Chapter 1

General Principles

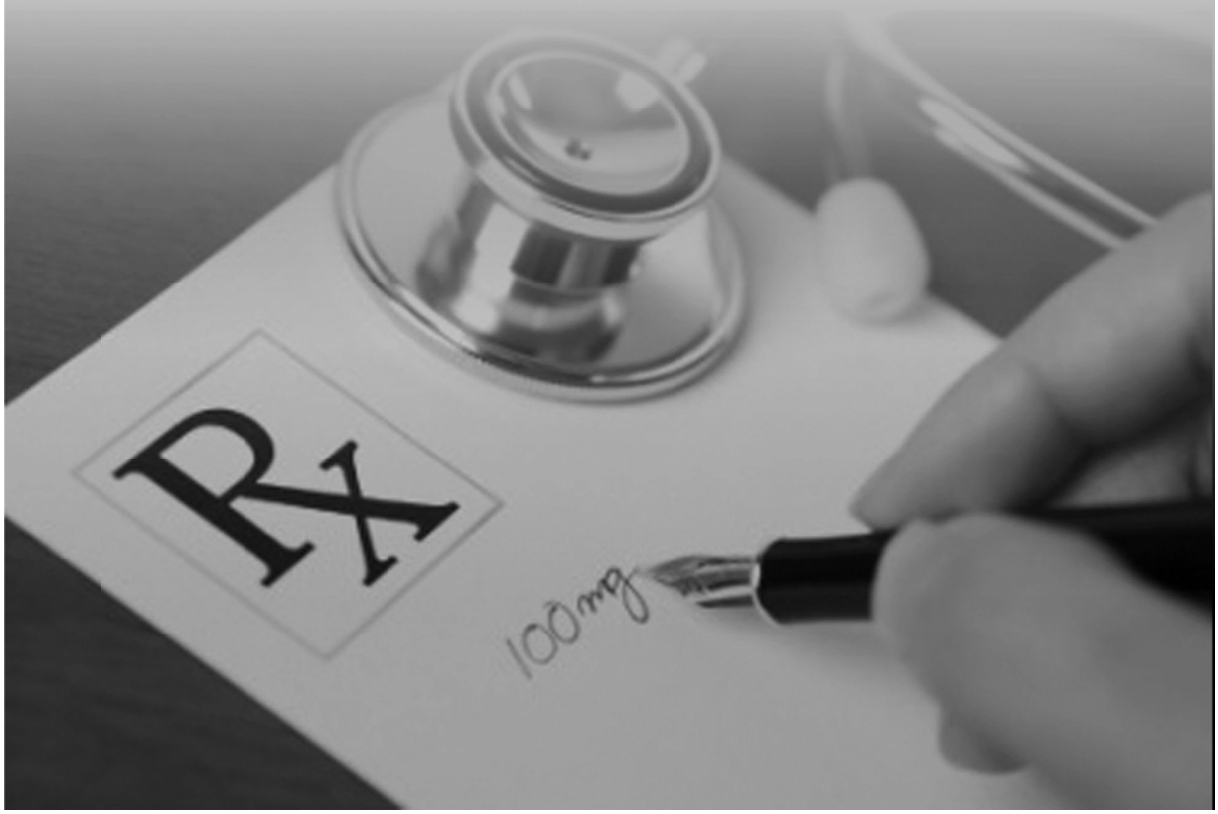


Table of Contents

CHAPTER 1: GENERAL PRINCIPLES

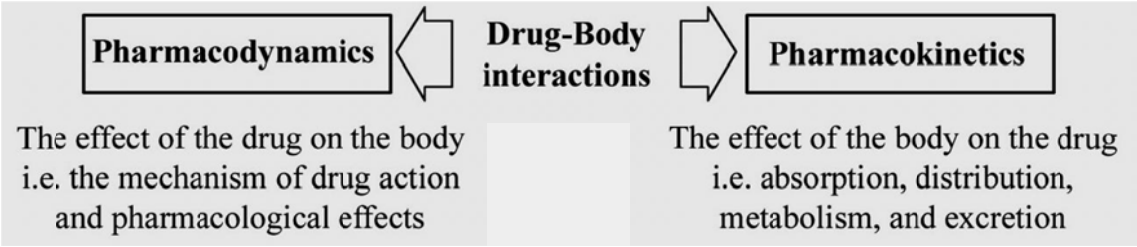
Chapter 1

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

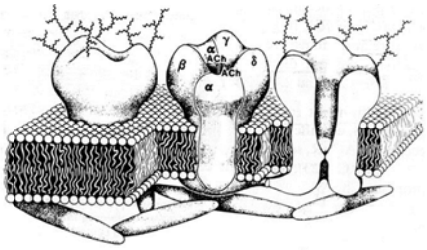
Receptors: they are protein macromolecules. When they combine with a drug, they may be activated or blocked.

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.

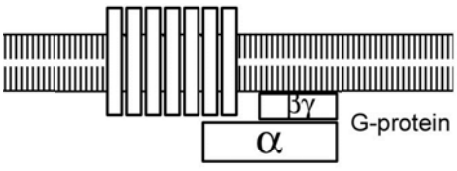
Types of receptors

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

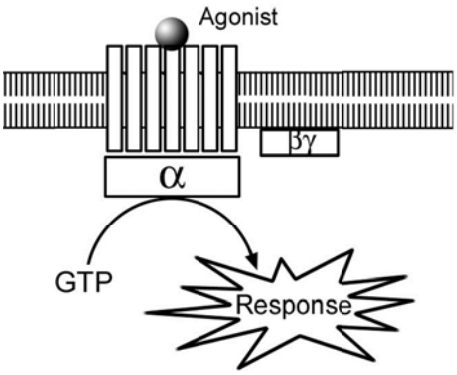


- The receptor is an ion channel consists of **5** transmembrane subunits (α_1, α_2, β, γ, δ).
- Binding of the agonist to the extracellular part of the receptor causes opening of the channel for a specific ion.
- The response of these receptors is very fast and their duration is very short.
- Examples:
  - *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.

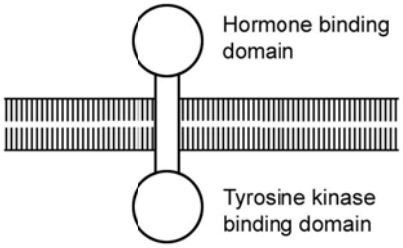


- **Stimulatory G-protein (Gs)** leads to increase *adenyl cyclase enzyme* → ↑ cAMP → activation of specific proteins (protein kinases). Examples of Gs-coupled receptors are the β1 and β2-adrenergic receptors.

- **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:

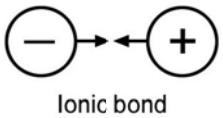


- The receptor consists of 2 large domains: an extracellular hormone-binding domain and an intracellular TK-binding domain connected by a transmembrane segment.
- Binding of the agonist to the hormone-binding domain causes activation of the intracellular domain to activate TK enzyme → activation of several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

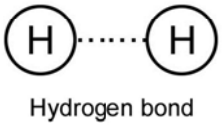
■ Intracellular receptors:

- 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.*

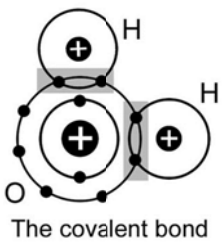
Types of drug-receptor bonds



■ **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.

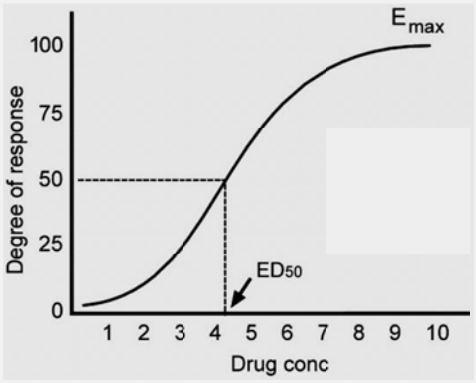
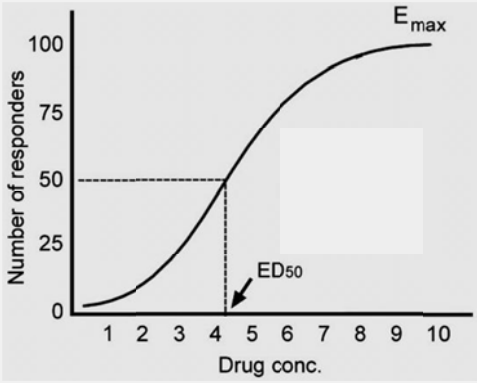
BIOLOGICAL RESPONSE TO DRUG-RECEPTOR BINDING (Dose-response relationship studies)

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:

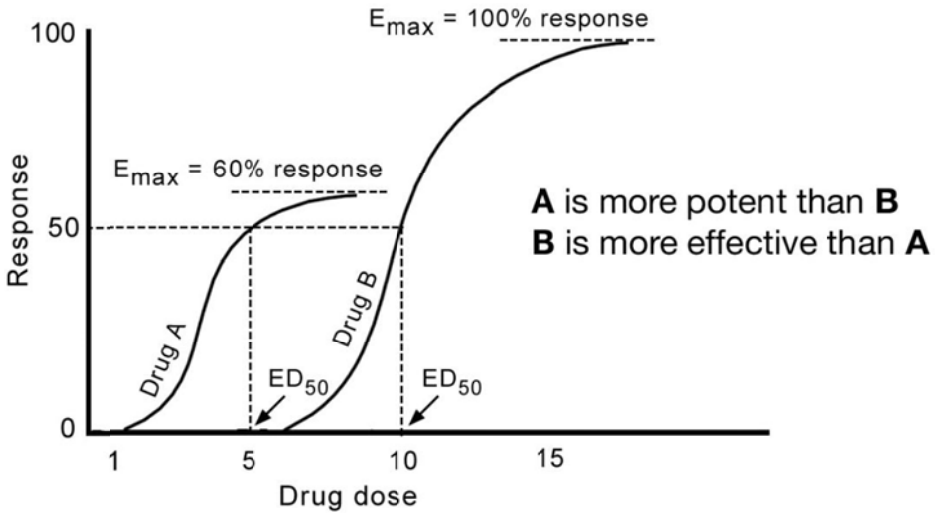
Graded response	Quantal response
– The response is increased **proportionally** to the dose of the agonist e.g. the response of the heart to adrenaline. – It is the response to **most** drugs. – The response could be tested in **one or more** animals.	– The response does not increase proportionally to 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

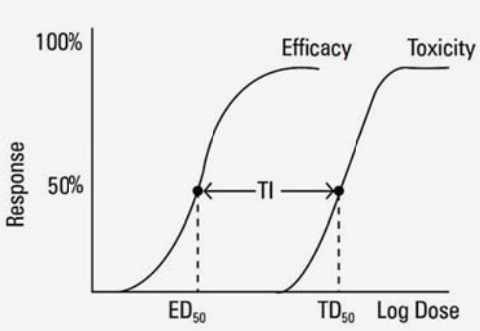


■ Potency

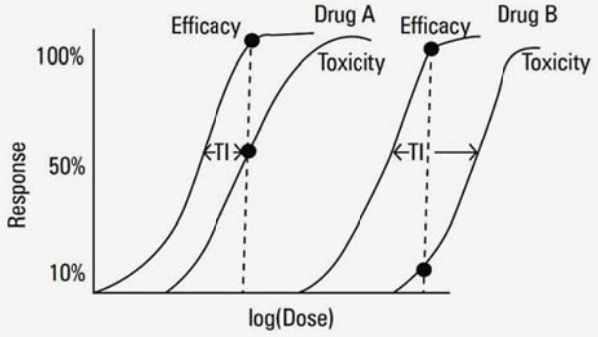
- **ED50 (Effective Dose)** is the dose of the drug that gives 50% of the Emax, or it is the dose that gives the desired effect in 50% of a test population of subjects.
- A drug that gives ED50 by smaller doses is described as **"potent"** drug.
- Potency of drugs is generally **less clinically important** 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

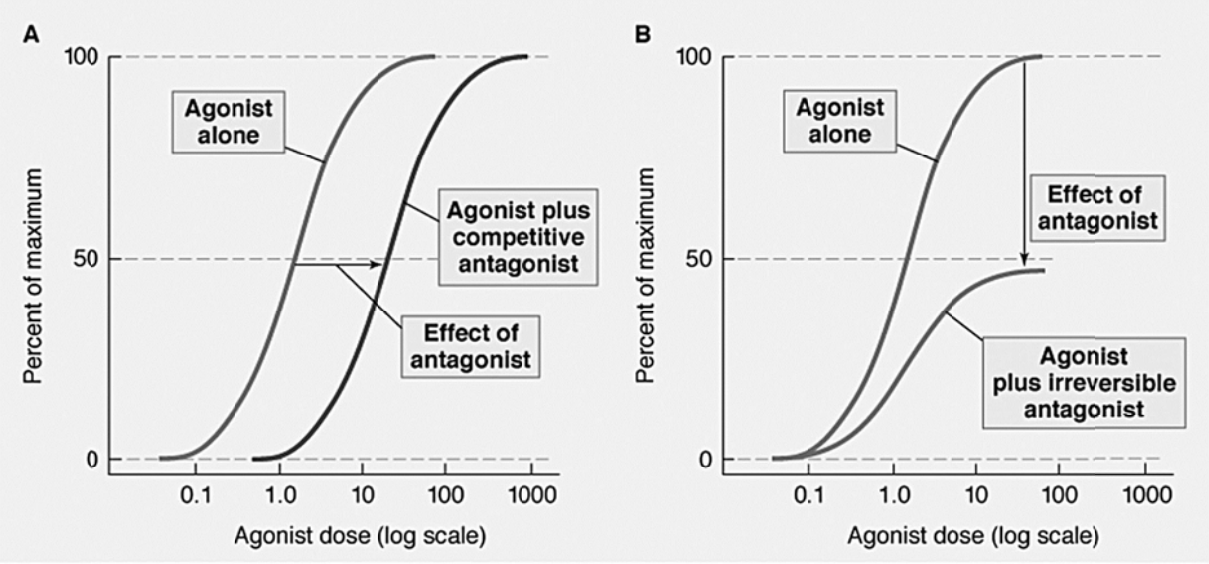


Drug A has a much narrower therapeutic index than Drug B. The dose of Drug A required to achieve a 100% therapeutic response will be toxic in 50% of patients. For Drug B, this is only 10%

- **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.

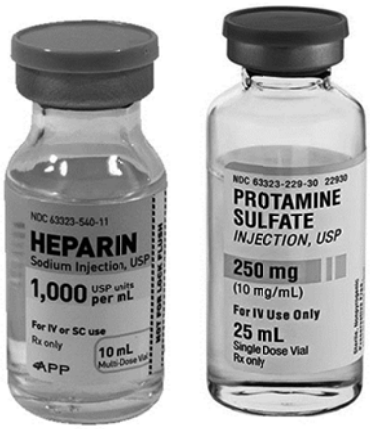


Reversible antagonism | Irreversible antagonism

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.

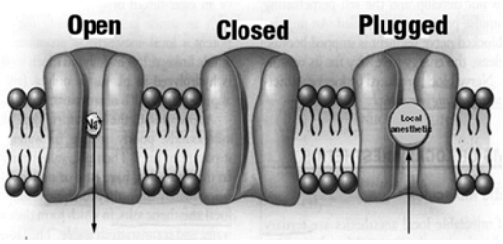
  Example: **adrenaline** is the physiological antagonist of **histamine** because while histamine causes hypotension and bronchoconstriction through activation of histamine H_1 receptors, adrenaline causes hypertension and bronchodilatation through activation of adrenergic α & β receptors respectively.

- **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

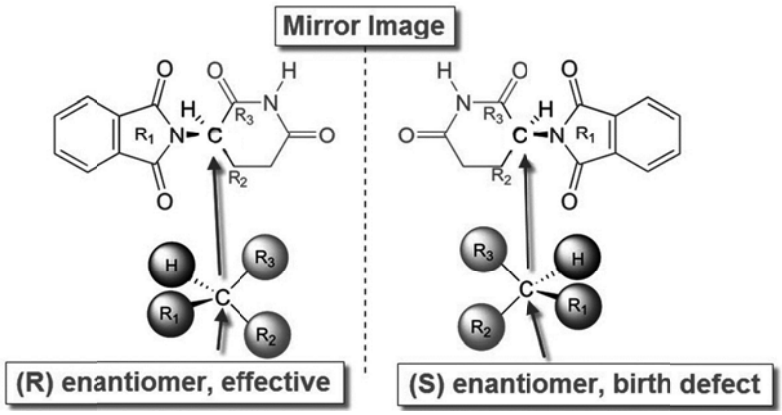
- These are small protein molecules that carry organic molecules across the cell membrane when they are too large or too polar.
- Drugs could affect carrier molecules by blocking their recognition site.

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:

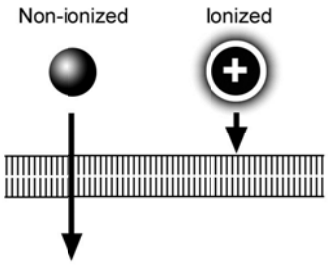
A. Factors related to the drug

- 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 bases. 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).

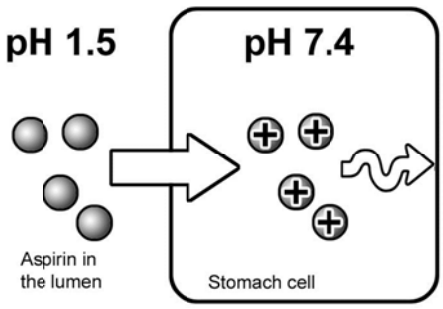
►When aspirin is put in the intestine:

- 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:

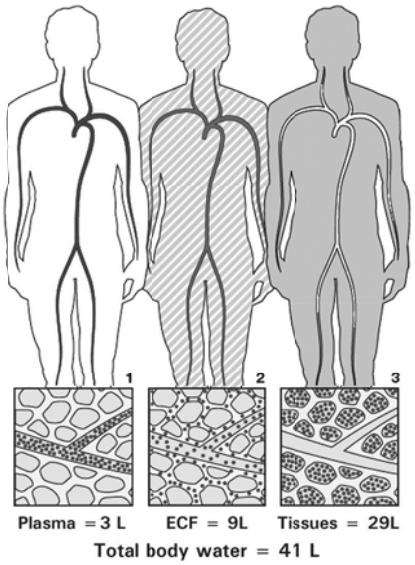
In the stomach, aspirin is more absorbable into stomach cells but once entered the cells, the pH changes from 1.5 outside to 7.4 inside the cell. So aspirin becomes ionized inside the cells and can't diffuse outside them again → gastric ulcer.



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.

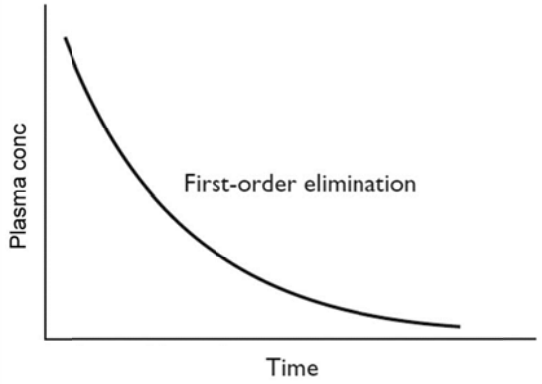
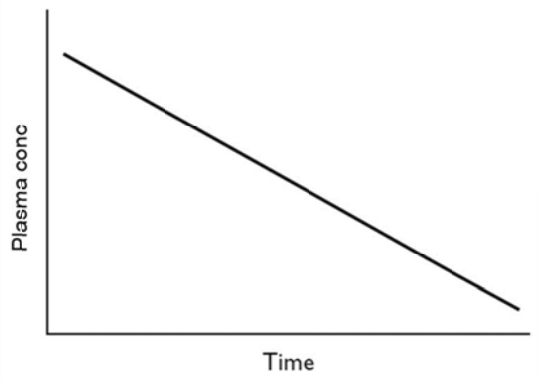
Clinical significance:

- 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):

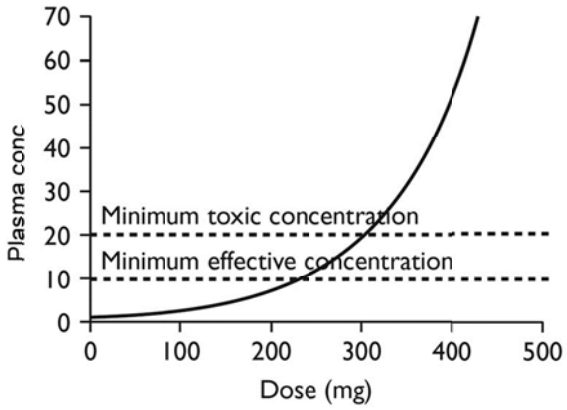
First-order elimination	Zero-order elimination
	
- Occurs to **most** drugs. - Constant **ratio (%)** of the drug is eliminated per unit time i.e. the rate of elimination is **proportional** to plasma concentration. The higher the concentration, the greater the rate of elimination. - Elimination **does 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.



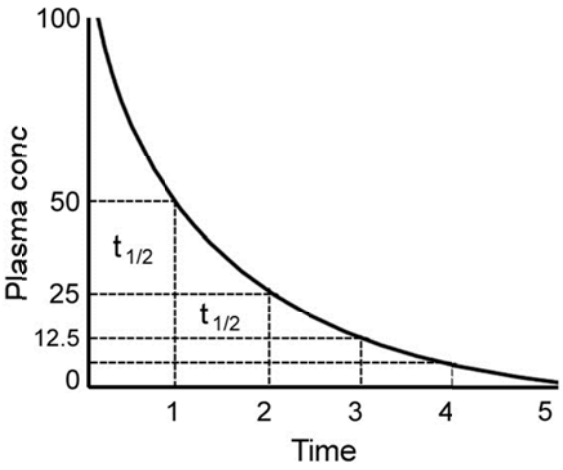
Elimination half-life ($t_{1/2}$)

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.**

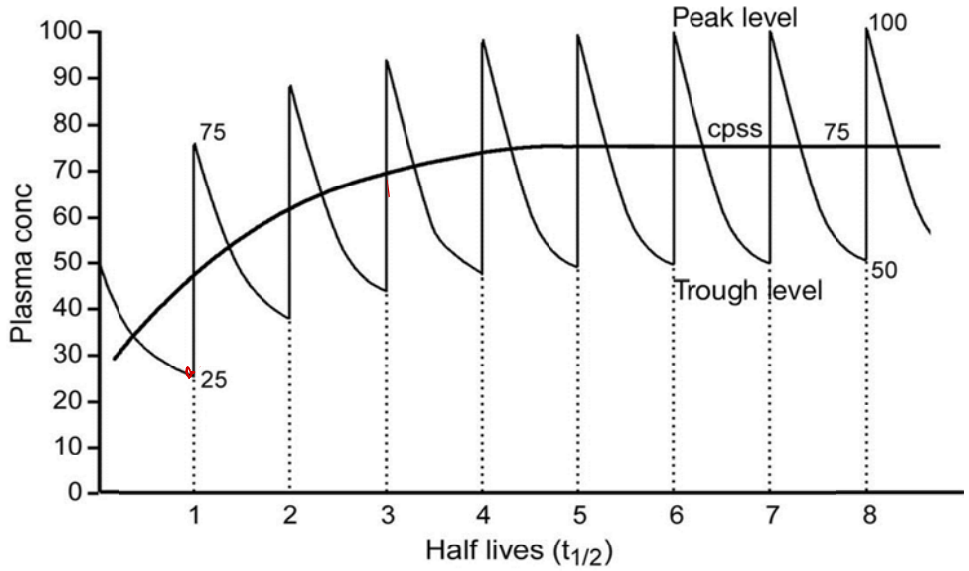
Steady-state plasma concentration (Cpss)

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

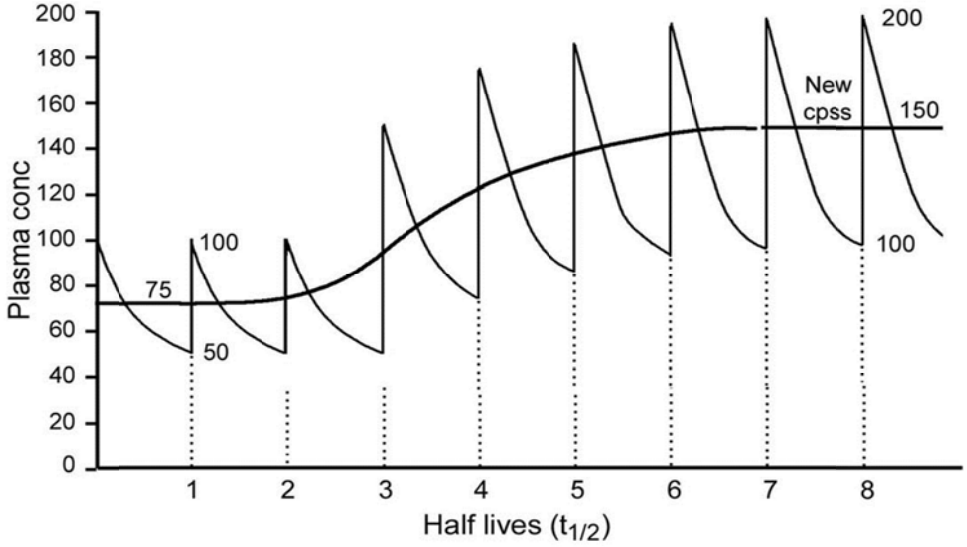
The rule of 5:

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

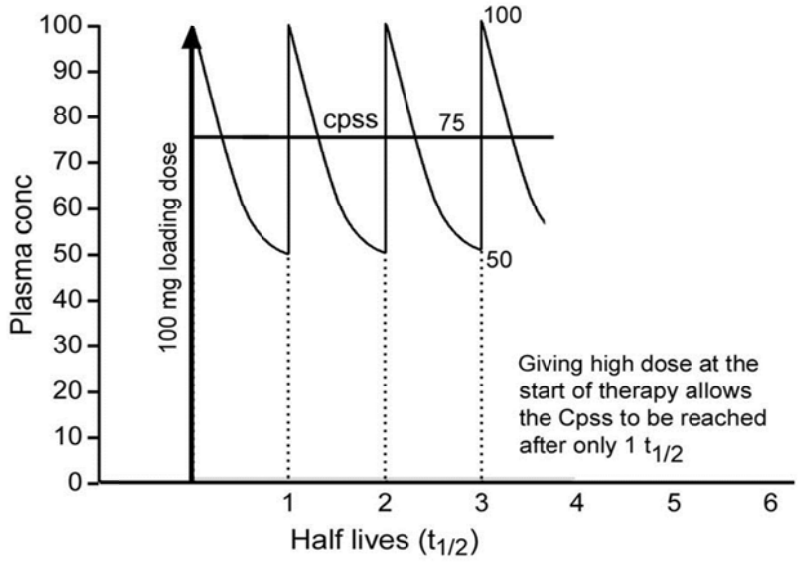
- If we changed the dose, the new Cpss is reached after 4-**5** $t_{1/2.}$
- If dosing stops, complete elimination of drug from plasma occurs after 4-**5** $t_{1/2.}$



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

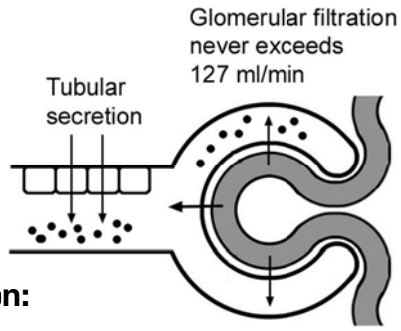
Definition: plasma clearance of a substance means the volume of plasma cleared from this substance per minute.

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)

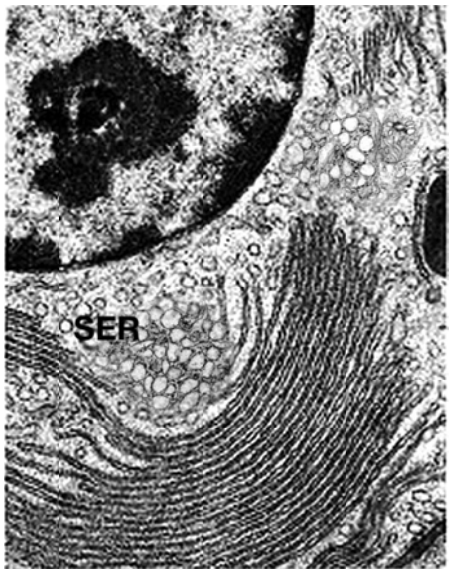
- The **liver** is the major site of drug metabolism but other organs can also metabolize drugs e.g. kidney, lungs, and adrenal glands.
- Many lipid soluble drugs must be converted into a **water-soluble form** (polar) to be excreted.
- Some drugs are not metabolized at all and excreted unchanged (**hard 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)

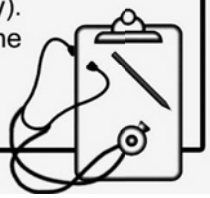
- It involve coupling of a drug or its metabolite to water-soluble substrate (usually glucuronic acid) to form water-soluble conjugate.
- **Glucuronyl transferase** is a set of enzymes that is responsible for the majority of phase II reactions. This set of enzymes is also located **inside liver**

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.

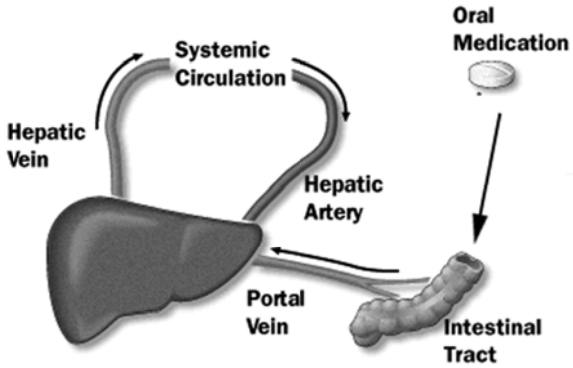


First-pass metabolism (pre-systemic elimination)

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.

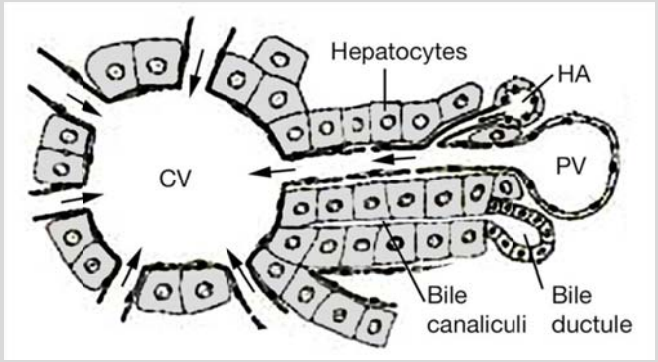
Type A (Augmented)	Type B (Bizarre)
– Predictable	– Unpredictable
– Dose-dependent	– Dose-independent
– High incidence	– Low incidence
– May respond to dose adjustment	– Generally need to stop the drug

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.

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