Lecture 41

Pharmacology

Definitions

1) Pharmacokinetics

The process by which a drug is absorbed, distributed, metabolized and eliminated by the body.
Pharmacokinetic properties of drugs may be affected by elements such as the site of administration and the dose of administered drug. These may affect the absorption rate.

2) Pharmacodynamics

The interactions of a drug and the receptors responsible for its action in the body. Pharmacodynamics places particular emphasis on dose-response relationships i.e. the relationship between drug concentration and effect. These effects can include those manifested within mammals (including humans), microorganisms, or combinations of organisms (e.g. malaria infection).

The Life Cycle of a Drug

1. Absorption

The process of a substance entering the blood circulation.

2. Distribution

The dispersion or dissemination of substances throughout the fluids of the body.

3. Degradation

The change of a chemical compound into a less complex compound.

4. Excretion

The removal of the substances from the body. In rare cases, some drugs irreversibly accumulate in body tissue.

Absorption

Absorption involves several phases. First, the drug needs to be introduced via some route of administration (oral, topical-dermal, *etc*.) and in a specific dosage form such as a tablet, capsule, solution and so on.
In other situations, such as intravenous therapy, intramuscular injection, enteral nutrition and others, absorption is even more straightforward and there is less variability in absorption and bioavailability is often near 100%. It is considered that intravascular administration (e.g. IV) does not involve absorption, and there is no loss of drug. The fastest route of absorption is inhalation, and not as mistakenly considered the intravenous administration

Faster Absorption

Parenterally (injection)

1. Intravenous (IV)

The infusion of liquid substances directly into a vein.

2. Intramuscular (IM)

The injection of a substance directly into a muscle.

3. Subcutaneous (SC)

A subcutaneous injection is administered as a bolus into the subcutis.

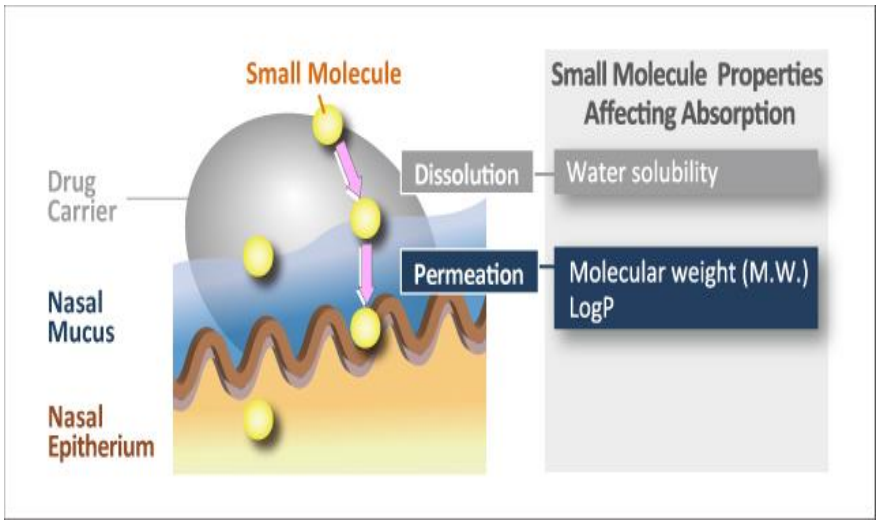
4. Intraperitoneal (IP)

The injection of a substance into the peritoneum (body cavity).eg Inhaled (through lungs).

Absorption and Solubility

The gastrointestinal tract is lined with epithelial cells. Drugs must pass or permeate through these cells in order to be absorbed into the circulatory system. One particular cellular barrier that may prevent absorption of a given drug is the cell membrane. Cell membranes are essentially lipid bilayers which form a semipermeable membrane. Pure lipid bilayers are generally permeable only to small, uncharged solutes. Hence, whether or not a molecule is ionized will affect its absorption, since ionic molecules are charged. Solubility favors charged species, and permeability favors neutral species. Some molecules have special exchange proteins and channels to facilitate movement from the lumen into the circulation.

The Henderson-Hasselbalch equation offers a way to determine the proportion of a substance that is ionized at a given pH. In the stomach, drugs that are weak acids (such as aspirin) will be present mainly in their non-ionic form, and weak bases will be in their ionic form. Since non-ionic species diffuse more readily through cell membranes, weak acids will have a higher absorption in the highly acidic stomach.

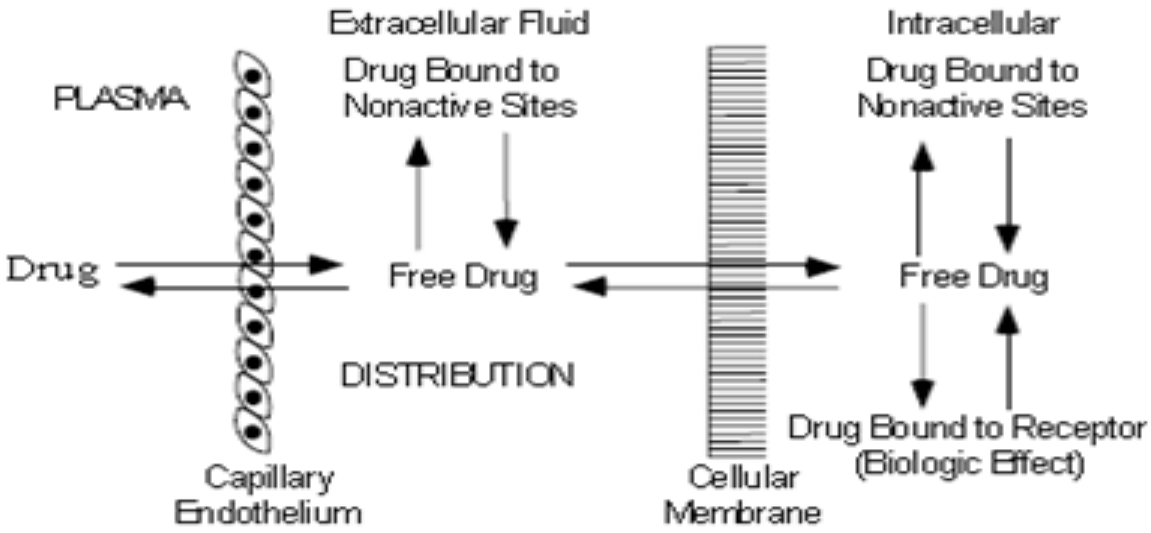


Distribution

1. Distribution in pharmacology is a branch of pharmacokinetics which describes the reversible transfer of drug from one location to another within the body.

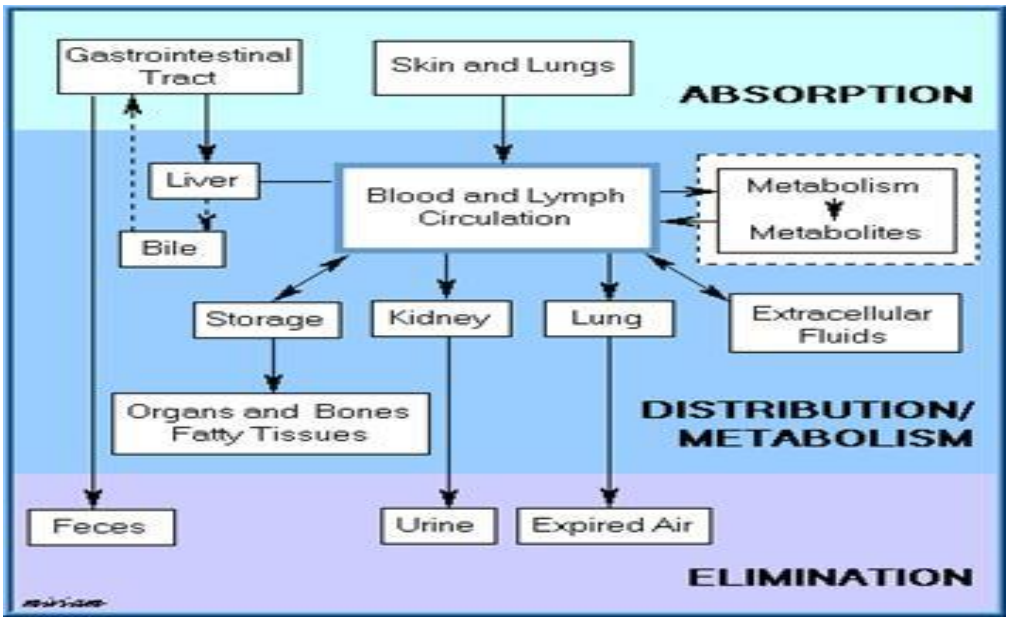
2. Once a drug enters into systemic circulation by absorption or direct administration, it must be distributed into interstitial and intracellular fluids. Each organ or tissue can receive different

doses of the drug and the drug can remain in the different organs or tissues for a varying amount of time. The distribution of a drug between tissues is dependent on vascular permeability, regional blood flow, cardiac output and perfusion rate of the tissue and the ability of the drug to bind tissue and plasma proteins and its lipid solubility. PH partition plays a major role as well. The drug is easily distributed in highly perfused organs such as the liver, heart and kidney. It is distributed in small quantities through less perfused tissues like muscle, fat and peripheral organs. The drug can be moved from the plasma to the tissue until the equilibrium is established (for unbound drug present in plasma).



Excretion

In pharmacology the elimination or excretion of a drug is understood to be any one of a number of processes by which a drug is eliminated from an organism either in an unaltered form (unbound molecules) or modified as a metabolite. The kidney is the main excretory organ although others exist such as the liver, the skin, the lungs or glandular structures, such as the salivary glands and the lacrimal glands. These organs or structures use specific routes to expel a drug from the body, these are termed elimination pathways:



Bioavailability

The fraction of an administered dose of drug that reaches the blood stream.

When the drug is administered orally the bioavailability depends on several factors:

1. Physicochemical properties of the drug and its excipients that determine its dissolution in the intestinal lumen and its absorption across the intestinal wall.
2. Decomposition of the drug in the lumen.
3. PH and perfusion of the small intestine.
4. Surface and time available for absorption.
5. Competing reactions in the lumen (for example of the drug with food).
6. Hepatic first pass effect

Depot Binding

Binding of a drug with various tissues of the body or with proteins in the blood; causes drugs to not reach their site of action.
E.g. Albumin a protein found in the blood that transports free fatty acids and can bind with some lipid-soluble drugs.
1. Can delay or prolong the effects of a drug.
2. Depot binding reduces bioavailability, slows elimination, can increase drug detection window.
3. Depot-bound drugs can be released during sudden weight loss.

Excretory Organs

The main organs responsible for drug excretion are the kidneys (renal excretion) and the liver (biliary excretion). Other organs can be involved in excretion, such as the lungs for volatile or gaseous agents. Drugs can also partially be excreted into sweat, saliva and tears. Breast milk is another pathway for drug excretion. Milk is more acidic than plasma; therefore, basic compounds can slightly concentrate in milk. This is an important factor for the estimation of the amount of drug administered to the breastfed baby.

Half Life

The plasma concentration of a drug is halved after one elimination half-life. Therefore, in each succeeding half-life, fewer drugs are eliminated. After one half-life the amount of drug remaining in the body is 50% after two half-lives 25%, etc. After 4 half-lives the amount of drug (6.25%) is considered to be negligible regarding its therapeutic effects.

The half-life of a drug depends on its clearance and volume of distribution. The elimination half-life is considered to be independent of the amount of drug in the body.

Factors affecting half-life
1. Age
2. Renal excretion
3. Liver metabolism
4.Protein binding

Drug Effectiveness

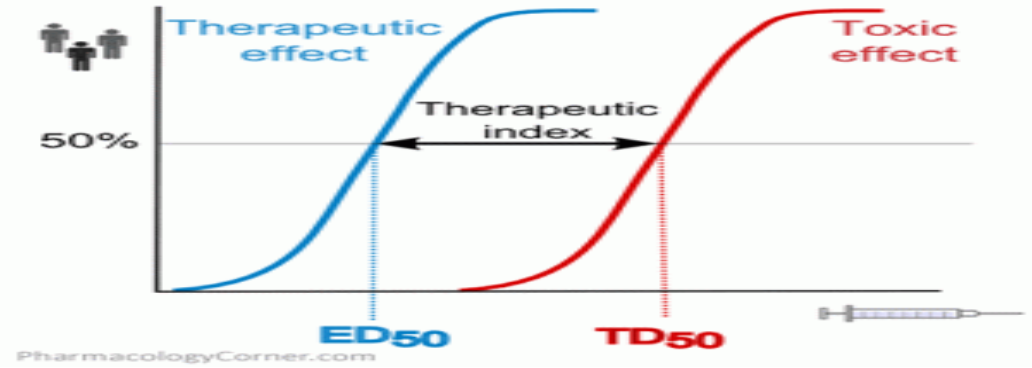
1. Drugs affect only the rate at which existing biologic functions proceed. Drugs do not change the basic nature of these functions or create new functions. For example, drugs can speed up or slow down the biochemical reactions that cause muscles to contract, kidney cells to regulate the volume of water and salts retained or eliminated by the body, glands to secrete substances (such as mucus, stomach acid, or insulin), and nerves to transmit messages.

2. Drugs cannot restore structures or functions already damaged beyond repair by the body. This fundamental limitation of drug action underlies much of the current frustration in trying to treat tissue-destroying or degenerative diseases such as heart failure, arthritis, muscular dystrophy, multiple sclerosis, Parkinson disease, and Alzheimer disease. Nonetheless, some drugs can help the body repair itself. For example, by stopping an infection, antibiotics can allow the body to repair damage caused by the infection.

Therapeutic Index

The therapeutic index (TI) is a comparison of the amount of a therapeutic agent that causes the therapeutic effect to the amount that causes toxicity.
TI refers to the ratio of the dose of drug that causes adverse effects at an incidence/severity not compatible with the targeted indication (e.g. toxic dose in 50% of subjects, TD50) divided by the dose that leads to the desired pharmacological effect (e.g. efficacious dose in 50% of subjects, ED50). In contrast, in a drug development setting TI is calculated based on plasma exposure levels

$$\text{Therapeutic index} = \frac{TD_{50}}{ED_{50}}$$



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