Biopharmaceutics & Pharmacokinetics

8th SEM

Miscellaneous factors affecting Drug Distribution

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ORGAN/TISSUE SIZE & PERFUSION RATE

- Perfusion Rate :- is defined as the volume of blood that flows per unit time per unit volume of the tissue (ml/min/ml)
- Perfusion rate is limited when

1) Drug is highly lipophilic
2) Membrane across which the drug is supposed to diffuse is highly permeable.

Distribution is permeability rate - limited in following cases-

1)When the drug is ionic/polar/water soluble

2)Where the highly selective physiology barrier restrict the diffusion of such drugs to the inside of cell.

- Drug is distributed in a particular tissue or organ depends upon the size of tissue (Volume) & Tissue/blood partition coefficient Ex.Thiopental i.v (liphopillic drug) has high tissue/blood partition coefficient towards brain & adipose tissue but brain is highly perfused organ so drug is distributed fast and shows rapid onset of action than poorly perfused adipose tissue.

- Miscellaneous factors

MISCELLANEOUS FACTORS

1) AGE:- Difference in distribution pattern is mainly due to:-

- Total body water -(both ICF &ECF) greater in infants
- Fat content - higher in infants & elderly
- Skeletal muscle - lesser in infants & elderly
- Organ composition – BBB is poorly developed in infants & myelin content is low & cerebral blood flow is high, hence greater penetration of drug in brain plasma
- Protein content- low albumin in both infants & elderly

2) PREGNANCY:-During Pregnancy, due to growth of uterus, placenta & foetus increases the volume available for distribution of drug. Foetus have separate compartment for drug distribution. Plasma & ECF volume also increase but albumin content is low.

3) OBESITY:-In obese persons, high adipose (fatty acid) tissue so high distribution of lipophilic drugs and perfusion through it is low.
4) DIET:-A diet high in fats will increases free fatty acid levels in circulation thereby affecting binding of acidic drugs (NSAIDs to albumin)
5) DISEASE STATES:-mechanism involved in alteration of drug distribution in disease states:-
   a)Altered albumin & other drug-binding protein concentration.
   b)Alteration or reduced perfusion to organ or tissue.
c) Altered tissue pH.
d) Alteration of permeability of physiological barrier (BBB)

Ex- BBB (in meningitis & encephalities) BBB becomes more permeable thus polar antibiotics ampicilin, penicilin G which do not normally cross gain access to the brain & patient suffering from CCF perfusion rate to entire body decreases it affect distribution.

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6) DRUG INTERACTIONS:- DI that affect distribution are mainly due to differences in plasma protein or tissue binding of drugs.

VOLUME OF DISTRIBUTION

$X \alpha C$ $X = Vd.C$

It is defined as hypothetical volume of body fluid into which a drug is dissolved or distributed.

$Vd = X/C$

Apparent Vd = amount of drug in the body/ plasma drug conc.

Apparent volume of distribution is dependent on concentration of drug in plasma. Drugs with a large apparent volume are more concentrated in extra vascular tissues and less concentrated intravascular.

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- The interacting molecules are generally the macromolecules such as protein, DNA or adipose. The protein are particularly responsible for such an interaction.
- The phenomenon of complex formation of drug with protein is called as protein binding of drug.
- As a protein bound drug is neither metabolized nor excreted hence it is pharmacologically inactive due to its pharmacokinetic and Pharmacodynamic inertness. –
- Protein + drug ⇌ Protein-drug complex
- Protein binding may be divided into: –
- 1. Intracellular binding. – 2. Extracellular binding.

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- INTRACELLULAR BINDING:- where the drug is bound to a cell protein which may be the drug receptor so binding elicits a pharmacological response.
- EXTRACELLULAR BINDING:- where drugs bound to an extracellular protein but the binding does not usually elicit a pharmacological response.
- MECHANISMS OF PROTEIN DRUG BINDING:- Binding of drugs to proteins is generally-
  - Reversible generally involves weak chemical bond such as:

1. Hydrogen bonds 2. Hydrophobic bonds 3. Ionic bonds 4. Van der waal's forces.

- Irreversible drug binding, though rare, arises as a result of covalent binding and is often a reason for the carcinogenicity or tissue toxicity of the drug.

- BINDING OF DRUG TO BLOOD COMPONENTS A. Plasma protein-drug binding:- • The binding of drugs to plasma proteins is reversible. • The extent or order of binding of drug to plasma proteins is: Albumin › 1-Acid glycoprotein ›Lipoproteins ›Globulins.à
- 6. 1. Binding of drug to human serum Albumin. • It is the most abundant plasma protein (59%), having M.W. of 65,000 with large drug binding capacity. •Both endogenous compounds such as fatty acid, bilirubin as well as drug binds to HSA. • Four diff. sites on HSA for drug binding. Site I: warfarin & azapropazone binding site. Site II: diazepam binding site. Site III: digitoxin binding site. Site IV: tamoxifen binding site.
- 7. 2. Binding of drug to α1-Acid glycoprotein: (orosomucoid) It has a M.W. 44,000 and plasma conc. range of 0.04 to 0.1 g%. It binds to no. of basic drugs like imipramine, lidocaine, propranolol, quinidine. 3. Binding of drug to Lipoproteins: Binding by: Hydrophobic Bonds, Non-competative. Mol wt: 2-34 Lacks dalton. Lipid core composed of: Inside: triglyceride & cholesteryl esters. Outside: Apoprotein. e.g. Acidic: Diclofenac. Neutral: Cyclosporin A. Basic: Chlorpromazine. LDL HDL VLDLChylomicrons Types
- 8. 4. Binding of drug to Globulins Globulin Synonym Binds to 1. α1 Globulin Transcortine /Corticosteroid Binding globulin Steroidal drugs, Thyroxin & Cyanocobalamine. 2. α2 Globulin Ceruloplasmine Vitamin A,D,E,K. 3. ß1Globulin Transferin Ferrous ions 4. ß2Globulin --- Carotinoids 5. γ Globulin --- Antigens

- B. BINDING OF DRUG TO BLOOD CELLS • In blood 40% of blood cells of which major component is RBC (95%). The RBC is 500 times in diameter as the albumin. The rate & extent of entry into RBC is more for lipophilic drugs. • The RBC comprises of 3 components. a) Haemoglobin: It has a M.W. of 64,500 Dal. Drugs like phenytoin, pentobarbital bind to haemoglobin. b) Carbonic anhydrase: Carbonic anhydrase inhibitors drugs are bind to it like acetazolamide & chlorthalidone. c) Cell membrane: Imipramine & chlorpromazine are reported to bind with the RBC membrane.

2. BINDING OF DRUG TO EXTRAVASCULAR TISSUE PROTEIN • Importance: 1. It increases apparent volume of distribution of drug. 2. localization of a drug at a specific site in body.
  - Factor affecting: lipophilicity, structural feature of drug, perfusion rate, pH differences.
  - Binding order: Liver ›Kidney › Lung › Muscles Tissue Binding of 1.Liver Irreversible binding of Epoxides of Halogenated Hydrocarbon & Paracetamol. 2.Lungs Basic drugs: Imipramine, Chlorpromazine, & AntiHistaminics.

Cont… Tissue Binding of 3.Kidney Metallothionin protein binds to Heavy metals & results in Renal accumulation and toxicity. 4.Skin Chloroquine & Phenothiazine binds to Melanin. 5.Eye Chloroquine & Phenothiazine also binds to Eye Melanin & results in Retinopathy. 6.Hairs Arsenicals, Chloroquine, & Phenothiazine. 7.Bones Tetracycline(yellow discoloration of teeth), Lead(replaces Ca & cause brittleness) 8.Fats Lipophilic drugs (thiopental), Pesticides (DDT) 9.Nucleic Acid Chloroquine & Quinacrine.

Thank You