Faculty of Pharmaceutical Sciences

Rama University Kanpur (U.P)

BP-404 T PHARMACOLOGY- 1(Theory)
B.PHARM 4th SEM.

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Pharmacokinetics- Membrane transport, absorption, distribution, metabolism and excretion of drugs .Enzyme induction, enzyme inhibition, kinetics of elimination

agonist are not altered. This type of antagonism is not surmountable by increasing the concentration of agonist.

PHARMACOKINETICS-

Pharmacokinetics is the quantitative study of drugmovement in, through and out of the body. Theoverall scheme of pharmacokinetic processes isdepicted The intensity of responseis related to concentration of the drug at the siteof action, which in turn is dependent on itspharmacokinetic properties. Pharmacokineticconsiderations, therefore, determine the route(s)of administration, dose, latency of onset, timeof peak action, duration of action and frequencyof administration of a drug.All pharmacokinetic processes involve transportof the drug across biological membranes.

Membrane Transportation-

Biological membrane This is a bilayer (about 100 Å thick) of phospholipid and cholesterol molecules, the polar groups (glyceryl phosphate attached to ethanolamine/choline or hydroxyl group of cholesterol) of these are oriented at the two surfaces and the nonpolar hydrocarbon chains are embedded in the matrix to form a continuous sheet. This imparts high electrical resistance and relative impermeability to the membrane. Extrinsic and intrinsic protein molecules are adsorbed on the lipid bilayer.A membrane that has *selective permeability* allows only substances meeting certain criteria to pass through it unaided. In the case of the cell membrane, only relatively small, nonpolar materials can move through the lipid bilayer (remember, the lipid tails of the membrane are nonpolar). Some examples of these are other lipids, oxygen and carbon dioxide gases, and alcohol. However, water-soluble materials—like glucose, amino acids, and electrolytes—need some assistance to cross the membrane because they are repelled by the hydrophobic tails of the phospholipid bilayer.All substances that move through the membrane do so by one of two general methods, which are categorized based on whether or not energy is required.

Passive transport is the movement of substances across the membrane without the expenditure of cellular energy. In contrast, ***active transport*** is the movement of substances across the membrane using energy from adenosine triphosphate (ATP).

Passive Transport

In order to understand *how* substances move passively across a cell membrane, it is necessary to understand concentration gradients and diffusion. A *concentration gradient* is the difference in concentration of a substance across a space. Molecules (or ions) will spread/diffuse from where they are more concentrated to where they are less concentrated until they are equally distributed in that space. (When molecules move in this way, they are said to move *down* their concentration gradient.) Three common types of passive transport include simple diffusion, osmosis, and facilitated diffusion.

Simple Diffusion is the movement of particles from an area of higher concentration to an area of lower concentration. A couple of common examples will help to illustrate this concept. Imagine being inside a closed bathroom. If a bottle of perfume were sprayed, the scent molecules would naturally diffuse from the spot where they left the bottle to all corners of the bathroom, and this diffusion would go on until no more concentration gradient remains. Another example is a spoonful of sugar placed in a cup of tea. Eventually the sugar will diffuse throughout the tea until no concentration gradient remains. In both cases, if the room is warmer or the tea hotter, diffusion occurs even faster as the molecules are bumping into each other and spreading out faster than at cooler temperatures. Having an internal body temperature around 98.6° F thus also aids in diffusion of particles within the body.

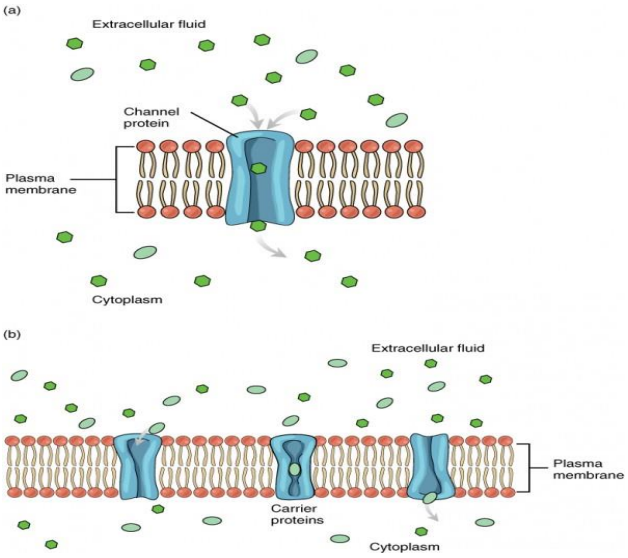
Whenever a substance exists in greater concentration on one side of a semipermeable membrane, such as the plasma membrane, any substance that can move down its concentration gradient across the membrane will do so.

Osmosis is the diffusion of water through a semipermeable membrane.Water can move freely across the cell membrane of all cells, either through protein channels or by slipping between the lipid tails of the membrane itself. However, it is concentration of solutes within the water that determine whether or not water will be moving into the cell, out of the cell, or both.

Osmosis is the diffusion of water through a semipermeable membrane down its concentration gradient. If a membrane is permeable to water, though not to a solute, water will equalize its own concentration by diffusing to the side of lower water concentration (and thus the side of higher solute concentration). In the beaker on the left, the solution on the right side of the membrane is hypertonic.

Solutes within a solution create osmotic pressure, a pressure that pulls water. Osmosis occurs when there is an imbalance of solutes outside of a cell versus inside the cell.

Facilitated diffusion is the diffusion process used for those substances that cannot cross the lipid bilayer due to their size and/or polarity (Figure 3.18). A common example of facilitated diffusion is the movement of glucose into the cell, where it is used to make ATP. Although glucose can be more concentrated outside of a cell, it cannot cross the lipid bilayer via simple diffusion because it is both large and polar. To resolve this, a specialized carrier protein called the glucose transporter will transfer glucose molecules into the cell to facilitate its inward diffusion. There are many other solutes that must undergo facilitated diffusion to move into a cell, such as amino acids, or to move out of a cell, such as wastes. Because facilitated diffusion is a passive process, it does not require energy expenditure by the cell.



a) Facilitated diffusion of substances crossing the cell (plasma) membrane takes place with the help of proteins such as channel proteins and carrier proteins. Channel proteins are less selective than carrier proteins, and usually mildly discriminate between their cargo based on size and charge. (b) Carrier proteins are more selective, often only allowing one particular type of molecule to cross.

Specialized transport

This can be carrier mediated or by pinocytosis. Carrier transport All cell membranes express a host of transmembrane proteins which serve as carriers or transporters for physiologically important ions, nutrients, metabolites, transmitters, etc. across the membrane. At some sites, certain transporters also translocate xenobiotics, including drugs and their metabolites.

Carrier transport is specific for the substrate (or the type of substrate, e.g. an organic anion), saturable, competitively inhibited by analogues which utilize the same transporter, and is much slower than the flux through channels. Depending on requirement of energy, carrier transport is of two types:

a. Facilitated diffusion The transporter, belonging to the super-family of solute carrier (SLC) transporters, operates passively without needing energy and translocates the substrate in the direction of its electrochemical gradient, i.e. from higher to lower concentration

b. Active transport It requires energy, is inhibited by metabolic poisons, and transports the solute against its electrochemical gradient(low to high), resulting in selective accumulation of the substance on one side of the membrane.

Active transport can be primary or secondary depending on the source of the driving force.

- Primary active transport
- Secondary active transport

ABSORPTION

Absorption is movement of the drug from its site of administration into the circulation. Not only the fraction of the administered dose that gets absorbed, but also the rate of absorption is important. Except when given i.v., the drug has to cross biological membranes; absorption is governed by the above described principles. **Other factors affecting absorption are:**

Aqueous solubility

Drugs given in solid form must dissolve in the aqueous biophase before they are absorbed.

Concentration

Passive diffusion depends on concentration gradient; drug given as concentrated solution is absorbed faster than from dilute solution.

Area of absorbing surface

Larger is the surface area, faster is the absorption.

Vascularity of the absorbing surface Blood circulation removes the drug from the site of absorption and maintains the concentration gradient across the absorbing surface. Increased blood flow hastens drug absorption.

Route of administration This affects drug absorption, because each route has its own peculiarities.

Drug Delivery Delivery -

Enteral Enteral Routes

• Oral- by far the most common route. The passage of drug from the gut into the blood is influenced by biologic and physicochemical properties.

• Sublingual (buccal) - Certain drugs are best given beneath the tongue or retained in the cheek pouch and are absorbed from these regions into the local circulation.

• Rectal -The administration of suppositories is usually reserved reserved for situations situations in which oral administration administration is difficult. This route is more frequently used in small children.

Parental Routes

• Intravenous injection – Used when a rapid clinical response is necessary, e.g., an acute asthmatic episode. – Achieve relatively precise drug concentrations in the plasma, since bioavailability is not a concern.

• Intra-arterial injection – Used in certain special situations, notably with anticancer drug ,s in an effort to deliver a high concentration of drug to a particular tissue. Typically, the injected artery leads directly to the target organ.

• Intrathecal injection – The blood-brain barrier limits the entry of many drugs into cerebrospinal fluid. life-threatening, antibiotics, antifungals and anticancer drugs are given via lumbar puncture and injection into the subarachnoid space.

• Intramuscular injection – Drugs may be injected into the arm, thigh or buttocks.

• Subcutaneous injection – Some drugs, notably insulin, are routinely administered SC. Drug absorption is generally slower SC than IM, due to poorer vascularity.

• Inhalation – Volatile anesthetics, as well as many drugs which affect pulmonary function, are administered as aerosols. Drugs administered via this route are not subject to first-pass liver metabolism.

• Topical application – Eye, intravaginal, intranasal, skin. – Alleviation of local symptoms symptoms.

Oral Drug Absorption

• The blood supply draining the gut passes through the liver before reaching the systemic circulation. – First-pass effect may reduce the amount of drug reaching the target tissue.

• Drug b d in ing – Many drugs will bind strongly to proteins in the blood or to food substances in the gut. – Plasma protein protein binding will in rease c the rate of passi ev absorption absorption by maintaining the concentration gradient of free drug.

• Food effects – Absorption Absorption can be reduced reduced by the presence presence of food in the gut – Absorption can be enhanced by food (bile secretion) – Some drugs are irritating and should be administered with meals to reduce adverse effects effects.

Plasma Protein Binding

• Drugs can bind to plasma proteins – Human serum albumin, lipoprotein, glycoprotein, and α, β, and γ globulins

• Protein Protein binding binding can influence influence the drug s' biological biological half-life – Fraction bound or free fraction – Warfarin is 97% protein bound

• Free fraction is an important consideration when looking at in vivo activity activity

• Protein binding can have implications in drug- drug interations

DISTRIBUTION

• Once in the blood, drugs are simultaneously distributed throughout the body and eliminated.

– Distribution is much more rapid than elimination, accomplished via the circulation, and influenced by regional blood flow.

A. Compartments –

Central Compartment- The central compartment includes the well- perfused organs and tissues (heart, blood, liver, brain and kidney) with which drug equilibrates rapidly.
– Peripheral Compartment- The peripheral compartment include those organs (e.g., adipose and skeletal muscle) which are less well- perfused, and with which drug therefore equilibrates more slowly.
– Speciail Copampartments - The cerebrospinal fluid (CS) central nervous system (CNS) is restricted by the structure of the capillaries and pericapillary glial cells.

Drugs also have relatively poor access to pericardial fluid, bronchial secretions secretions and fluid in the middle ear. thus making the treatment of infections in these regions difficult.

B. **Protein Binding-** Many drugs bind to plasma proteins. Weak acids and neutral drugs bind particularly to albumin, while basic drugs tend to bind to alpha-1-acid glycoprotein (orosomucoid). Some drugs even bind to red cell surface proteins.

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1. Effects on drug distribution Only that fraction of the plasma drug concentration which is freely circulating (i.e., unbound) can penetrate cell membranes. Protein binding thus decreases the net transfer of drug across membranes. Drug binding to plasma proteins is generally weak and rapidly reversible, however, so that protein-bound drug can be considered to be in a temporary storage compartment. The protein concentration of extravascular fluids (e.g., CSF, lymph, synovial fluid) is very low. Thus, at equilibrium (when the concentrations of free drug are equal), the total drug concentration in plasma is usually higher than that in extravascular fluid. The extent of protein binding must be considered in interpreting "blood levels" of drugs.

2. Effects on drug elimination The effects of plasma protein binding on drug elimination are complex. For drugs excreted only by renal glomerular filtration, protein binding decreases the rate of elimination since only the free drug is filtered. For example, the rates of renal excretion of several tetracyclines are inversely related to their extent of plasma protein binding. Conversely, however, if drug is eliminated by hepatic metabolism or renal tubular secretion, plasma protein binding may promote drug elimination by increasing the rate that that drug is presented for elimination.

3. Tissue binding Binding to tissue proteins may cause local concentration of drug. For example, if a drug is bound more extensively at intracellular than at extracellular sites, the intracellular and extracellular concentrations of free drug may be equal or nearly so, but the total intracellular drug concentration may be much greater than the total extracellular concentration.

C. Apparent volume of distribution (AVD or Vd). The volume of distribution, or more properly the apparent volume of distribution, is calculated from measurements of the total concentration of drug in the blood compartment after a single IV injection. Suppose that we injected someone IV with 100 mg of a drug, and measured the blood concentration of the drug repeatedly during the next several hours. We then plot the blood concentrations (on a log scale) against time, and obtain the following graph:

DRUG METABOLISM

Drug metabolism is the metabolic breakdown of drugs by living organisms, usually through specialized enzymatic systems. More generally, xenobiotic metabolism (from the Greek xenos "stranger" and biotic "related to living beings") is the set of metabolic pathways that modify the chemical structure of xenobiotics, which are compounds foreign to an organism's normal biochemistry, such as any drug or poison. These pathways are a form of biotransformation present in all major groups of organisms and are considered to be of ancient origin. These reactions often act to detoxify poisonous compounds (although in some cases the intermediates in xenobiotic metabolism can themselves cause toxic effects). The study of drug metabolism is called pharmacokinetics.
Drug metabolism is divided into three phases.
In phase I, enzymes such as cytochrome P450 oxidases introduce reactive or polar groups into xenobiotics. These modified compounds are then conjugated to polar compounds in.
phase II reactions. These reactions are catalysed by transferase enzymes such as glutathione S-transferases. Finally, in
phase III, the conjugated xenobiotics may be further processed, before being recognised by efflux transporters and pumped out of cells. Drug metabolism often converts lipophilic compounds into hydrophilic products that are more readily excreted.
Phase I – modification
In phase I, a variety of enzymes act to introduce reactive and polar groups into their substrates. One of the most common modifications is hydroxylation catalysed by the cytochrome P-450-dependent mixed-function oxidase system. These enzyme complexes act to incorporate an atom of oxygen into nonactivated hydrocarbons, which

can result in either the introduction of hydroxyl groups or N-, O- and S-dealkylation of substrates.[5] The reaction mechanism of the P-450 oxidases proceeds through the reduction of cytochrome-bound oxygen and the generation of a highly-reactive oxyferryl species.
Phase I reactions (also termed nonsynthetic reactions) may occur by oxidation, reduction, hydrolysis, cyclization, A common Phase I oxidation involves conversion of a C-H bond to a C-OH.

Phase II – conjugation

In subsequent phase II reactions, these activated xenobiotic metabolites are conjugated with charged species such as glutathione (GSH), sulfate, glycine, or glucuronic acid. Sites on drugs where conjugation reactions occur include carboxy (-COOH), hydroxy (-OH), amino (NH2), and thiol (-SH) groups. Products of conjugation reactions have increased molecular weight and tend to be less active than their substrates, unlike Phase I reactions which often produce active metabolites. The addition of large anionic groups (such as GSH) detoxifies reactive electrophiles and produces more polar metabolites that cannot diffuse across membranes, and may, therefore, be actively transported.

Phase III – further modification and excretion

After phase II reactions, the xenobiotic conjugates may be further metabolized. A common example is the processing of glutathione conjugates to acetylcysteine (mercapturic acid) conjugates. Here, the γ-glutamate and glycine residues in the glutathione molecule are removed by Gamma-glutamyl transpeptidase and dipeptidases. In the final step, the cysteine residue in the conjugate is acetylated.

Conjugates and their metabolites can be excreted from cells in phase III of their metabolism, with the anionic groups acting as affinity tags for a variety of membrane transporters of the multidrug resistance protein (MRP) family. These proteins are members of the family of ATP-binding cassette transporters and can catalyse the ATP-dependent transport of a huge variety of hydrophobic anions, and thus act to remove phase II products to the extracellular medium, where they may be further metabolized or excreted.

EXCRETION-

Excretion is the passage out of systemically absorbed drug. Drugs and their metabolites are excreted in:

1. Urine Through the kidney. It is the most important channel of excretion for majority of drugs.

2. Faeces Apart from the unabsorbed fraction, most of the drug present in faeces is derived from bile. Liver actively transports into bile organic acids organic bases (by OCT), other lipophilic drugs (by P-gp) and steroids by distinct nonspecific active transport mechanisms.
Certain drugs are excreted directly in colon,
e.g. anthracene purgatives, heavy metals.

3. Exhaled air Gases and volatile liquids (general anaesthetics, alcohol) are eliminated by lungs, irrespective of their lipid solubility. Alveolar transfer of the gas/vapour depends on its partial pressure in the blood. Lungs also serve to trap and extrude any particulate matter that enters circulation.

4. Saliva and sweat These are of minor importance for drug excretion. Lithium, pot. iodide, rifampin and heavy metals are present in these secretions in significant amounts. Most of the saliva along with the drug in it, is swallowed and meets the same fate as orally taken drug.

ENZYME INDUCTION

Enzyme induction is a process in which a molecule (e.g. a drug) induces (i.e. initiates or enhances) the expression of an enzyme.

ENZYME INHIBITION

Enzyme inhibition can refer to the inhibition of the expression of the enzyme by another molecule interference at the enzyme-level, basically with how the enzyme works.
This can be competitive inhibition, uncompetitive inhibition, non-competitive inhibition or partially competitive inhibition.
If the molecule induces enzymes that are responsible for its own metabolism, this is called auto-induction (or auto-inhibition if there is inhibition). These processes are particular forms of gene expression regulation.

KINETICS OF ELIMINATION

The knowledge of kinetics of elimination of a drug provides the basis for, as well as serves to devise rational dosage regimens and to modify them according to individual needs. There are three fundamental pharmacokinetic parameters, viz. bioavailability (F), volume of distribution (V) and clearance (CL) which must be understood

BIOAVAILABILITY (F)

The rate and extent to which an active drug ingredient is absorbed and becomes available at the site of drug action. By definition, for intravenous drugs, F = 1. Oral bioavailability can be determined by comparing the area under the curve (AUC) (of the plot of plasma drug concentration vs. time) after an oral dose to that for an intravenous dose, i.e., F = AUCoral/AUCIV

Relative Bioavailability The extent to which an oral drug product (e.g., a generic drug product) is absorbed in comparison to the trade name, or currently marketed drug product. This is usually determined by comparing the area under the curve (AUC) (of the plot of plasma drug concentration vs. time) of the new product to that of the trade name product, i.e., Relative F = AUCgeneric/AUCtrade name.

CLEARANCE (CL)
Clearance refers to the volume of plasma cleared of drug (by all processes) per unit time, i.e., Cl = ke x Vd

VOLUME OF DISTRIBUTION (V)
In pharmacology, the volume of distribution (VD, also known as apparent volume of distribution, literally, volume of dilution) is the theoretical volume that would be necessary to contain the total amount of an administered drug at the same concentration that it is observed in the blood plasma. In other words, it is the ratio of amount of drug in a body (dose) to concentration of the drug that is measured in blood, plasma, and un-bound in interstitial fluid.
The volume of distribution is given by the following equation:

Vd= total ammount of drug in the body/drug blood plasma concentration