PHARMACOLOGY
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RECALL:
Medicines differ in their characteristics, either:

1. **Narrow therapeutic index**: if the dose of toxicity is close to the dose of the effect \([\text{TD50 close to ED50}]\)
   SO, margin safety is a little bit.

2. **Wide therapeutic index**: if the dose of toxicity is far away from the dose of the effect \([\text{TD50 far away to ED50}]\) SO, margin safety is high.

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

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

1. Digoxin (0.8 – 2) ng/ml
2. Cyclosporine (100-400) ng/ml
3. Quinidine (2-6)
4. Carbamazepine (4-10)
5. Phenotin (10-20)

**How do we measure margin safety or therapeutic index?**
- It is measured by concentration of drug in plasma

Ex.: In digoxin (0.8 – 2) ng/ml

(ف بهاي الحالة بقدر اعطي الجرعة الي بدي اياها من الدوا لا حدوث التسمم الدوائي قليل بكون)

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

![Graphs showing therapeutic index](image-url)
Now, let’s start with

**Pharmacokinetics**

It describes the condition of how the drug moves inside a person [contains 4 stages]:

1. **Absorption** (in most cases absorption take place in intestine and stomach)
2. **Distribution** (if drug reach the plasma, it will distribute to target tissue in the body (periphery – 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:

**DRUG TRANSPORT**

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

- **Drug can cross cellular membrane** 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. **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

**Diagram:**
- **Orange color**: active transporter
- **Blue color**: passive transporter

**Note:**
- VMAT and VAChT induction of substance into nucleus
- ACTIVE TRANSPORTER such as MRP1-4 takes hydrophobic anions and get them outside the cell.

**Legend:**
- MRP1-4: hydrophobic anions transporter
- MDR1, MDR3 and BSEP: hydrophobic cations
- MATE1-2: organic cations
- ENT1, ENT2, CNT1, CNT2, CNT3: for enteri
- OCTs at all: for organic ions.

**From picture:**
- MRP1-4: hydrophobic anions transporter
- MDR1, MDR3 and BSEP: hydrophobic cations
- MATE1-2: organic cations.
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

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.

- 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.

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

- P-gp (P-glycoprotein)

Explain: drugs generally enter the body, and 90% of them are taken by mouth and absorbed through the intestine 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 grapefruit juice ... the grapefruit inhibits pgp, and this enters the body 13 times more because it is not present, then the repelled substance will decrease.
P-gp is mediated DDi involving (Lop, QND) IF they are taken together, May toxic occur

Lop: drug to antidiarrheal
QND: drug to arrhythmia

Explaining: When we only give lop, it will become inhibition to p-gp, meaning the amount of lop that enters the body is enormous and may happen respiratory depression. If lop take with QND (It has nothing to do with lop but has to do with pgp) It is inhibition to p-gp. 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**

- An important determinant of the rate and efficiency of absorption, divided into three category:

  A- **Alimentary routes**, such as oral, rectal, and sublingual.
a. **Parenteral routes**, such as intravenous (in the vein), intramuscular (in the muscle), subcutaneous (under skin), and Intrathecal (inside backbones).

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

1. **Topical administration**, useful in treatment of local conditions (موضعي: كريمات)
2. **Inhalation**, provides a rapid access to circulation (take the drug with inhaler through lungs rapidly, it’s an effective and fast way) like ventolin.

Another type of drugs taken by similar way is intranasal (take the drug by nose).

— At the alveoli there are a lot of blood supply, that makes the inhalation very fast way to achieving the activity.

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**Again:**

1. **Oral**

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

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.  

The advantages of Oral route consider the safest and the most convenient for the patients.
The main disadvantages are the absorption variation and irritation of mucosal surfaces. It depends on the 1) genetics. 2) physiology of your patient. For example: the ladies have p-gp differ than men. Also depends on the food. Some patient has a constipation (that makes drug being long in the body and increase absorption) or diarrhea (that make the drug extracted quickly, and decrease the absorption).

Doxacyclin is drug that given to patients with acne, but in 5% of people it caused Heartburn, so we recommend take a lot of water with this drug.

**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.

In the angina case, the heart suffers lack of oxygen, so we make a dilation to vessel by nitrate drugs like nitroglycerin. Under the tongue we have a high blood supply, so the drug enter the circulation faster than orally and the pain go-out in about 5 min.

**Advantages:**

1- Avoid hepatic first pass metabolism.

- First of all, the drugs enter the stomach —> to the intestines (where drug absorption takes place) —> to the liver (drugs cemetery) by portal vein. The liver do detoxification (because the drug is a toxic material) and destroy the drugs.

- So the drug is reduced by stages (stomach-> intestines-> liver) and the amount of drugs absorption are more less than the drug has taken.

- 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.

- The first pass metabolism converts the drug from lipophilic to lipophobic (water soluble) then go to the kidney which secretes it out of the body.

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.
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.
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 and sepsis

**FROM INTERNET:**
“The first pass effect (also known as first-pass metabolism or presystemic metabolism) is a phenomenon of drug metabolism whereby the concentration of a drug, specifically when administered orally, is greatly reduced before it reaches the systemic circulation. “
+ it’s depend on liver enzymes , and enzymes differ from one to another (cuz we are different genetically.
Alsa it convert the drug from lipophilic to lipophobic so when drugs reach kidney we lost it