pharmacokinetic

pharmacokinetic:-the action of the body on the drug include :- (absorption, distribution, elimination of drug) .(ADME).

Absorption of drug:-is the transfer of drug from site of administration into blood stream.

The rate and efficiency of absorption depend on:- the route of administration.In I.V. administration there is complete absorption . other route of administration there is partial absorption.

The methods of passage of drug through the cell membrane:-

1-passive diffusion:-

A-Most important means by which the drug enters tissues.

B-The driving force is concentration gradient across the membrane between the compartments.

C-No energy required, dose not required carrier.

D-The process dose not become saturated.

E-Lipid-soluble drugs readily move across most biological membranes, whereas water –soluble drugs penetrate the cell membrane through aqueous channels.

2-active transport:-

A-Drug entry involves specific carrier proteins present on the cell membrane .

B-The process is energy dependant, driven by hydrolysis of ATP to ADP.

C-Capable of moving drugs against concentration gradient.

D-The process shows saturation kinetics .e.g iron absorption

3-faciliated diffusion:-a-carrier mediated transport that dose not require energy. e.g. vit. B12.

4-Filtrationa:-Some low molecular weight chemicals, water, urea, cross membranes better than predicted on the basis of their lipid solubility, suggesting that membranes possess pores/channels.

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5-Pinocytosis:- This is a minor method for drug absorption, but it may be important inthe absorption process for some polypeptides, bacterial toxins, antigens, and food proteins by the gut.

Effect of PH on the drug absorption:-most drugs weak acids or weak bases..

1-weak acidic drug is lipid soluble in acidic media & water soluble in basic media.

2-Weak basic drug is lipid soluble in basic media & water soluble in acidic media.

3-The ratio between ionized & non ionized forms depends on PH at site of absorption& on strength of weak acid or weak base.

Other Physical factors affecting absorption:-

1-Blood flow to the absorption site.

2-Total surface area for absorption.

Blood – Brain Barrier:-

The barrier consist of a continuous layer of endothelial cells joined by tight junction and surrounded by pericytes .

The brain is consequently in accessible to many drugs including anti-cancer drugs and some antibiotics such as the aminoglycosides ,with a lipid solubility that is insufficient to allow penetrating of the blood brain barrier .However , inflammation can disrupt the integrity of the blood –brain barrier allowing normally impairment substances to enter the brain. Penicillin give I.V.to treat bacterial meningitis .Dopamine antiemetic dopamine receptor antagonist .

Bioavailability :-Is the fraction of administered drug that reach the systemic circulation. Bioavailability is a determined by comparing plasma levels of a drug after a particular rout of administration .e

plasma drug levels achieved 100%by IV injection . When the drug is given orally only part of administered dose appears in the plasma.

Factors that influence bioavailability.

1-First-passhepatic metabolism.

2-Solubility of drug.

3-Chemical instability.

4-Nature of the drug formulation.

First –pass metabolism :

The drugs are extracted so efficiently by the liver or gut wall that the amount reaching the systemic circulation is considerably less than the amount absorbed .

This is known as a first –pass or pre systemic metabolism and reduces bioavailability .A much problem because larger dose of the drug is needed when it is given orally than when it is given by other routes.

Drug distribution:-Is the process by which a drug reversibly leaves the blood stream and enters the interstitium (ECF).& or the cells of the tissues.

Distribution of drug depends on :-

1-**blood flow:-**blood flow to brain , liver & kidney is greater than that to the skeletal muscles, whereas adipose tissue has a still lower rate of blood flow

2-C**apillary permeability :**a capillary structure: present or absence of slit junction or tight junction, in the basement membrane between capillary. E.g. the tight junction in brain tissues forming BBB that prevents passage of protein –bound drugs while the liver & spleen endothelium have large pores allowing the passage.

3-**Drug structure**: non ionized (lipid soluble) or ionized (water soluble).

4-**Binding to plasma protein & tissues,** high drug protein binding reduced distribution.

The drug present in the plasma in two states:

1-free fraction is pharmacologically active.

2-Protein bound fraction is a reservoir of inactive drug.

Tissue binding :-e.g. benzodiazepines (lipid soluble) -------enter fat --stores .e.g. chlorquine------binds to melanin containing tissues .extensive tissue binding delays elimination & prolong half -life .

Volume of distribution(Vd) :-

Is the volume of fluid required to contain the total amount of drug in the body at the same concentration as that present in the plasma

Calculation of Vd :Vd = D| C D= total amount of drug in the body (dose)C= plasma concentration of the drug

Distribution of an absorbed drug in the body depends on protein binding ,blood flow, and solubility.

Distribution of drugs from plasma to other body fluids & tissues varies depending on the nature of drug.

1-If drug is extensively bound to plasma proteins, it will be retained mainly in blood or plasma (has large molecular weight & high protein binding) then it has small volume of distribution like(warfarin)

2-the drug is widely distributed in the tissues (has low molecular weight & high lipid solubility) .it will have a large Vd like propranolol .

Drug metabolism:

chemical transformation within the body to change the drug in 2 major ways:-

1-reducing lipid solubility

2-altering biological activity.

Reducing lipid solubility :-make a drug molecule progressively more-water soluble to favor its elimination in urine.

Altering biological activity:-an end result is the abolition of biological activity through various steps:-

1-an active drug may be metabolized into inactive metabolites e.g. warfarin.

2-An active drug may change into other active metabolites increasing duration of action e.g. codeine is converted into morphine.

3-Conversion of pharmacologically inactive drug (prodrug) into a drug e.g. L-dopa to dopamine.

Reaction of drug metabolism :-

(phases of drug metabolism) metabolized in the liver using two general sets of reactions, called phase I, and phase II.

Phase I:-Oxidation. Reduction ,or hydrolysis .Oxidation : undertaken by mixed function microsomal oxidases (cytochrom p450).Cytochrome p450 isoenzymes are grouped into families called CYP.

Phase I reactions not involving P450 system:e.g. catecholamine oxidation by COMT enzyme Ethanol oxidation by alcohol dehydrogenase.

Phase II reaction:-This phase consist of conjugation reaction .Conjugation of drug may occur with glucuronic acid, sulfuric acid , acetic acid or an amino acid.

Enzyme induction:-The capacity of the body to metabolize drugs can be altered by certain drugs or other substances, especially when used long term-------increase in amount & activity of metabolizing enzyme (enzyme induction).e.g. enzyme inducers : chronic ethanol. Tobacco smoke, rifampicin

Enzyme inhibition :--more selective than enzyme induction.-basis of a number of drug interactions : e.g. cimetidine inhibits hepatic drug metabolism by inhibiting p450 enzymes leading to increased blood levels & possibly more adverse effects of the metabolized drug like warfarin & theophylline.

Pro-drugs:-are inactive precursors that metabolized to active metabolites e. g Levadopa , Zudovudine ,Aciclovir.

Drug elimination:-Drugs are eliminated from the body after being partly or wholly converted to water soluble metabolites.

1-renal elimination(excretion)a-glomerular filtration.

2-fecal elimination(rectal elimination).

3-pulmonary elimination .

Half-life(t1\2):-The time it takes to eliminate 50% of the drug from the body . some chemicals are quickly excreted from the body. Other drugs remain for a long time. because these rates are usually the same for most individuals, the half-life helps explain the dose, frequency, and duration for different drugs.

The half –life of a drug is increased by:-

1-diminished renal plasma flow, (in heart failure, or hemorrhage).

2-A second drug that displaces the first from albumin … increases the VD of the drug.

3-Decreased excretion (renal disease)

4-Decreased metabolism. (hepatic insufficiency).

Clearance :-clearance relates the rate of elimination to the plasma concentration

Clearance = rate of elimination of drug Plasma drug concentration A drug elimination with first –order kinetics, clearance is a constant.Clearance depends upon the drug and condition of the organs of elimination in the patient.

CL (total)= CL hepatic + CL renal + CL pulmonary + CL other total clearance .

Steady –state drug :-The rate of drug input equals the rate of elimination. , the condition in which the total amount of drug in the body does not change over multiple dosing intervals.

Tachyphylaxis:-Is the rapid loss of efficacy or response due to foregut repeated administration in a short period of time (day or hours) example is rapid loss of

thee bronchodilator effect of ephedrine over days due to depletion of neurotransmitter noradrenalin in bronchi.

Tolerance:-Is reduction in response to drugs following continued drug administration & may occur due to decrease efficacy due to down –regulation of receptors or may be due to increase in drug metabolism. When this occurs higher doses are needed to produce the previous effect .

Cross –tolerance; occur between drugs of similar structure like the benzodiazepines .

Additive effect;-result of drug interaction that occur when two drugs with similar actions are given together.

Elimination of drugs:-the rate of elimination determines the duration of action for most drugs., therefore, the time course of concentration in plasma is important in predicting the intensity and duration of effect for most drugs

first-order elimination:- -the rate of elimination proportionate to the concentration, the higher the concentration ,the greater the amount of drug eliminated per unit time.

The drugs concentration in plasma decreases exponentially with time.

Half-life of elimination that constant regardless of the amount of drug in the body.

The concentration of such a drug in the blood will decrease by 50% for every half life.

zero –order elimination:-

a-the rate of elimination is constant regardless of concentration

b-a few drugs saturate their elimination mechanisms even at low concentrations .

c-the drugs concentration in plasma decreases in a linear fashion over time .(ethanol, phenytoin, aspirin).