less common
Endocrinal side effects	Less common	Common
Agranulocytosis	Less common	Common

Part 9: Antiparkinsonian Drugs

Parkinsonism is a movement disorder characterized by ms rigidity, tremors, and postural instability due to loss of **dopaminergic neurons in substantia nigra and locus ceruleus** resulting in imbalance of dopaminergic (inhibitory) and cholinergic (excitatory) influences on the extrapyramidal system. Recently, a heroin substitute (MPTP) was found to cause irreversible damage of the negrostriatal dopaminergic neurons and a parkinsonism-like state.



Diminished dopaminergic neurons in substantia nigra seen in Parkinsons disease

Classification of antiparkinsonian drugs:

- **Dopaminergic drugs:**
  - **Dopamine precursors:** Levodopa (L-dopa).
  - **COMT inhibitors:** Tolcapone - Entacapone
  - **Selective MAO-B inhibitors:** Selegiline
  - **Dopamine agonists:** Bromocriptine
  - **Release of dopamine** and inhibition of its reuptake: Amantadine
- **Antichloinergic drugs:**
  - **Synthetic atropine substitutes:** Benztropine – Orphenadrine – Trihexyphenidyl

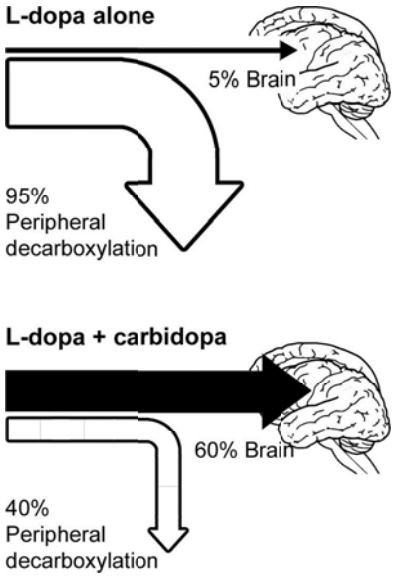
1. Levodopa (L-dopa)

Pharmacokinetics

- Absorbed rapidly from the small intestine.
- It has **short $t_{1/2}$** (1-2 h). This short $t_{1/2}$ may produce "*on-off phenomenon*" i.e. rapid fluctuation of the clinical state in the form of sudden tremors & immobility after short period of recovery.
- **Amino acids** (e.g. leucine & isoleucine) compete with L-dopa absorption from the gut so it should be taken on an empty stomach.

Mechanism of action

- Dopamine can't cross BBB but L-dopa can. It is considered the **1st line** treatment of parkinsonism.
- More than 95% of the administered dose is rapidly decarboxylated into dopamine in the peripheral tissues. Only a small fraction escapes and crosses BBB.
- Peripheral decarboxylation can be minimized by administration of a decarboxylase inhibitor which can't cross BBB e.g. **carbidopa** or **benserazide.**
- Such a combination helps to reduce the dose of L-dopa and hence the adverse effects



Adverse effects

- **GIT:** nausea & vomiting *(domperidone is the drug of choice to treat this vomiting because it does not cross the BBB. It acts on the bare area of the barrier).*
- **CNS:**
  - Mood changes, hallucinations and nightmares.
  - Dyskinesia: involuntary movements of the head, lips, and tongue.
  - On-off phenomenon: rapid fluctuation of the clinical state in the form of sudden tremors and immobility after a short period of recovery due to the short $t_{1/2}$ of the drug.
- **Autonomic:** postural hypotension, arrhythmias, mydriasis and acute rise of IOP.
- **Brownish** body secretions & red urine due to the metabolite *homovanilic acid.*

Interactions

- **Food:** amino acids (e.g. leucine & isoleucine) compete with L-dopa absorption**.**
- **Dopamine blockers** (antipsychotic drugs and metoclopramide) antagonize the effects of L-dopa.
- **Pyridoxine** (vitamin B6) enhances peripheral decarboxylation into dopamine.
- **COMT inhibitors** and **selective MAO-B inhibitors:** make synergism with L-dopa.

2. COMT inhibitors (L-Dopa adjuvants): Tolcapone - Entacapone

Mechanism of action

- They inhibit COMT enzyme selectively & reversibly, the enzyme that converts L-dopa to 3-O-methyldopa (3OMD) in the gut and liver.

- By inhibiting COMT enzyme, tolcapone increases the efficacy of L-dopa and stabilizes dopamine levels in the striatum and improves motor function.

Adverse effects

- Same side effects of L-dopa (nausea, vomiting, hallucination, mood changes).
- Tolcapone causes fulminating hepatic necrosis.

3. Selective MAO-B inhibitors: Selegiline

Mechanism of action

- It is a selective MAO-B inhibitor **decreasing breakdown** of dopamine in the brain.
- Unlike MAO-A inhibitors, it does not precipitate **"cheese reaction"** since tyramine is metabolized in the liver by MAO-A.

Adverse effects

- Nausea, vomiting & GIT upset.
- Hallucinations & mood changes.
- Insomnia.

4. Dopamine agonists: Bromocriptine

- It is dopamine (D_2) agonist derived from ergot alkaloids.
- It differs from L-dopa in: **Faster** onset, **longer** duration, **No** on-off effect.

Other uses

- To treat hyperprolactinemia and to suppress lactation (dopamine agonists ↓ prolactin secretion from pituitary gland).
- Acromegaly (dopamine agonists ↓ GH secretion from pituitary gland).

Adverse effects

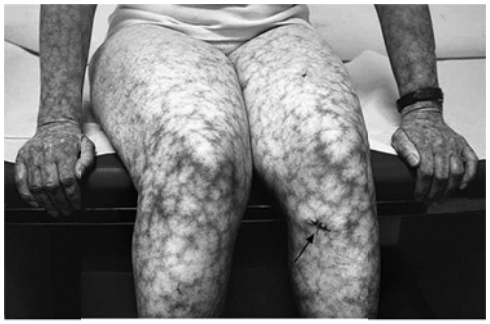
- Nausea, vomiting & GIT upset.
- Hallucinations & mood changes in large doses.
- Postural hypotension.

5. Dopamine release stimulation: Amantadine

- It is an antiviral drug for influenza A2 virus.
- The antiparkinsonian mechanism is unclear but may be due to ↑ dopamine release, ↓ dopamine reuptake, or direct action on dopamine receptors.

Adverse effects

- Nausea, vomiting & GIT upset.
- Hallucinations & mood changes in large doses.
- Postural hypotension.
- Skin pigmentation.



Skin pigmentation "levido reticularis" caused by amantadine.

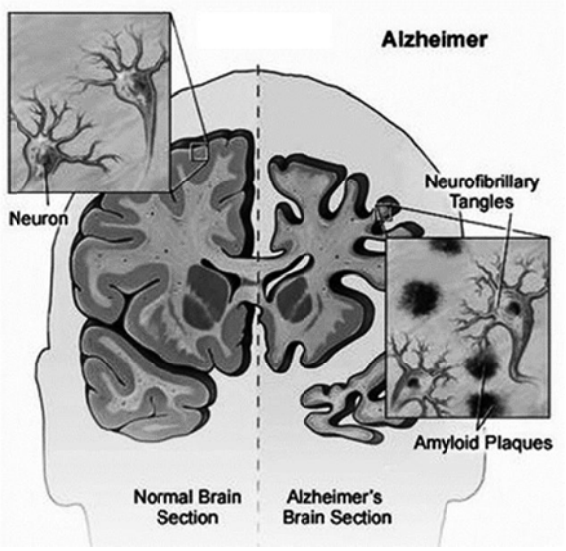
6. Anticholinergic drugs:

Benztropine – Orphenadrine – Trihexyphenidyl

- These drugs have **greater selectivity** for blocking central than peripheral muscarinic receptors.
- They produce moderate improvement of tremors and **sialorrhea** but little effect on muscle rigidity.
- They are used also to control acute drug-induced extrapyramidal side effects.
- These drugs are **contraindicated** in patients with **prostatic** hypertrophy, obstructive GI disease (e.g., paralytic ileus) and narrow-angle **glaucoma**.
- In patients suffering from Parkinsonism, there is some degree of **dementia** associated with atrophy of cortical neurons. Anticholinergic drugs may aggravate dementia and memory loss.

Part 10: Drugs Used in Alzheimer's Disease

Alzheimer is a neurodegenerative disease characterized by progressive loss of memory and dementia due to **loss of cholinergic neurons** and deposition of abnormal protein "amyloid plaques". Overstimulation of **glutamate receptors** may be responsible for this neurodegenerative process.



The aim of therapy is to either improving cholinergic transmission within the CNS or preventing the excitatory actions of NMDA glutamate receptors in selected brain areas.

1. Cholinesterase inhibitors: Donepezil - Rivastigmine

- They are more selective for ChE enzyme in the CNS
- They provide a modest reduction in the rate of loss of cognitive functions.
- **Side effects:** nausea, vomiting, anorexia, and muscle cramps.

2. NMDA receptor antagonist: Memantine

- It is a derivative of amantadine
- It prevents rate of memory loss in both vascular-associated and Alzheimer dementia.
- **Side effects are rare:** confusion, agitation, restlessness.

3. Recent trials:

- **β & γ-secretase inhibitors:**
  The enzymes β & γ-secretase are responsible for formation of amyloid proteins Aβ40 and Aβ42 that are found in the brain of Alzheimer patients. Inhibition of these enzymes reduces deposition of theses amyloid deposits.
- **Ibuprofen and indomethacin**
  These NSAIDs reduce formation of Aβ42 by inhibition of γ-secretase enzyme which is unrelated to their COX inhibition. Aspirin and corticosteroids do not produce this effect.
- **Copper and zinc chelating agents:**
  Removal of these metals promotes dissolution of amyloid plaques in brain tissue.

Part 11: General Anesthetics

General anesthesia is characterized by a loss of consciousness, analgesia, amnesia, skeletal ms relaxation, and inhibition of autonomic and sensory reflexes.

Balanced anesthesia

- Balanced anesthesia refers to a combination of drugs used to take advantage of individual drug properties and minimizing their adverse actions.
- In addition to anesthetic drugs and neuromuscular blocking drugs, other drugs are administered preoperatively, intraoperatively, and postoperatively to ensure smooth induction, sedation, and smooth recovery (e.g., benzodiazepines, opioids).

Stages and planes of anesthesia

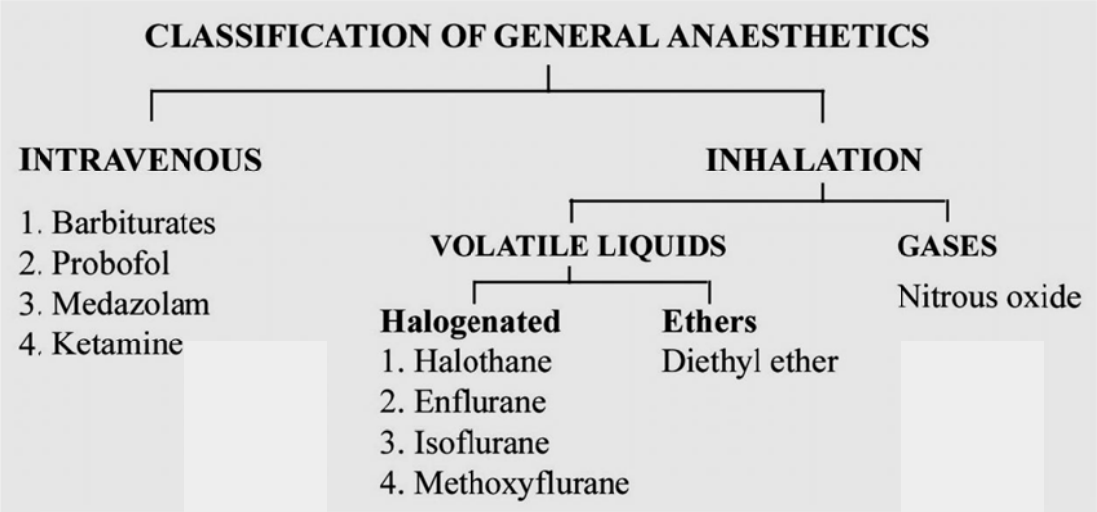
- The stages and planes of anesthesia identify the progression of physical signs that indicate the depth of anesthesia. Newer, more potent agents progress through these stages rapidly, and therefore, the stages are often obscured.
- Mechanical ventilation and the use of adjunct drugs also obscure the signs indicating the depth of anesthesia.
  - **Stage I:** Analgesia and amnesia.
  - **Stage II:** Excitation.
  - **Stage III:** Surgical anesthesia: loss of consciousness.
    - Four planes have been described relating to increased depth of anesthesia.
    - Plane IV includes maximal pupil dilation, apnea, and circulatory depression.
    - The loss of the eyelash reflex and a pattern of respiration that is regular in rate and depth are the most reliable signs of stage III anesthesia.
  - **Stage IV:** Medullary depression: respiratory and cardiovascular failure.

Mechanism of anesthetic action

Inhalation and IV anesthetic agent interaction with **discrete protein binding sites in nerve endings to activate ligand-gated ion channels:**

- **GABA-A-receptor chloride channels:** anesthetic agents directly and indirectly facilitate a GABA-mediated increase in chloride conductance to hyperpolarize and inhibit neuronal membrane activity.
- **Ligand-gated potassium channels:** anesthetic agents increase potassium conductance to hyperpolarize and inhibit neuronal membrane activity.
- **NMDA receptors:** certain anesthetics (e.g., nitrous oxide, ketamine) inhibit excitatory glutamate gated ion channels.

Classification of general anesthetics



INTRAVENOUS ANAESTHETICS

1. Ultrashort acting barbiturates: thiopental

Advantages

- Produces rapid and pleasant induction with rapid recovery.
- Does not increase intracranial pressure.
- Used for induction before stronger anesthetic and for short procedures.

Disadvantages

- Poor analgesia and skeletal muscle relaxation.
- Induce cough, laryngospasm, bronchospasm and apnea avoided by atropine and ready artificial respiration.
- Extravasation induces necrosis.
- Contraindicated absolutely in cases of prophyria (defect of ALA synthetase) barbiturates increase synthesis of porphyrins which precipitates acute attack inducing paralysis and death.

2. Etomidate

Advantages: It is very similar to thiopental but:

- Larger margin between the anaesthetic dose and the dose producing respiratory and cardiovascular depression than with thiopental.
- It is more rapidly metabolized than thiopental and, therefore, less likely to cause a prolonged hangover.
- It is used only as an induction agent, and is preferable to thiopental in patients at risk of circulatory failure.

Disadvantages

- More likely to cause involuntary movements during induction.
- And to cause postoperative nausea and vomiting.
- Suppresses the adrenal cortex with prolonged use which has been associated with an increase in mortality in severely ill patients.

3. Propofol

Advantages

- Rapid and pleasant induction with rapid recovery and clarity of mental status.
- Does not increase intracranial pressure.
- Used for induction or maintenance.

Disadvantages

- Respiratory center depressant less than thiopental.
- Markedly decreases the blood pressure.

4. Midazolam (see under Benzodiazepines)

- They are used in conjunction with anaesthetics to sedate the patient.
- The most commonly employed is midazolam.
- Diazepam and lorazepam are alternatives. All three facilitate amnesia while causing sedation.

Advantages

- Used for induction
- 3-4 times as potent as diazepam.
- Does not cause local irritation after injection as diazepam.
- Little cardiovascular or respiratory depression.

Disadvantages

- Light anaesthesia.
- Can cause respiratory depression.
- Anterograde amnesia which lasts for at least 2 hours.

5. Ketamine (Dissociative Anaesthesia)

Advantages

- Profound analgesia and amnesia
- The only intravenous anesthetic that routinely produces cardiovascular stimulation through central sympathetic stimulation (increases Bl.P. H.R and C.O.). So, it is beneficial in cases of shock.
- No respiratory depression and has a potent bronchodilator effects.

Disadvantages

- Increases intracraneal pressure (due to increased cerebral blood flow).
- Unpleasant dreams.
- Recovery often is accompanied by delirium and psychomotor activity).
- Diplopia and nystagmus may occur due to increased muscle tone.
- Contraindicated in cases of hypertension and stroke.

INHALATION ANAESTHETICS

An important characteristic of an inhalation anaesthetic is the speed at which the arterial blood concentration, which governs the pharmacological effect, follows changes in the concentration of the drug in the inspired air.

Measure of potency

- Through the minimum alveolar concentration (MAC). It is the anaesthetic (MAC) alveolar concentration at 1 atmosphere that will produce loss of movement in 50% of subjects exposed to a noxious stimulus.
- Methoxyflurane is highly potent while nitrous oxide is of low potency.

Rapidity of induction

- Gas of little solubility in blood as nitrous oxide has a high blood gas tension, a small Vd, with a consequent rapid induction and rapid recovery.
- Gas of high solubility in blood e.g. methoxyflurane has a low blood gas tension, a big Vd, with a slow induction and a slow recovery.

Pharmacological effects

- Inhalation anaesthetics produce descending depression of all brain functions in the following order: Cortex >Subcortex> Mid-brain > Spinal cord > Medullary centers.
- The highly developed functions like memory are the first to be lost, but the vital functions as respiration and circulation are the last.
- With modern balanced anaesthesia no more notable staging. Loss of consiousness, analgesia and muscle relaxation is produced with a combination of drugs rather than with a single anaesthetic agent.
- Unconsciousness rapidly produced with an i.v. induction agent (e.g. propofol), to maintain unconsciousness and produce analgesia with one or more inhalation agent which might be supplemented with an i.v. analgesic agent, and to produce muscle paralysis with a neuromuscular blocking drug.
- The following table shows points of difference in between the currently used inhalation anesthetics:

Inhalation anesthetics

	Ether	Nitrous Oxide	Halothane	Enflurane	Methoxy Flurane
1- MAC	1.9	> 100 (the least potent)	0.75	1.7	0.16 (the most potent)
2- Induction and recovery	rapid	rapid	Slow	slow	slow
3- Analgesia	good	good	Inadequate	potent	potent (continues after recovery)
4- Skeletal muscle relaxation	good	not relaxant	Inadequate	good	good
5- C.V.S	--------	--------	Bradycardia, arrhythmias and hypotension	less than halothane	less than halothane
6- Respiration	Bronchodilataion by the sympathetic stimulation	Diffusion hypoxia at the termination	Respiratory center depression	- more respiratory center depression - Inhibits bronchoconstriction	more
7- Liver	Increased glycogenolysis by the sympathetic stimulation	-----	autoimmune hepatitis	less than halothane (rare)	less than halothane (rare)
8- Uterus	----------	No uterine relaxation	potent uterine relaxant	less uterine relaxation	No uterine relaxation
9- Hyperthermia	----------	-------	rare	rare	rare
10- Use	* Suitable for most types of operations * Of wide safety margin	* The most widely used * Obstetric anesthesia . * Neuroleptanaesthesia	- Safe for children and for asthmatics	lower incidence of arrthythmias than halothane	* Limited use because of nephrotoxicity * Obsetetric anaesthetic.
11- Disadvantages	* Inflamable * Irritant * Precipitaes convulsions	* Weak anaesthetic * Has no skeletal muscle relaxant effect * Diffusion hypoxia	* Hepatitis * Malignant hyperthermia * Contraindicated in cardiac	* Nephrotoxic * EEG. seizure activity (contraindicated in epileptics)	Nephrotoxic (damage of tubules by the liberated fluoride diabetes insipidus induced by fluoride)

Preanesthetic medications (anesthetic adjuvant):

They are drugs given to reduce anxiety, providing analgesia and amnesia, and prevent salivation, bradycardia, and other side effects of anesthesia.

- **Anxiolytics (e.g. diazepam):** given at night preoperatively to provide sedation & amnesia.

- **Opioid analgesics (e.g. morphine, fentanyl, or alfentanil):**
  - They are given 1½ hrs before anesthesia to inforce low potency anesthetics as nitrous oxide.Alfentanyl may offer faster recovery than fentanyl.

- **Anticholinergic drugs (e.g. atropine or scopolamine):**
  - They are given 1½ hrs before anesthesia to reduce respiratory secretions and prevent occurrence of aspiration pneumonia.
  - They block the reflex vagal stimulation induced by some inhalation anesthetics.

- **Muscle relaxants & others drugs:** e.g. **vasopressors** to prevent hypotension and **hypothermics** (chlorpromazine) to lower the normal body temperature in cases of cardiac surgery.

Part 12: Local Anesthetics

Classification

There are two classes of local anesthetics: **amides** and **esters**. The primary differences between the two classes are in their relative metabolism (amides have primarily a hepatic metabolism, whereas esters are metabolized by plasma cholinesterases) and their potential for allergic reactions (esters more than amides).

	Esters	Amides
Members	Cocaine, procaine, tetracaine, benzocaine	Lidocaine, prilocaine, mepivacaine, bupivacaine
Metabolism	Plasma cholineestrase	Liver
Hypersensitivity reactions	May occur	Rare

Mechanism of action

- Local anesthetics block voltage dependent Na^+ channels within the nerve fibers →↓ nerve conduction.
- In general, small nerve fibers (that carry pain sensation) are more sensitive to local anesthetics than large fibers (motor and other sensations).
- Myelinated fibers are blocked before non-myelinated fibers of the same diameter.

Pharmacological properties

	Chemistry	Anesthetic potency	Duration	Onset
Procaine	Ester	Low	Short	Moderate
Mepivacaine	Amide	Moderate	Moderate	Fast
Prilocaine	Amide	Moderate	Moderate	Fast
Lidocaine	Amide	Moderate	Moderate	Fast
Tetracaine	Ester	High	Long	Moderate

Adjuvants of local anesthetics

- **Vasoconstricotors e.g. adrenaline:**
  - They are added to produce local VC; this will reduce wash of the anesthetic by the local blood flow and thus prolongs the duration of the anesthetic.

- Vasoconstrictors should not be added for ring block of hands, feet, fingers, toes, and ear pinna to avoid tissue damage.

- **Sodium bicarbonate:**
  - All local anesthetics are weak **bases**. Addition of bicarbonate to the anesthetic solution maintains the anesthetic in the non-ionized state and this increases lipid solubility and enhances penetration of the anesthetic into the nerve sheath.

Techniques and clinical uses

- **Surface (topical) anesthesia:** is used for anesthetization of the skin, mucous membranes, or cornea.
  - Treatment of itching caused by insect bites or irritant condition.
  - To relieve pain caused by oral, laryngeal, or rectal disorders e.g. piles.
  - Corneal anesthesia in ophthalmic surgery.

- **Infiltration anesthesia:** injecting an anesthetic directly into the subcutaneous tissue for minor surgical procedures e.g. dental procedures. Epinephrine may be added to prolong the duration of action.

- **Nerve block:** injecting the local anesthetic close to the appropriate nerve trunk proximal to the intended area of anesthesia e.g. radial nerve block or retro-orbital block for ocular surgery.

- **Spinal anesthesia:** is used for surgeries of the lower limb or pelvic structures. A local anesthetic is injected into the subarachnoid space below the terminal end of the spinal cord (usually between 3rd and 4th lumber vertebra).

- **Epidural anesthesia:** the anesthetic is infused into the space between the dura mater and the connective tissue lining the vertebral canal as alternative to subarachnoid anesthesia.

Adverse effects

- **Surface anesthesia:** allergic dermatitis.

- **Infiltration anesthesia:** faulty intravascular injection can lead to:
  - CNS excitation: irritability and convulsions
  - CVS depression: bradycardia, hypotension, myocardial depression or cardiac arrest.

- **Vasovagal syncope**: vasovagal (also called neurocardiogenic) syncope is usually associated with bradycardia (rather than tachycardia) and pallor (rather

than flushing). These differences can be helpful in distinguishing it from anaphylaxis.

– **Spinal anesthesia:**
  - Spinal shock due to sympathetic outflow paralysis.
  - Headache due to CSF leakage.
  - Respiratory paralysis.
  - Septic meningitis.

Recommendations

- The **choice** of local anesthetic for infiltration depends on several factors, including duration of the procedure, need for hemostasis, patient sensitivity to catecholamines, and patient allergy to local anesthetics.
- Prior to infiltration, the clinician should determine if the patient has any **history of allergy.** Patients with a true allergic reaction to a local anesthetic need evaluation by an allergy specialist.
- Local anesthetic infiltration is **contraindicated** in the following conditions:
  – If the area needed to be anesthetized is so large because the amount of anesthetic needed exceeds the maximal safe dose.
  – If the patient has history of allergy to local anesthesia.

Treatment of spinal shock

- **Place the patient in the supine position with the legs elevated.**
- **Airway support:** oxygen and artificial respiration.
- **If there are convulsions, give i.v. diazepam.**
- **If there is hypotension**, give i.v. fluids plus vasoconstrictors.
- Cardiopulmonary resuscitation (CPR) is necessary when cardiac function is interrupted.

Notes

Review Questions

Long questions:

1. Classify **opioid analgesics** and discuss mechanism, uses, &contraindications of morphine.
2. Anxiety is a common medical disorder. Classify **antianxiety drugs** and discuss in details the differences between barbiturates and benzodiazepines.
3. **Depression is an important medical disease. Classify** antidepressant drugs; **mention their mechanism, indications and side effects.**
4. Classify **antiepileptic drugs**; mention their mechanism, indications and side effects.
5. **Dopamine** is found in many areas in the CNS. Discuss the drugs that act by inhibiting these central dopamine sites.
6. **Dopamine** is found in many areas in the CNS. Discuss the drugs that act by activating these central dopamine sites.

Short questions:

1. **Give an account on:**
   a) Mechanism and treatment of paracetamol toxicity
   b) Drug treatment of Alzheimer's disease.

2. **Discuss the pharmacodynamic principles underlying the use of:**
   a) Morphine in acute pulmonary edema.
   b) Acetylcysteine in paracetamol toxicity
   c) Naloxone in acute opioid toxicity.
   d) Selegiline in parkinsonism.

3. **Discuss on pharmacological basis of each of the following:**
   a) Nalorphine is contraindicated to relive pain in addict patient.
   b) Reserpine is contraindicated with MAOIs.
   c) Anticholinergic drugs are not preferred to treat parkinsonism in old patients.

4. **Mention drug interactions of each of the following drugs:**
   (1) L-Dopa (2) MAOIs

5. **Mention the main differences between:**
   a) Valproic acid and lamotrigine
   b) L-Dopa and bromocriptine.
   c) Chloropromazine and olanzapine

Of each of the following questions, select ONE BEST answer:

1. Morphine, all are true EXCEPT:
A. Acts as an agonist at opioid receptors (especially μ) in the brain and spinal cord
B. Causes pupillary constriction by stimulation of the Edinger–Westphal nucleus in the mid-brain
C. Acts as an antihistamine
D. Is subject to presystemic metabolism
E. Stimulates the chemoreceptor trigger zone

2. Which of the following is not true for meperidine?
A. It has less analgesic potency than morphine
B. It has less spasmogenic effect than morphine
C. It can cause histamine release and bronchoconstriction
D. It has greater bioavailability than morphine
E. It does not cause physical dependence

3. Morphine causes all of the following EXCEPT:
A. Diarrhoea
B. Increased intrabiliary pressure
C. Histamine release
D. Reduced sensitivity of the respiratory centre to carbon dioxide
E. Hypotension

4. The following are particularly sensitive to the pharmacological actions of morphine EXCEPT:
A. Young children
B. The elderly
C. Patients with hepatic failure
D. Patients with renal failure
E. Patients with hyperthyroidism

5. The pharmacologic effects of acetylsalicylic acid include:
A. Reduction of high body temperature
B. Promotion of platelet aggregation
C. Reduction of pain by stimulation of PGs synthesis
D. Efficacy equals to that of probenecid as uricosuric agent
E. Less gastric irritation than other NSAIDs

6. Aspirin reduces the synthesis of the following eicosanoids EXCEPT:
A. TXA2
B. PGE2
C. PGF2α
D. LTB4
E. PGI2

7. The following statements about NSAIDs are correct EXCEPT:
A. Diclofenac may cause permanent platelet dysfunction
B. Indomethacin may cause neurological side effects (neurotoxicity).
C. Sulindac is a prodrug
D. They may impair renal function
E. Aspirin may displace coumarin anticoagulants from plasma proteins

8. The following statements about aspirin are correct EXCEPT:
A. May cause GIT hemorrhage after a single dose
B. Enteric-coated tablets cause less gastric bleeding
C. May cause metabolic alkalosis in high doses
D. May cause Rye's syndrome in children
E. Its toxicity may require treatment with hemodialysis

9. Which one of the following statements concerning Cox-2 inhibitors is correct:
A. They show greater analgesic activity than traditional NSAIDs
B. They show anti-inflammatory activity greater than traditional NSAIDs
C. They harm the stomach as do non-selective cox inhibitors
D. They increase platelet aggregation
E. They are cardio protective

10. Non-narcotic analgesics are all of the following drugs EXCEPT:
A. Paracetamol
B. Acetylsalicylic acid
C. Codiene
D. Ketorolac
E. Dipyrone

11. Which one of the following non-narcotic agents inhibits mainly cyclooxygenase (COX) in CNS?
A. Paracetamol
B. Ketorolac
C. Acetylsalicylic acid
D. Ibuprofen
E. Celecoxib

12. For which of the following conditions could aspirin be used prophylactically?
A. Noncardiogenic pulmonary edema
B. Peptic ulcers
C. Thromboembolism
D. Metabolic acidosis
E. Periodontitis

13. Nefopam:
A. Is associated with gastrointestinal haemorrhage
B. Causes miosis
C. Causes more respiratory depression than morphine
D. Potentiates the dysrhythmogenic effect of halothane anaesthesia
E. Is contraindicated in epilepsy

14. Indicate the benzodiazepine, which has the shortest elimination half-life:
A. Nitrazepam
B. Alprazolam
C. Triazolam
D. Diazepam
E. Clorazepate

15. Which of the following benzodiazepines is preferred for elderly patients?
A. Clorazepate
B. Clonazepam
C. Triazolam
D. Prazepam
E. Diazepam

16. Which of the following benzodiazepines is preferred for patients with liver disease?
A. Clorazepate
B. Nitrazepam
C. Lorazepam
D. Prazepam
E. Diazepam

17. The following drug can be given to reverse benzodiazepine overdose:
A. Cocaine
B. Flumazenil
C. Buspirone
D. Picrotoxin
E. Diazepam

18. Indicate the anxiolitic agent, which relieves anxiety without causing marked sedative effects:
A. Diazepam
B. Buspirone
C. Lorazepam
D. Clorazepate
E. Zolpidem

19. Local anesthetics produce:
A. Analgesia, amnesia, loss of consciousness
B. Blocking pain sensation without loss of consciousness
C. Alleviation of anxiety and pain with an altered level of consciousness
D. A stupor or somnolent state
E. Physical dependence

20. Local anesthetics act by:
A. Blocking voltage-gated sodium channels
B. Blocking voltage-gated calcium channels
C. Blocking voltage-gated potassium channels
D. Blocking chloride conductance
E. Blocking NMDA receptors

21. Which of the following local anesthetics has short duration?
A. Procaine
B. Mepivacaine
C. Prilocaine
D. Lidocaine
E. Tetracaine

22. Which drug does not activate opioid receptors, has been proposed as a maintenance drug in treatment programs for opioid addicts, and with a single oral dose, will block the effects of injected heroin for up to 48 h?
(A) Fentanyl
(B) Nalbuphine
(C) Naloxone

(D) Naltrexone
(E) Propoxyphene

23. Which drug is a full agonist at opioid receptors with analgesic activity equivalent to morphine, a longer duration of action, and fewer withdrawal signs on abrupt discontinuance than morphine?
(A) Fentanyl
(B) Hydromorphone
(C) Methadone
(D) Nalbuphine
(E) Oxycodone

24. Which drug used in the maintenance treatment of patients with tonic-clonic or partial seizure states increases the hepatic metabolism of many drugs including both phenytoin and warfarin?
(A) Buspirone
(B) Clonazepam
(C) Eszopiclone
(D) Phenobarbital
(E) Triazolam

25. A patient with liver dysfunction is scheduled for a surgical procedure. Lorazepam or oxazepam can be used for preanesthetic sedation in this patient without special concern regarding excessive CNS depression because these drugs are
(A) Actively secreted in the renal proximal tubule
(B) Conjugated extrahepatically
(C) Eliminated via the lungs
(D) Reversible by administration of naloxone
(E) Selective anxiolytics like buspirone

26. This drug used in the management of insomnia facilitates the inhibitory actions of GABA. Its actions are antagonized by flumazenil.
(A) Buspirone
(B) Temazepam
(C) Eszopiclone
(D) Ramelteon
(E) Phenobarbital

27. A 9-year-old child is having learning difficulties at school. He has brief lapses of awareness with eyelid fluttering that occur every 5–10 min. Which drug would be effective in this child without the disadvantages of excessive sedation?
(A) Clonazepam
(B) Diazepam
(C) Ethosuximide
(D) Gabapentin
(E) Phenobarbital

28. Which antiepileptic drug is most likely to elevate the plasma concentration of other drugs administered concomitantly?
(A) Carbamazepine
(B) Clonazepam
(C) Phenobarbital
(D) Phenytoin
(E) Valproic acid

29. With chronic use in seizure states, the adverse effects of this drug include coarsening of facial features, hirsutism, and gingival hyperplasia.
(A) Carbamazepine
(B) Ethosuximide
(C) Zonisamide
(D) Tiagabine
(E) Phenytoin

30. The mechanism of antiseizure activity of carbamazepine is
(A) Block of sodium ion channels
(B) Block of calcium ion channels
(C) Facilitation of GABA actions on chloride ion channels
(D) Glutamate receptor antagonism
(E) Inhibition of GABA transaminase

31. Which statement about phenytoin is accurate?
(A) Displaces sulfonamides from plasma proteins
(B) Drug of choice in myoclonic seizures
(C) Half-life is increased if used with phenobarbital
(D) Isoniazid (INH) decreases steady-state blood levels of phenytoin
(E) Toxic effects may occur with only small increments in the dose

32. Which of the following drugs is the most effective in the emergency management of malignant hyperthermia?
(A) Atropine
(B) Dantrolene
(C) Haloperidol
(D) Succinylcholine
(E) Vecuronium

33. Which drug is most likely to cause hyperkalemia leading to cardiac arrest in patients with spinal cord injuries?
(A) Baclofen
(B) Dantrolene
(C) Pancuronium
(D) Succinylcholine
(E) Vecuronium

34. Tolcapone may be of value in patients being treated with levodopa-carbidopa because it:
(A) Activates COMT
(B) Decreases the formation of 3-*O*-methyldopa
(C) Inhibits monoamine oxidase type A
(D) Inhibits neuronal reuptake of dopamine
(E) Releases dopamine from nerve endings

35. Concerning the drugs used in parkinsonism, which statement is accurate?
(A) Dopamine receptor agonists should never be used in Parkinson's disease before a trial of levodopa
(B) Levodopa causes mydriasis and may precipitate an acute attack of glaucoma
(C) Selegiline is a selective inhibitor of COMT
(D) The primary benefit of antimuscarinic drugs in parkinsonism is their ability to relieve bradykinesia
(E) Therapeutic effects of amantadine continue for several years

36. Which drug is an antagonist at 5-HT2 receptors and can be used for the management of insomnia?
(A) Estazolam
(B) Flurazepam
(C) Trazodone
(D) Triazolam
(E) Zolpidem

37. Which of the following drugs is most likely to be of value in obsessive-compulsive disorders?
(A) Amitriptyline
(B) Bupropion
(C) Sertraline
(D) Trazodone
(E) Venlafaxine

38. A patient under treatment for a major depression is brought to the emergency department after ingesting 30 tablets of imipramine. Which of the following would be LEAST useful?
(A) Administer bicarbonate to correct acidosis.
(B) Administer lidocaine to control cardiac arrhythmias.
(C) Initiate hemodialysis to hasten drug elimination.
(D) Maintain heart rhythm by electrical pacing
(E) Use intravenous diazepam to control seizures

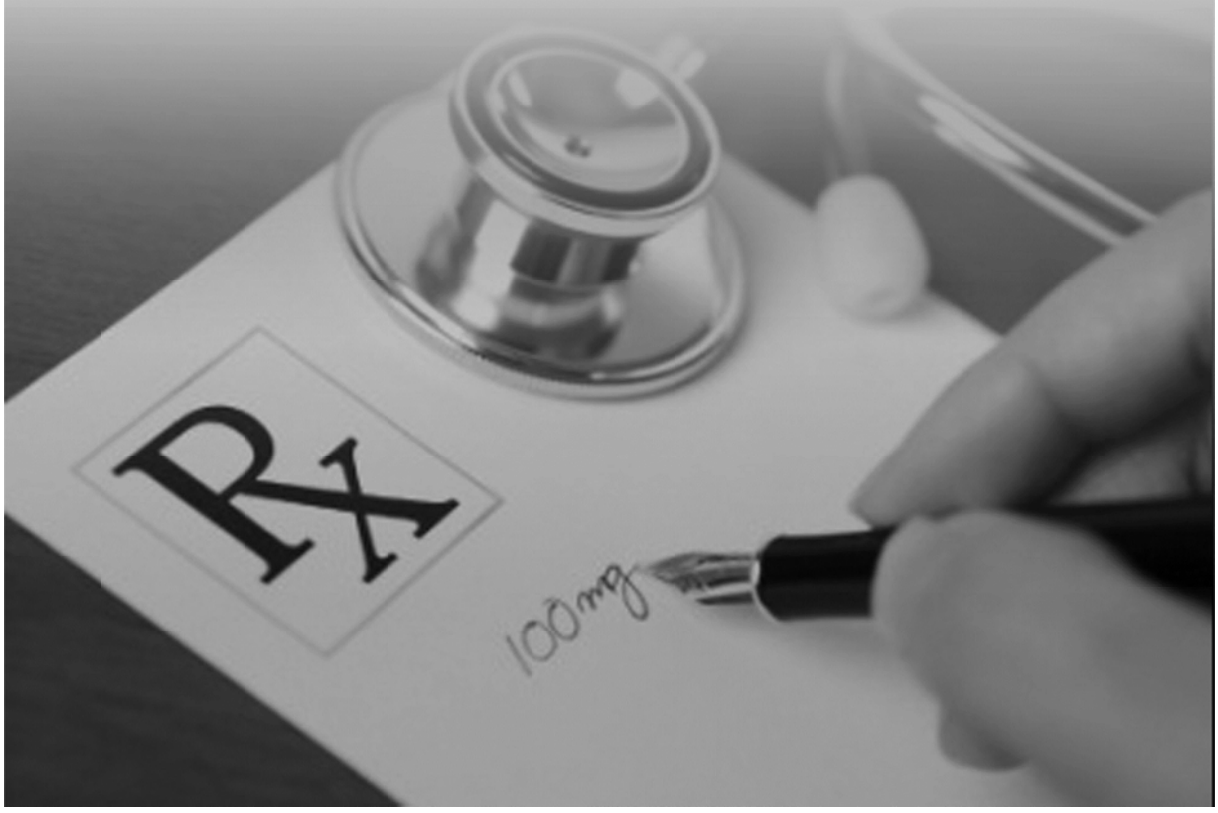
39. A 36-year-old woman presents with symptoms of major depression. Drug treatment is to be initiated with sertraline. In your information to the patient, you would tell her that
(A) Sertraline may take 2 wk or more to become effective
(B) It is preferable that she take the drug in the morning
(C) Muscle cramps and twitches can occur
(D) She should notify you if she anticipates using other prescription drugs
(E) All of the above

Answers

1 C	10 C	19 B	28 E	37 C
2 E	11 A	20 A	29 E	38 C
3 A	12 C	21 A	30 A	39 E
4 E	13 E	22 D	31 E	
5 A	14 C	23 C	32 B	
6 D	15 C	24 D	33 D	
7 A	16 C	25 B	34 B	
8 C	17 B	26 B	35 B	
9 D	18 B	27 C	36 C	

Chapter 11

Antimicrobial Drugs



Chapter 11

Antimicrobial Drugs

Part 1: Basic Principles of Antimicrobial Drugs

Chemotherapy is the killing of a living organism whether being bacteria, fungi, protozoa, or virus.

Bacteria are prokaryotic cells. Some bacteria are pathogenic to humans and can cause serious infections; the principal treatment of infections is with **antibiotics**.

CLASSIFICATION OF ANTIMICROBIAL DRUGS

A. According to source:

- **Natural compounds**: e.g. *penicillin, chloramphenicol.*
- **Synthetic compounds**: e.g. *sulfonamides, quinolones.*
- **Semisynthetic compounds:** e.g. *ampicillin.*

B. According to the effect on microorganisms:

- **Bactericidal agents:** that kills the microorganism e.g. *penicillin.*
- **Bacteriostatic agents:** arrest growth of the microorganism e.g. *sulfonamides.*

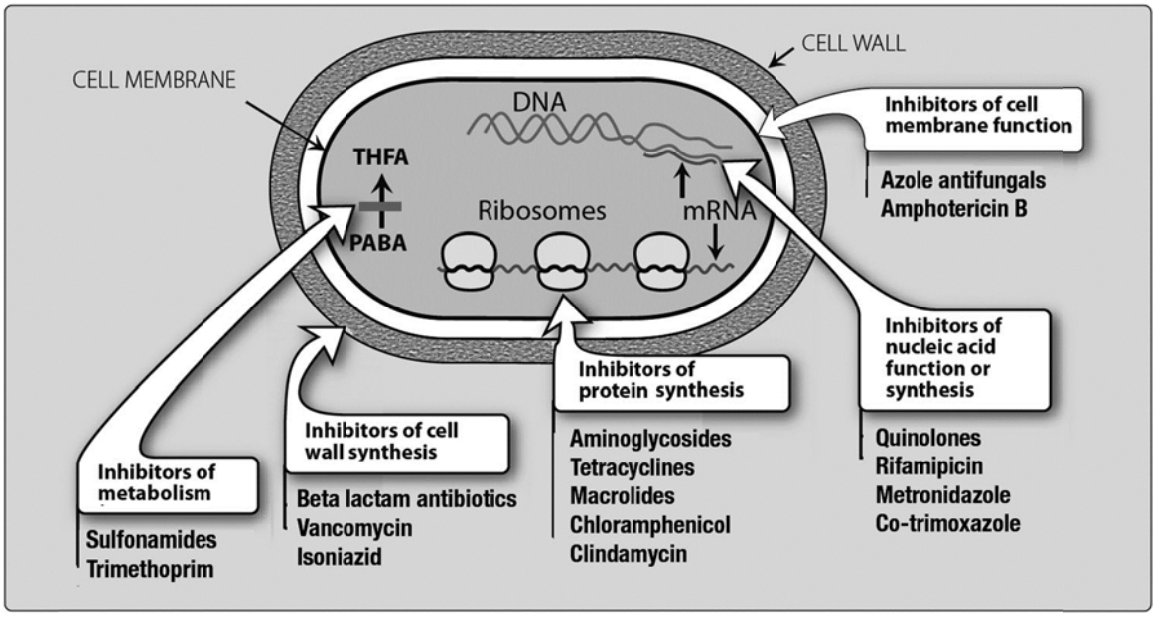
C. According to mechanism of action:

- Agents act by inhibition of **cell wall** synthesis: e.g. *penicillin.*
- Inhibition of **cell membrane** function e.g. *amphotericin B and azoles.*
- Agents act by inhibition of **nucleic acid** synthesis: e.g. *quinolones.*
- Agents act by inhibition of **protein** synthesis:
  - *By acting on ribosomal **30 S** subunit e.g. aminoglycosides.*
  - *By acting on ribosomal **50 S** subunit e.g. macrolides.*
- Agents act by inhibition of bacterial **metabolism**: e.g. *sulfonamides.*

D. According to antimicrobial spectrum:

Species pluralis (spp.), Latin abbreviation for multiple species.

- **Narrow spectrum drugs:**
  - Drugs affect mainly Gram +ve spp. e.g. *benzyl penicillin*.
  - Drugs affect mainly Gram –ve spp. e.g. *aminoglycosides.*
- **Extended spectrum drugs:** agents that affect Gram +ve & Gram –ve spp..
- **Broad spectrum drugs:** agents act on wide range of Gram +ve & Gram –ve spp. and others (protozoa) e.g. *tetracyclines.*



COMBINATION OF ANTIBIOTICS

Indications:

- To obtain broader **spectrum** e.g. *amoxicillin + clavulanic acid → co-amoxiclav.*
- To obtain **synergism** e.g. sulfonamides + trimethoprim → *co-trimoxazole.*
- In **mixed** bacterial infections e.g. diabetic foot or peritonitis.
- In **serious** bacterial infections e.g. bacterial meningitis or septicemia.
- To overcome **bacterial resistance** e.g. TB and pseudomonas infection.
- To **reduce toxicity** of one drug by using smaller doses of two drugs.

Results:

- Bactericidal + bactericidal → **synergism:** e.g. penicillin with aminoglycosides.
- Bacteriostatic + bacteriostatic → **addition:** e.g. tetracyclines with sulfonamides.
- Bactericidal + bacteriostatic → **antagonism or synergism:**
  - **Antagonism:** when bacteri**cidal** drug acts by inhibiting cell wall synthesis (i.e. kills rapidly multiplying bacteria e.g. penicillin) is combined with

bacterio**static** drug (e.g. erythromycin) which arrests the organism and prevents its multiplication.

- **Synergism:** in special cases e.g. combination between **sulfadiazine** + **penicillin** in meningococcal meningitis (both drugs attain high concentrations in CSF when meninges are inflamed).

CLINICAL APPROACHES FOR RATIONAL PRESCRIBING OF ANTIBIOTICS

A. Confirm the presence of an infection

Fever:

- Fever is considered a hallmark of most infectious diseases.
- Fever is defined as repeated oral temperatures > 37.2 ◦C.
- Fever may be **present in absence of infection** e.g. in autoimmune disorders and several malignancies.
- Fever may be **absent in presence of infection** if the immune system is depressed.

White blood cell count:

- Normal WBC is 4000-10,000 cells/mm3.
- **Bacterial** infections are associated with elevated **granulocyte** counts (neutrophils, basophils, and eosinophils).
- **Viral, TB** and **fungal** infections are associated with elevated **lymphocytic** count.
- **Parasitic** infections and **allergic** reactions are associated with increased **eosinophilic** count.

B. Selection of antimicrobial agents

Identification of the infecting organism:

- Infected body materials (e.g., blood, sputum, urine, wound drainage, etc.) must be sampled and cultured **before** initiating treatment.
- **Empirical therapy** before identification of the organism is necessary in the following conditions:
  - In all **acutely ill patients** with infections of unknown origin.
  - Infection in a **neutropenic** patient, or a patient with **meningitis** *(characteristically described by severe headache, neck rigidity, and sensitivity to bright lights)*. In such conditions any delay in the treatment could be fatal.

- **Patient factors:**

- **In neonates**, the use of *chloramphenicol* can lead to shock and cardiovascular collapse (gray baby syndrome) because liver functions are not well developed. Also, the use of *sulfonamides* may lead to kernicterus (brain damage) due to displacement of bilirubin from serum albumin.
- **In growing children**, the use of *fluoiroquinolones* can lead to arthropathy (joint swelling, stiffness and cartilage damage). Also, the use of *tetracyclines* can bind to growing bones and teeth resulting in abnormal teeth and bone formation.
- **In old age** (> 65 years) the incidence of renal toxicity with *aminoglycosides* is greater than in younger patients.
- **In immunocompromised patients**, the use of **bactericidal** agents is necessary, as the host's immune system is not capable of final elimination of the bacteria.
- **Pregnancy:** many antibiotics cross the placenta and cause adverse effects to the fetus e.g. *aminoglycosides* and *tetracyclines*.

- **Tissue penetration:**

- The capillary lining in some tissues, e.g. prostate, the vitreous body of the eye, and brain form **natural barriers** to drug delivery due to presence of tight junctions of the capillary wall.
- Lipid soluble antibiotics e.g. *chloramphenicol* and *metronidazole* can cross these barriers in normal conditions. *Penicillin* is ionized at physiologic pH and cannot cross these barriers unless **inflammation** is present.
- **Poor perfusion** of some area, e.g. diabetic foot, reduces the amount of antibiotic reaching this area, making treatment is difficult.

C. Determinants of the rational dosing

The dose and frequency of an antibiotic is based on three important properties. Understanding of these concepts can improve clinical outcomes and decrease the development of resistance.

- **Concentration-dependent killing:**

Certain antibiotics *(e.g. aminoglycosides)* show enhanced bacterial killing in concentration above the MIC. Giving these antibiotics by a **single large dose** per day achieves high peak levels and cause rapid killing of bacteria.

Minimum inhibitory concentration (MIC):

The MIC is the lowest concentration of antibiotic in body tissues and fluids that inhibits bacterial growth.

- **Time-dependent killing:**

By contrast, *β-lactam antibiotics, macrolides, clindamycin,* and *linezolid* do not exhibit this concentration-dependent property; instead, the clinical efficacy depends on the **time** of the drug concentration remains above the MIC. So, preparations with long duration kill more bacteria.

- **Post-antibiotic effect (PAE):**

The PAE is a persistent bacterial suppression after levels of antibiotic fall below the MIC. Antimicrobials with long PAE (e.g. *aminoglycosides* and *fluoroquinolones*) usually require one dose per day.

ANTIBIOTIC RESISTANCE

The development of antibiotic resistance is a major problem in clinical practice. Methicillin-resistant *Staph aureus* (MRSA) and some strains of *Mycobacteria tuberculosis* are examples of multidrug-resistant bacteria.

- **Innate resistance:**

Innate resistance is a feature of a particular species of bacteria e.g *Pseudomonas*. The gene(s) of resistance can be transferred between bacteria by transfer of naked DNA (transformation), by conjugation with direct cell-to-cell transfer of extrachromosomal DNA (plasmids), or through bacteriophage (transduction).

- **Acquired resistance:**

Acquired resistance is when bacteria that were sensitive to certain antibiotic become resistant with time. Mechanisms responsible for this resistance include:

- Production of enzymes that inactivate the drug.
- Alteration of drug binding site.
- Reduction in drug uptake by the organism.
- Development of altered metabolic pathways.

ADVERSE EFFECTS OF ANTIMICROBIAL AGENTS

The adverse effects associated with the use of antimicrobial agents include:

- <u>General adverse effects</u>

- **Hypersensitivity** or allergic reactions: In form of fever, skin rash, arthralgia, cholestatic jaundice or hemolysis. More serious reactions are agranulocytosis, bone marrow aplasia or anaphylactic reaction.

- Reactions related to alterations in normal body flora, **superinfection or vitamin B deficiency** may follow the use of broad-spectrum antimicrobials. It is due to inhibition of bacterial flora that suppresses commensal micro-organisms which present in gut or that forms these vitamins, respectively.
- **Resistance**

- **Direct toxic reactions,** resulting from high doses or drug interactions, on hemopoietic system, liver, kidney, GIT, nervous system or CVS.

SUPERINFECTION (Opportunistic infection):

Administration of antimicrobials usually alter bacterial flora but with no ill effect in most cases however, broad-spectrum antibiotics if used for long time may alter or kill bacterial flora. So, the bacteria and fungi that are normally inhibited by bacterial flora will multiply leading to superinfection (its early manifestation may by diarrhea). It is caused by staphylococci, Pseudomonas, proteus, Candida albicans or *Clostridia difficile...* etc. Superinfection may be vaginal, oral, pharyngeal or even systemic infection e.g. staphylococcal enterocolitis, candidiasis or Pseudomembranous colitis (= antibiotic-associated diarrhea).

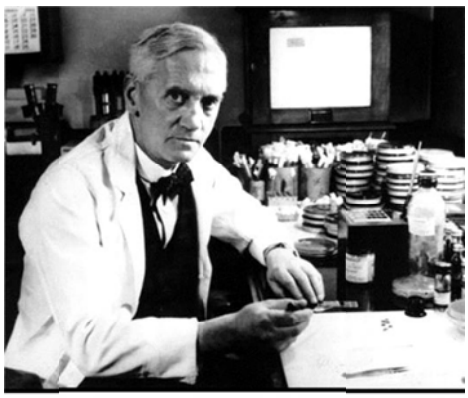
Treatment:
Stop the causative agent and give drug, which kill the organisms responsible for superinfection e.g. staphylococcal enterocolitis, which is treated by **metronidazole or vancomycin** orally, antifungal nystatin for candidiasis.

GENERAL PRINCIPLES OF THERAPY WITH ANTIMICROBIALS

- Antimicrobials should only be given when necessary and after antimicrobials susceptibility test whenever possible.
- The pharmacokinetics of the drug should be taken into consideration e.g. the state of hepatic and renal functions of the patient.
- In serious infection it is better to start with a parentral loading of a bactericidal agent to avoid emergence of resistant strains by giving adequate dosage for sufficient duration and adapting proper combination regimens.
- Antimicrobials should be continued for 3 days after apparent cure is achieved to avoid relapse.

Part 2: Individual Classes of Antibiotics

A. CELL WALL INHIBITORS

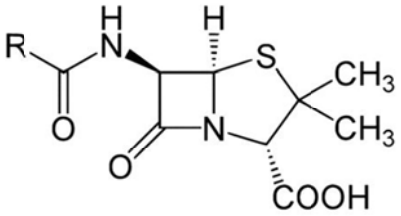


Alexander Fleming, who is credited with discovering penicillin in 1928

β-LACTAM ANTIBIOTICS

They share a β-lactam ring in their molecular structure which is required for antibacterial activity.

- **Penicillin**
- **Cephalosporins**
- **Monobactams**
- **Carbapenem**



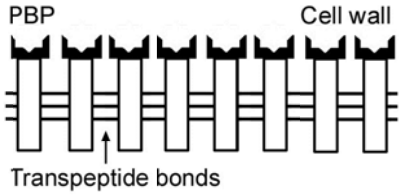
Penicillin core structure, where "R" is the variable group

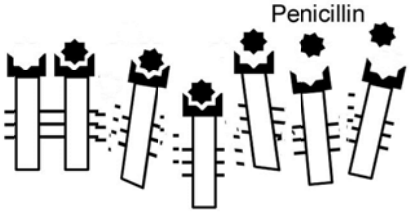
Penicillins

Antibacterial spectrum:

- *Gram-positive cocci,* e.g. streptococci, pneumococci and staphylococci.
- *Gram-negative cocci:* gonococci and meningococci.
- *Gram-positive bacilli:* anthrax bacillus, C. diphtheria and clostridia.
- *Gram-negative bacilli:* shigella, salmonella, pseudomonas…etc.
- *Spirochetes:* Treponema pallidum.
- *Actinomyces.*

Mechanism of action:





- Penicillins bind to **penicillin binding proteins** (PBPs) on the bacterial cell wall and inhibit transpeptidation reaction essential for **bacterial cell wall synthesis.**
- The next step is activation of intracellular autolytic enzymes (**autolysins**) leading to cell rupture. *Thus, the antibacterial effect of penicillin is the result of both inhibition of cell wall synthesis and destruction of existing cell wall by autolysins.*
- Penicillins are **bactericidal** especially for **Gram-positive** bacteria which have thick cell walls.
- The major cause of resistance is the production of **β-lactamase** *(penicillinase)*.

Pharmacokinetics:

- Absorption of oral penicillins is decreased by food. They must be administered **1**hr before or 2 hr after meals.
- Route of administration of a B-lactam antibiotic is determined by the stability of the drug to gastric acid and by the severity of the infection.
  - Oral in moderate infection and acid stable preparations e.g. penicillin V.
  - Paraentral in severe infection and acid sensitive preparations e.g. penicillin G
- Penicillins can penetrate to CSF and ocular fluid only during meningitis. They cross placental barrier but they are not teratogenic.
- Most penicillins are excreted through organic acid secretory system via the kidney. The renal excretion in proximal tubules could be decreased by co-administration of probenecid which prolongs its duration of action.

PREPARATIONS OF PENICILLINS:

1.BENZYL PENICILLIN (PENICILLIN G) and RELATED DRUG:

Effectiveness: active against gram-negative and positive cocci, gram-positive bacilli and spirochetes. It is sensitive to penicillinase enzyme.

Classification:

A. Injectable Short-acting preparation e.g. benzyl penicillin (penicillin-G):

- It is the prototype of all penicillin family.
- Primarily covers **gram-positive organisms** (*Pneumococci, streptococci, staphylococci (*non-penicillinase-producing)*, Cl. perfringens,C. diphtheria*) with **little gram-negative** coverage (*Gonococci* and *meningococci[but not bacilli]*), making it **ineffective** in urinary tract infection.
- ***Others:*** *Treponema pallidum* (syphilis).
- It has some limitations:
  - It is acid labile and must be given parentrally.
  - It has a short half-life, so frequent injections are required.
  - It is easily inactivated by β-lactamase enzyme.
  - It has narrow spectrum.

B. Injectable Long-acting preparation

i. Penicillin G Procaine:

It is a suspensions of combination of penicillin G with procaine that have longer duration (12-24 hrs) allowing reduced frequency of injections. So it is injected just once every day, intramuscularly.

ii. Benzathine Penicillin: This preparation produces low blood levels lasting from few days to 4 weeks depending on the dose. So it is used in chemoprophylaxis and in the treatment of syphilis.

C. Oral Penicillin V: it is an acid stable form of penicillin G (given orally).

2. PENICILLINASE OR β-LACTAMASE RESISTANT PENICILLINS (ANTI-STAPH PENICILLINS)

[Methicillin, cloxacillin, dicloxacillin, flucloxacillin, and **nafcillin]**

- They are effective against β-lactamase producing *Staphylococci*.
- They have low or **no activity** against **other gram-positive and gram-negative organisms**.
- The use of these agents is now declining due to increased incidence of methicillin-resistant *S. aureus* (MRSA).

3. EXTENDED SPECTRUM PENICILLINS

[Ampicillin and **amoxicillin]**

- They maintain gram-positive coverage with extended coverage of more **gram-negative bacteria** e.g. *Salmonella*, H. influenza, Proteus, and Shigella (but not *Pseudomonas*).
- They can be given orally (acid resistant) and by injection (IM and IV).
- They are inactivated by β-lactamase, so they are usually combined with **clavulanic acid** or **sulbactam** (β-lactamase inhibitors) to cover β-lactamase producing bacteria. **[Amoxicillin/clavulanic acid** (co-amoxiclav) - **Ampicillin/sulbactam** (Unasyn)].
- **Ampicillin** is concentrated in bile so it is effective in gall bladder disease and typhoid carrier.
- **Ampicillin**is more active on shigella and H. influenza.
- **Pro-drugs of ampicillin** e.g. pivampicillin and talampicillin are esters of ampicillin which themselves are microbiologically inactive but after oral administration they are de-esterified in the gut mucosa or liver to release ampicillin to the systemic circulation. They are better absorbed from the gut than ampicillin itself, so gives higher levels in blood and tissues and they have no effect on the gut flora and less G.I. upset.
- **Amoxicillin** has better absorption and tissue penetration than ampicillin. So, it has no effect on the gut flora and less G.I. upset.

Common organisms capable of producing penicillinase:

Staphylococcus aureus,
Escherichia coli,
H. influenzae
Pseudomonas aeruginosa
Neisseria gonorrhoeae
Proteus
*Bacteroides*species.

- **Amoxicillin** is more active against Salmonella and Streptococcal fecalis.
- **Amoxicillin** can penetrate mucoid and purulant sputum, so it is useful in chronic bronchitis.

4. ANTIPSEUDOMONAL PENICILLINS

[Ticarcillin, Azlocillin, and **Piperacillin]**

- They are broad-spectrum, but should only be used for pseudomonas infection and ampicillin resistant proteus. Also they have activity against anaerobic gram negative bacteria e.g. Bacteroids fragilis (a common pathogen in intra-abdominal sepsis)
- They have synergistic effect when they are used with aminoglycosides.
- They are inactivated by β-lactamase so they are combined with **clavulanic acid forming Timentin** to cover β-lactamase producing bacteria.

	PENICILLIN G	ANTI-STAPH PENICILLINS	EXTENDED SPECTRUM PENICILLINS	ANTI-PSEUDOMONAL PENICILLINS
		Cloxacillin Flucloxacillin Nafcillin	**Ampicillin Amoxicillin**	**Ticarcillin Azlocillin Pipracillin**
Spectrum	Gram +ve spp. and few Gram –ve *cocci* *T. pallidum*	*Staphylococci*	Gram +ve and Gram –ve spp. (except *Pseudomonas*)	*Pseudomonas* and Gram –ve spp.
β-lactamase susceptibility	Yes	No	Yes	Yes
			They are combined with **clavulanic acid or sulbactam** to cover β-lactamase producing bacteria.	

Therapeutic uses of penicillins:

A. Treatment: Penicillins may be used in the treatment of:

- Streptococcal infections, e.g. wound sepsis, acute throat infections, subacute bacterial endocarditis,.. etc.
- Staphylococcal infections of skin, mucous membrane and bone.
- Pneumococcal infections e.g. pneumonia.
- Syphilis (5 million units single dose) and gonorrhoea.
- Meningococcal infections: Penicillin diffuses into the CSF only when the meninges are acutely inflamed.
- Typhoid and paratyphoid fevers: ampicillin and amoxycillin.

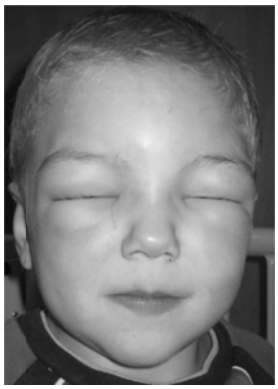
- Pseudomonas infection: (ticarcillin or piperacillin)
- Actinomycosis, Anthrax and H. influenza infections.
- Diphtheria, tetanus and gas gangrene. (Penicillin may be used together with the specific antitoxins).

B. Prophylaxis: Penicillins may be used prophylactically in the following conditions:

- To prevent recurrence of rheumatic fever: Benzathine penicillin, 1.2 million units IM once a month.
- To prevent subacute bacterial endocarditis due to bacteraemia resulting from operative procedures such as dental extraction, tonsillectomy…etc. in patients with congenital or acquired valvular disease or immunocompromised patient.

Adverse effects:

- **Hypersensitivity reactions:**
  - It occurs in ~10% of patients receiving penicillin.
  - It occurs with all types of penicillin. Allergy is not due to penicillin itself but to degradation product common to all penicillin
  - It is more common after parenteral than oral administration.
  - All types of reactions, from simple rash to **acute anaphylaxis and angioedema**, can occur within 2 minutes (**early or type I** hypersensitivity) or up to 12 days (**delayed or type II**) after administration.



  - True anaphylaxis is rare (1:10'000 of cases).
  - Penicillin allergy is unpredictable i.e. an individual who tolerated penicillin in the past may develop allergy later on and *vice versa.*

  Prevention:
  - Never give penicillin if there is history of penicillin allergy.
  - Test for hypersensitivity

  Management of anaphylactic shock: see CVS.

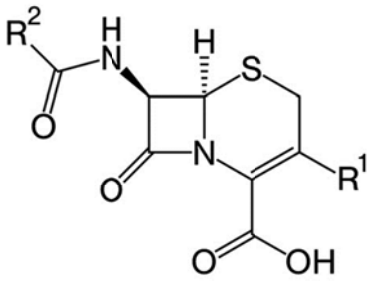
- **Other adverse effects:**
  - Penicillin in high doses can cause neurotoxicity and seizures in patients with renal failure.
  - Nafcillin is associated with neutropenia and thrombocytopenia.
  - Methicillin causes interstitial nephritis (and is no longer used for this reason).
  - Co-amoxiclav and flucloxacillin cause hepatotoxicity (cholestatic jaundice).

Drug interactions:

- **Bacteriostatic drugs** (e.g. tetracycline, chloroamphenicol, erythromycin) interfere with the action of penicillin because penicillin acts by inhibiting cell wall synthesis (i.e. kills rapidly multiplying bacteria) while bacterio**static** drugs arrest the organism and prevents its multiplication.
- **Antipseudomonal penicillins** (acidic drugs, —ve charged) form complex with **aminoglycosides** (basic drugs, +ve charged) if they are mixed in the same infusion fluid.

Cephalosporins

- Cephalosporins also have a **β-lactam** ring and have the **same mechanisms** of action like penicillins.
- Each newer generation of cephalosporins is increasingly **resistant to β-lactamase.**



Core structure of the cephalosporin antibiotics

Pharmacokinetics:

- Cephalosporins are widely distributed in body fluids; members of the third and fourth generations can penetrate to CSF *(except cefoperazone)*.
- Like penicillins, most cephalosporins are excreted via the kidneyand hence the dose must be adjusted in patient with renal insufficiency. The renal excretion is also decreased by probenecid.
- Cefoperazone and ceftriaxone (third generation) are primarily excreted in bile and its serum level is not greatly influenced by renal failure.

Antibacterial spectrum And Classification:

They are divided into 1st, 2nd, 3rd, and 4th generations. The difference among the groups is marked by changes in antibacterial spectrum. In general, the activity against gram-positive bacteria decreases from first to third generation while activity against gram-negative organisms increases.

1. First-generation cephalosporins:

[Cephalexin (Keflex), **cephradine** (Velosef), **cefadroxil** (Duricef)].

- Primarily cover **gram-positive organisms** (similar to penicillin G) with **some gram-negative coverage** (*E. coil, Klebsiella*), making them **effective** in urinary tract infection.
- They are **sensitive to β-lactamase.**
- They **do not penetrate to CSF** (even in presence of meningitis).
- There is partial cross allergenicity between them and penicillins.

2. SECOND-GENERATION CEPHALOSPORINS

[Cefoxitin, **cefuroxime** (Zinnat), **cefaclor**].

- They maintain gram-positive coverage with enhanced coverage of gram**-negative bacteria** e.g. *H. influenza, Neisseria, Proteus,* (but not *Pseudomonas*).
- They are used primarily in the management of **urinary and respiratory tract, bone, and soft-tissue infections** and **prophylactically** in various surgical procedures.
- They are relatively resistant to β-lactamases.
- They **do not penetrate to CSF** (even in presence of meningitis, *except cefuroxime*).

3. THIRD-GENERATION CEPHALOSPORINS

[Cefotaxime (Clarofan), **Ceftazidine**, **Cefoperazone** (Cefobid), **Ceftriaxone** (Rocephin)

- They maintain gram-positive coverage with excellent coverage of **gram-negative bacteria**(including *Pseudomonas*)and active against **anaerobes.**
- They can **penetrate to CSF** in presence of meningitis *(except cefoperazone).*
- They are excreted by the kidney, except *cefoperazone*and *ceftriaxone* which are excreted **biliary** allowing their use in **renal failure**.
- They are highly resistant to β-lactamase.
- They have long duration (12 hrs) and ceftriaxone has longer duration (24 hrs)

4. FOURTH-GENERATION CEPHALOSPORINS

- **Cefepime** has a powerful coverage against most **Gram-positive** and **Gram-negative bacteria** (including *Pseudomonas*) and **anaerobes.**
- **Ceftaroline** is sometimes described as **"FIFTH GENERATION"** drug. **.**

Therapeutic uses:

- Severe undiagnosed sepsis especially in immunosuppressed patient.
- Treatment of infection of respiratory tract, urinary tract, skin, soft tissue, bones and joints due to susceptible organisms.
- Gram-negative bacterial meningitis may be treated by cefotaxime (third generation) and ceftriaxone that reach the C.N.S.
- Biliary infection: 3rd generation (cefoperazone or ceftriaxone).
- Gonorrhoea due to penicillin-resistant Gonococci. It is treated by single IM injection of ceftriaxone.
- Pseudomonal infection when aminoglycosides are not desirable.

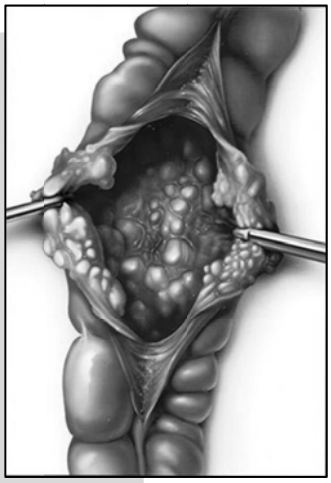
	1ST GENERATION	2ND GENERATION	3RD GENERATION	4TH GENERATION
	Cephalexin Cephradine Cefadroxil	**Cefoxitin Cefuroxime Cefaclor**	**Cefotaxime Cefoperazone Ceftriaxone**	**Cefipime**
Spectrum	Mainly Gram +ve spp. and few Gram –ve bacilli	Maintain Gram +ve coverage and enhanced Gram –ve coverage	Excellent Gram –ve coverage (including *Pseudomonas*)	Wide Gram +ve and Gram –ve coverage including *Pseudomonas*
β-lactamase susceptibility	Yes	Yes	No	No
Penetration to CSF	No even in meningitis	No *(except cefuroxime)*	Yes *(except cefoperazone)*	Yes
Cross allergy with penicillin	High	Moderate	Low	Low
Elimination	Renal	Renal	Renal & biliary	Renal & biliary

Adverse effects:

- **Hypersensitivity reactions**: 10% of penicillin-sensitive persons share hypersensitivity to cephalosporins. The cross hypersensitivity with penicillin is much lower with the 3rd and 4th generation drugs.
- Some **first generation** cephalosporins are **nephrotoxic** especially when administered with loop diuretics or aminoglycosides.
- Some **third generation** cephalosporins (e.g. cephoperazone) inhibit the enzyme *vitamin K epoxide reductase* leading to **hypoprothrombinemia** (could be prevented by vitamin K).
- **Superinfection with *C. difficile* (pseudomembranous colitis):** Cephalosporins are the main cause of hospital-acquired *C. difficile* colitis, a potentially life-threatening infection.

Pseudomembranous colitis

Pseudomembranous colitis (= antibiotic-associated diarrhea or *C. difficile* colitis), can occur following antibiotic treatment. When antibiotics are given, most of the resident intestinal bacteria are killed with sparing of some types like *Clostridia difficile*. The normally harmless *C. difficile* grow rapidly because of lack of competition with other flora, and produce toxins. These toxins damage the inner wall of the intestines and cause abdominal pain, fever and diarrhea. Severe cases can be life-threatening.



Treatment:
- Stop all antibiotics whenever possible.
- Oral **metronidazole** 250 mg /6 hr (1st choice).
- If metronidazole failed, give oral **vancomycin** solution 125 mg/6 hr

Drug interactions:

- If IV **ceftriaxone** is added to any IV **calcium-containing solution** (e.g. Ringer's or parenteral nutrition) dangerous particulates of **ceftriaxone-calcium** can result and precipitate in the lungs and kidney. Separate between IV ceftriaxone and any IV calcium-containing solution by at least 48 hours.
- Some **third generation** cephalosporins inhibit the enzyme *aldehyde dehydrogenase*. If they are co-administered **with alcohol**, acetaldehyde accumulates in blood leading to nausea and vomiting (**disulfiram-like reaction**).

OTHER beta-LACTAM DRUGS

Aztreonam (Azactam)

- Aztreonam is a monobactam that share similarity in structure and mechanism with penicillin but is highly **resistant to β-lactamase.**
- Aztreonam is especially effective against β-lactamase producing **gram-negative bacteria**. It could be used as alternative to aminoglycosides in **severe** respiratory, urinary, biliary, GIT and female genital tracts infections.
- It has **no cross-hypersensitivity** with penicillins or cephalosporins.
- Most of the Adverse effects reported have been, for example, hematological effects, nephrotoxicity and pseudomembranous colitis,.

Carbapenems [Imipenem-cilastatin, meropenem]

- They are **broad spectrum** antibiotics that share similarity in structure and mechanism with penicillin but they are highly **resistant to β-lactamase.**
- They are one of the **antibiotics of last resort** for many bacterial infections.
- The ease of penetration (due to its low molecular weight) and resistance to β-lactamase imparts a broad-spectrum of antimicrobial activity against most aerobic and anaerobic bacteria (Gram-positive and gram-negative) with the exception of occasional Pseudomonas strains.
- If imipenem is given alone it is inactivated by dihydropeptidase enzyme in kidney leading to low urinary excretion and significant renal toxicity in animals, therefore it is combined with **cilastatin** (Tienam) to inhibit renal dihydropeptidase enzyme.
- **Meropenem** does not undergo metabolism by renal dihydropeptidase enzyme.

Adverse effects:

- Blood disorders.
- Seizures in high doses. Meropenem is less likely to provoke seizures.
- G.I.T: nausea, vomiting, etc.

OTHER CELL WALL INHIBITORS

Vancomycin

- Vancomycin **inhibits cell wall synthesis** and enhances cell lysis.
- It is active against **gram-positive organisms.**
- It is given by slow i.v. infusion to treat **serious MRSA infections** in patients allergic to penicillins or cephalosporins.
- Because it is not absorbed orally, it is used by this route to treat **antibiotic-associated enterocolitis** (*C. difficile* colitis) and other infection by susceptible organisms.
- Rapid infusion of vancomycin may cause anaphylactoid reactions and **"red man" syndrome** (skin rash and flushing due to histamine release).
- Rarely, high levels of vancomycin may cause permanent auditory impairment (**ototoxicity)** and **nephrotoxicity**.

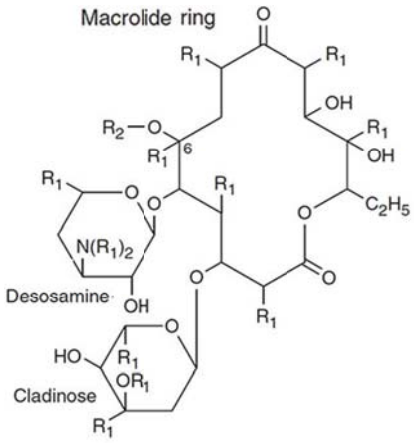
Bacitracin

- Bacitracin inhibits the building of peptidoglycan blocks (cell wall units).
- It is most active against **gram-positive bacteria**.
- It is used **only topically** in combination with **neomycin or polymyxin** for minor skin infections due to serious nephrotoxicity.

B. INHIBITORS OF BACTERIAL PROTEIN SYNTHESIS

Macrolides

[Erythromycin (prototype), azithromycin, clarithromycin, roxithromycin]



Mechanism of action:

- They bind reversibly to the **50S ribosomal subunit** and **inhibit bacterial protein synthesis.**
- They are **bacteriostatic** in low concentrations and bacteri**cidal** in high concentrations.

Antibacterial spectrum:

Macrolids are effective against a number of organisms, including **gram-positive bacteria,** e.g. pneumoncocci, staphylococci, streptococcus species, C. diphtheria, **some gram-negative** bacteria, e.g. Neisseria, H. influenza, and intracellular microorganisms (Mycoplasma species, legionella and Chlamydia).

Pharmacokinetics:

- Absorption of erythromycin is affected by food and HCl. To minimize destruction and enhance absorption, erythromycin is administered as esters salts.
- Newer macrolides are acid stable and can be given orally.
- They reach all body fluids including prostate, placenta and milk but only **small amounts** can penetrate to CSF.
- Azithromycin and roxithromycin are **concentrated** in neutrophils, macrophages and lung tissue, so they have long $t_{1/2}$ (given once daily) and they are useful against **intracellular organisms.**
- Macrolides are concentrated in liver and excreted **primarily in active form via bile** with only low levels found in urine.
- Azithromycin and clarithromycin are converted into **active** metabolites.

Therapeutic uses:

- Treatment and prevention of infections caused by staphylococci, streptococci and pneumococci (**gram-positive**) in penicillin-hypersensitive individuals.
- Eradication of C. diphtheriae from pharyngeal carriers (1st choice).
- Azithromycin and roxithromycin are especially effective against **intracellular** and **atypical bacteria** *(chlamedia, mycoplasma, legionella)*
- **Clarithromycin** has activity against *Toxoplasma*. It is also effective against *Helicobacter pylori* in peptic ulcer**.**
- It is a second line drug for the treatment of gonorrhea and syphilis.
- Treatment of middle ear and sinus infections, since the causative agents, *H. influenza* and *Strep pneumonia* are usually sensitive.

Adverse effects:

- **Epigastric distress** especially with erythromycin.
- Erythromycin may cause **cholestatic hepatitis** probably due to hypersensitivity reaction to the oral estolate form or hepatoxic effect when drug therapy lasts longer than 10 days or repeated courses are prescribed.
- Erythromycin and clarithromycin **inhibit hepatic CYP450**– metabolism of some drugs e.g. warfarin and phenytoin *(Azithromycin is devoid of this side effect)*.
- **Bacterial resistance** if it is used more than one week.
- **Hypersensitivity reactions**: fever, rashes and cholestatic hepatitis.

Interactions:

- Combination of the therapeutic dose of erythromycin with penicillin antagonizes the bactericidal effect of penicillin.
- Erythromycin decreases CYP450 enzymes, thus increase serum concentration of theophylline, oral anticoagulants, cyclosporins, and digoxin.

Lincosamides: Clindamycin

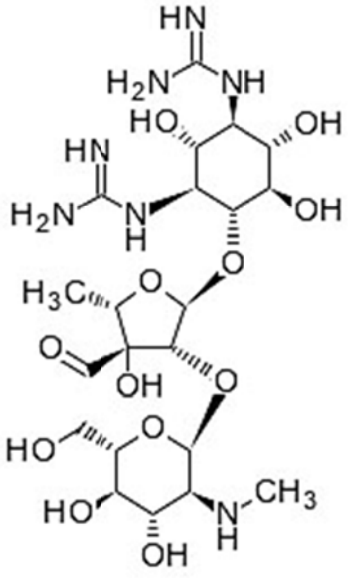
- The lincosamide family of antibiotics includes lincomycin and clindamycin. Clindamycin is semisynthetic derivative of lincomycin and is more potent than lincomycin.
- Clindamycin is similar, in the mechanism and kinetics, to **erythromycin** but has activity against **anaerobic bacteria**.
- It is used as an alternative drug for treatment of **anaerobic infections**. Topical preparations are used for treatment of **acne.**
- Food in the stomach does not interfere with the absorption of clindamycin. So it is completely absorbed after oral administration.
- Approximately 90 % are plasma protein bound. Clindamycin penetrate most tissues well, including bone. Therefore, **bone and joint** infections caused by susceptible organisms respond well to treatment with clindamycin.
- It is associated with high incidence of diarrhea and **pseudomembranous colitis** as side effect due to superinfection by resistant clostridia in addition to side effects of erythromycin.

Aminoglycosides

[streptomycin (prototype), Gentamicin, tobramycin, amikacin, kanamycin, neomycin]

Mechanism of action

- Aminoglycosides are transported across the inner cell membrane by active transport system present **only in Gram-negative aerobic spp**.
- Inside the cell, they bind to **30S ribosomal subunit** and **inhibit bacterial protein synthesis**.
- They are bacteri**cidal.** Bacterial killing is **concentration-dependent** i.e., the higher the concentration, the more bacteria are killed, so they are better given as a single large dose daily.
- A **post-antibiotic effect** is also present *i.e.,* residual bactericidal activity is present after the serum concentration falls below the MIC.



Structure of streptomycin

Antimicrobial spectrum:

They have **narrow spectrum** against mainly **Gram negative bacilli**, very few Gram positive cocci, and Mycobacteria TB.

Pharmacokinetics:

- All aminoglycosides are **not absorbed orally** (must be given parentrally) and **cannot penetrate to CSF** because they are highly **polar** compounds.
- They can cross the **placental barrier** and may cause **congenital deafness**.
- They are excreted **unchanged** in urine by glomerular filtration *(dose adjustment is necessary in renal dysfunction)*. They become more active in **alkaline urine**.

Penicillins and aminoglycosides

The antibacterial effects of all β-lactam antibiotics are **synergistic** with the aminoglycosides. Because penicillin inhibits cell wall synthesis and facilitate the entry of aminoglycosides to inside the bacterial cell.

*[**Note:** these drugs should never be combined in the same infusion fluid because the **basic** aminoglycosides form inactive complex with the **acidic** penicillin]*

Therapeutic uses:

The role for aminoglycosides has decreased substantially due to their **narrow spectrum** and **potential toxicity**.

- Streptomycin is currently used only for **plague**, **brucellosis** and it is one of the 1st line drugs for **TB**.
- Gentamicin and tobramycin are used in the treatment of **gram-negative infections** e.g. urinary tract and respiratory infections.
- They are used in **gram-negative septicemia,** usually combined with penicillin and/or metronidazole.
- **Pseudomonas infections**: they are more efficient when combined with antipseudomonal penicillin
- A combination of vancomycin and gentamicin is useful in the treatment of **enterococcal endocarditis**.
- Neomycin is used **orally** for **hepatic encephalopathy** to suppress intestinal bacteria that produce ammonia.
- Neomycin is used orally for **sterilization of intestine** before surgery and bacillary dysentery.
- Neomycin and gentamycin are used **topically** for skin and eye infections often in combination with polymixin B or bacitracin.

Adverse effects:

Aminoglycosides have a **narrow therapeutic index;** it may be necessary to monitor serum concentrations and individualize the dose especially in **old age**.

- **Nephrotoxicity:**
  - It is due to accumulation of aminoglycosides in the renal tubular cells.

- It ranges from mild reversible effect to severe irreversible toxicity.
- It is increased by co-administration of other nephrotoxic drugs e.g. cephalosporins.

- **Ototoxicity**:
  - It is due to accumulation of aminoglycosides in the endolymph and perilymph of the inner ear causing damage to the hair cells in the organ of Corti.
  - It may affect the cochlear (auditory) or vestibular functions.
  - Deafness may be irreversible.
  - It is increased by co-administration of other ototoxic drugs e.g. loop diuretics and in old age and with renal diseases.

- **Neuromuscular block:**
  - Often occurs after direct intraperitoneal or intrapleural application of large doses of aminoglycosides leading to skeletal muscle weakness.
  - It is treated by immediate administration of calcium gluconate or neostigmine.

- **Malabsorption:**
  - Occasionally observed following the **oral administration** of streptomycin, neomycin, kanamycin. It is due to binding with bile salts and inhibition of pancreatic lipase leading to steatorrhoea and diarrhoea.

Drug interactions:

- **With antibiotics:**
  - With cephalosporins nephrotoxicity increases.
  - Anti-pseudomonal penicillins, and cephalosporins decrease the antibacterial effect of gentamicin if combined together in th**e same syringe (in-vitro)** because penicillins are acidic and aminoglycosides are alkaline.

- **Skeletal muscle relaxants:**
  - Aminoglycosides increase the effect of non-depolarizing NMB agents (see ANS). It could be reversed by neostigmine and calcium gluconate.
  - Aminoglycosides should be administered with great caution during surgery or in the post-operative period.

- **Anticoagulants:**
  - With oral anticoagulants: oral aminoglycosides impair vitamin K production by intestinal bacteria potentiating the effect of anticoagulants.
  - Heparin precipitate aminoglycosides (**avoid their mixing in the same syringe**).

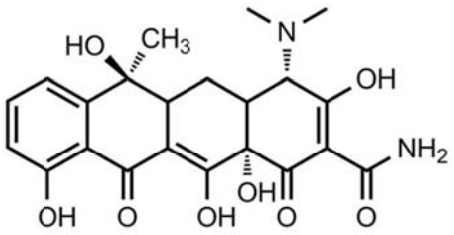
- **Diuretics**: Diuretics e.g. ethacrynic acid, and mannitol potentiate ototoxicity of aminoglycosides.

Tetracyclines

[Oxytetracycline (prototype), doxycycline, tigecycline]

Mechanism of action:

- Tetracyclines bind reversibly to the **30S ribosomal subunit** and **inhibit bacterial protein synthesis.**
- They are bacterio**static**.



Core structure of tetracyclines

Antibacterial spectrum:

Tetracyclines display **broad-spectrum** activity and are effective against:

- Most gram-positive, many gram-negative bacteria and Brucella.
- Rickettsia, Coxiella, Mycoplasma and Chlamydia (intracellular organisms).
- Spirochetes, Actinomycines, Protozoa.
- Helicobacter pylori.

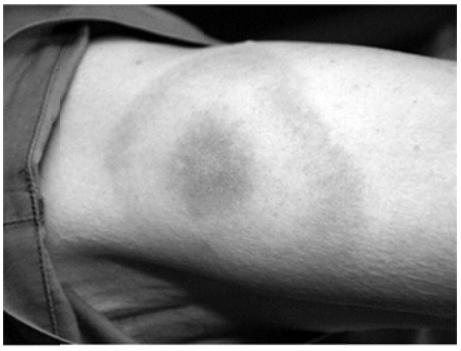
Pharmacokinetics:

- These antibiotics are **partially absorbed** from the stomach and upper gastrointestinal tract and the amounts remaining may alter bacterial flora **leading to super infection**. Because absorption of **doxycycline** is rapid and complete, it has weak effect on intestinal flora.
- Calcium (milk and Ca. antacids), magnesium (Mg hydroxide), aluminum hydroxide and iron interfere with their absorption since they form insoluble chelates with tetracyclines.
- They reach all body fluids and placenta due to its lipid solubility but only **small amounts** can penetrate to CSF (**Doxycycline is the most lipid-soluble**).
- Because of their chelating properties with calcium they tend to be deposited in growing bones and teeth causing yellow discoloration of teeth.
- The primary route of elimination **is renal**. ***Doxycycline* is excreted in stool** and **does not accumulate** in patients with renal impairment.

Therapeutic uses:

- Tetracyclines have broad spectrum activity against both **Gram-positive** and **Gram-negative** organisms, but their use is now declining because of increased resistance and the development of safer drugs.
- Doxycycline is used as **alternative to macrolides** in *Chlamydia, Mycoplasma,* and *Legionella* infections.
- They have broader spectrum than macrolides against **other atypical bacteria** (*Borrelia, Rickettsia, Coxiella)*:

- *Borrelia burgdorferi:* is the cause of **Lyme disease,** a spirochetal infection transmitted by infected ticks. The disease consists of skin rash, fever, and arthritis.
- *Rickettsia:* is a genus of small obligate intracellular bacteria causing **typhus** and **Rocky Mountain spotted fever**.
- *Coxiella burnetii:* is a small obligate intracellular bacterium causing **Q fever.**

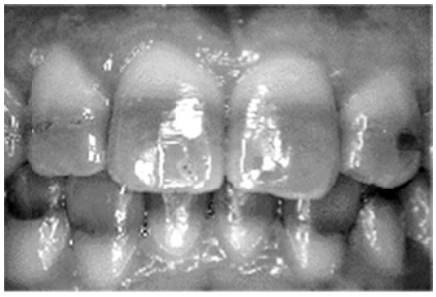


The typical "bull's-eye" rash at the site of a tick bite is a common early symptom of Lyme disease

- **Doxycycline** is used orally (100 mg/12h for 3 months) for treatment of **acne vulgaris**.
- **Doxycycline** is effective in treatment of **cholera** (300 mg single oral dose).

Adverse effects:

- **Epigastric distress** (nausea, vomiting, **epigastric burning and hyperacidity**) resulting from irritation of gastric mucosa. This can be prevented by giving tetracycline after meals.
- **Yellow staining** of both the deciduous and permanent teeth and dental enamel hypoplasia (increased susceptibility to caries, as well as retardation of bone growth) because of their chelating properties with calcium. This can occur if tetracyclines are administered after the fourth month of gestation or if they are given to children less than 8 years of age, this is a further **reason for avoiding their use during pregnancy**.



Teeth discoloration caused by tetracyclines

- **Cholestatic hepatitis** particularly in **pregnant** women and at large doses.
- **Phototoxicity:** skin reaction in the form of sunburn, occurs when a patient taking tetracyclines is exposed to sunlight or ultraviolet rays.
- **Superinfection** with resistant *staphylococci* or *C. difficile* (*C. difficile* colitis). Also, decreased synthesis of Vit. B12 leads to sore tongue & black hairy tongue
- **Teratogenesis,** when administered early in pregnancy.

Contraindications:

- Severe hepatic disease and renal disease.
- It should be avoided in patients with peptic ulcer,
- In children (less than 8 years of age)
- In pregnancy and lactation.

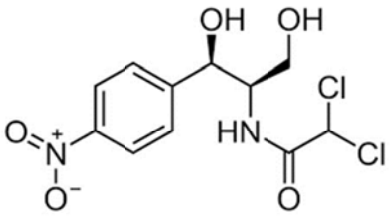
Interactions:

- Avoid simultaneous ingestion of dairy products (milk & cheese), antacids, or iron with tetracyclines because of chelating action of tetracyclines.
- Tetracyclines decrease vitamin K synthesis in intestinal lumen due to inhibition of intestinal flora leading to potentiation of oral anti-coagulant effect.

Chloramphenicol

Mechanism of action:

- Chloramphenicol binds to the **50S ribosomal subunit** and **inhibits bacterial protein synthesis.**
- The drug is either **bacteriostatic** (more common) or bactericidal depending on the organism.



Structure of chloramphenicol

Pharmacokinetics:

- Due to its lipophilic nature, chloramphenicol is **absorbed rapidly**, so there is less alteration of bacterial flora with less susceptibility to superinfection and distributed throughout body fluids.
- Therapeutic levels can penetrate to the CSF and placenta.
- Chloramphenicol is inactivated in the liver by **glucuronyl transferase.**
- Elimination is mainly renal. About 10 % of the administered drug is excreted unchanged (so it is not useful in UTI).

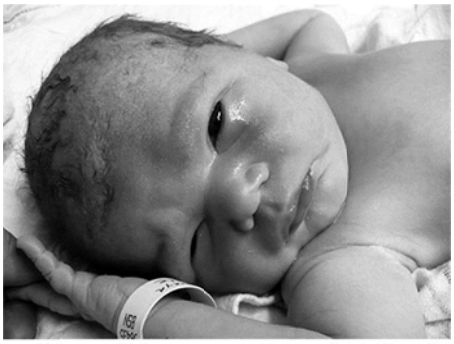
Therapeutic uses:

- Chloramphenicol has broad spectrum against both **Gram-negative and Gram-positive spp.,** but its use is **limited** because of its severe toxicity.
- It could be used as an alternative to macrolides and tetracyclines for diseases caused by **atypical bacteria** *(Mycoplasma, Legionella, Rickettsia, Coxiella, etc).*
- As an alternative to penicillin and cephalosporins for treatment of **meningitis** (due to *H. influenza*), **typhoid fever**, and **anaerobic infections**.
- Used as eye drops (0.5%) for **eye infections**.

Adverse effects:

- **Aplastic anemia** and **bone marrow suppression:**
  - It is dose dependent – rare but fatal.
  - It may occur weeks or months after stopping of the drug.
  - It may be a result of the inhibition of human mitochondrial protein synthesis.
  - Management of BM suppression: see blood.

- **Gray baby syndrome:**
  - It occurs in neonates because their liver cannot metabolize chloramphenicol.
  - It consists of cyanosis, collapse, abdominal distension, and shock.
  - Mortality is high (40%).



Gray baby syndrome

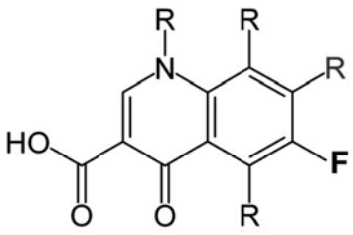
- **Inhibition of cytochrome P-450 enzymes** can increase levels of other drugs.

C. INHIBITORS OF BACTERIAL NUCLEIC ACID SYNTHESIS

Fluoroquinolones

[Ofloxacin, norfloxacin, ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin]

Quinolones are synthetic analogues of Nalidixic acid. The earlier quinolone nalidixic acid did not achieve systemic antibacterial levels and is useful only as urinary antiseptic. Fluorination was found to produce compounds with greater antibacterial activity, achieving useful drug levels in the blood and tissues.



Core structure of fluoroquinolones.
R are variable groups

Members:

- First generation: Nalidixic acid.
- Second generation: Pipemidic acid.
- Third generation: Most are fluorinated. They include **ciprofloxacin, ofloxacin (tarivid), levofloxacin** etc…
- Fourth generation: e.g. **moxifloxacin, trovafloxacin**, they are like third generation with enhanced gram-positive and anaerobes activity.

Mechanism of action:

- They inhibit **type II DNA topoisomerase (DNA gyrase)** that is necessary for bacterial replication.
- Quinolones are **bactericidal**. Like aminoglycosides, they exhibit concentration-dependent killing and a post-antibiotic effect.
- Resistance is due to point mutations in the target enzyme.

Pharmacokinetics:

- The absorption of fluoroquinolonesis is ↓ by stomach contents especially **milk, iron** and **antacids**.

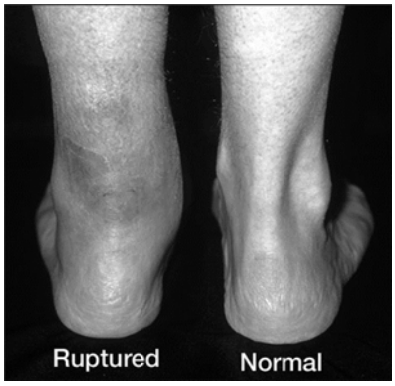
- They reach all body tissues but only **small amounts** can reach CSF.
- Newer fluoroquinolones *(e.g. levofloxacin and moxifloxacin)* accumulate in neutrophils and macrophages, so they have **long $t_{1/2}$** (given once daily) and they are useful against **intracellular organisms.**
- They are excreted primarily **unchanged** in urine, so they are useful in UTIs.

Therapeutic uses:

- Fluoroquinolones are especially indicated in **resistant infections**. Empiric use of these agents in minor infections should be discouraged.
- 3rd generation e.g. Ciprofloxacin have greater activity against **gram-negative bacteria** and moderate activity against **gram-positive organisms and anaerobes.** Newer compounds (moxifloxacin, trovafloxacin) have equal activities against all**.**
- Levofloxacin and moxifloxacin are known as **"respiratory quinolones"** due to their high activity against *S. pneumonia* and other **atypical respiratory pathogens** (*legionella, mycoplasma*).
- 3rdgeneration are used for most **severe systemic infections** e.g. GIT infection, urinary tract infections and prostatitis, respiratory infections, skin and Bone infections (osteomyelitis).
- Treatment of **pseudomonas** infection.
- Ciprofloxacin for **salmonella**; enteric fever

Adverse effects:

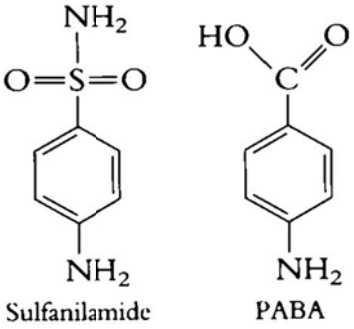
- **GIT upset:** nausea, vomiting (the most common).
- **Arthropathy** (in experimental animals):
  - It was manifested as articular damage & erosions in weight-bearing joints.
  - Although this side effect has not been reported in human, the use of fluoroquinolones is **not recommended in children** <18 years.
- **Tendinitis and tendon rupture:** there is increased risk of tendinitis and spontaneous tendon rupture especially with ciprofloxacin. The Achilles tendon is the most frequently affected.
- **CNS (1-2%):** seizures and psychiatric problems. Fluoroquinolones should be used cautiously in patients with **epilepsy**.
- **Prolongation of QT interval** and ↑ risk of torsade de pointes.
- **Inhibition of cytochrome P-450 isozymes** can increase levels of other drugs.



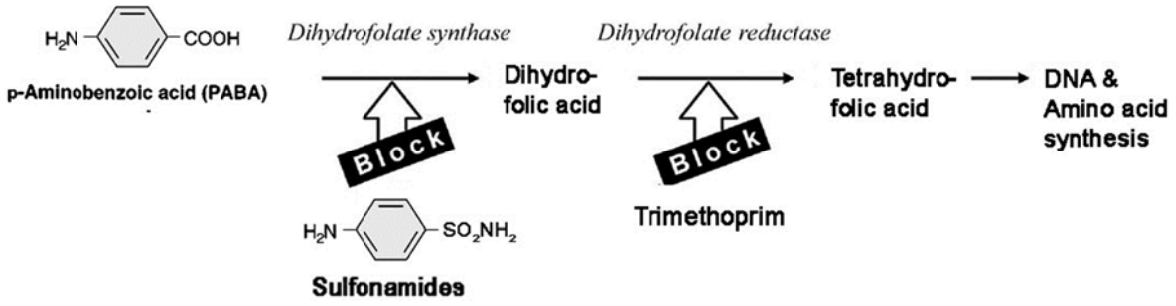
D. INHIBITORS OF BACTERIAL METABOLISM

Sulfonamides and trimethoprim

Mechanism of action:



- Bacteria cannot utilize preformed folic acid; they use *P*-aminobenzoic acid (PABA) as a precursor for synthesis of **dihydrofolic acid** (by the enzyme *dihydrofolate synthase),* then to the active form **tetrahydrofolic acid** (by the enzyme *dihydrofolate reductase),* necessary for bacterial nucleic acid synthesis.
- **Sulfonamides** are structural analogs of PABA. They compete with PABA at the enzyme *dihydrofolate synthase* resulting in inhibition of **dihydrofolic acid** synthesis.
- **Trimethoprim** acts by inhibition of next step (formation of the active form **tetrahydrofolic acid**) via inhibition of *dihydrofolate reductase* enzyme.
- Both sulfonamides and trimethoprim are bacterio**static** drugs.
- **Co-trimoxazole** is a combination of **sulfamethoxazole** (400 mg) and **trimethoprim** (80 mg) to produce **sequential block** of folic acid synthesis.
- Bacterial resistance occurs by development of alternative metabolic pathway for folic acid synthesis.



Pharmacokinetics:

- Most sulfonamides are adequately absorbed from the GIT *(except sulfasalazine)*.
- They reach all body fluids including CSF *(even without meningitis)*.
- Sulfonamides are metabolized in the liver and excreted by the kidney. The acetylated products can precipitate and crystalize in **acidic urine** leading to urinary stones **(crystalluria)**.
- **Alkalinization** of urine can enhance activity of sulfonamides and reduce crystalluria.

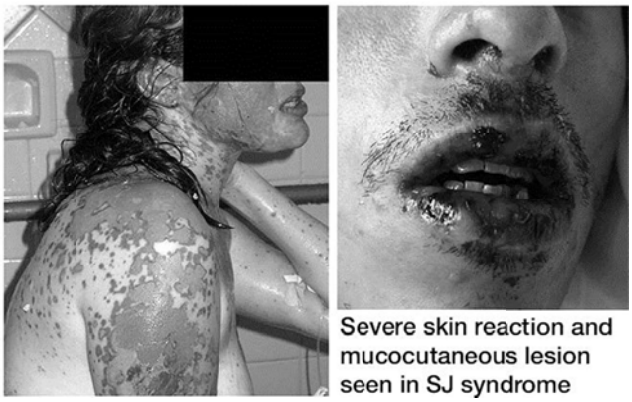
Therapeutic uses:

- **Co-trimoxazole:**
  - Treatment of upper respiratory tract infections and bronchitis caused by *S. pneumonia* and *H. influenza.*
  - Treatment of non-complicated **UTIs** and **prostatitis**.
  - The drug of choice for treatment of ***Pneumocystis carinii*** **pneumonia (PCP)** and **toxoplasomosis** in AIDS patients.

- **Other sulfonamide combinations:**
  - **Fansidar** is a combination of sulfadoxine + pyrimethamine is used as an alternative treatment of malaria caused by **chloroquine-resistant *Plasmodium falciparum* malaria**
  - **Sulfasalazine** is poorly absorbed combination of sulfapyridine + 5-aminosalicylic acid used to treat **ulcerative colitis**.
  - **Silver sulfadiazine** is used topically for the treatment of **burn**.

Adverse effects:

- **Hypersensitivity reactions:**
  - Fever and rash are the most common.
  - ***Steven-Johnson syndrome*** is a rare, but fatal form of extensive skin and mucus membrane lesions due to hypersensitivity reaction.



Severe skin reaction and mucocutaneous lesion seen in SJ syndrome

- **Crystalluria:** due to precipitation of sulfonamide metabolites in **acidic** urine leading to colic, hematuria and even anuria.
- **Kernicterus:** sulfonamides cause displacement of bilirubin from plasma protein binding sites. When they are given to **neonates** (or in the last 2 weeks of pregnancy), high free bilirubin levels in the blood can cross BBB and cause permanent brain damage.
- **Anemia:**
  - ***Megaloblastic anemia:*** due to folic acid deficiency (can be prevented by giving folic acid supplementation)
  - ***Aplastic anemia*** leading to granulocytopenia and thrombocytopenia.
  - ***Hemolytic anemia*** in patients with G-6-PD deficiency.

E. MISCELLANEOUS AND LESS COMMON ANTIBACTERIAL AGENTS

Metronidazole

- **Metronidazole** was introduced as an antiprotozoal agent but it is also active against **anaerobic bacteria** such as *Bacteroides*, *Clostridia*, and some *Streptococci* (see antiamebic drugs)
- It is effective in the therapy of **pseudomembranous colitis**, and serious **anaerobic infections** (e.g. sepsis secondary to bowel disease).

Fusidic acid

- **Fusidic acid** is a narrow-spectrum steroid antibiotic active mainly against **Gram-positive bacteria**. It acts by inhibiting bacterial **protein synthesis**.
- It is used in combination with other antistaphylococcal agents in **staphylococcal sepsis**, and **topically** for staphylococcal infections (e.g. as eye drops).
- It is associated with GIT upset (common), skin eruptions and jaundice.

Streptogramins: Quinupristin and dalfopristin

- **Quinupristin** and **dalfopristin** are new class of protein synthesis inhibitors. They inhibit bacterial **protein synthesis** by binding to the 50S ribosomal subunit.
- Individually, they exhibit only mild bacterio**static** activity, but **combined together** as an intravenous injection, they exert **bactericidal** activity against drug-resistant **Gram-positive spp.** including vancomycin-resistant *Enterococci* and MRSA.
- Their use is limited to **serious bacterial infections** when other antibiotics fail.
- Bacterial resistance is still uncommon.
- Both drugs undergo **extensive first-pass** hepatic metabolism and must be given as an **intravenous infusion**.
- **Adverse effects** include inflammation and pain at the infusion site, arthralgia, myalgia and GIT upset.

Oxazolidinones: Linezolid

- **Linezolid** is the first member of this new class of protein synthesis inhibitors (approved in 2000). They inhibit bacterial **protein synthesis** by binding to the **50S** ribosomal subunit.
- It is active against a wide variety of drug-resistant **Gram-positive bacteria** such as vancomycin-resistant *Enterococci* and MRSA. The drug is also effective against some **anaerobes**, such as *C. difficile*.

- Its use is limited to **serious bacterial infections** when other antibiotics fail.
- Bacterial resistance is still uncommon.
- **Adverse effects** include thrombocytopenia and GIT upset.

Rifaximin

- It is a **poorly-absorbed** antibiotic related to rifampicin (see antiTB drugs). It has activity against many Gram positive and Gram negative bacteria. Like rifampin, it inhibits bacterial **DNA and RNA synthesis**.
- It is used **orally** for **hepatic encephalopathy** to suppress intestinal bacteria that produce ammonia.
- It is recently approved to reduce symptoms of abdominal bloating and flatulence associated with **irritable bowel syndrome**.

Nifuroxazide (Antinal)

- It is a **poorly-absorbed** antibiotic related to nitrofurantoin (see UTI). It has activity against many Gram positive and Gram negative enteropathogenic bacteria. The exact mechanism is unclear.
- Bacterial resistance is still uncommon.
- It is used orally as **intestinal antiseptic** in cases of infectious **diarrhea**.

Polymixins

- The polymixin antibiotics are **polymixin B** and **colistin** (polymixin E). They exert their antibacterial action by disrupting the **outer cell membrane**.
- They have selective and rapid bactericidal action on **Gram-negative bacilli**, especially *Pseudomonas* and coliform spp.
- They are **not absorbed** from the GIT.
- Due to their **high toxicity**, they are used only **locally** for eye and skin infections.

Antipseudomonal drugs

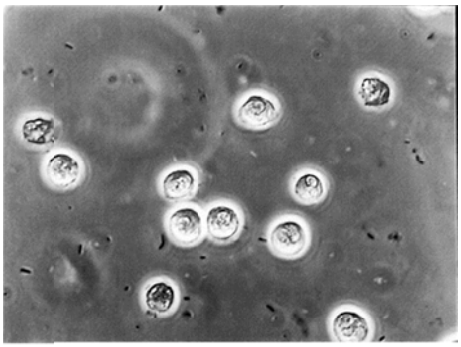
- Antipseudomonal penicillins: e.g. ticarcillin, piperacillin, etc.
- Monobactams: e.g. aztreonam
- Carbapenems: e.g. imipenem, meropenem.
- 3rd and 4th generation cephalosporins: e.g. ceftazidime & cefipime
- Fluorinated quinolones: e.g. ciprofloxacin.
- Tobramycin and gentamycin.

Part 3: CASE STUDY
Treatment of Urinary Tract Infections (UTI)

Definition: infection of the urinary tract indicated by presence of **> 10 pus cells/HPF** in centrifuged urine sample **(pyuria).**

Sterile pyuria: presence of pus cells without organisms. It occurs in some conditions e.g. ***renal TB, analgesic nephropathy, and bladder tumors.***

Bacteriuria: urine culture proves presence of bacteria in urine with or without symptoms of UTI.



Multiple bacilli shown as black and bean-shaped between pus cells in urinary microscopy. These changes are indicative of a UTI.

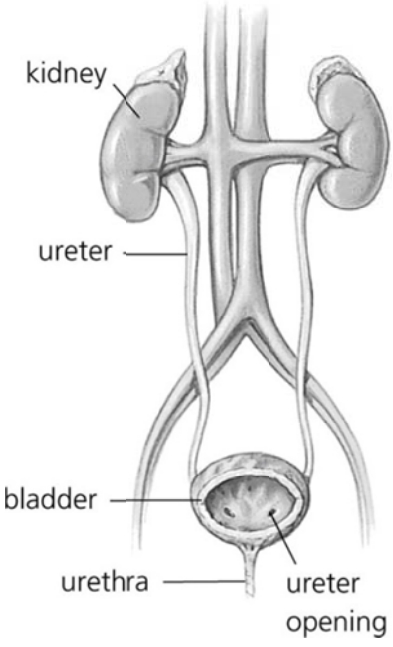
Predisposing factors

- Females > males due to short urethra – Children > adults due to bad hygiene.
- Immunosuppression e.g. in cases of diabetes mellitus.
- Presence of obstruction to urine flow e.g. congenital abnormalities, urethral strictures, and stones.

Causative organisms

- ***E-coli*** is the most **common organism** (80%) in uncomplicated infection.
- *Staphylococcus saprophyticus* (10%).
- Other Gram-negative bacilli e.g. *Proteus, Pseudemonus & Klebsiella* are the commonest organisms. in complicated infection.

Clinical picture



- **Upper UTI (pyelonephritis):** inflammation of the renal tissue or pelvis.
  Manifestations: loin pain, chills, & fever.
- **Lower UTI (cystitis):** inflammation of the bladder & urethra.
  Manifestations: dysuria (burning micturition), urgency & frequency of urination.
- **Uncomplicated (simple) UTI:** occurs for the 1st time without complications. It is usually lower UTI.
- **Complicated (recurrent) UTI:** usually upper UTI with complications e.g. renal stones or anatomical dysfunction.

Laboratory investigations

- **Urine analysis:** the most common test.
  - Macroscopic: color, pH, glucose, protein, etc.
  - Microscopic: WBCs, RBCs, epithelial cells, crystals, casts, ova, etc.
- **Urine culture & sensitivity test:**
  - Culture and sensitivity test is essential in **recurrent UTI** because mixed infection and drug resistance are common.
  - **Does the *in-vitro* test necessarily reflect the *in-vivo* response to drugs? NO because:**
    - The antibacterial drug is **not** excreted in sufficient amount in urine or excreted in urine but as inactive metabolite.
    - Presence of contraindications of the drug e.g pregnancy or children.
  - Most bacteria causing UTI cause alkaline urine, but **strongly alkaline** urine is suggestive of ***Proteus*** infection because it is urease +ve and splits urea into ammonia (NH_3) in the urine.
- **Plain X-ray & i.v. pyelography:** to exclude stone or obstruction**.**
- **Serum creatinine** to avoid use of nephrotoxic drugs.

Management of UTI

1. Specific treatment: Antimicrobial drugs:

- **In lower UTI (usually simple):**
  - The antimicrobial drug should be excreted in large amount in urine.
  - Drugs used routinely: **co-trimoxazole, amoxycillin or nitrofurantoin.**
  - Duration of treatment: **3-5** days.
  - In some cases, simple UTI could be treated by **single** large dose of **fosfomycin** (3g oral once) but with lower cure rates.
- **In upper UTI (usually recurrent):**
  - The antimicrobial drug should be bactericidal of high tissue penetration e.g. **aminoglycosides, fluorinated quinolones or 3rd gen cephalosporins**.
  - Duration of treatment: **10-14** days followed by **chemoprophylaxis** for **15-30** days to prevent recurrence.
  - Indications of chemoprophylaxis: recurrent upper UTI and UTI in pregnancy and children.
  - Drugs used routinely in chemo-prophylaxis: co-trimoxazole, amoxycillin or nitrofurantoin.

2. Changing the urinary pH:

- Normal urine pH is 5.2-6.5. It is possible, by the use of pharmacological agents, to produce urinary pH values ranging from ~ 5.0 to 8.5.

Drug	% Renal excretion of unchanged drug
Ampicillin	75-92
Amoxicillin	60-98
Piperacillin	75-90
Ticarcillin	80-98
Aztreonam	65-95
Imipenem	5-40
Meropenem	62-83
Cephalexin	91-100
Ceftriaxone	65-95
Ciprofloxacin	30-50
Levofloxacin	61-86
Moxifloxacin	20
Gentamycin	>90
Topramycin	>90
Nitrofurantoin	27-56
Co-trimoxazole	50-75

■ Alkalinization of the urine:

Indications:

- To enhance the activity of sulfonamides & aminoglycosides.
- To prevent uric acid stones and sulfonamides crystalluria.
- To relieve dysuria (burning micturition) in some cases of bladder infection.
- *E. coli* is inhibited in alkaline medium.

Alkalinizing agents:

- **Oral:** sodium and potassium citrate salts: citrate is metabolized into bicarbonate which is excreted in urine.
- **Intravenous** bicarbonate solution: contains 5% $NaHCO_3$.

■ Acidification of the urine:

Indications:

- To enhance the activity of nitrofurantoin, fosfomycin, and hexamine.
- Acidifying agents can lead to dangerous systemic acidosis in cases of renal or hepatic impairment.

Acidifying agents:

- **Oral:** ascorbic acid > 2 g/d.
- **Intravenous** ammonium chloride (NH_4Cl) solution.

3. Urinary antiseptics:

■ Hexamine (Methenamine)

- In acidic urine, hexamine is hydrolyzed into ammonia and **formaldehyde**. Formaldehyde is bactericidal and lacks bacterial resistance. Urine must be **acidified** (pH below 5.5) to get this effect.
- **Side effects:** Chemical cystitis.

■ Nitrofurantoin

- Nitrofurantoin causes bacterial **DNA damage** by an unclear mechanism
- It is used **only** as a **urinary antiseptic** in **lower simple UTI** against ***E. coli.*** Other urinary tract Gram-negative bacteria are often resistant.
- It becomes more active in **acidic** urine.
- It is **contraindicated** in renal failure.
- **Adverse effects** include hemolytic anemia in patients with G-6-PD deficiency, peripheral neuritis, and dark brown urine.

■ Fosfomycin

- Fosfomycin inhibits bacterial **cell wall** synthesis.
- It is a **broad spectrum** antibiotic against many **Gram positive** and **negative** spp.
- It is used **only** as a **urinary antiseptic** in **lower simple UTI**.
- It becomes more active in **acidic** urine.

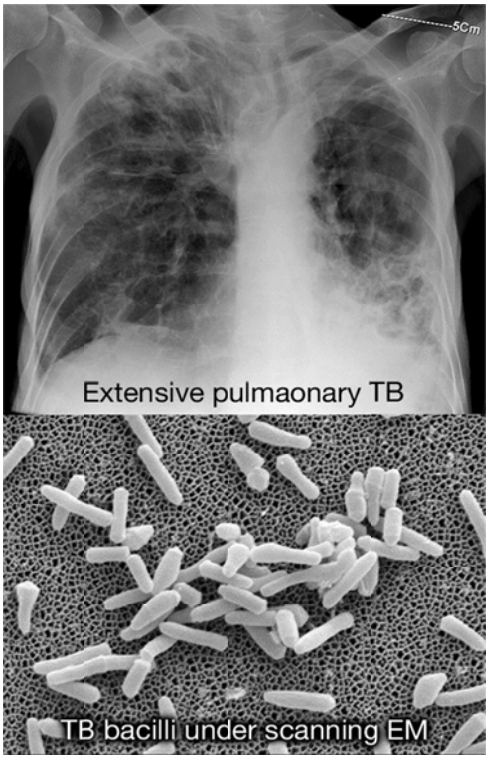
Causes of failure of treatment:

- Improper choice, dose, or duration of drug treatment.
- Bacterial resistance.
- Presence of complications e.g. renal calculi, ureteric stricture, etc.
- Renal failure.
- Immunocompromized patient: e.g. DM

	Contraindicated drugs	Recommended drugs
UTI with Renal Failure	▪ Nitrofurantoin: absolutely contraindicated because it is nephrotoxic and needs acidic urine to act while we cannot acidify urine in renal failure. ▪ K salts and acidifying agents: absolutely contraindicated because they can cause dangerous acidosis or hyperkalemia. ▪ Aminoglycosides.	▪ Penicillin ▪ Most cephalosporins ▪ Co-trimoxazole
UTI in Pregnancy and lactation	▪ Sulfonamides → kernicterus. ▪ Fluorinated quinolones → arthropathy. ▪ Aminoglycosides → congenital deafness. ▪ Tetracyclines → teratogenic and cause yellow staining of teeth. ▪ Chloramphenicol → grey baby syndrome.	▪ Penicillin ▪ Most cephalosporins

Part 4: Chemotherapy of TB and Leprosy

Overview:



- *Mycobacterium tuberculosis*, one of a number of mycobacteria, can lead to serious infections of the lungs, genito-urinary tract, skeleton, and meninges.
- Worldwide estimations record 9 million new cases every year, and approximately 2 million die of the disease each year.
- Treatment of TB (and other mycobacteria) presents therapeutic problems because:
- Tubercle bacilli are either extracellular (metabolically active), intracellular (metabolically inactive) or inactive inside necrotic caseous material. However, most of tubercle bacilli are intracellular with slow growth rate. Resistant strains occur naturally to any agent given as sole drug.
- Bacterial **resistance** is common, particularly in patients non-adherent to the treatment protocol.
- The organism grows slowly and may require 6-24 months of treatment.

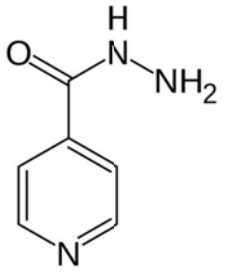
General rules during TB therapy:

- **Never treat TB by a single drug:** at least two of the first line drugs, are used to prevent emergence of resistant strains.
- **Never add a single drug to a failing regimen!**
- Treatment must be continued for long period (6-24 months) to eradicate bacilli.
- **Poor patient compliance** is the commonest cause of therapeutic failure, so it is better to give drugs in a single daily dose to enhance patient compliance.
- The patient must be **followed up** for detection of adverse effects of drugs and/or therapeutic failure.

FIRST LINE ANTI-TUBERCULOUS DRUGS

- **Isoniazide**
- **Rifampicin (Rifampin)**
- **Ethambutol**
- **Pyrazinamide**
- **Streptomycin**

1. Isoniazid (INH)



Mechanism of action

- INH is an analog of pyridoxine (vitamin B6).
- INH is a **prodrug** that is activated inside *M. tuberculosis* into active metabolite which inhibits the synthesis of **mycolic acid**, an essential component of the **mycobacterial cell wall (bactericidal).**
- **Mycolic acid** is present only in *M. tuberculosis,* so INH has **no activity** on other bacteria or atypical mycobacteria.
- **Resistance** is due to mutations in the enzyme responsible for conversion of INH into the active metabolite.

Pharmacokinetics

- Absorption of INH is good after oral administration. It penetrates most body fluids including the CSF.
- It accumulates in caseated lesions and can attack both extra- and intracellular bacilli.
- INH is acetylated in the liver. The rate of acetylation is genetically determined ("rapid acetylators" and "slow acetylators").

N.B.

INH exerts **competitive antagonism with pyridoxine** for enzyme apotryptophan leading to clinical picture of pyridoxine deficiency (neurotoxicity).

Therapeutic uses

- **Treatment of TB:** INH is **administered in combination** with one or more other first-line drugs to minimize the development of resistance.
- For **prophylaxis** (close contacts), INH is used alone.

Adverse effects

I **Inhibition** of CYP450 (↓ metabolism of other drugs, especially phenytoin).

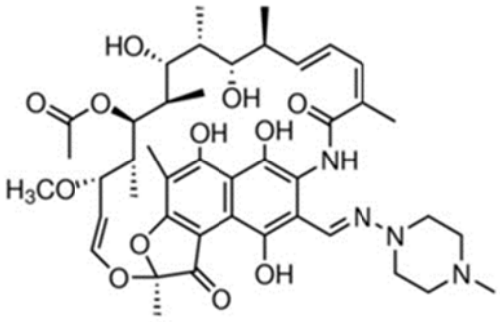
N **Neurotoxicity:**
- High levels of INH compete with pyridoxine at the enzyme *pyridoxal kinase* leading to **peripheral neuropathy**.
- It is more common in **slow acetylators**.
- It could be minimized by co-administration of **pyridoxine** (vitamin B6).

H **Hepatotoxicity** with jaundice (3%)**:**
- It is due to accumulation of toxic metabolites in the liver.
- It is more common in **rapid acetylators** and in individuals over 35 years.

H **Hypersensitivity reactions** with rash and fever (2%).

H **Hemolytic anemia** in patients with G-6PD deficiency

2. Rifampin (Rifampicin)



Mechanism of action

- Rifampin selectively inhibits bacterial **DNA-dependent RNA polymerase enzyme** leading to ↓ RNA synthesis (human enzyme is not affected).
- Rifampin is **bactericidal** for both intra- and extracellular *M. tuberculosis*, and atypical mycobacteria.
- It is also effective against many **Gram-positive** and **Gram-negative** bacteria.
- **Resistance** develops rapidly if the drug is used **alone**. It is due to a change in the polymerase enzyme.

Pharmacokinetics

- Rifampin is absorbed orally and can reach all body tissue and fluids including the CSF, pleural and ascetic fluids.
- It can reach TB cavities, sputum and penetrate macrophage killing intra- and extracellular TB bacilli.
- It enters **enterohepatic circulation** and **induces** hepatic microsomes to **decrease the half-lives** of other drugs.
- It is excreted through the bile and urine. Its metabolites cause ***orange-red*** discoloration of urine, stool, tears, and sweat; the patient should be **warned**.

Therapeutic uses

- Treatment of **TB** in combination with ***INH*** and ***pyrazinamide***. Rifampin and INH are the most effective antituberculous drugs.
- Although rifampin has activity against many Gram positive and negative bacteria but should be used **only against TB** to prevent development of resistance.
- Treatment of **leprosy** in combination of ***dapsone*** and ***clofazemine***.
- Used **prophylactically** for individuals exposed to **meningitis** caused by *Meningococci* or *H. influenzae*.

Adverse effects

- **Hepatotoxicity (rare):** abnormal liver enzymes, jaundice, etc. especially in old patients and patients with chronic liver disease.
- **Microsomal enzyme induction** leading to decrease half-lives of other drugs.
- **Flu-like symptoms:** with intermittent therapy.
- **Red tears and urine:** harmless, but can stain contact lenses.
- **GIT** upset (nausea and vomiting) and skin **rash**.

3. Ethambutol

Mechanism of action

- Ethambutol inhibits ***arabinosyl transferase*** involved in **cell wall** biosynthesis.
- Ethambutol is specific bacterio**static** for *M. tuberculosis.* It is active against intra- and extracellular TB bacilli.
- Relatively **less toxic** and resistant strains develop **slowly**.

Therapeutic uses

- Treatment of TB in combination with INH and rifampin to minimize **resistance**.
- Treatment of **TB during pregnancy** because it is **the least toxic**.

Adverse effects

- **Peripheral neuropathy and visual disturbances (1-5%)**:
  - Optic neuropathy manifested by field defects and red-green color blindness. These effects are reversible on stopping the drug.
  - There is no specific treatment other than stopping of the drug.
- **Hyperuricemia** and **gout**: due to ↓ uric acid excretion.
- **GIT disturbance** & hypersensitivity reactions.

4. Pyrazinamide

Mechanism of action

Pyrazinamide is taken up by the macrophages and is converted into the active product by the **acidic** medium of the lysosomes inside the macrophages. It inhibits mycobacterial **cell wall** functions.

Therapeutic uses: In combination with INH and rifampin to minimize resistance

Adverse effects

- **Hepatotoxicity** is the major side effect.
- **Hyperuricemia** and **gout**: due to ↓ uric acid excretion.

5. Streptomycin

- It is one of the aminoglycosides. It is bacteri**cidal** for **extracellular** bacilli but it is ineffective against intracellular bacilli. Why?
- **Therapeutic uses:** in combination with INH & rifampin to treat **resistant**

pulmonary TB and **renal TB** (because 50-90% is excreted unchanged via the kidney). It is given by IM injections.

- **Adverse effects:** nephrotoxicity, ototoxicity (8th nerve damage), and NM block.

SECOND-LINE ANTI-TUBERCULOUS DRUGS

- **Para aminosalicylic acid**
- **Ethionamide**
- **Cycloserine**
- **Fluoroquinolones**
- **Capreomycin**

1. Para aminosalicylic acid (PAS)

PAS is an analog of PABA; it works similar to sulfonamides but only against mycobacteria.

2. Ethionamide

Ethionamide, like isoniazid, blocks the **synthesis of mycolic acids.** Resistance develops rapidly. It commonly produces severe GI disturbances.

3. Other drugs: fluoroquinolones, cycloserine, etc.

REGIMEN OF TB THERAPY

- **Patients with active TB:**
  - **Initial phase (first 2-4 months)**: **4 drugs** are used **(RIPE)**: (**Rifampin + INH + Pyrazinamide + Ethmabutol**). ***N.B.*** *Recent guidelines now recommend giving a 'fourth drug' such as Ethambutol routinely - previously this was only added if drug-resistance was suspected.*
  - **Continuation phase (next 4-6 months):** at least **2 drugs** are used (**INH + rifampin**).

- **Patients with latent TB** *(i.e. patients with +ve Tuberculin skin test and had history of contact to a person proved to have TB):* **INH** alone for 6 months or dual Rifampicin + INH for 3 months.

- **Patients with meningeal TB:** are treated for a prolonged period (12-18 months) with the addition of **steroids.**

- **TB during pregnancy:** the only anti-TB drug which is absolutely contraindicated is streptomycin because of the high risk of congenital deafness. The other first line anti-TB drugs are safe for use in pregnancy.

- **TB with liver disease:** INH, rifampin, and pyrazinamide are hepatotoxic but because of their effectiveness, they should be used depending on monitoring of liver function tests. In severe liver damage, only one drug can be used.

CHEMOTHERAPY OF LEPROSY

1. Dapson

- Structural analogue of PABA and chemically related to sulfonamides.
- **Mechanism of action:** similar to sulfonamides (bacteriostatic).
- **Therapeutic uses:** treatment of leprosy with rifampin for 2-5 years.
- **Adverse effects:**
  - Nausea, vomiting, skin rash
  - Hemolysis and methemoglobinemia,
  - Exacerbation of skin lesion of lepromatous leprosy.

2. Clofazimine

- **Mechanism of action:** inhibit mycobacteria DNA synthesis (bactericidal).
- **Therapeutic uses:** in combination with dapson and rifampin to prevent resistance.
- **Adverse effects:** abdominal pain, brown urine, atropine-like actions.

3. Rifampin: is the most active antilepromatous drug available.

Part 5: Antiviral Drugs

ANTI-HERPES VIRUS AGENTS

1. Acyclovir

- **Acyclovir** is a purine analog that **inhibits the activity of viral DNA polymerase.**
- It is active against **herpes simplex virus (HSV)** types I and II, and to a lesser extent against **Epstein–Barr virus, varicella-zoster virus,** and **cytomegalo virus** (**CMV).**
- **Adverse effects:** reversible nephrotoxicity and neurotoxicity

2. Gancyclovir

- Similar to acyclovir but highly active against **CMV.**
- **Adverse effects:** reversible neutropenia and thrombocytopenia

ANTI-INFLUENZA AGENTS

1. Amantadine and rimantadine

- Amantadine and rimantadine inhibit the **uncoating** and replication of the viral RNA in infected cells.
- They are used to treat **influenza A** infections when administered within the first **48 hours** of symptoms, and as prophylaxis during flu season.
- **Adverse effects:** mild CNS effects (insomnia, nervousness) and some GI dysfunction. Patients with a history of **seizures** require close monitoring.

2. Ribavirin

- Ribavirin, a guanosine analog that appears to inhibit viral RNA polymerases; the mechanism of action is **not clear.**
- It is used to treat **respiratory syncytial virus (RSV)** and **influenza A and B**.
- **Adverse effects:** Hemolytic anemia and teratogenic in pregnancy.

3. Zanamivir and Oseltamivir (Tamiflu)

- Zanamivir, (administered by inhalation), and oseltamivir, (administered orally), are **neuraminidase inhibitors.**
- They are used for the treatment and prophylaxis of **acute uncomplicated influenza** infection. The agents are effective against both influenza A and B.
- Abdominal pain and **GI dysfunction** are common with oseltamivir. Zanamivir may cause **bronchospasm**.

ANTI-RETROVIRAL DRUGS

1. Reverse Transcriptase Inhibitors (RTIs):

- **Nucleoside analogs (NRTI):** zidovudine, lamivudine, tenofovir
- **Non-Nucleoside analogs (NNRTI):** efavirenz, nevirapine

Adverse effects:

- All agents: peripheral neuropathy and interaction with CYP450.
- Zidoviodine: myopathy and anemia.

2. Protease inhibitors: ritonavir, lopinavir, atazanavir

Adverse effects:

- All agents: diabetes, hypertriglyceridaemia and hypercholesterolaemia
- Ritonavir is the most potent inhibitor of CYP450 known.

3. Fusion receptor protein inhibitors: Enfuvirtide.

- It competes with the **gp41 subunit** of the HIV-1 viral envelope and prevents fusion to the cell membrane CD4 receptors.

4. Integrase inhibitors: Raltegravir

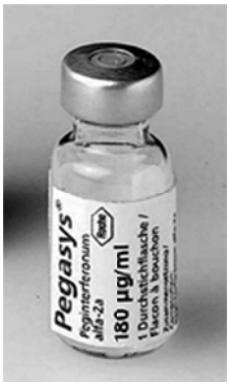
- It is a **new class** of drugs that inhibit the viral enzyme **integrase** to prevent HIV replication and viral integration into the host cell.

ANTI-HEPATITIS VIRUS DRUGS

1. Interferon-alpha and peginterferon-alpha (Pegasys)

- Interferons are group of natural cytokines released by host cells in response to infection. They have several classes; all have antiviral effects and regulate the immune function.
- Genetically engineered interferon-α is used, in combination with **ribavirin**, for both **HBV** and **HCV**. Peginterferon has long duration (injected **once-weekly s.c.).**

- **Antiviral mechanism:**
  - Interferon binds to cell membrane receptors to initiate a series of reactions leading to inhibition of viral replication.
  - They promote apoptosis of viral-infected cells.



- **Adverse effects:**
  - Flu-like symptoms: muscle pain, fever, and **fatigue**.
  - Bone marrow depression: neutropenia.
  - Neuropsychiatric effects: depression, convulsions.

2. Lamivudine

- It is a nucleoside reverse transcriptase inhibitor (NRTI) used for **HBV infections**, providing effective and rapid response in most patients, and slows progression of liver fibrosis.

3. Sofosbuvir (Sovaldi®)

- It is a nucleotide analog used for treatment of **HCV** in combination with ribavirin and interferon.
- It works by inhibition of **viral RNA polymerase**.

4. Grazoprevir/Elbasvir (Zepatier®)

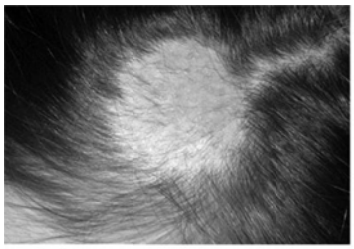
- It is a recently approved combination for treatment of **HCV** (genotypes 1, 3, 4).
- **Grazoprevir** is a NS3/4A protease inhibitor. This protease enzyme enables the C virus to survive and replicate in host cells. **Elbasvir** is a NS5A inhibitor. NS5A is a protein needed by the virus for various stages of infection.
- The effectiveness and adverse effects of sofosbuvir, grazoprevir, and elbasvir are under current investigation.

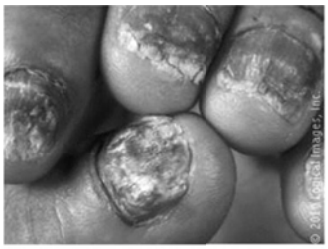
Management of chronic HCV infection

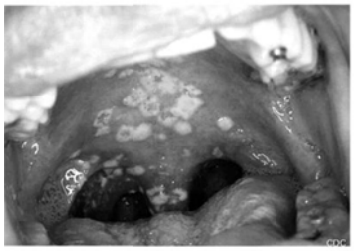
- Treatment with interferon-α **alone** gives 10-15% success rate in achieving long term clearing of plasma hepatitis C RNA. A combination of **interferon and ribavirin** gives 50% success rate.
- About 50% of successfully treated patients will **relapse** despite treatment.
- **HCV genotype** will give guidance to the **length of treatment** and **response rate**:
  - Those with genotype **2** and **3** can achieve SVR after **24** weeks as they have better response to treatment.
  - In genotype **1** and **4**, therapy is continued for **48** weeks due to **lower** response rate.
- The following also predict **a good long term response to interferon:**
  - Younger age.
  - Female gender.
  - Absence of cirrhosis on liver biopsy.
  - Non-black racial origin.
  - Low hepatic iron.
- **No HCV vaccine** is currently available.

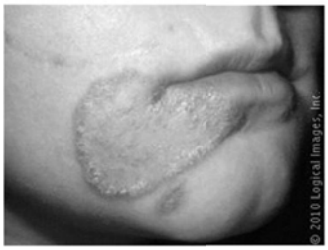
Part 6: Chemotherapy of Fungal Infections

Fungal infection is termed **mycosis**


Ringworm of the scalp


Onychomycosis of nail


Oropharyngeal candidiasis


Tinea of the face

Types of fungal infections:

- **Mucocutaneous (superficial) infections:**
  - Dermatophytes: cause infection of **skin**, **hair**, and **nails**: e.g. tinea capitis (scalp), tinea cruris (groin), tinea pedis (foot), onychomycosis (nails).
  - Yeasts: cause infections of moist skin and mucous membranes: e.g. ***Candida albicans*** causing oral, pharyngeal, vaginal, & bladder infections.
- **Systemic mycoses:** are fungal infections affecting internal organs. It occurs in immunocompromized patients e.g. cryptococcosis, and aspergillosis (lung).

Classification of antifungal drugs:

A. Drugs for mucocutaneous infections:	**Systemic drugs**	▪ **Azoles:** Fluconazole, Itraconazole, Voriconazole. ▪ Griseofulvin ▪ Terbinafine
	Topical drugs	▪ **Azoles:** Ketoconazole, Miconazole, Clotrimazole, Tioconazole, etc. ▪ Nystatin ▪ Terbinafine. ▪ Other drugs: Tolnaftate, Ciclopirox, Naftifine, Whitfield ointment, Gentian violet, Castellani paint, Tincture iodine.
B. Drugs for systemic infections:		▪ **Azoles:** Fluconazole, Itraconazole, Voriconazole. ▪ Amphotericin-B ▪ Flucytosine ▪ Caspofungin

1. Azoles

[Ketoconazole, Miconazole, Fluconazole, Itraconazole, Voriconazole]

Mechanism of action

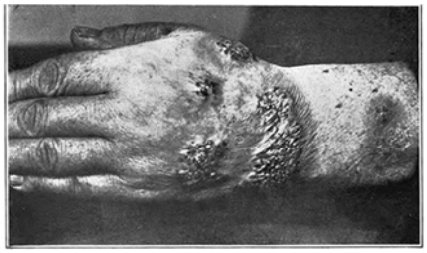
- Azoles inhibit fungal **cytochrome P450** necessary for **ergosterol synthesis**, a major component of fungal cell membrane. This will alter membrane permeability and disrupt its function.
- They are **broad spectrum** fungistatic against many **dermatophytes and candida.**

Pharmacokinetics

- Absorption of azoles from stomach if affected by food and gastric HCl.
- Fluconazole can reach the CSF with good concentrations. The other drugs cannot.
- Fluconazole is excreted in the urine mostly unchanged

Therapeutic uses

- **Superficial fungal infections: [ketoconazole – itraconazole – miconazole]**
  - Dermatophytes infection of the **skin** (tinea), **hair**, and **nails** (onychomycosis):
    - For **skin** infection: treatment continued for **2-4** weeks.
    - For **hair** infection: treatment continued for **6-8** weeks.
    - For **nail** infection: treatment continued for **3-6** months.
  - Mucocautaneous candidiasis: oropharyngeal, vulvovaginal, etc.
- **Systemic fungal infections: [itraconazole – fluconazole – voriconazole]**
  - **Itraconazole** (orally or IV) is the drug of choice for systemic ***blastomycosis***.
  - **Fluconazole** (orally or IV) is the drug of choice for systemic candidiasis, and ***cryptococcal meningitis*** (because it the only azole that can cross to CSF with good concentration).
  - **Voriconazole** is the drug of choice for ***invasive aspergillosis*** of the lung.



Skin lesions of blastomycosis

N.B. Itraconazole has largely replaced ketoconazole in most uses.

Adverse effects

- **Hepatotoxicity** and ↑ of serum transaminases.
- **Azoles inhibit hepatic CYP450 enzymes** (fluconazole is the least among them).
- **Ketoconazole** causes **antianderogenic effects:** gynecomastia and impotence due to ↓ gonadal steroid synthesis.
- **Voriconazole** causes **transient visual disturbances.**

2. Amphotericin-B

Mechanism of action

Amphotericin B is polyene macrolide that binds to ergosterol of fungal cell membranes and forms **"pores"** that alter membrane stability and allow **leakage of cellular contents.**

Pharmacokinetics

- Amphotericin B is **polar** compound that **cannot be absorbed** from the GIT or cross the CSF. It should be administered **IV** or intrathecal.
- Half-life is **15 days**. Dialysis is **ineffective** in case of toxicity.
- Because of significant toxicity, amphotericin B is available in **liposomal form** in which the drug is enclosed in lipid microspheres **"liposomes"**. These lipid microspheres bind preferentially to ergosterol in the fungal cell membrane with lower affinity to mammalian cell membranes.

Therapeutic uses

Amphotericin B has the **broadest spectrum** of activity. It is used to treat **severe systemic fungal infections**, including those caused by *Candida albicans, Histoplasma capsulatum, Cryptococcus neoformans, Coccidioides immitis, Blastomyces dermatitidis, Aspergillus spp., and Sporothrix schenckii.*

Adverse effects

- Amphotericin B is highly **toxic** drug. It causes **nephrotoxicity** in 80% of patients which is dose-dependent and may be irreversible.
- **Chills** and **fever** in 50% of patients.
- Seizures and neurotoxicity
- Hypokalemia and thrombocytopenia

OTHER ANTIFUNGAL DRUGS

Flucytosine

- Flucytosine is actively transported into fungal cells and is converted to the uracil form **5-fluorouracil (5-FU)** which inhibits **nucleic acid synthesis.** Human cells lack the ability to convert large amounts of flucytosine into 5-FU.
- It is often used in **combination with other antifungal agents** (because of rapid development of resistance) to treat **severe systemic** fungal infections.
- **Adverse effects:** Flucytosine is relatively nontoxic; the major adverse effect is **depression of bone marrow** at high doses and **hair loss**.

Griseofulvin

- Griseofulvin binds to **microtubules** and prevents **spindle formation and mitosis in fungi.** It is fungi**static** and requires long duration of therapy.
- The drug binds to keratin structures and **accumulates in skin, hair, and nails.**
- Griseofulvin is used orally for long-term therapy of **dermatophyte infections of the hair and nail.**
- **Adverse effects: hepatotoxicity** (liver functions should be checked during therapy), hypersensitivity reactions (skin rash), and CNS effects.

Terbinafine

- Terbenafine inhibits the fungal enzyme ***squalene epoxidase***. This leads to the accumulation of the sterol squalene, which is toxic to the organism.
- Like griseofulvin, it accumulates in keratin structures and used orally or topically for treatment of **dermatophyte infections of the hair and nail.**

Nystain

- Nystatin is polyene macrolide very similar in kinetics and mechanism to amphotericin B.
- It is **too toxic** for parenteral administration and is used only topically.
- It is active mainly against **Candida,** and is used topically for oralpharyngeal and vaginal candidiasis.

Caspofungin

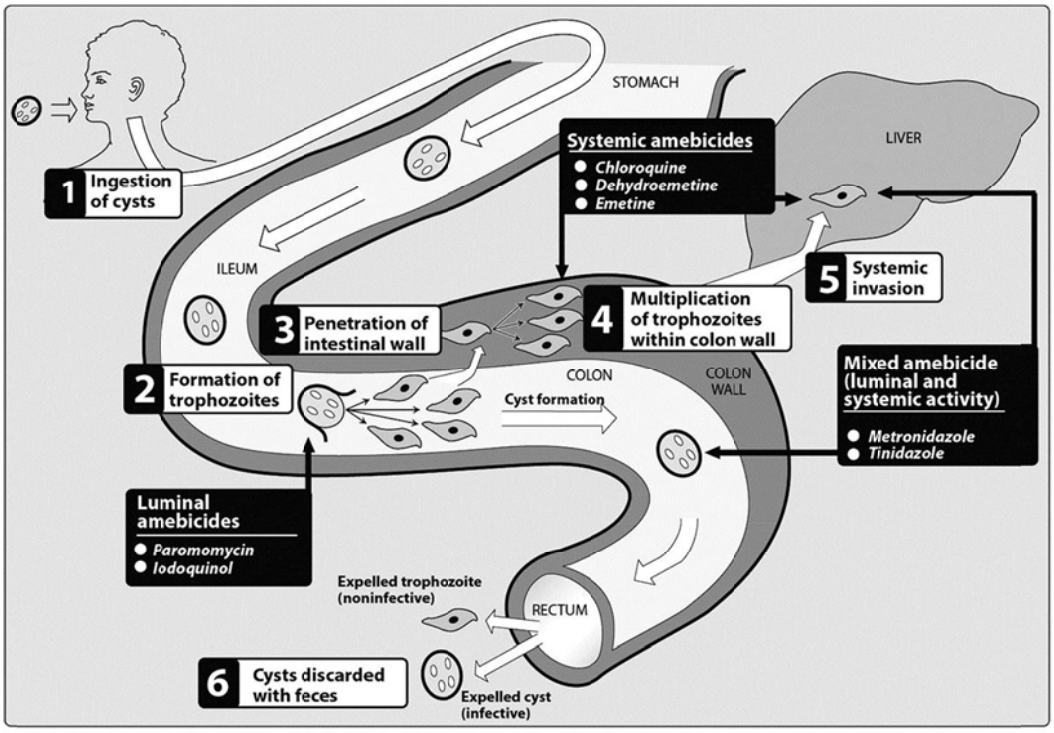
- It is large cyclic peptide that **disrupts the fungal cell wall** resulting in cell death.
- **Caspofungin** is used by i.v. route for salvage therapy in patients with **severe invasive aspergillosis** or **esophageal candidiasis** who failed to respond to amphotericin B (second line drug).

Ciclopirox

- Broad-spectrum antifungal effective against **dermatophytes and yeasts**. The mechanism is **unclear.**
- It is used topically for skin and nail infections.

Part 7: Antiamoebic Drugs

- The causative organism for amoebiasis is ***Entamoeba histolytica***. Initial infection occurs by ingestion of the **cyst** form. The infectious cysts pass into the colon, where they develop into **trophozoites**. These motile organisms adhere to colonic epithelial cells. Here, the trophozoites feed, multiply, encyst and eventually pass out in the feces **"asymptomatic carrier"**.
- The motile organism invades the colonic mucosa causing **"amoebic dysentery"**. They may also spread to the liver causing acute **"amoebic liver abscess"**.



Classification of antiamoebic drugs:

A. Luminal amoebicidal drugs: these agents destroy the trophozoites of *E. histolytica* that eventually form into cysts in the intestine.	▪ **Diloxanide** ▪ **Iodoquinol** ▪ **Paromomycin**
B. Tissue amoebicidal drugs: they destroy the invading **trophozoite** in the tissues (e.g. liver) but are ineffective against the trophozoites in the intestinal lumen. **Their use now is very limited.**	▪ **Emetine and dehydroemetine** ▪ **Chloroquine:** active only against liver infection.
C. Mixed tissue and luminal amoebicides:	**Metronidazole, tinidazole, ornidazole.**

1. Mixed amebicides: Metronidazole

Structure and mechanism of action

- Metronidazole is 5-nitroimidazole compound. Anaerobic protozoa & bacteria lack mitochondria; instead, they have *ferredoxin oxidoreductase enzyme* in the cytoplasm to generate ATP.
- This enzyme system can transfer electron to the 5-nitro groups of metronidazole converting it into **cytotoxic product**. This product causes DNA damage and inhibits DNA repair.
- Metronidazole is active against **anaerobic organisms** including *anaerobic bacteria: (e.g. Bacteroids, C. difficile), E. histolytica, G. lamblia, T. vaginalis, B. coli.*

Therapeutic uses

- **Amebiasis:** Metronidazole is the most effective agent available for the treatment of all forms of amoebiasis except asymptomatic person that excrete cysts. Metronidazole kills trophozoites but not cysts.
- **Urogenital trichomoniasis:** 250 mg t.d.s. for 7 days is the treatment of choice. The other partner should be treated simultaneously.
- **Giardiasis:** 250 mg t.d.s. for 5 days.
- **Balantidiasis:** 750 mg t.d.s. for 5 days
- **Severe anaerobic infections:** e.g. puerperal sepsis, peritonitis, acute ulcerative gingivitis, etc.

Adverse effects

- **GIT:** nausea, vomiting & metallic taste.
- **CNS:** insomnia, headache, vertigo, parasthesia, ataxia, & seizures.
- **Blood:** bone marrow depression, leukopenia & thrombocytopenia.
- **Disulfiram-like reaction:** metronidazole causes accumulation of acetaldehyde if alcohol is consumed leading to nausea & vomiting.
- **Dark brown urine.**

N.B. Disulfiram is a drug used for treatment of chronic alcoholism. It blocks metabolism of acetaldehyde by the enzyme *aldhyde dehydrogenase* leading to accumulation of acetaldehyde → nausea, vomiting, flushing, etc.

2. Luminal amebicidal drugs:

- **Diloxanide:** Is active against both trophozoite and cyst forms in the intestinal lumen but **not** in the intestinal wall or extraintestinal tissues. The mechanism is **unknown**.

- **Iodoquqinol:** it is iodinated quinolone derivative. Is active against both trophozoite and cyst forms in the intestinal lumen but **not** in the intestinal wall or extraintestinal tissues. The mechanism is **unknown**.

  Because it contains iodine, it can cause **dermatitis** and **persistent diarrhea** (iodine intolerance).

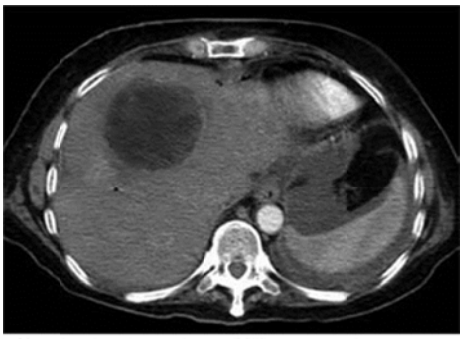
- **Paromomycin:** it is a poorly-absorbable aminoglycoside antibiotic. It is used as alternative to iodoquinol and diloxanide. The antiamoebic mechanism is **unclear** but may be due to alteration of the cell membrane permeability and leakage of cell contents.

Uses of luminal drugs

- They are used for treatment of asymptomatic or mild intestinal infection.
- They can also be added to metronidazole in acute amoebic dysentery as well as hepatic abscess to eradicate cysts in the lumen which may cause relapse.

3. Tissue amebicidal drugs:

- **Emetine and dehydroemetine:** Emetine is a plant alkaloid. Dehydroemetine is a potent derivative. All have significant toxicity.
- **Chloroquine:** it is a synthetic drug (see treatment of malaria).
- Both drugs can be used as alternative to metronidazole in the treatment of **amoebic liver abscess** or extraintestinal amoebiasis, however, their use now is **very limited**.



CT scan showing amebic liver abcess

Part 8: Antimalarial Drugs

Life cycle of malaria and sites of drug actions

A. Sexual cycle in the female mosquito.

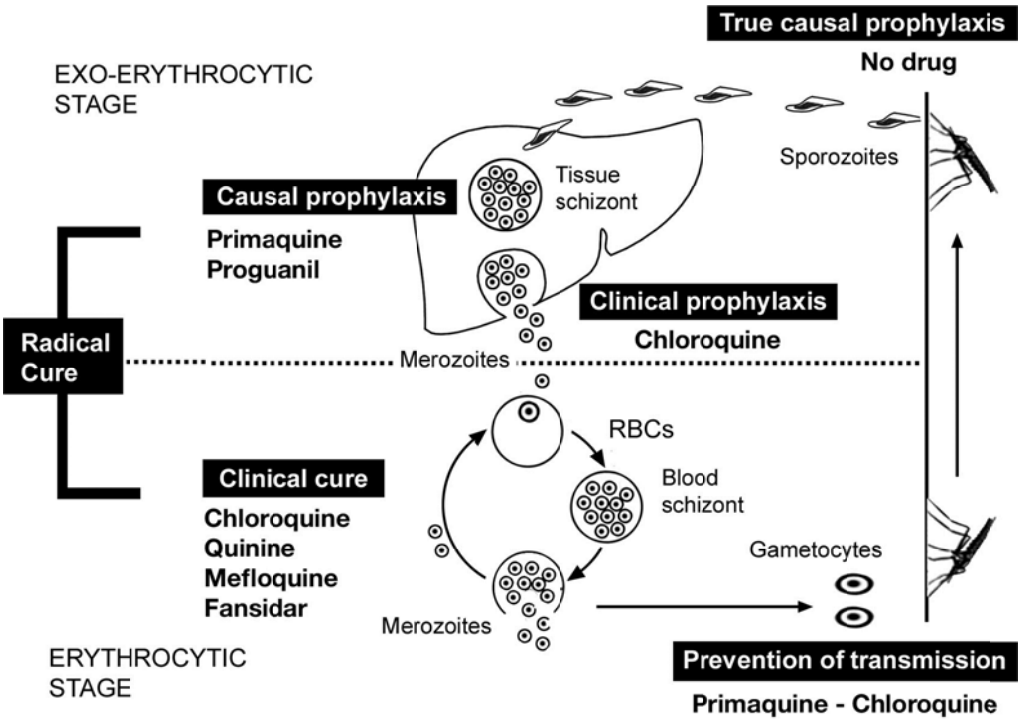
B. Asexual cycle in man and consists of:

- **Sporozoite stage:** sporozoites injected by the mosquito rapidly enter the liver.
- **Exo-erythrocytic (liver) stages:**

  Pre-exo-erythrocytic stage (primary liver stage):
  Sporozoites in the liver undergo multiplication to form **tissue schizont** which eventually ruptures and releases **merozoites** to infect RBCs. During this stage the patient is asymptomatic.

  Secondary exo-erythrocytic stage (persistent liver stage):
  Sporozoite of *P. vivax* or *P. ovale* form dormant **hypnozoites** in the liver that can persist and reactivated after a latent period causing relapse of malaria.

- **Erythrocytic stage:** merozoites liberated from ruptured liver schizont will invade RBCs to form **blood schizont**. This blood schizont will eventually rupture to liberate merozoites and toxic products causing fever and clinical manifestations of malaria (every 3rd day in tertiary malaria).
- **Gametocytes stage: s**ome merozoites develop into gametocytes which will be sucked by the mosquito to complete the sexual cycle.



Types of treatment:

I. Chemoprophylaxis: (Killing the parasite before multiplication inside RBCs)

- **Causal prophylaxis:** killing the parasite in the liver:
  Proguanil and primaquine.
- **Clinical prophylaxis:** killing the parasite as soon as they reach the RBCs:
  Proguanil and chloroquine.

II. Suppressive or clinical cure: (killing the parasite in the RBCs)

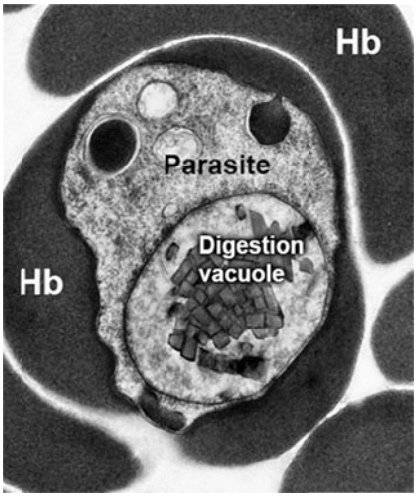
- Chloroquine: for chloroquine-sensitive malaria.
- Quinine and mefloquine: for chloroquine-resistant malaria.
- Artemisinin and its analogs: for chloroquine-resistant malaria.
- Sulfonamides and pyrimethamine: Fansidar (sulfadoxine + pyrimethamine).

III. Radical cure: (clearing the dormant hypnozoite from the liver to prevent relapse)
Primaquine + chloroquine

IV. Prevention of transmission: (killing the gametocytes)
Proguanil, primaquine, and pyrimethamine.

Chloroquine

Mechanism of action



- Inside RBCs, the malarial parasite digest hemoglobin in a vacuole inside the parasite cell to acquire amino acids essential for multiplication.
- Chloroquine enters the digestion vacuole by simple diffusion. The acidic pH inside the vacuole makes chloroquine **ionized** and, thus, cannot diffuse outside the vacuole and becomes trapped inside it.
- Inside the vacuole, the ionized chloroquine reacts with the digestive products of **heme** molecule and forms a **highly toxic complex** that kills the parasite.
- Chloroquine is a **blood schizonticide** for *Plasmodium vivax, P. ovale, and P. malariae* but **not** for *P. falciparum* which is usually resistant.

Pharmacokinetics

- Absorption from the GIT is good and complete.
- It binds to melanin-rich tissue e.g. skin, eye, etc.
- Chloroquine has **very high Vd** (100-1000L/Kg) and slow rate of elimination.

Therapeutic uses

- **Malaria** (except *P. falciparum*):
  - For treatment of acute attack: 1g IV followed by 500 mg after 6, 24, 48h.
  - For chemoprophylaxis: 500 mg once/week orally.
- As a 2nd line for treatment of **amoebic liver abscess:** 500 mg daily for 14 days.
- As a 2nd line (after metronidazole) for treatment of **giardiasis.**
- Treatment of **rheumatoid arthritis** and **SLE**: 500 mg/day then 250 mg/day.

Adverse effects

- **Long term administration:**
  - **Skin:** pruritus (common), dermatitis, bleaching of hair, and alopecia.
  - **Visual disturbances**: corneal deposits, optic atrophy, and retinopathy.
- **Rapid i.v. injection** causes hypotension, ECG changes, and **cardiac arrest**. Parenteral administration is better avoided or should be infused **slowly.**
- **Hemolysis** in G-6PD deficient persons.

Quinine (and Quinidine)

Structure and mechanism of action

- Both quinine and quinidine are derivatives from the park of cinchona tree. Quinidine is the D-isomer of quinine.
- Quinine is highly active **blood schizonticide** against the **four** species of human malaria parasites, but it is primarily used to treat **chloroquine-resistant *P. falciparum***, often in combination with **doxycycline**.
- The exact antimalarial mechanism is **unknown**.

Therapeutic uses: treatment of **chloroquine-resistant *P. falciparum***.

Adverse effects (more common with i.v. administration)

- **Cinchonism:** tinnitus, ringing in ears, blurred vision, headache, and vomiting.
- **CVS:** hypotension, **syncope**, cardiac arrhythmias and ↑ **QT** interval.
- **Hypoglycemia** is important and may be **fatal** side effect with i.v. administration. It is due to stimulation of insulin release).

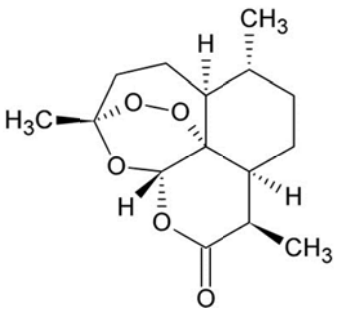
- **Blackwater fever (rare):** massive hemolysis with fever, hemoglobinurea, and dark urine. The pathogenesis is unclear.
- **Hemolysis** in G-6PD deficient persons.
- Hypersensitivity reactions.

N.B.

Although quinine causes **uterine contractions** but the WHO guidelines consider **pregnancy is NOT a contraindication of quinine.**

Artemisinin and its analogs

Structure and mechanism of action



- Artemisinin is the active component of a Chinese herb. The compound contains unusual **peroxide bridge**. Cleavage of this peroxide bridge inside the digestion vacuole liberates **oxygen free radicals** which are lethal to the parasite.
- Artemisinin and its analogs are very rapidly acting **blood schizonticides** against **all** human malaria parasites. They have no effect on hepatic stages.

Pharmacokinetics

- Artemisinin is insoluble and can be used **only orally**.
- **Artesunate** and **artemether** are semisynthetic analogs with improved solubility to be suitable for **parenteral** administration.

Therapeutic uses

- Combination of artemisinin and other antimalarials is now the standard treatment of **falciparum malaria** in nearly all endemic areas.
- **IV artesunate** is now recommended by the WHO in preference to IV quinine due to fewer side effects.

Adverse effects: GI disturbances and, rarely, allergic reactions and hemolysis.

Mefloquine

Structure and mechanism of action

- Mefloquine is structurally related to quinine.
- Strong **blood schizonticide** against *P. falciparum* by **unknown** mechanism.
- It is given **only orally** because parenteral administration causes severe irritation.

Therapeutic uses: treatment of chloroquine-resistant falciparum malaria.

Adverse effects: neurotoxicity: headache, vertigo, psychosis, and confusion.

Primaquine

Mechanism of action

Primaquine is a **hepatic schizonticide** (for *P. vivax and P. ovale*) and **gametocide** (in all 4 types of malaria), through an **unknown mechanism.**

Therapeutic uses

- **Radical cure:** after successful treatment, it is given orally for 15 days to kill the dormant hypnozoites in the liver and prevent **relapse**.
- **Causal prophylaxis:** but prolonged course of primaquine should be avoided.
- **Prevention of transmission:** by killing the gametocytes in all 4 types of malaria.

Adverse effects

– **Methemoglobinemia** nearly in **all** patients.
– **Severe hemolysis** in patients with G-6PD deficiency.
– GIT upset, visual disturbance, and leucopenia.

Antifolate drugs
(Pyrimethamine, Proguanil, Fansidar)

Mechanism of action: ↓ folic acid synthesis necessary for DNA synthesis.

Therapeutic uses

- **Fansidar** is a combination of sulfadoxine + pyrimethamine. It produces sequential block of folic acid synthesis. It is used to treat the acute attack of **chloroquine-resistant malaria** in combination with quinine or artemisinin.
- **Proguanil** is used for prophylaxis and for prevention of transmission.
- **Pyrimethamine** is used for clinical cure and for prevention of transmission.

Part 9: Anthelmintic Drugs

Helminths can be divided into three main groups:

Nematodes (round worms)	Trematodes (flukes)	Cestodes (tape worms)
Intestinal nematodes: *Ascaris lumbricoides* *Ankylostoma duodenale* *Enterobius vermicularis* *Trichuris trichiura* *Strongyloides stercoralis* *Trichostrongylus* **Tissue nematodes:** *Filaria.* *Guinea worm.* *Cutaneous and visceral Larva migrans.*	*Schistosomes* **Intestinal flukes:** *Heterophyes heterophyes* *Metagonimus yokogawia* *Fasciolopsis buski* **Liver flukes:** *Fasciola hepatica* **Lung flukes:** *Paragonimus westermani*	*Taenia saginata* *Taenia solium* *Diphyllobothrium latum* *Hymenolepis nana.* *Hydatid tape worm.*

DRUGS EFFECTIVE AGAINST NEMATODES

1. Benzimidazoles
[Albendazole – Mebendazole – Thiabendazole]

Mechanism of action

These agents inhibit **microtubule synthesis** and **glucose uptake** by the worms. The two effects lead to ↓ ATP production and paralysis of the worm.

Therapeutic uses

Benzimidazoles are broad-spectrum anthelmintic drugs.

- **For intestinal nematodes:** (400 mg once daily on an empty stomach for 2-3 days).
- **For tissue nematodes:** (400 mg twice daily with a fatty meal for 10 days).
- **For hydatid disease**: (400 mg twice daily for one month).
- **Neurocysticercosis:** albendazole is the drug of choice (400 mg twice daily with a fatty meal for 21 days). It is given with corticosteroids to minimize the immune reaction caused by the dying organisms.

Adverse effects: usually mild and mainly GIT upsets.

2. Pyrantel pamoate

- It causes depolarizing neuromuscular blockade and inhibits ChE enzyme in the parasite → paralysis of the worm.
- It is used for intraluminal round worms.
- **Adverse effects:** very few.

3. Diethylcarbamazine (Hetrazan)

- It causes paralysis of **microfilaria** and alters their surface structure, making them more susceptible to destruction by host defense mechanisms. The mechanism is **unknown.**
- **Therapeutic uses:** treatment of **filariasis** (Wucheraria bancrofti and Loa loa).
- **Adverse effects:** sudden death of the microfilaria can produce **severe allergic reactions** e.g. fever, leukocytosis, eosinophilia, edema, rashes, tachycardia and headache (**corticosteroid**s may be needed to suppress these allergic reactions).

DRUGS EFFECTIVE AGAINST TREMATODES AND CESTODES

1. Praziquantel

Mechanism of action

It increases cell membrane permeability of Ca^{2+}. This leads to rapid and prolonged muscle contraction and paralysis of the worm.

Therapeutic uses

- **Treatment of schistosomiasis:** it is active against adult worm and all immature forms in all species (40 mg/kg single dose orally).
- **Other flukes:** *e.g. H. heterophyes, Fasciolopsis buski, Paragonimus westermani.*
- **Cestodes:** *T. saginata, T. solium, D. latum, and H. nana.*

Adverse effects

- Nausea, vomiting, drowsiness, arthralgia, myalgia and low grade fever.
- Mild elevation of liver enzymes.

Contraindications and cautions:

Praziquantel is contraindicated in **ocular cysticercosis**, because parasite destruction in the eye may cause immune reaction and irreversible damage. Some workers also caution against use of the drug in **neurocysticercosis** for the same reason.

2. Bithinol

- It inhibits the parasite respiration.
- It is an alternative to triclabendazole for **Fasciola hepatica** (sheep liver fluke infection) and as an alternative to praziquantel for **pulmonary paragonimiasis**.

3. Niclosamide

- It is a second line drug for most tape worm (cestodes) infections.
- It appears to act by inhibition of oxidative phosphorylation and ↓ energy production.
- It is given as 2g once on an empty stomach.
- Adverse effects are minimal because the drug is not absorbed.

Infecting Organism	Drug of Choice	Alternative Drugs
Roundworms (nematodes)		
Ascaris lumbricoides (roundworm)	Albendazole or pyrantel pamoate	Ivermectin, piperazine
Trichuris trichiura (whipworm)	Mebendazole or albendazole	Ivermectin
Necator americanus (hookworm); *Ancylostoma duodenale* (hookworm)	Albendazole or mebendazole or pyrantel pamoate	
Strongyloides stercoralis (threadworm)	Ivermectin	Albendazole or thiabendazole
Enterobius vermicularis (pinworm)	Mebendazole or pyrantel pamoate	Albendazole
Trichinella spiralis (trichinosis)	Mebendazole or albendazole; add corticosteroids for severe infection	
Trichostrongylus species	Pyrantel pamoate or mebendazole	Albendazole
Cutaneous larva migrans (creeping eruption)	Albendazole or ivermectin	Thiabendazole (topical)
Visceral larva migrans	Albendazole	Mebendazole
Angiostrongylus cantonensis	Albendazole or mebendazole	
Wuchereria bancrofti (filariasis); *Brugia malayi* (filariasis); tropical eosinophilia; *Loa loa* (loiasis)	Diethylcarbamazine	Ivermectin
Onchocerca volvulus (onchocerciasis)	Ivermectin	
Dracunculus medinensis (guinea worm)	Metronidazole	Thiabendazole or mebendazole
Capillaria philippinensis (intestinal capillariasis)	Albendazole	Mebendazole
Flukes (trematodes)		
Schistosoma haematobium (bilharziasis)	Praziquantel	Metrifonate
Schistosoma mansoni	Praziquantel	Oxamniquine
Paragonimus westermani (lung fluke)	Praziquantel	Bithionol
Fasciola hepatica (sheep liver fluke)	Bithionol or triclabendazole	
Fasciolopsis buski (large intestinal fluke)	Praziquantel or niclosamide	
Heterophyes heterophyes; Metagonimus yokogawai (small intestinal flukes)	Praziquantel or niclosamide	
Tapeworms (cestodes)		
Taenia saginata (beef tapeworm)	Praziquantel or niclosamide	Mebendazole
Diphyllobothrium latum (fish tapeworm)	Praziquantel or niclosamide	
Taenia solium (pork tapeworm)	Praziquantel or niclosamide	
Cysticercosis (pork tapeworm larval stage)	Albendazole	Praziquantel
Hymenolepis nana (dwarf tapeworm)	Praziquantel	Niclosamide, nitazoxanide
Echinococcus granulosus (hydatid disease); *Echinococcus multilocularis*	Albendazole	

Notes

Review Questions

1. Mention the antibacterial mechanism of action and the major adverse effects of each of the following drugs:
   - Penicillin
   - Clarithromycin
   - Aminoglycosides
   - Tetracyclines
   - Vancomycin
   - Isoniazid
   - Ethambutol

2. Mention the antiviral mechanism of action and the major adverse effects of each of the following drugs:
   - Interferon-alpha
   - Acyclovir
   - Amantadine

3. Mention the antifungal mechanism of action and the major adverse effects of each of the following drugs:
   - Itraconazole
   - Amphotricin B

4. Mention the antiprorozoal mechanism of action and the major adverse effects of each of the following drugs:
   - Metronidazole
   - Chloroquine
   - Artemisinin

5. Give a short account on the drug management and drug(s) of best choice in the following infections:
   - Bacterial meningitis
   - Community-acquired pneumonia
   - Bites (human or animal)
   - Typhoid fever
   - Pseudomembranous colitis
   - Gonorrhea

6. Discuss drug treatment of hepatitis C virus. Mention the mechanism of action and major adverse effects of interferon-alpha.
7. Discuss drug treatment of amebic liver abscess. Mention the mechanism of each drug.
8. Discuss drug treatment of chloroquine-resistant *P. falciparum* malaria. Mention the mechanism and major adverse effects of each drug.

Of each of the following questions, select ONE BEST answer:

1. The penicillin G preparation with the longest duration of action is
A. Benzathine penicillin
B. Sodium penicillin
C. Potassium penicillin
D. Procaine penicillin
E. Pipracillin

2. If a patient gives history of urticaria, itching and swelling of lips following injection of penicillin G, then
A. He will develop milder reaction whenever penicillin is injected
B. He can be given ampicillin safely
C. He can be given cephalosporins safely
D. He can be given oral phenoxymethyl penicillin safely
E. All natural and semisynthetic penicillins are contraindicated for him

3. The most important reason for highly restricted use of penicillin G injections in present day therapeutics is its
A. Narrow spectrum of activity
B. Potential to cause hypersensitivity reaction
C. Short duration of action
D. Neurotoxicity
E. Nephrotoxicity

4. Cefotaxime act by the following mechanism:
A. Inhibition of bacterial protein synthesis
B. Inhibition of bacterial cell wall synthesis
C. Inhibition of bacterial nucleic acid synthesis
D. Inhibition of bacterial folic acid synthesis
E. Inhibition of bacterial cell division

5. Benzathine penicillin injected once every 4 weeks for 8 years or more is the drug of choice for
A. Agranulocytosis patients
B. Prophylaxis of bacterial endocarditis in patients with valvular defects
C. Prophylaxis of rheumatic fever
D. Treatment of anthrax
E. Treatment of sinusitis

6. Amoxicillin is inferior to ampicillin for the treatment of the following infection
A. Typhoid
B. Tonsilitis
C. Shigella enteritis
D. Subacute bacterial endocarditis
E. Gonorrhoea

7. Which one of the following statements about ampicillin is false?
A. Its activity is enhanced by sulbactam
B. It causes maculopapular rashes
C. It is the drug of choice for Listeria monocytogenes infection
D. It eradicates most strains of MRSA
E. Pseudomembranous colitis may occur with its use

8. The mechanism of antibacterial action of azithromycin involves
A. Binding to a component of the 50S ribosomal subunit
B. Inhibition of translocase activity
C. Blockade of binding of aminoacyl – tRNA to bacterial ribosomes
D. Selective inhibition of ribosomal peptidyl transferases
E. Inhibition of DNA–dependent RNA polymerase

9. In the empiric treatment of severe bacterial infections of unidentified etiology, this drug, often used in combination with an aminoglycoside, provides coverage against many staphylococci
A. Amoxicillin
B. Clavulanic acid
C. Erythromycin
D. Nafcillin
E. Tetracycline

10. *C. difficile* colitis is more common complication with the use of:
A. Cephalosporins
B. Vancomycin
C. Co-trimoxazole
D. Meropenem
E. Flucoloxacillin

11. Beta – lactamase production by strains of Haemophilus influenzae,

Moraxella catarrhalis, and Neissera gonorrhoeae confers resistance against penicillin G. which one of the following antibiotics is most likely to be effective against all strains of each of the above organisms?
A. Ampicillin
B. Ceftriaxone
C. Clindamycin
D. Erythromycin
E. Piperacillin

12. A 19-year-old woman with recurrent sinusitis has been treated with different antibiotics on several occasions. During the course of one such treatment she developed a severe diarrhea and was hospitalized. Sigmoidoscopy revealed colitis, and pseudomembranes, were confirmed histologically. Which of the following drugs, administered orally, is most likely to be effective in the treatment of colitis due to C difficile?
A. Ampicillin
B. Azithromycin
C. Clindamycin
D. Metonidazole
E. Tetracycline

13. The drug of choice for Lyme disease is:
A. Doxycycline
B. Sulfonamides
C. Penicillin
D. Erythromycin
E. Topramycin

14. The drug of choice for anaerobic infections is:
A. Tetracycline
B. Sulfonamides
C. Penicillin
D. Erythromycin
E. Metronidazole

15. The drug of choice for typhoid fever is:
A. Tetracycline
B. Sulfonamides
C. Penicillin G
D. Ciprofloxacin
E. Metronidazole

16. Methicillin resistant staphylococci do not respond to β-lactam antibiotics because
A. They produce a β-lactamase which destroys methicillin and related drugs
B. They elaborate an amidase which destroys methicillin and related drugs
C. They have acquired a penicillin binding protein which has low affinity for β-lactam antibiotics
D. They are less permeable to β-lactam antibiotics

17. Indicate the sulfonamide whose sodium salt yields a nearly neutral solution which is suitable for topical use in the eye
A. Sulfadiazine
B. Sulfacetamide
C. Sulfamerazine
D. Sulfamethizole

18. Which of the following is not true of sulfonamides?
A. They are primarily metabolized by acetylation
B. They are more likely to produce crystalluria in alkaline urine in which they are less soluble
C. They may exert bactericidal action in the urinary tract
D. Used alone, they have become therapeutically unreliable for serious infections

19. Clavulanic acid is combined with amoxicillin because
A. It kills bacteria that are not killed by amoxicillin
B. It reduces renal clearance of amoxicillin
C. It counteracts the adverse effects of amoxicillin
D. It inhibits beta lactamases that destroy amoxicillin

20. Which toxic effect of aminoglycoside antibiotics is most irreversible in nature?
A. Optic neuropathy
B. Ototoxicity
C. Hepatotoxicity
D. Muscle weakness
E. Kidney damage

21. Highest incidence of antibiotic associated pseudo membranous enterocolitis has been noted with the use of
A. Ampicillin
B. Chloramphenicol
C. Vancomycin
D. Clindamycin
E. Gentamycin

22. Which antibiotic class can cause teeth staining and dental enamel hypoplasia if given to small children?
A. Fluoroquinolones
B. Cephalosporins
C. Tetracyclines
D. Aminoglycosides
E. Macrolides

23. Antiviral agents that are active against cytomegalovirus (CMV) include which of the following?
A. Ganciclovir
B. Acyclovir
C. Amantadine
D. Oseltamivir
E. Ribavirin

24. Which one of the following drugs is least likely to be effective in the treatment of esophageal candidiasis, it is used by the oral route?
A. Amphotericin B
B. Clotrimazole
C. Fluconazole
D. Griseofulvin
E. Ketoconazole

25. Which one of the following drugs is most appropriate for oral use in vaginal candidiasis?
A. Clotrimazole
B. Griseofluvin
C. Fluconazole
D. Flucytosine
E. Nystatin

26. The antiviral actions of this drug include inhibition of both RNA and DNA synthesis. The drug is used for the treatment of severe respiratory syncytial virus infections in neonates.
A. Amantadine
B. Amprenavir
C. Oseltamivir
D. Ribavirin
E. Ritonavir

27. The primary mechanism of antibacterial action of penicillin involves inhibition of:
A. Beta-lactamases
B. Cell membrane synthesis
C. N-acetylmuramic acid synthesis
D. Peptidoglycan cross-linking
E. Transglycosylation

28. Fluid expressed from the penile chancre of a patient revealed to be infected with *Treponema pallidum*, the best course of action would be to:
A. Administer a single oral dose of fosfomycin
B. Administer a single oral dose of gentamycin
C. Inject intramuscular benzathine penicillin G
D. Treat with oral tetracycline for 7 d
E. Treat with vancomycin

29. Which of the following statements about beta-lactam antibiotics is false?
A. Cephalexin and other first-generation cephalosporins do not cross the blood-brain barrier
B. Ceftriaxone and nafcillin are both eliminated mainly via biliary secretion
C. Instability of penicillins in gastric acid can limit their oral absorption
D. Renal tubular reabsorption of amoxicillin is inhibited by probenecid
E. Ticarcillin has activity against several gram negative rods

30. A patient needs antibiotic treatment for native valve, culture positive infective enterococcal endocarditis. His medical history includes a severe anaphylactic reaction to penicillin G during the last year. The best approach would be treatment with
A. Amoxicillin-clavulanate
B. Aztreonam
C. Ceftriaxone
D. Ticarcillin
E. Vancomycin

31. If ampicillin and piperacillin are used in combination in the treatment of infections resulting from Pseudomonas aeruginosa, antagonism may occur. The most likely explanation is that

A. Ampicillin is bacteriostatic
B. Ampicillin induces beta-lactamase production
C. Autolytic enzymes are inhibited by piperacillin
D. Piperacillin blocks the attachment of ampicillin to penicillin-binding proteins
E. The 2 drugs form an insoluble complex

32. Which statement about vancomycin is accurate?

A. Active against methicillin-resistant staphylococci
B. Bacteriostatic
C. Binds to PBPs
D. Hepatic metabolism
E. Oral bioavailability

33. A 52 years old patient with signs and symptoms suggestive of typical bacterial meningitis. Treatment of this patient should be initiated immediately with intravenous administration of

A. Amoxicillin
B. Cephalexin
C. Benzylpenicillin G
D. Nafcillin
E. Piperacillin

34. The mechanism of antibacterial action of azithromycin involves:

A. Antagonism of bacterial translocase activity
B. Binding to a component of the 50S ribosomal subunit
C. Inhibition of DNA-dependent RNA polymerase
D. Interference with binding of aminoacyl-tRNA to bacterial ribosomes
E. Selective inhibition of ribosomal peptidyl transferases

35. If a patient had been scheduled for elective colonic surgery, optimal prophylaxis against infection would be achieved by the use of

A. Intravenous cefoxitin
B. Intravenous third-generation cephalosporin
C. Oral amoxicillin
D. Oral ciprofloxacin
E. Oral neomycin

36. Clarithromycin and erythromycin have very similar spectra of antimicrobial activity. The major advantage of clarithromycin is that it

A. Does not inhibit hepatic drug-metabolizing enzymes
B. Eradicates mycoplasmal infections in a single dose
C. Has greater activity against *H pylori*
D. Is active against methicillin-resistant strains of staphylococci
E. Is active against strains of streptococci that are resistant to erythromycin

37. The primary mechanism of resistance of gram-positive organisms to macrolide antibiotics including erythromycin is

A. Changes in the 30S ribosomal subunit
B. Decreased drug permeability of the cytoplasmic membrane
C. Formation of drug-inactivating acetyltransferases
D. Formation of esterases that hydrolyze the lactone ring
E. Methylation of binding sites on the 50S ribosomal subunit

38. A suitable treatment for community-acquired pneumonia with little risk of drug interactions can be achieved with

A. Azithromycin
B. Clindamycin
C. Doxycycline
D. Erythromycin
E. Vancomycin

39. Regarding the toxicity of aminoglycosides which statement is accurate?

A. Gentamicin and tobramycin rarely cause renal damage
B. Ototoxicity includes vestibular dysfunction, which may be irreversible
C. Ototoxicity is reduced if loop diuretics are used to facilitate the renal

excretion of aminoglycoside antibiotics
D. Reduced blood creatinine is an early sign of aminoglycoside nephrotoxicity
E. Skin reactions are very rare following topical use of neomycin

40. Your 23-year-old female patient is pregnant and has gonorrhea. The medical history includes anaphylaxis following exposure to amoxicillin. The most appropriate drug to use is
A. Azithromycin
B. Cefixime
C. Ceftriaxone
D. Ciprofloxacin
E. Doxycycline

41. In a patient suffering from pseudomembranous colitis due to C difficile with established hypersensitivity to metronidazole the most likely drug to be of clinical value is
A. Amoxicillin
B. Chloramphenicol
C. Doxycycline
D. Levofloxacin
E. Vancomycin

42. Trimethoprim-sulfamethoxazole is established to be effective against which of the following opportunistic infections in the AIDS patient?
A. Cryptococcal meningitis
B. Herpes simplex
C. Oral candidiasis
D. Toxoplasmosis
E. Tuberculosis

43. A 65-year-old woman has returned from a vacation abroad suffering from traveler's diarrhea, and her problem has not responded to antidiarrheal drugs. A pathogenic gram-negative bacillus is suspected. Which drug is most likely to be effective in the treatment of this patient?
A. Ampicillin
B. Ciprofloxacin
C. Sulfadiazine
D. Trimethoprim
E. Vancomycin

44. Silver sulfadiazine is clinically used for:
A. Treatment of Rocky Mountain spotted fever
B. To prevent infections of skin burns
C. Treatment of typhoid fever
D. Treatment of Legionella pneumonia
E. Treatment of lead toxicity

45. Which statement about the fluoroquinolones is accurate?
A. Antacids increase their oral bioavailability
B. Contraindicated in patients with hepatic dysfunction
C. Fluoroquinolones are drugs of choice in a 6-year-old child with a urinary tract
D. Gonococcal resistance to fluoroquinolones may involve changes in DNA gyrase
E. Modification of dosage is required in patients renal impairment.

46. Which adverse effect is most common with sulfonamides?
A. Stevens Johnson syndrome
B. Hematuria
C. Kernicterus in the newborn
D. Neurologic dysfunction
E. Skin rash

47. Which statement about ciprofloxacin is accurate?
A. Antagonism occurs if used with dihydrofolate reductase inhibitors
B. Ciprofloxacin is active against MRSA strains of staphylococci
C. Most "first-time" urinary tract infections are resistant to ciprofloxacin
D. Organisms that commonly cause ear infections are highly resistant
E. Tendinitis may occur during treatment

48. Supplementary folinic acid may prevent anemia in folate-deficient persons who use this drug
A. Ciprofloxacin
B. Levofloxacin
C. Linezolid
D. Clarithromycin
E. Trimethoprim

49. Supplementary pyridoxin may prevent neurotoxicity in persons who use this drug
A. Ciprofloxacin
B. Isoniazid
C. Linezolid
D. Clarithromycin
E. Trimethoprim

50. Which statement regarding ethambutol is correct?
A. It is contraindicated in pregnancy
B. Visual adverse effects are very rare
C. It inhibits arabinosyl transferase involved in cell wall biosynthesis
D. Ocular toxicity of ethambutol is prevented by thiamine
E. Resistance is common and rapid.

51. Interactions between this drug and cell membrane components can result in the formation of pores lined by hydrophilic groups present in the drug molecule.
A. Caspofungin
B. Flucytosine
C. Griseofulvin
D. Nystatin
E. Terbinafine

52. Which statement about fluconazole is accurate?
A. Does not penetrate the blood-brain barrier
B. Drug of choice in treatment of aspergillosis
C. Induces hepatic drug-metabolizing enzymes
D. Has the least effect of all azoles on drug metabolism
E. Oral bioavailability is less than that of ketoconazole

53. The following is the drug of choice for invasive aspergillosis
A. Voriconazole
B. Ketoconazole
C. Miconazole
D. Fluconazole
E. Itraconazole

54. The drug most likely to suppress herpetic infections and provide prophylaxis against CMV retinitis in AIDS patient is
A. Fluconazole
B. Gancyclovir
C. Indinavir
D. Rifabutin
E. Trimethoprim-sulfamethoxazole

55. Which of the following statements about interferon-alpha is false?
A. At the start of treatment, most patients experience flu-like symptoms
B. Therapeutic outcome is low when used alone for HCV
C. It is used in the management of hepatitis B and C
D. Lamivudine interferes with its activity against hepatitis B
E. Toxicity includes bone marrow suppression

56. A 22-year-old man with gonorrhea is to be treated with cefixime and will need another drug to provide coverage for possible urethritis caused by *Clmydia trachomatis.* Which of the following drugs is least likely to be effective in non-gonococcal urethritis?
A. Azithromycin
B. Ciprofloxacin
C. Co-trimoxazole
D. Nitrofurantoin
E. Tetracycline

57. The drug regimen most likely to be effective in treating severe extraintestinal amebiasis is
A. Chloroquine
B. Diloxanide furoate plus iodoquinol
C. Emetine plus diloxanide furoate plus chloroquine
D. Chloroquine followed by primaquine
E. Tinidazole plus diloxanide furoate

58. Metronidazole is not effective in the treatment of
A. Amebiasis
B. Infections due to *Bacteroides fragilis*
C. Infections due to *Pneumocystis carinii*
D. Pseudomembranous colitis
E. Trichomoniasis

59. Which statement about antiprotozoal drugs is accurate?

A. Chloroquine is an inhibitor of plasmodial dihydrofolate reductase
B. Mefloquine destroys secondary exoerythrocytic schizonts
C. Primaquine is a blood schizonticide and does not affect secondary tissue schizonts
D. Artemisinin is not useful for *P. falciparum* malaria
E. Intravenous quinine can cause serious arrhythmia

60. Plasmodial resistance to chloroquine is due to:
A. Change in receptor structure
B. Decreased accumulation of the drug in the food vacuole
C. Increased activity of DNA repair mechanisms
D. Increased synthesis of dihydrofolate reductase
E. Induction of drug-inactivating enzymes

61. Which drug should be used for treatment of the acute attack of *P vivax* malaria but does not eradicate exoerythrocytic forms of the parasite?
A. Chloroquine
B. Mefloquine
C. Primaquine
D. Pyrimethamine-sulfadoxine
E. Quinidine

62. After successful treatment of malaria, which drug should be given later to eradicate schizonts and latent hypnozoites in the patient's liver?
A. Artesunate
B. Fansidar (Pyrimethamine-sulfadoxine)
C. Chloroquine
D. Primaquine
E. Quinine

Answers

1 A	14 E	27 D	40 A	53 A
2 E	15 D	28 C	41 E	54 B
3 A	16 A	29 D	42 D	55 D
4 B	17 B	30 E	43 B	56 D
5 C	18 B	31 E	44 B	57 E
6 C	19 D	32 A	45 D	58 C
7 D	20 B	33 C	46 E	59 E
8 A	21 D	34 B	47 E	60 B
9 D	22 C	35 E	48 E	61 A
10 A	23 A	36 C	49 B	62 D
11 B	24 D	37 E	50 C	
12 D	25 C	38 A	51 D	
13 A	26 D	39 B	52 D	