**Pharmacology**

**sheet 5**

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Revision:

* In which form does the drug exist in the plasma? Lipid soluble.
* Which form of the drug cross membranes? Free form &Lipid soluble.(the bound will not cross because the protein is large)

**Slide13**

-Drug distribution is the passage of the drug from blood to different tissues including the site of action,

-What we need is the drug at the site of action in the proper concentration, good enough to produce the desired effect but without producing side effects.

-What determine the proper conc. at the site of action are the kinetic parameters.

-Our body contains fluid as 1)Plasma 2)Extracellular fluid 3)Intracellular fluid, now look at the example in the slide we see that the plasma is almost 3L and ECF is 10L and ICF constitutes the major part of the fluid of the body

as we know the free form is the one which crosses the membrane and reaches equilibrium -> then does its effect at the site of action after that it is metabolised and excreted or excreted directly without metabolism then more of the drug will dissociate into the site of action and this will go on until we finish the whole drug in the blood.

So the duration of action of the drug depends on 3 factors:

1. Absorption
2. Metabolism/ excretion
3. Binding to protein

The factor which increases the blood conc. is the absorption on the other hand metabolism/excretion lower blood conc. because they'll get rid of the drug from the body.

-The volume in which the drug distributes in the body could be measured by a constant known as AVD =apparent volume of distribution

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**AVD = Dose (mg)/C0 (mg/L)**

e.g.: if the given dose is 500mg and C0=500mg/L then how much is the AVD?

Answer: 1L ... Where do think this 1L is? Since the volume is very small, most probably the drug will only be present in the plasma.

-If the AVD is 500L then it's found in all compartments and it's lipid soluble.

**Slide 15**

As a general rule drugs with high AVD are lipid soluble and drugs with small AVD they'll be water soluble and given by IV, and if it's very very high then of course its lipid soluble but it also indicates extensive tissue binding and this could reflect some side effects to the drug like severe retinal damage.

**Slide 16**

-compartmental selectivity means that the drug is selective to a specific compartment.

-organ selectivity means that the drug only goes to a specific organ this could be of an advantage if we want the drug to act in the site where its specific.

-protein binding is the major factor because the protein holds the drug in the plasma note: what's the major factor affecting absorption? Lipid solubility, while the major factor affecting distribution is protein binding

- Natural barriers, sometimes we need the drug to cross the barrier to work and others not to cross because they'll produce side effects.

Placenta is an excellent barrier and we need it to prevent the passage of drugs from the mother to the fetus. Usually we chose the drugs that do not cross the placenta.

Mammary glands are very easy, even if the drug passes through the milk we just ask the lady not to feed the baby however if the drug was long acting we try not to find an alternative drug.

**Slide 17**

-Drug metabolism: a change in the chemical structure of the drug from the initial chemical structure to another and it's a major process.

- the concept of metabolism in general means changing the chemical structure of the drug by adding a hydrophilic(water-soluble) group to a drug so we're transforming it from lipid to water soluble drug and then excreted by the kidney.

- Alot of the drugs do not need any help, they produce their effect, PH of the medium changes it to water soluble then excreted.

-The metabolism of the drug has nothing to do with the benefit and harm of the drug

-As a result of drug metabolism we have by products called metabolites, what are the ideal requirements of metabolites?

1) Water-soluble. 2) Not pharmacologically active. 3) Not toxic.

-There's a concept known as T half life which is the duration by which the conc. of a substance reaches half.

e.g.: the T half life of a certain drug is 1 hour, what do u expect the duration of action to be? 5 hours

But if we said for example the T half life is 1hr and the duration of action is 2 days then we expect the metabolites of that drug are pharmacologically active.

**Slide18**

-major site of drug metabolism is liver

-Drug metabolism involves a number of enzymes.

-We have **two major pathways**, Pathway one involves oxidation reduction reactions (microsomal enzymes) it is also known as mixed function oxidase system and cytochrome P450 system.

**Slides 19/20/21**

***\*Structures are not required \****

Aromatic hydroxylation, aliphatic hydroxylation (if we add an alcohol group to the alkyl it becomes more watersoluble), O-dealkylation (removal of the alkyl group), N-dealkylation,N-oxidation;N-hydroxylation,sulfoxidation, hepatic reduction (azoreduction and nitroreduction)

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-Nonmicrosomal oxidation and reduction in the liver but at different site than microsomal

-Hydrolysis can not only occur in the liver but also in the intestine including enzymes known as esterases and water.

Note all examples above are pathway I

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Pathway II: conjugation reactions

-methylation, acetylation their enzymes are known as transferases that require a donar that will provide acetyl group.

-glucuronic acid conjugate (the glucuronate itself attach to the drug)

-etheneal sulphate (ether containing)

-glycine conjugate a major pathway foe detoxification include the production of mercaptopuric acid

**QUICK revision:** *We have two pathways: Pathway one involves oxd/red reactions that could be microsomal or non-microsomal or hydrolysis and we have pathway two which is conjugation reactions.*

**Slide 24**

The idea of this slide is that each drug has its own properties, for example we can administer a drug that is inactive (Prodrug) and then it is converted to an active form in the body or we can administer the drug directly in the active form after that it produces its action and then it could be excreted without metabolism or maybe it only needs to be metabolized by pathway one only or two only or both of them (one then two OR two then one).

**Slide 25**

-We already mentioned the characteristics.

-Sites of drug metabolism major one is liver but metabolism could occur anywhere CNS, skin, intestines ...etc

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1-Genetic factors: as we know metabolism requires enzymes like oxidases, esterases, transferases ... they are all proteins produced from DNA so if a mutation or a deficiency in a certain enzyme is present then by the end of the second dose we will have accumulation and toxicity such a patient requires to change the drug or if there is no other drug that can be given we lower the dose

We also have species differences, people are divided to slow and rapid metabolizers. e.g: sulfadrugs are metabolized by acetylation pathway 2, then people are divided to be slow acetylators and others are rapid acetylators. Those who are slow acetylators will require a lower dose to prevent accumulation&toxicity and vice versa for rapid acetylators.

Q) How to test for rapid or slow metabolites? By testing the urine if we have low metabolites then this person is a slow metabolizer.

2- Sex (they say female have a lower capacity for metabolising the drug compared to males?)

3-drug-drug interaction

4-Age:

Consider the following case: paracetamol is safer to children than when compared to adults where as chloramphenicol is safer to adults than in children, take metabolism in consideration and explain!

Extra note: paracetamol parent drug is not toxic but produces highly toxic metabolites however; chloramphenicol parent drug is very toxic while metabolites are not.

Answer: Children do not have similar capacity in metabolising the drug as in adults (the enzymes are not mature) so it's very safe to give chloramphenicol to children.

5-General health of patients and nutritional status: The better the health the better the metabolism!

6-Dose and frequency of administration: increasing the dose requires more enzymes.

**Slide27**

First pass effect: the oral drug goes first to the liver then to circulation if it was metabolised in the liver then the drug is ineffective orally.

Enterohepatic circulation: the drug is given orally reaches intestines then goes to the liver something occurs there in the liver then returns back to the intestines to be absorbed into the circulation. Why is it imp.?The drugs that are given in the inactive form will be activated in the liver. Why do we administer a drug in the inactive form? To lower its side effects.