SHEET NO. 6

PHARMACOLOGY

DOCTOR 2019 | MEDICINE | JU

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RECALL:-

Medicines differ in their characteristics, either :

1- Narrow therapeutic index : if the toxic dose is close to the effective dose [TD50 close to ED50] . Then the margin of safety is little and narrow .

2- Wide therapeutic index: if the toxic dose is far away from the effective dose [TD50 far away to ED50] , the marginof safety is high.

(بهاي الحالة بقدر اعطي جرعة كبيرة من الدوا بدون حدوث تسمم دوائي ، وفقا للحاجة طبعا)

Ex.. antibiotic, because it does not have target in human system.

The doctor ranked dugs in slide (28) according to Narrowest widest

1- Digoxin (0.8 – 2)ng/ml

2- Cyciosporine (100-400) ng/ml

3- Qunindine (2 -6)

4- Carbamazepine (4-10)

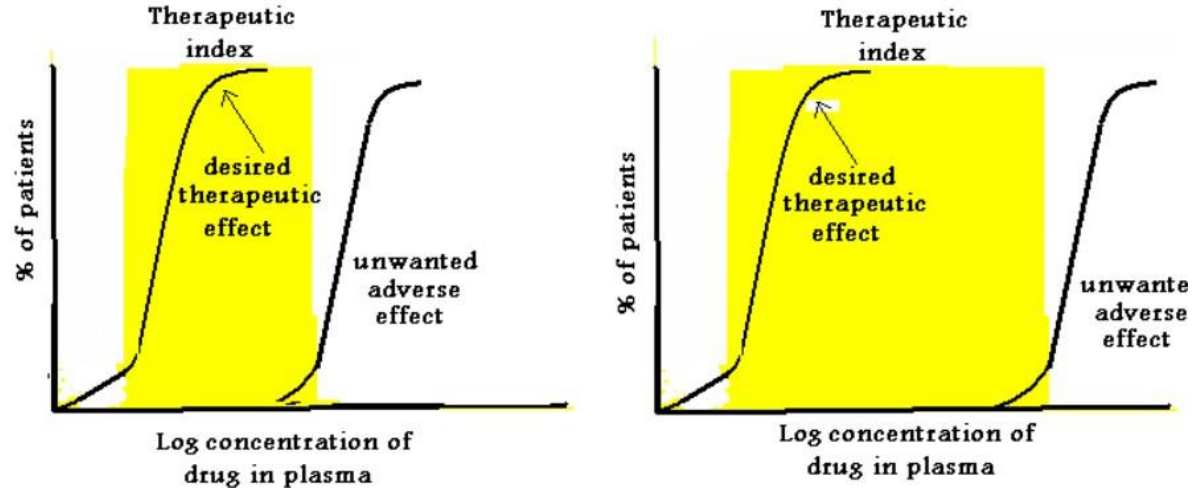
5- Phenotin (10-20)

How do we measure the margin of safety or the therapeutic index ?

-It is measured by the concentration of drug in the plasma not by the given dose .

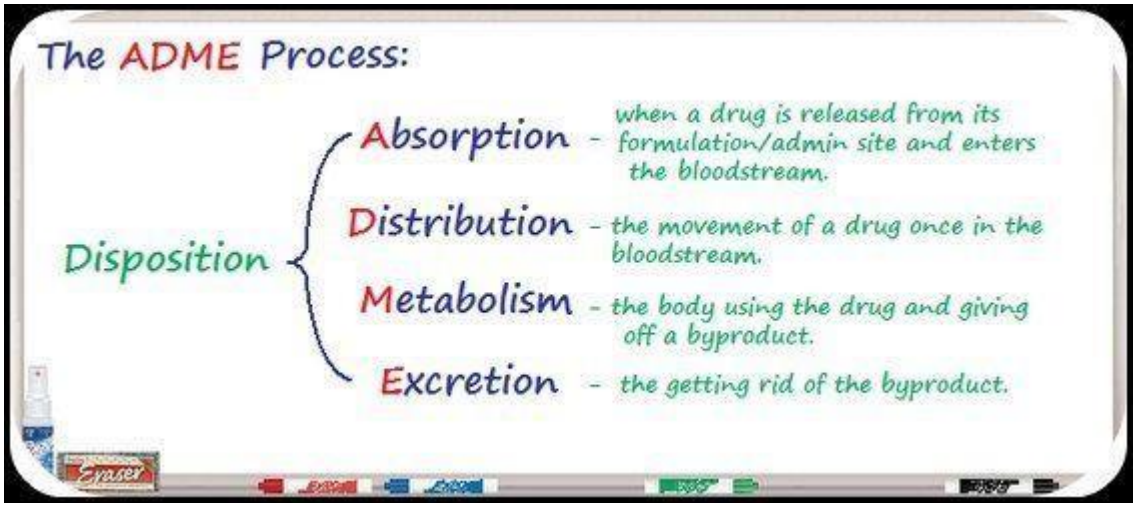
Ex.. In digoxin (0.8 – 2) ng/ml.

(هاد المثال بوضحلي الكمية الي بناخد فيها جرعة الدوا وبتكون نسبتها بالبلازما ضمن مستوى الامان.)



Now , let's start with

Pharmacokinetics



It describes the movement of drug inside the human body.

[contains 4 stages]:

1- Absorption: (in most cases absorption takes place in intestine and stomach)

2- Distribution (if drug reaches the plasma, it will distribute it to target tissue in the body (peripherally – liver – kidney …)

3- Metabolism (transfer medication from lipophilic to hydrophilic), so we can get it out of the body.

4- Elimination (the drug leaves the body by kidney or different ways).

So, to understand how drugs enter the body we must take about drug transportation:

اذا كان الدوا Lipopholic بيقدر يمر بسهولة عبر الغشاء

DRUG TRANSPORT:

-*DEFINITION*: the movement of drug molecules in the body affect the absorption, distribution, and elimination.

-Drug can across cellular membrane by passive diffusion or by an active transport.

A-Passive diffusion (it does not need energy) :

1-Lipid diffusion of un-ionised molecules, Majority of drug gain access to the body by this mechanism

2-Size and charge, the lipid-water partition coefficient being the most important factors.

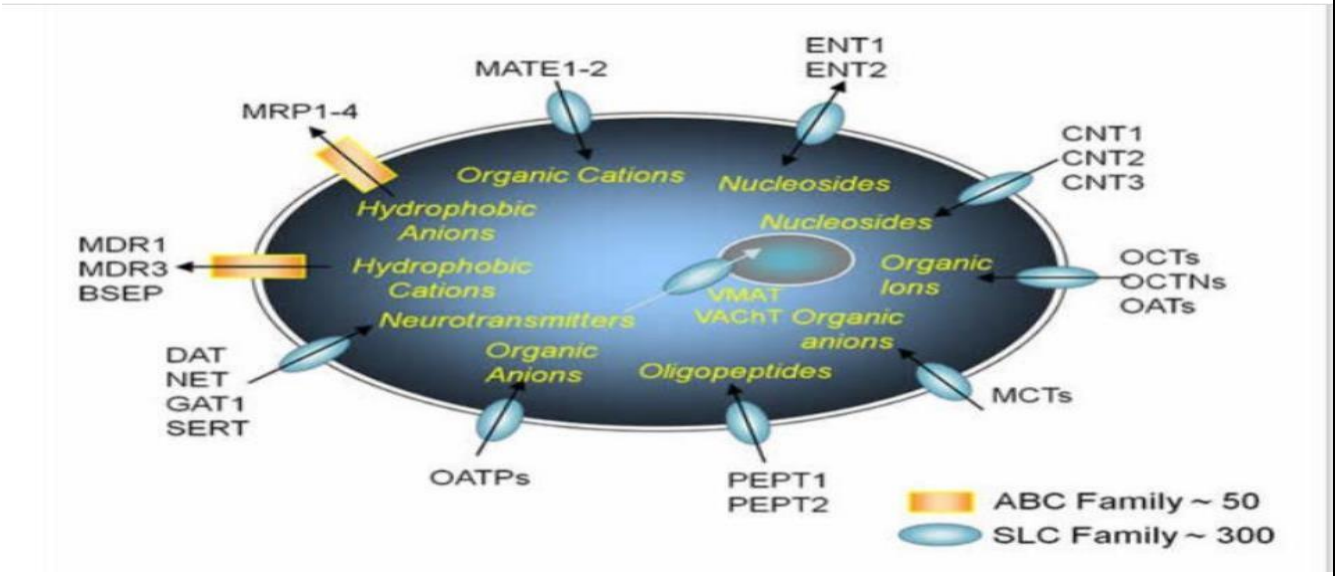
3-Does not require metabolic energy.

4- High conc. gradient to low conc. gradient.

B- Active transport :

1-Movement through the membrane is facilitated by a Macromolecules, [such as channels but require energy].

2-Selective for chemical structure and it is saturable process
3- A few drugs that closely resemble the naturally occurring metabolites are transport by this process.
Because of its selective to structure of drug [in most cases it will be saturable]
-Need metabolic energy and can transports molecules against a concentration gradient



orange color : active transportation
blue color : passive transportation

from picture : active
MRP1-4 hydrophobic anions
transporter MDR1, MDR3 and
BESEP hydrophobic cations

METE1-2: Organic Cations (passive)
Note:
-VMAT and VAChT induction of substance into nucleus
-ACTIVE TRANSPORTER such as MRP1-4 takes hydrophobic anions and get them outside the cell .

-MATE1-2 : work as transporter of organic cations from outside to inside the cell.
-ENT1 + ENT2+ CNT1+CNT2+CNT3 : for entering nucleosides.
-OCTs at all : for organic ions.

Relevance of Drug Transporters

Definition : Modulation of transporter function through inhibition or induction could result in changes in drug absorption distribution and excretion--drug-drug interactions.

Imagine this drug transporter could happen

Increase or decrease the expression will affect at level of drug within the blood of the patient, that means if induction or the organic cationic take place, it will enter more and more , And vice versa.

In some drugs , they work induction or inhibition to transport, for example, the first drug we take, then we take the second drug and the indication works on its transporter, so it will affect the level of the drug in the body.

For drug - drug interaction, They can be inhibited or induced

For example, Drug A given in patient and Drug B ***inhibit*** the transportation of drug A Meaning that it is drug A that will not enter the body Or they ***induce*** transportation meaning that it is drug A that will enter the body .

1) A source of inter-individual variability in drug response:

expression level of protein is different between people ..... so expression level of transporter is also different between people..... This is our first source for a variety between patient. We encounter some patients, and the effect of the drug between them such as some people reach the effect to 5 and other 15....

Example. .. Women are different from men on MDR1 So, men have more p-glycoproteins than ladies … In women, this leads to higher drug concentration, better drug response, and even more side effects than men.

2) A source for nonlinear kinetic: [we will take about it later on.]

-P-gp (P- glycoprotein) MDR1

Explain: drugs generally enter the body, and 90% of them are taken by mouth and absorbed through the intestine (duodenum) or stomach (most cases are intestinal). But when the drug enters the cell, it finds itself under the effect p-gp.

Note : Whatever inhibition to p-gp means that p-gp is absent and that the drug concentration increases in the body and becomes toxic.

Example: statin ... because after taking the drug and then drinking grap fruit juice, the grap fruit inhibits pgp, and this enters the body 13 times more because it is not present, then the repelled substance will decrease .

• FDA concept paper on drug interactions recommends that new drug candidates be evaluated as substrates, inhibitors, and inducers of Pgp to assess the potential forclinical drug-drug interactions.

Every drug we put on the market needs to be tested if it is inducer or inhabitior or substrate to it

Clinical Study: P-gp Mediated DDI Involving Loperamide and Quinidine

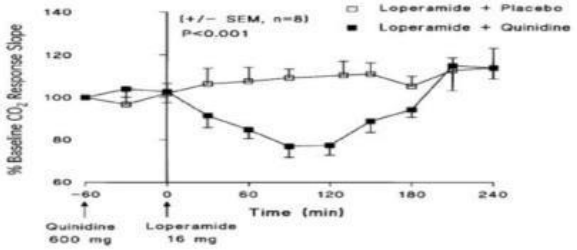


Fig 2. Effect of quinidine on slope of the carbon dioxide response curve after administration of loperamide after placebo *(open boxes)* or quinidine *(solid boxes)*.

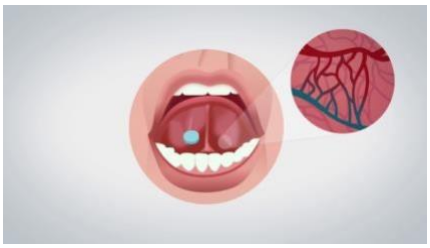
- LOP: potent opiate/anti-diarrheal; no CNS effects at normal doses
- When LOP (16 mg) given with QND (600 mg) AUC increased ~2.5 fold
- Respiratory depression produced by LOP only when co-administered with QND
- Authors conclude: QND inhibited the P-gp mediated efflux of LOP at the BBB
- Example of transporter mediated DDI with potential for toxic effect in humans

P-gp is mediated Drug – Drug interactions, involving (Lop, QND), if they are taken together, may toxicity occur.
Lop : drug to antidiarrheal
QND: drug to arrhythmia
Explnaning: lop is a substrate that will release outside, and if lop is taken with QND (It has nothing to do with lop but has to do with pgp), it will inhibit p-gp. As a result, the level of lop will become very high and the chance of a patient's respiratory depression is high and sometimes death may occur.

Route of administration (طريقة إعطاء الدواء)

The route is an important determinant of the rate and efficiency of absorption. It is divided into three categories :

A- **Alimentary routes**, such as oral, rectal, and sublingual (تحت اللسان).

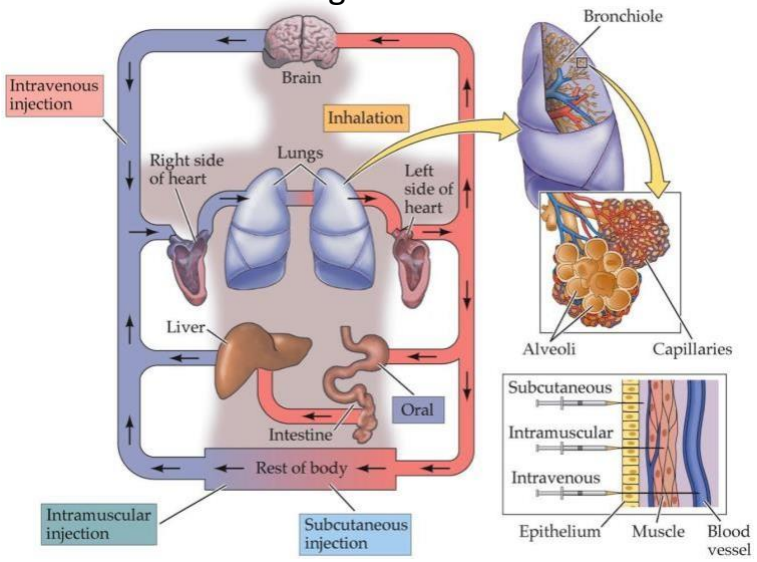


a. **Parenteral routes**, such as intravenous (in the vein), intramuscular (in the muscle), subcutaneous(under skin), and Intrathecal(in the vertebral column).

b. **Miscellaneous routes**, such as:

1. Topical administration, useful in treatment of local conditions , like ointments . (موضعي:كريمات)
2. By inhalation, which provides a rapid access to circulation , like : Ventolin , which is an inhaler takes as a beta 2 agonist .

Why does the drug taken as an inhaler have a fast response effect?
Because around each alveoli there is a huge number of blood capillaries that directly delivers the drug to our blood circulation , resulting in a fast drug response .



1-Oral

Oral routes are the most common, but it is the most variable and involve most complication to the tissue (like irritation), mainly the stomach acidity (that degrades some of the drug taken) and first pass effect at the liver.

1) The delivery of the drug into circulation is slow after oral Administration, so that rapid and high blood levels are avoided and adverse effect are less likely.
2) The advantages of Oral route is that it is considered the safest and the most convenient for the patients.
3) The main disadvantages are the absorption variation (when the patient suffers from constipation , the drug movement will be slower and more of the drug will be absorbed , while in case of diarrhea less will be absorbed) and irritation of mucosal surfaces.
4) depends on **1) genetics. 2)pathophysiology** of the patient.
5) Genetics : females have less p-gp than men , so more effects of the drug are felt ..

6) Pathophysiology : like having peptic ulsers , chronic diseases and others that effect the stomach acidity .
7) Ex : doxycycline is drug given to patients to treat acne, but causes in irritation in the esophagus in 5% of the peoplulation it , so it is recommended to a lot of water with this drug.
8) Glucophage is another drug given in gradually increased doses , so the patient can build tolerance against its effects like irritation and diarrhea .

What is liver's first pass effect ?

It refers to the detoxification and metabolization of a portion of the drug after its taken (especially orally).

More explanation : After the drug is administrated (especially orally) , part of it goes to the stomach then duodenum to be absorbed . Meanwhile a bigger portion is delivered to the liver where its converted from lipophilic to hydrophilic (inactivated) then eliminated from our body with urine (through the kidney) .

So when a drug like Aciclovir (antiviral drug) is taken , only 15% of the dose affects the body , the other 85% are either degraded by the liver enzymes or pumped out by p-glycoprotein .

2-Sublingual route

Some drugs are taken as small tablets which are held under the tongue (sublingual tablet).

Ex:- Nitroglycerin, as a softer sublingual tablet [2 min disintegration time], may be used for the rapid relief of angina.(ذبحة صدرية)

In the angina case, the heart suffers lack of oxygen with increased demand , so nitroglycerin causes vasodilation which reliefs the pain .

And because we have a good blood suplly sublingually , the drug will enter the circulation **faster** than orally and the pain will vanish in about 2-5 mins.

Advantages:

1-Avoid hepatic first pass metabolism. (prevent absorption variations)

-Because the liver detoxification depends on the liver enzymes which is proteins, and this proteins are variable between people, the activity of the first pass metabolism are variable between people too.
That should explain the variability of the oral route.

2- Rapid absorption - Because of the good blood supply to the area, absorption is usually quite rapid.

3- Drug stability - pH in mouth relatively neutral , while in the stomach its quite acidic.

4-Rectal route

Most commonly by suppository.

Advantages:

1- By-pass liver - Some of the veins draining the rectum lead directly to the general circulation, thus by-passing the liver. Reduced first-pass metabolism effect.(explained lastly)

2- Useful - This route may be most useful for patients unable to take drugs orally (unconscious patients) or with younger children (effective in giving the right dose to that people) and if patient is nauseous or vomiting.
-useful way with patient with Inflammation of the inner ear, to avoid vomiting during giving the drug

4-Parenteral routes (Injections)

When to use this routes and mainly INJECTIONS :

A. Drug is poorly absorbed through mucous membranes (hydrophobic).
B. To avoid first-pass metabolism inactivation in the liver.
C. To avoid uncertainty about amount absorbed (by avoiding first pass metabolism).
D. To give a rapid response , in emergent cases .
E. The drug causes vomiting, ex: anticancer drugs.

The main disadvantages are:

a. More rapid absorption may lead to increase adverse effect .

b. A sterile formulation and aseptic techniques are required.(يستوجب تعقيم عالي)

** It Requires a very practical provider, to avoid emboli (air given with injection) and sepsis (bacterial contamination leading to excessive bacterial growth in the blood)

If you don't sacrifice for what you want , what you want becomes the sacrifice .

هذا و بالله التوفيق و له الحمد و المنة