PREMIUM EDITION FOR NURSING STUDENTS

PHARMACOKINETICS

NOTES READY TO STUDY

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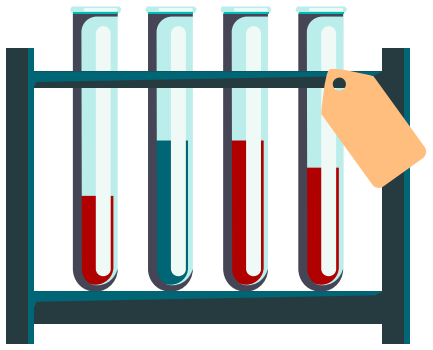
PHARMACOKINETICS

Pharmacokinetics is the examination of how drugs move within the human body.



Pharmacokinetic Processes

1. *Absorption*
2. *Distribution*
3. *Metabolism (Bio-transformation)*
4. *Elimination*

Frequently Utilized Pharmacokinetic Parameters

1. *Bio-availability*
2. *Volume of distribution*
3. *Half-Life*
4. *Clearance*

Every pharmacokinetic process necessitates the drug's passage through the cellular membrane. This cellular membrane comprises a bilayer of amphipathic lipids, with the hydrocarbon chains facing inward, creating a continuous hydrophobic phase, while their hydrophilic heads point outward. Drugs traverse this membrane using either passive mechanisms or mechanisms that entail the active involvement of membrane components

A. Passive Transport

1. *Simple Diffusion: This is the most common form of passive transport, often observed with lipid-soluble drugs. For instance, drugs like Propranolol, Diazepam, and Thiopentone Na demonstrate this mode of movement across cell membranes.*
2. *Paracellular Transport: In addition to simple diffusion, drugs may also utilize paracellular transport to pass through the intercellular space between adjacent cells in a tissue*

B. Active Transport

1. *Facilitated diffusion, as exemplified by substances like vitamin B12 (B12) and folic acid, involves the assisted movement of these compounds across cell membranes with the aid of carrier proteins, all without requiring an input of external energy.*
2. *Drug transporters are involved in facilitated transport, a mechanism where carrier proteins assist in the movement of substances across cell membranes without requiring an external input of energy. This process helps substances like drugs to traverse cell membranes efficiently and is a fundamental aspect of drug absorption, distribution, and elimination within the body.*

Absorption It is the movement of a drug from its site of administration into the central compartment and the extent to which this occurs.

Variables influencing Absorption

Pharmaceutical factors (extrinsic factors) pertain to aspects related to the drug itself

Physical state of the drug: Drugs administered in aqueous or liquid forms are absorbed more quickly. For instance, colloids like dextran and albumin are absorbed more slowly compared to crystalloids such as saline and glucose Water/Lipid solubility: Drugs administered in aqueous or liquid forms are absorbed more quickly. For instance, colloids like dextran and albumin are absorbed more slowly compared to crystalloids such as saline and glucose Particle size: Drugs administered in aqueous or liquid forms are absorbed more quickly. For instance, colloids like dextran and albumin are absorbed more slowly compared to crystalloids such as saline and glucose Ionisation of the drug: Drugs administered in aqueous or liquid forms are absorbed more quickly. For instance, colloids like dextran and albumin are absorbed more slowly compared to crystalloids such as saline and glucose Disintegration-time of the drug: This refers to the time it takes for a solid drug dosage form (e.g., a tablet) to completely break down into finer particles in the gut. Longer disintegration times result in slower absorption rates Dissolution-Time of a drug: It represents the time it takes for a solid dosage form, such as a tablet, to dissolve in the gut after disintegration. Shorter dissolution times lead to faster absorption rates Enteric-coated tablet: These tablets are coated with materials like cellulose or phthalate. They resist disintegration and dissolution in gastric juice but allow for breakdown and dissolution in the alkaline environment of the gut. Enteric-coated tablets are designed for prolonged action, such as sustained-release (S.R.) tablets

Human factors/other factor

Concentration of the drug: Passive diffusion relies on the concentration gradient. A higher concentration of the drug leads to a faster rate of absorption Area of the absorbing surface: A larger surface area results in increased absorption Vascularity of the absorbing surface: Greater blood flow to the absorbing surface enhances both the amount and speed of absorption Route of absorption

Factors Influencing Oral Absorption

The epithelial lining of the gastrointestinal tract (GIT) is lipoidal, making lipid-soluble drugs better absorbed Some drugs are susceptible to degradation in the acidic environment of the stomach; for example, insulin Ionized drugs, such as basic drugs like morphine, are better absorbed in the duodenum The presence of food in the stomach can affect the absorption of other drugs.

As a general rule, the presence of food in the stomach slows down the absorption of certain drugs, including Rifampicin, Ampicillin, Iron, and Isoniazid (Isonicinil). For Rifampicin, it is most effective when taken on an empty stomach. The presence of fatty food enhances the absorption of certain drugs

Ribaviri Albendazole
/Mebendazol Effaviren
Atovaquon

Vitamin C increases absorption of Iron Phytates and oxalates can decrease the absorption of iron There is an interaction between iron and tetracycline, as tetracycline chelates iron Phenytoin and sucralfate, with sucralfate decreasing the absorption of phenytoin, exhibit an interaction.

The rate at which a drug is absorbed increases as the rate of gastric emptying becomes faster. However, during pregnancy, gastric emptying is delayed, which can result in decreased drug absorption when administered orally.

Migraines can also lead to a condition called gastroparesis, which is the delayed emptying of the stomach. In the management of gastroparesis, combinations of medications are sometimes used: PCM + Metoclopramide
Rabeprazole + Domperidone in Gastroparesi

In pathological conditions
CCF→Mucosal oedema delays absorption
GIT→Malabsorption B. Parenteral: Intramuscular /
Subcutaneous Rout

Factors such as heat, muscular exercise, or massage can cause vasodilation, thereby increasing the absorption of drugs administered through intramuscular or subcutaneous routes Vasoconstrictors like Epinephrine can decrease drug absorption and extend the duration of action, especially when combined with a drug like Lignocaine (Lidocaine).

C. Topica

Inflammation or denuded areas of the skin exhibit increased vascularity, significantly enhancing the absorption of applied drugs to the extent that toxicity can occur The contact time of a drug with the site of absorption is critical. If a drug moves quickly through the gastrointestinal tract, as in cases of severe diarrhea, it may not be effectively absorbed. Note that anything delaying the transport of a drug from the stomach to the intestine also slows down the rate of absorption, as exemplified by Dicyclomine.

Bio-Availability

Bioavailability is defined as the proportion of the administered drug dose that reaches the systemic circulation without alteration after pre-systemic elimination, making it available for its intended action. It is often expressed as a percentage.

The relative bioavailability of a drug is determined by comparing the amount of the drug absorbed via a specific route of administration to the amount of the drug administered by any route. This comparison helps assess the efficiency of drug absorption and its effectiveness in producing the desired therapeutic effect.

Bio-availability
IV route : 100%
Oral: 0- 100%

Incomplete Bio-availability may be due t
Incomplete absorptio
First-pass metabolism

Absolute Bio-availability is calculated by
AUC after oral dose x 100 AUC after IV
dose

Various factors can affect drug bioavailability:

Route of administration Presence of food or other drugs in the gastrointestinal tract Pre-systemic elimination Entero-hepatic recycling Drug distribution and plasma protein binding Pharmaceutical factors, including drug properties, dosage form, particle size, and dissolution rate.

Entero-hepaticRecycling

Entero-hepatic recycling is a drug re-circulation process. In this process, the drug travels from the intestine to the liver through the portal vein and then returns to the intestine via the bile duct. β-Glucuronidase plays a crucial role in entero-hepatic recycling by facilitating hydrolysis, which is necessary for drug reabsorption to occur.

Example of Drugs undergoing EHR

Several drugs and endogenous substances undergo entero-hepatic recycling

NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) - Most NSAIDs except for Nabumetone. Examples: Paracetamol (PCM), Indomethacin, Diclofenac Opioids: Drugs in this category include Morphine, Buprenorphine, and Methadone Other Medications: Diazepam, Oral Contraceptive Pills (OCP), Amoxicillin, Ampicillin, Sulfonamides, Tamoxifen, Digoxi Endogenous Substances: Vitamin D3, Estrogen, Progesterone, Vitamin B12, Thyroxine

These substances undergo entero-hepatic recycling, which contributes to their pharmacokinetics and overall effectiveness in the body.

The significance of entero-hepatic recycling (EHC) includes

Prolongation of Drug Action: EHC can extend the duration of a drug's action within the body. However, it often reduces the drug's potency, meaning that more of the drug may be required to achieve the desired therapeutic effect.

2. Treatment of Drug Toxicities: Some drugs can inhibit EHC, and these inhibitors can be useful in treating toxicities caused by drugs capable of undergoing entero-hepatic recycling. For example:e.g Activated charcoal Anion exchange resin for Digoxin

Drug Distribution

Drug distribution is the dynamic process involving the reversible movement of a drug between the bloodstream and the various extravascular fluids and tissues in the body. These tissues can include fat, muscle, and brain tissue, among others. This process is critical as it affects how the drug is distributed throughout the body, impacting its concentration at different sites and ultimately influencing its pharmacological effects.

Distribution is a passive process

Distribution is indeed a passive process in pharmacokinetics. The primary driving force behind this process is the concentration gradient between the drug in the bloodstream and the drug in the various tissues and organs of the body. The drug moves through the tissues by diffusing from areas of higher concentration to areas of lower concentration until equilibrium is reached. This equilibrium establishes a balance in drug distribution throughout the body, influencing its therapeutic effects and duration of action.

Drug distribution in the body is uneven because different tissues receive drugs at varying rates and to varying degrees. After absorption or systemic administration, drugs disperse into interstitial and intracellular fluids within the body's diverse tissues and organs. This non-uniform distribution is a fundamental aspect of drug action and impact.

First Distribution Phase

Initially, well-perfused organs like the liver, heart, kidneys, and brain receive the drug through the bloodstream.

Second Distribution Phase

This phase may take minutes to several hours for the drug's concentration in tissues to reach equilibrium with that of the blood. It involves a larger fraction of the body and includes less well-perfused organs such as adipose tissue, muscles, and the skin.

Apparent volume of Distribution,Vd

The "Apparent Volume of Distribution" (Vd) is a concept that represents the hypothetical volume needed to accommodate all the drug in the body if the drug's concentration were the same throughout the body, effectively assuming the body behaves as a single, homogeneous compartment.

Vd =Amount of drug in body

Conc of drug in blood/ plasma

Redistribution

Redistribution of highly lipid-soluble drugs, whether administered intravenously or by inhalation, initially directs them toward organs with robust blood flow, such as the brain, heart, and kidneys. If the drug's intended action occurs in one of these highly perfused organs, its onset of action is rapid. For instance, intravenous administration of thiopental in general anesthesia (IV GA) illustrates this phenomenon.

Subsequently, less vascular but larger tissues, including muscles and fat, begin to accumulate the drug. As a result, the drug's concentration in the bloodstream decreases, leading to its withdrawal from these tissues. In such cases, redistribution contributes to the termination of the drug's action.

It's worth noting that the drug's rate of redistribution is influenced by its lipid solubility. When a drug is administered repeatedly or continuously over extended periods, the less perfused but high-capacity sites gradually fill up, leading to prolonged drug activity. For example, Nitrazepam initially has a sedative effect lasting 6-8 hours, but with prolonged use, its half-life (t1/2) increases to 30 hours.

The actual volume of distribution has physiological relevance and is related to the body's total water content, which is approximately 42 liters.

Several factors can impact drug distribution in the body

The drug's ability to permeate various tissues affects its distribution

Lipid solubility and the influence of pH gradients across cell membranes can alter how drugs distribute The pKa of a drug, especially for weak acids or bases, plays a role in distribution The size of the drug molecule can affect how it distributes in different tissues The partition coefficient, representing the drug's concentration in lipids versus water, affects distribution Anatomical and physiological barriers in the body can either hinder or facilitate drug diffusion

Proportionate attachment to plasma protein

Threshold for the concentration of the unbound drug.

Note: Drugs with significant binding to plasma protein are mostly confined within the vascular compartment, resulting in a low distribution volume. e.g Warfarin 99% PPB

Vd: 9.8 L/70kg

Variables influencing the distribution of a drug

Accumulation within tissues

The volume of distribution (Vd) for these drugs greatly exceeds both the total body water and body mass. Morphine: 230L/70kg Digoxin: 500L/70kg Chloroquine: 13000L/70k

The existence of particular tissue transporters

e.g P-gP Organ / Tissue size and perfusion rat

Abnormal medical conditions

CCF / Cirrhosis /anaemia / Obesity Alternate of distribution of water Permeability of Mb altere

Drug interaction during pregnancy.

Medical importance.

For drugs with an exceptionally large volume of distribution, their concentration in extravascular tissue significantly surpasses that in the vascular compartment, resulting in heterogeneous distribution. Conversely, drugs with a small volume of distribution exhibit homogeneous distribution In instances of drug poisoning involving drugs with a low volume of distribution, hemodialysis is typically beneficial, as these drugs are confined mainly to the vascular compartment.

N.B: Drugs that are primarily restricted t

Blood /Plasma : small Vd 5-10

Drugs going beyond vasc comp (e.g tissue) Vd =10-20

Drugs sequestered in tissues, Vd 500-50,000L

When Vd exceeds total body water (<42L), it means that there is sequestration of the drug in tissues.

Plasma Protein Binding

Numerous drugs travel within the bloodstream while attached to plasma proteins. Typically, this binding is reversible. However, occasional covalent binding may occur with reactive drugs like alkylating agents.

Albumin-major carrier for acidic drugs.
Examples of drugs that bind to albumin:
NSAIDs
Warfarin
Barbiturates
Benzodiazepines
Sulfonamides

Albumin-major carrier for acidic drugs.
Examples of drugs that bind to albumin:
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Kinetics of Drug-Protein Binding

The dynamics of reversible drug-protein binding in a protein with a single binding site can be explained by the law of mass action, which involves the formation of a drug-protein complex: Protein + Drug Drug-Protein Complex.
⇌Factors Determining the Function of Bound Drugs in Plasma

Drug concentratio Affinity
for the binding site Number
of binding sites

Therefore Plasma Protein binding is non-linear & saturable process

Disease related factors:

e.g Hypoalbuminaemia secondary to liver disease / Nephrolic syndrome decrease PPB and increases the unbound fraction. Condition leading to ↑ Acute Phase response: Cancer /Crohn's Disease /MI leads to an increase in α1 –Acid glycoprotein and enhanced binding of basic drugs

Drug-Drug interaction.

Implications of Plasma Protein Binding (PPB)

Highly plasma protein-bound drugs are primarily confined to the vascular compartment, resulting in a low volume of distribution (Vd) The bound fraction of the drug is not available for immediate action; it acts as a drug reservoir Extends the drug's duration of action. Only subject to metabolism or excretion if actively extracted by liver or kidney tubules. Restricts drug filtration in the glomerulus.

N.B: In general, plasma protein binding (PPB) does not impede renal tubular secretion or biotransformation because as the concentration of free drug decreases, dissociation from plasma proteins will take place

A single drug can attach to multiple sites on the albumin molecule, and multiple drugs can also bind to the same albumin molecule simultaneously Interaction between drugs

Drugs with higher affinity displace those with lower affinity. If a drug has high affinity for various sites, no interaction occurs. Acidic drugs do not displace basic drugs Significant displacement interactions includ

Salicylates with Sulfonylureas, Phenytoin with Warfarin, Aspirin & Warfarin

Binding within tissues.

Numerous drugs tend to accumulate in tissues at significant concentrations rather than in the extracellular fluid (ECF). For example: Quinacrine-Liver, Chloroquine-Relina, Iodine-thyroid, Thiopentone-Adipose tissue, Tetracycline –Bone / teeth Tissue binding involves cellular components like proteins, phospholipids, and, in some cases, nuclear proteins. This binding is typically reversible. Tissue binding acts as a reservoir, extending the drug's duration of action. Consequences include drug accumulation and tissue binding, leading to local toxicity. For example: e.g Chloroquine –retinopathy, Gentamicin—ototoxicity /nephrotoxicity.

The Central Nervous System (CNS) and Cerebrospinal Fluid (CSF).

The distribution of drugs from the blood into the Central Nervous System (CNS) is distinct. The endothelial cells of brain capillaries are tightly connected, forming continuous tight junctions. As a result, drug penetration into the brain relies more on transcellular transport rather than paracellular transport.

This distinct feature of tight junctions in brain capillary endothelial cells and capillary cells comprises the Blood-Brain Barrier (BBB).
At choroid Plexus →Blood-CSF barrier (epithelial cells joined by height junctions rather than endothelial cells)

N.B: Only lipid-soluble drugs can enter and affect the CNS, with additional mechanisms to prevent drug entry into the brain

Efflux transporters P-gP, organic anion transporter Polypeptide (OATP) control the drug
Enzymatic BBB

Enzymes like MAO and cholinesterase hinder the passage of catecholamines, 5HT, and ACH into the brain in their active state.

The Blood-Brain Barrier is compromised at the CTZ (located at the floor of the 4th ventricle), making even lipid-insoluble drugs induce vomiting.

Inflammation of the meninges or brain can increase the permeability of these barriers

Significance

Crucial for drug design, such as second-generation anti-histamines
Results in lower sedation due to reduced lipid solubility.

Drug Transfer Across the Placenta

Key Factors in Placental Drug Transfe

Lipid Solubilit
Plasma Protein Bindin
Ionization of Weak Acids/Bases

Fetal Plasma Slightly More Acidic (pH 7.0-7.2 vs. 7.4) Leading to Basic Drug Trapping Presence of

P-Gp and Other Transporters Limits Fetal Exposure to Harmful Substances Note: The Placental

Barrier Isn't Absolute; Fetus Exposed to Maternal Drugs to Some Extent.

Drug Metabolism

Drug Elimination primarily occurs through bio-transformation and excretion via urine or bile. The liver is the primary site of drug metabolism, with other tissues, including the kidney, intestine, and lung, also playing a role.

Half-life
Plasma half-life

Half-life (T1/2) represents the duration for a drug's plasma concentration to decrease by half during elimination, especially noticeable during a constant infusion.

$$T1/2=\frac{\ln 2 \times Vd}{CL}$$

Note

Many drugs exhibit an alpha T1/2 and remain in the plasma due to distribution. Certain drugs have a beta T1/2, meaning they possess two half-lives: one in plasma related to distribution and another in tissues associated with elimination.

Examples of half-life of some drugs
Adenosine: 10 second
Esmolol: 10 minute
Aspirin: 15 minute
Digoxin: 4 hour
Digitoxin: 40 hour
Amiodarone: 100 days

In first T1/2: 50% of drug is eliminate
In second T1/2: 75% of drug is eliminate
In third T1/2: 87.5% of drug is eliminate
In fourth T1/2: 93.75% of drug is eliminate
In fifth T1/2: 97% of drug is eliminated
hus almost complete elimination occurs in about 4-5 T1/2

Factors affecting T1/

Clearanc
Volume of distributio
Plasma-protein bindin
Types of elimination kinetics (zero/first order
Pathological state
Active metabolite
Entero-hepatic recycling.

Significance of Knowing Plasma T1/2

Helps Determine Drug's Duration of Actio Facilitates Planning Effective Dosage and Schedul Enables Calculation of Time to Steady-State and Complete Drug Elimination

Clinical Scenarios Elevating Plasma T1/2

Reduced Renal Plasma Flow (e.g., CCF, Cardiogenic Shock, Hemorrhage Increased Volume of Drug Distributio Impaired Drug Excretion (e.g., Renal Disease Decreased Drug Metabolism (e.g., Cirrhosis).

Biological T1/2

The time it takes for a drug or its active metabolite's pharmacological effect to decrease by half.
Applicable to drugs with prolonged effects, such as anti-cancer medications.

Accumulation Factor

With repeated drug doses, accumulation occurs until dosing stops because it theoretically takes an infinite time to eliminate all of the drug from the body.

In practice, if dosing intervals are shorter than 4 times the T1/2, accumulation becomes noticeable.

$$\text{Accumulation factor} = \frac{1}{\text{Fraction lost in one dosing interval}}$$

Example

For a drug given once every T1/2,

Accumulation factor = 1/0.5=2.

Plateau Principle and Steady-State Plasma Concentration (Cpss)

Cpss is achieved when a drug's absorption rate equals its elimination rate, so subsequent doses have no effect on plasma concentration.

Cpss is reached after 5 times the T1/2.

$$\text{Cpss} = \frac{\text{dose rate}}{\text{Clearance}}$$

Note: Drugs with shorter T1/2 reach Cpss more quickly.

Target Level Strategy

Employed for drugs with a narrow safety margin and unquantifiable effects, like anti-arrhythmics and anti-epileptics. In such cases, the goal is to attain a specific plasma concentration within the therapeutic range.

Loading Dose

A single or rapidly repeated initial dose to achieve the target concentration quickly, influenced by bioavailability and volume of distribution.

Loading dose = $\frac{\text{target Cpss x Vd}}{\text{F}}$

Examples: Insulin in diabetic ketoacidosis, Digitalis in rapid digitalization.

Maintenance Dose

Regularly administered doses at intervals to maintain steady-state plasma concentration, balancing elimination.

MD =CL x target plasma conc

Clearance

Fraction of the theoretical volume of fluid (plasma) completely cleared of the drug per unit of time. CL = $\frac{\text{rate of elimination}}{\text{Plasma conc of the drug}}$

Significant for establishing proper dosing regimens and maintaining steady-state concentration.

Dosing rate = CL x Cpss

Kinetics of Elimination

First-Order Kinetics (Linear Kinetics) Rate of drug elimination directly proportional to drug concentration, with constant clearance.

Approximately 95% of drugs at therapeutic levels follow first-order kinetics. Examples: Paracetamol, Diclofenac, Amoxicillin, Dexamethasone, Diazepam.

Zero-Order Kinetics (Non-linear)

Rate of drug elimination remains constant, regardless of drug concentration, leading to decreasing clearance with higher concentrations.

Only a few drugs exhibit zero-order kinetics. Examples: Alcohol, Paclitaxel, Azlocillin.

First-Order Kinetics

Consistent fraction of drug is eliminated. Rate of elimination directly correlates with the drug's plasma concentration.

Clearance remains constant.

Half-life (T1/2) remains constant.

Zero-Order Kinetics

Consistent amount of drug is eliminated. Rate of elimination is unaffected by the drug's plasma concentration.

Clearance is higher at low concentrations and lower at high concentrations.

Half-life (T1/2) is shorter at low concentrations and increases with higher plasma drug concentrations.

Michaelis-Menten Kinetics (Mixed-Order Kinetics/Dose-Dependent Kinetics)

Examples include Aspirin, Phenytoin, Digoxin, Warfarin, Tolbutamide, Theophylline. At low doses, drugs follow first-order kinetics, but as plasma drug concentration rises, elimination kinetics shift from first order to zero order.

This shift may occur due to

Saturation of the metabolizing enzyme
Saturation of the elimination process.

Significance: Clinical use of these drugs requires careful monitoring and maintenance of their plasma concentration, as even small increases can lead to drug toxicity.

Elimination of Drugs

Drugs exit the body either unchanged through excretion or after conversion via metabolism. Note: Lipid-soluble drugs are not easily eliminated; they need to be metabolized into more polar forms. The kidney plays a crucial role in drug excretion.

- Renal excretion
- Glomerular filtration
- Active tubular secretion
- Passive tubular reabsorption

Glomerular filtration depends on

1. GFR (N 110-130 ml/min
2. Extent of Plasma binding.

Only unbound drug is filtered.
Tubular secretion
Active Process
The process requires a carrier and supply of energy
They are also subjected to competitive inhibition e.g(Penicillin + Probenecid)
e.g substance secreted para-amino hippuric acid.
The Process is saturable.

Tubular Reabsorption Passive reabsorption of lipid-soluble drugs occurs in the distal tubule. Only a few drugs, like electrolytes, glucose, and vitamins, undergo active reabsorption. Note: Drugs present in the glomerular filtrate can be reabsorbed in the tubules. In the proximal and distal tubules, weak acids and bases in their non-ionized forms undergo net passive reabsorption.

When tubular urine is made more alkaline, weak acids become largely ionized, resulting in their more rapid and extensive excretion.
Example: The combination of aspirin and $NaHCO_3$ illustrates this effect.

Biliary & Fecal Excretion

Applicable to substances primarily unabsorbed after oral ingestion, including drugs or their metabolites, which are excreted via bile or secreted into the intestinal tract and not reabsorbed.

Examples include Cromoglygate, Morphine glucuronide, Chloramphenicol, Erythromycin, and moxifloxacin.

Zero-Order Kinetics (Non-linear)

Exhaled Air
The lung serves as the major organ of excretion for gaseous and volatile substances, such as anesthetic gases
.

Other Routes
Sweat, tears, hair, and skin can serve as sensitive detection methods for drugs, holding forensic significance. Examples include lithium, KI, Clofazimine, and Rifampicin.

Salivary Excretion
While not a true method of drug excretion (since the drug is swallowed and reabsorbed), some drugs' concentrations in saliva parallel those in plasma. Saliva can be useful in determining drug concentration when obtaining blood samples is inconvenient. Examples include Lithium and
Rifampicin
.

Breast Milk
Milk is more acidic than plasma, and certain basic lipids may be slightly more concentrated in milk. For instance, β-Blockers can be excreted in breast milk
.

1. Methods of Prolonging Drug Action

Advantages of Prolonging Drug Action Reduced frequency of administratio
Improved patient compliance (less disruption, fewer chances of forgetting
Minimization of large plasma fluctuations (reducing side effects related to peak plasma levels shortly after dosing)

Eliminates the need to convert short-acting drugs (e.g., hypnotics or headache remedies) into long-acting forms.

Methods of Prolonging Drug Action:

Retarding Drug Absorptio
Slowing Drug Metabolism (typically in the liver
Delaying Renal Excretion of the Dru
Utilizing Compounds with High Plasma Protein Bindin
Modifying the Molecular Structure of the Drug

Retarding Drug Absorption:

Oral absorption can be retarded by
Giving the drug on full stomach
Giving the drug in form of SR-tablet, Spansules , Capsules.

Drug with t1/2 ≤ 4hr are suitable for SR formulation. If t1/2 ≥ 12hr, there is no need for such formulation.

Controlled release tablet (semi-permeable Mb to control release of drug from the dosage form); Prolong the action by (4-8hrs)

Parenteral absorption is retarded by
Decrease vascularity of the absorption surface

e.g Epinephrine with lignocaine (LA), (1:50,000-1:`00,000) Epinephrine decreases the rate of entry of LA from Local site to systemic circulation and prolongs duration of action and decrease systemic toxicity of bloodless field.

b. Reduction in solubility of the drug.

Achieved by combining the drug with a compound having poor liquid lipid solubility or by giving the drug in suspension form

e.g Insulin + Zinc suspension (20-24hr)

Penicillin + Procaine 12-24 hrly

Benzathine penicillin 2-4 weekly.

c. Administration of the drug in oily solution or along with water-repellent substance.

e.g Aluminium monosterate delays absorption of water repellent.

d. Combination of the drug with protein from which it is slowly released

e.g Protamine-zinc-insulin (really used now)-24-36 hrs.

e. Depot preparation

e.g DMPA (Depo-Medroxyprogestone Acetate) → 1-3 mth

Give drugs in form of pellet implantation / sialistic & Bio-degradable implants.

2. Modification of Chemical Structure

Esterificatio
Steroidal sex hormone: testosterone / oestrogen ↓ When esterified with carboxylic acids ↓ Give like propiorate /Benzoate ↓

Slowly absorbed.

Pegylation (combination with polyethylene glycol)
Interferon→usually administered thrice weekly
Interferon + Polyethylene
↓
Absorb more slowly -permitting weekly dosing.

Transdermal Delivery system
e.g Fentanyl patch, Nitroglycerine patch

3. Retarding Drug Metabolism

Hepatic Microsomal Enzymes Required for Biotransformation: ↓

Inhibited by certain enzyme e.g MAO inhibitors

Levodopa's duration of action is increased by combining it with the peripheral dopa-decarboxylase inhibitor, carbidopa.

Allopurinol enhances the duration of action of Mercaptopurine, as Mercaptopurine is degraded by xanthine oxidase, and allopurinol inhibits xanthine oxidase.

Note: Depression of biotransformation can alter the body's internal environment by delaying the inactivation of endogenous products, such as steroid hormones.

4. Retarding Renal Excretion of Drugs:

Renal Excretion Involves: Glomerular Filtration Tubular

Reabsorption Tubular Secretion (Active Process) Excretion by

glomerular filtration cannot be blocked / slowed ↓

Harmful effect on kidney But tubular secretion of certain lipid can be blocked by employing agents that shares the same tubular secretory pathway.

e.g: Probenecid is used to decrease penicillin excretion /Ampicillin

↓

Prolongation of duration of action

5. Increased Protein binding of the drug in Plasma

Long-acting sulfonamides, such as Sulfadoxine binds to plasma protein more strongly than shorter acting sulfonamides such as sulfadiazine (50%).

Suramin- drug used in trypanosomiasis; Extensive PPB →long duration of action.

6. Drug sequesterd in Adipose tissue

e.gQuinesterol (cyclopentylester of estradiol) ↓

Prolonged duration of action.