Toxicokinetics

Effect of the body on the drug. Consist of four process (ADME)

1) Absorption

Is the process whereby toxicants Transfer into the body from the site of administration to the systemic circulation.

Sites of a Absorption: skin, lungs and gastrointestinal tract, (GIT) is the most Important in toxicology are ingested orally. The lungs are clearly important for all airborne compounds whereas the skin is only rarely a significant site for absorption.

Mechanism of Absorption:

1: Simple diffusion (Lipid diffusion)

o From high conc . to low conc . (Along concentration gradient) .

o Depend on lipid solubility .

o Not needed energy and carrier .

o **The drug must be lipid soluble and small in molecular weight (Mwt .) .**

¬ Factors affecting simple diffusion :

1: Dose concentration (Increase dose concentration Increase absorption

2:Molecular weight & size (Increase Mwt . Decrease absorption) .

3 : Ionization (Water soluble drug (Ionized) > Decrease absorption)

4 PH at the site of absorption.

Most of drugs are weak acids or weak bases

Weak acid drugs less ionized in acidic medium---decrease ionization --- Increase Absorption,Weak base drugs less ionized in basic medium---decrease ionization--Increase Absorption

2 : **Facilitate Diffusion** :

- From high concentration to low concentration (Along concentration gradient .
- Need carrier and not need energy

3:**Active transport** :

-From low concentration to high concentration (Against concentration gradient

- Need carrier and need energy

4 **: Pinocytosis or Endocytosis :**

- Drugs of exceptionally large size .

- Engulfment of a drug molecule by the cell membrane . - Eg (Vitamin B1 + intrinsic factor) complex

► **Factors affecting absorption of drugs** :

1 : **Patient - Related factors** :

Route of administration IV > IM > SC > Oral > Skin.

Absorbing surface area Increase surface - Increase absorption .

Systemic circulation Shock and heart failure decrease absorption .

Presence of other drugs Adrenaline SC=Vasoconstriction(VC) leads to decrease absorption .Specific factors E.g. intrinsic factor for Vit . B12 .

2: **Drug - Related factors:**

o Lipid solubility : High lipid solubility drug - High absorption .

o Ionization: Non - ionized drugs High absorption .

o Valency: Ferrous iron (Fe^{+2}) absorbed more than ferric iron (Fe^{+3}) .

o Nature Inorganic (Small molecules) > Organic (Big molecules) .

o Pharmaceutical preparation Solution > Suspension > Tablet

o PH of the drug .

2) Distribution

Is the process whereby an absorbed chemical moves away from the site of absorption to other areas of the body (extracellular fluid) and tissue.

Distribution of toxic Depend on:

1-Blood flow

Increase blood flow---Increase distribution,Blood flow to the vessel-rich organs (brain, liver and kidney) is greater than that to the skeletal muscles, adipose tissue and viscera.

2-**Capillary permeability:**

- it depend on capillary structure and the chemical nature of the drug.

In the liver and spleen (high capillary permeability)—large plasma proteins can pass. In the brain only lipid soluble drugs can pass through blood brain barrier (BBB).

3-**Binding to plasma protiens:**

ϖ Albumin is the major drug-binding protein and may act as a drug reservoir.

ϖ Bound fraction of the drug ---not active

ϖ Free fraction of the drug --- active

ϖ The concentration of free drug decrease due to elimination ---the bound drug dissociates from the protein (to maintain equilibrium between free-drug and bound-drug).

4- **Volume of distribution**(Vd):

The apparent volume of fluid into which an administrated drug is dispersed.

Vd (Volume of distribution) = Q (Total amount of drug in the body) /Cp (Plasma concentration of the drug)

- If the drug has high Vd that means The drug has low affinity to binding to PP.
- If the drug has low Vd that means The drug has high affinity to binding to PP.

the primary sites for toxicant storage are adipose tissue , bone , liver & kidney. Lipid soluble toxicants are often stored in adipose tissue. - another major site for storage is bone.

Metabolism-(biotransformation)

Is conversion of drug from non-polar (active)◊ to Polar (less or not active) to facilitate excretion.

Classification:- Phase I

Phase I Reactions:

1: **Oxidation**

2: Reduction

3: Hydrolysis

Phase II

This phase consists of conjugation reactions.

Conjugation may be with :

1: Acetic acid (Acetylation)

2: Sulfate

3: Methylation

4: Glycine

5**: Glucuronic acid, the cytochrome P-450 system metabolizes**

Metabolism Enzymes:- Microsomal Enzymes, Non-Microsomal Enzymes

Factors Affecting Metabolism:-

- Age
- Sex differences:
- Genetic factor:
- State of health:

Excretion

Is the last toxicokinetic step for a xenobiotic and involves removing the xenobiotic out of the body by a number of passages.

Routes of drug excretion (elimination):

1-Kidney:- Through: 1: Glomerular filtration: For water soluble non bound drugs (Most)

2-GIT :- through Saliva and Bile.

3-Skin :- through sweat gland(Rifampecin) and Breast (milk) Nicotine and Morphine.

4-Lung:- e.g. Anesthetic Gases e.g Nitrous oxide & Halothane .