10

Pharmacology

Doctor 2017 | Medicine | JU

Sheet ○ Slides

Done By

Tamer Barakat

Contributed in the Scientific Correction

Abdul Aziz ALShamali

Contributed in the Grammatical Correction

Abdul Aziz ALShamali

Doctor

Dr. Alia

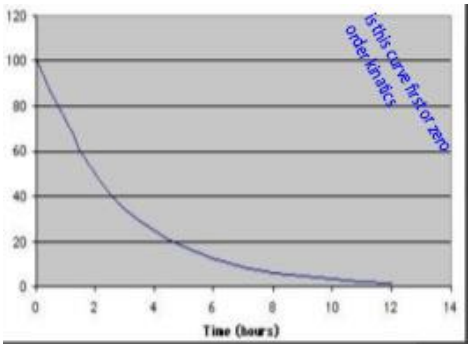
Refampin is used to treat TB not malaria (Quinacrine is used for malaria)

Elimination:

- ⇨ It's the opposite process of absorption. It's the process in which drugs are transferred from internal environment (the body) to external one.
- ⇨ Elimination can take a place by:
  1- Kidney (urine), which is the most important way. **The drug needs to be polar (water soluble)**, But why? Because if the drugs are lipid soluble, they will be reabsorbed from the urine, that's why modifications (phase I, phase II)occur.
  2- Bile, intestine ***(drugs that are not absorbed after oral administration or that are secreted directly into the intestines or into bile are eliminated in the face)***, lungs or through mother's milk. **The drug needs to be lipid soluble**.

- ⇨ **Metabolism** usually results in inactive metabolites which are also water soluble and, therefore, excreted by the kidneys.
- ⇨ Any disease that affects the function of the kidney will affect its elimination.
  Kidney disease => low elimination => high active drug or metabolites => toxicity
  That's why some drugs have restricted use in patients with kidney dysfunction.
- ⇨ Like absorption, elimination also depends on the PH. Weakly acidic drugs are excreted faster in alkaline urine, why? Because when they get ionized in the urine, they can't diffuse back to the unprotonated form. Hence, they can't diffuse back to blood. The same occurs with alkaline drugs through acidic environment.

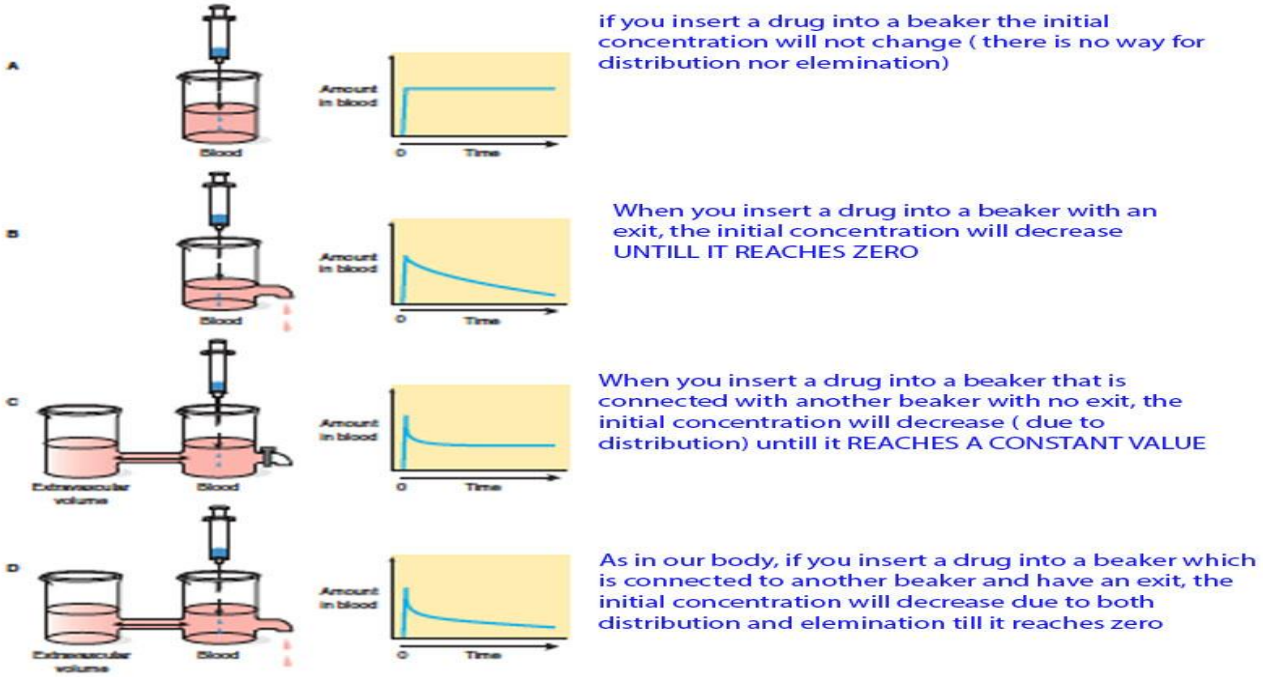
- ⇨ **Elimination** of drugs usually follows **first order kinetics**, in other words, the **higher** the drug **concentration**, the **higher** the **elimination** $([drug] \propto elemination)$
- ⇨ **Half-life ($t_{1/2}$):** is the time needed for the drug concentration to drop 50%. For instance, the $t_{1/2}$ of this curve is 2 hours (Conc. dropped from 100 to 50 in 2 hours).



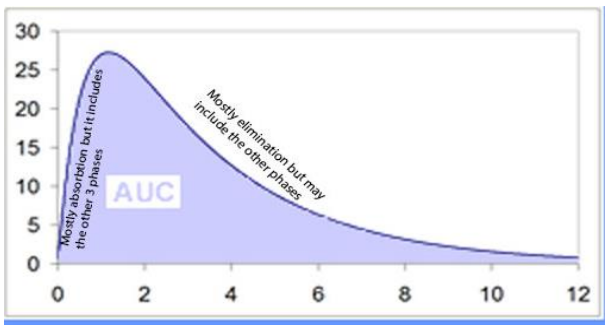
- ⇨ Some drugs, such as **Aspirin**, follow **zero order kinetics**, in which the elimination of the drug doesn't depend on the concentration, in other words, the elimination rate is fixed.
  But why do some drugs follow first order while the others follow zero order? It depends on **the way of transport**. First order drugs use active or passive diffusion to get into the urine, so the higher the conc. is plasma, the higher the amount that will

diffuse to urine. On the other hand, zero-order drugs need transporters to move to the kidney, so no matter what the conc. of the drug is. The transporters are responsible for the amount found in urine. You can think of it this way, even if you have a higher drug conc. in zero order, the transporters won't increase (saturable), so the amount that reaches the urine is constant.

- ⇨ Zero-order depends on transporters *(the capacity, rate of function and the availability)*.
- ⇨ From the equation $t_{1/2}=0.7 * \frac{V}{CL}$ you can see that **half time** depends on both **Clearance** and **apparent volume**.
- ⇨ Clearance (CL): It's the **VOLUME** of plasma from which a substance is completely removed per unit time, which is usually mL/min.
- ⇨ $CL = \frac{Rate\ of\ elemination}{[drug]}$ *(Remember that rate of elimination also depends on distribution of the drug).*
- ⇨ The following picture helps you understand the curve of elimination in your body:



- ⇨ Always remember that the **4 phases** of the drug **(absorption, distribution, metabolism and elimination) happen at the same time** (overlapping). However,the difference is in the rates. To illustrate. the absorption would be high at the beginning, while the elimination would be low (but it still exists). What we see in the conc./ time curve reflects the net of what happens to drug's concentration.

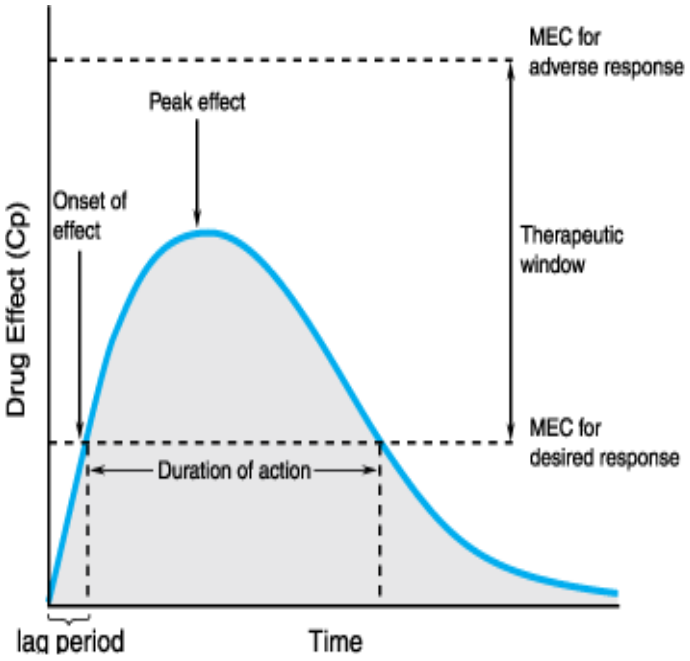


Dosage regimens:

A- Single Administration:

⇨ Let's start by the following antibiotic pill concentration in a patient:

1- The [drug] will be absorbed as the **concentration below MES(Minimal Effective Concentration)** in the absorption phase is **called** the **lagging period** (no effect). Then the [drug] will become higher than MES and we would enter the **Therapeutic window** (the effect of the drug continues through it).



Sub-therapeutic conc.: conc. below MEC (no

2- We would reach the peak conc. (highest conc. of the drug)

3- Elimination rate **>** absorption rate. Therefore, we exit the therapeutic window and finally we reach zero.

⇨ The time required for full elimination of a drug depends on the drug itself, but in terms of half-lives, it actually would need 5($t_{1/2}$) s (**I.e.** *the first $t_{1/2}$ around 50% stays in body, the 2nd around 25%, the 3rd 12.5%, the 4th around 6.25%. Finally, 3% remain after the fifth half-life (neglectable))*

⇨ The duration of a drug's action is determined by the time period over which concentrations exceed the MEC (therapeutic window).

⇨ **MEC (Minimal Effective Concentration)** exists for each adverse response. Further, if the drug's concentration exceeds this, a toxicity will result *(Note that MEC for adverse effect is also called maximum safe concentration)*

⇨ The therapeutic goal is to obtain and maintain concentrations within the therapeutic window for desired response with a minimum level of toxicity.

⇨ Drug response below the MEC for the desired effect will be sub-therapeutic**.**

B- **Frequent** administration:

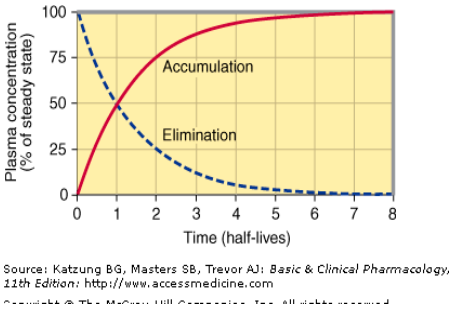
The time course of drug accumulation and elimination .

Solid line: Plasma concentrations reflecting **drug accumulation** during a constant-rate infusion of a drug .50% of the steady-state concentration is reached after one half-life, whereas 75% after two half-lives and over 90% after four half -lives. This means, if you take a pill and wait for 1 $t_{1/2}$, the [drug] in your body would be 50%, at that moment, if you take another pill and waited for another $t_{1/2}$, the [drug] in your body would be 75% (50% of the new pill would remain, while only 25% would remain from the old pill (because 2 $t_{1/2}$ passed from its perspective). If you continue this approach with a third and a fourth pills, you would reach the steady state.

You need to give 1 pill every $t_{1/2}$ to reach the steady state (usually it takes 4-5 half-lives).

Dashed line: Plasma concentrations reflecting drug elimination after a constant rate infusion of a drug had reached steady state .Fifty percent of the drug is lost after one half-life, 75% after two half-lives ,etc.

The **"rule of thumb" suggests** that four/five half-lives must elapse after starting a drug-dosing regimen before full effects will be seen is based on the approach of the accumulation curve to over %90 of the final steady-state concentration.



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

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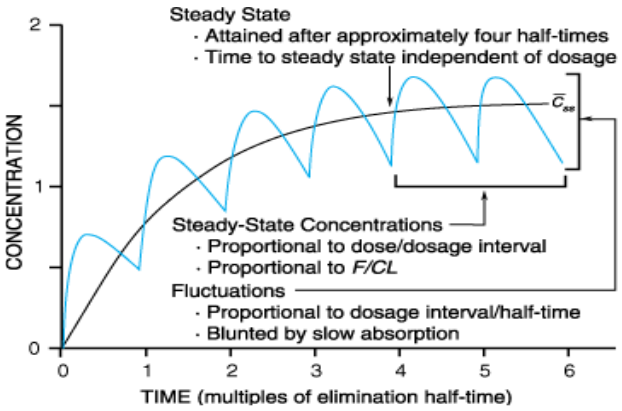
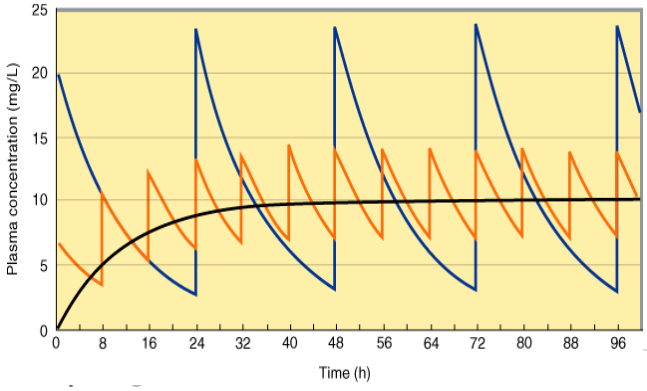
- ⇨ Maintenance dose: after reaching the steady state, we need to preserve it by giving a pill every $t_{1/2,}$ this continues until the treatment is over.
- ⇨ Loading dose: its used to get to the steady state faster by letting patient take 2 pills together to reach the steady state initially, then he can use the maintenance dose to preserve the steady state.



⇨ ***Note* that this method can't be used for toxic drugs because we reach high conc. at first**



The fluctuations are always present in frequent administration method, so we need to make sure the top of it doesn't reach a toxic level, also that the bottom of it doesn't get under MEC

(for drugs that reach a toxic level, frequent administration is not usually used)

Sources of Variability in Therapeutic Responses

Similar drugs usually produce similar qualities of responses in patients but might produce different intensities and duration of effects. The difference effects are either due to *the way of administration* or **related to the patients.**

1- **Body weight and size**
2- *Dose، dosage schedule, route of administration and formulation.*
3- *Results from repeated administration of drug (drug resistance, drug tolerance-tachyphylaxis and drug allergy.*
4- Diurnal variation "Chronopharmacology."
5- **Age and sex of the patient.**
6- Drug reactions**.**
7- *Drug interactions. Chemical or physical, GI absorption, protein binding or distribution, metabolism (stimulation/inhibition), excretion (pH/ transport processes), receptor (potentiating/ antagonism), change in ph and electrolytes, other drugs ،diet ،and environment.*
8- **Placebo effect.**
9- **Intercurrent illnesses (condition of health), if a patient has a disease in liver, you shouldn't give him a drug that is eliminated by it.**
10- Tolerance.
11- **Genetic or radical factors. "Pharmacokinetics"**

So why did the Dr go back to **metabolism**? to emphasizing its **importance in**:

1- Site of Drug-Drug interactions:

A- At the site of absorption. For instance, tetracycline/doxycycline are antibiotics that interact with Ca ion and precipitates, that's why you should take Ca supplement capsule at the same time as them.

B- During metabolism/biotransformation in Cytochrome P450.

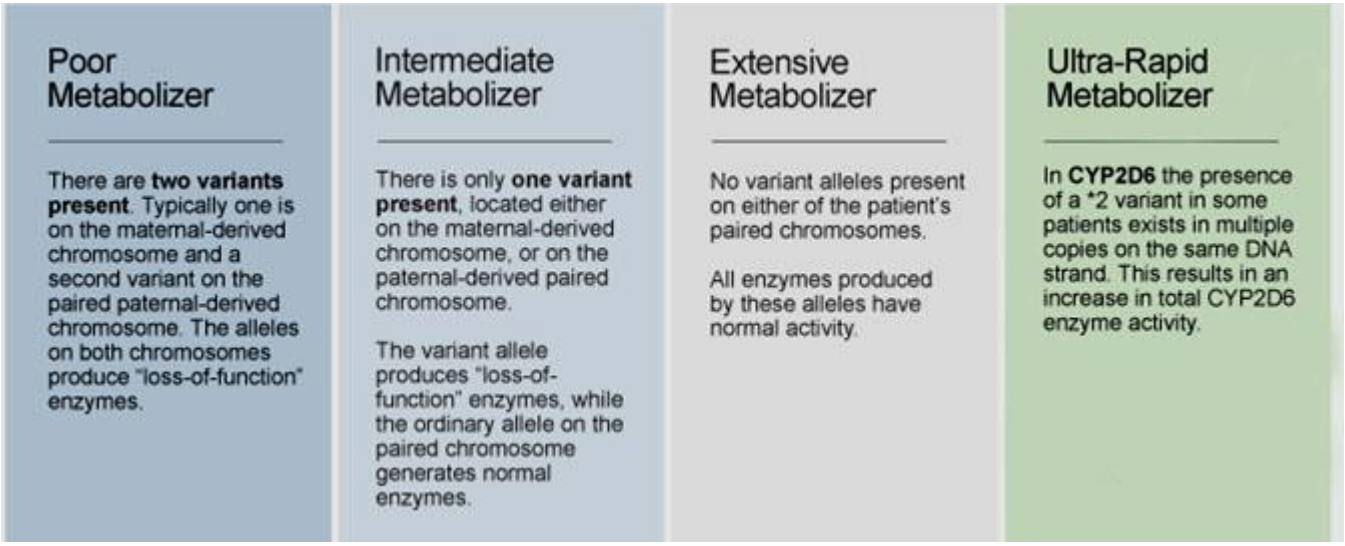
C- At the site of action. *(All the antagonistic and active effect of pharmacodynamics occur here).*

D- During excretion, if we have two drugs that use the same transporters to leave the body, they will compete on binding to the transporters, the one with higher affinity would be excreted first. E.g. **digoxin** (heart failure drug) and **quinidine** (arrhythmia drug), since quinidine has higher affinity, it will be excreted first. In the same time, digoxin would be toxic.

E- During distribution, mainly the affinity of the drugs to plasma proteins (warfarin vs. phenylbutazone) **or** (aspirin vs. methotrexate "chemotherapeutic agent") .

2- The site affecting the way we give the patient a drug (mainly in **phase I**) **due to:**

A- Genetic polymorphism



⇨ There are 12 isoforms for P450, each of these isoforms has 4 phenotypes (polymorphism).

b- Inducers/inhibitors that affect P450.

Adverse Effect:

⇨ **Undesirable** effect that may be even dangerous & can occur. They can be **predictable** as the ones **mentioned in the drug's leaflet**, or **unpredictable**; which happens mostly due to patient's **hypersensitivity or allergy**.

⇨ Adverse effects also take place with overdoses (toxicity).

⇨ Giving a drug with adverse effects depends on the condition of the patient, so the question that you shall ask yourself before prescribing a drug is:

Does the benefit of the drug outweigh the adverse effect?

*This is called **Risk-Benefit ratio**.*

⇨ A good example is chemotherapeutic drugs, they kill both cancerous and normal high replicating cells.

In Pregnancy

Table 27.1 FDA classification on safety of medicines used in pregnancy.

FDA Category	Comments
A	Human studies did not show a risk to the developing fetus in pregnancy
B	Animal studies did not show a risk to the developing fetus in pregnancy but there are no studies done in pregnant women
C	Animal studies did show harmful effects on the developing fetus in pregnancy but there are no studies done in pregnant women. Medicine ***should be given*** if the potential benefits justifies the potential risks to the fetus
D	Human studies did show harmful effects on the developing fetus but the benefits from use in pregnant women may be acceptable despite the risk (Examples: the medicine is used in a life-threatening or serious illness)
X	Both human and animal studies show serious harmful effects on the developing fetus. The medicine is ***strictly prohibited*** in pregnancy **(Examples: Chemotherapy drugs and oral isotretinoin.)**

→ **Paracetamol**

Sign NOT to get pregnant while using any of X drugs

X drugs:

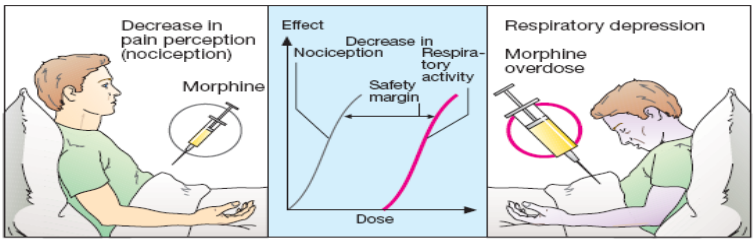
A- thalidomide treats nausea and vomiting, but causes fetuses to lose their limbs :/
Later on, they discovered that this drug can be used to treat multiple myeloma (THE PATIENT MUST TAKE CONTRACIPTIVES WITH THIS DRUG)

B- isotretinoin, used to treat acne, causes abnormal fetuses

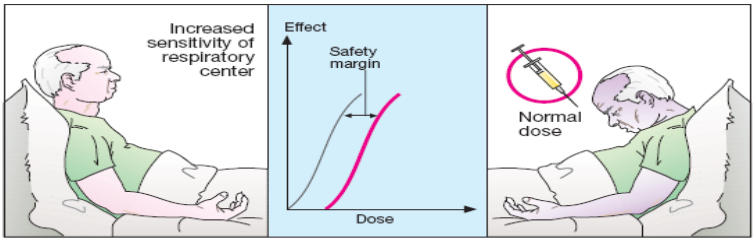
Variation of drug responses due to age:

1- elderly people have some pharmacodynamic changes in their bodies (receptors) that make them more sensitive for some types of drugs. E.g. Painkillers and opioids.

⇨ If you give a dose of morphine for a young and an elderly patient, you might find that the dose is toxic for the elderly, but it isn't toxic for the young, that's due to change in safety margin curve.



A. Adverse drug effect: overdosing



B. Adverse drug effect: increased sensitivity

⇨ What about pharmacokinetics?

- We have decrease in water content, so the distribution would be different.
- increase in lipid mass (drugs that are lipid soluble can accumulate in more places.
- metabolism usually declines with age (low active P450) => decrease of clearance => high active drug.
- elimination rate which is measured by GFR[1] decreases with age. The decrease can reach 50%. However, it depends on the patient
  - 30% have low decrease, 30% intermediate and 30% high decrease.

Age	Scr	CrCl
30	1.1	65
50	1.1	53
70	1.1	41
90	1.1	30

Note that Serum creatinine didn't change with age, unlike creatine clearance

WE SHOULD PUT AGE IN CONSIDERATION WHEN PRESCRIBING A DRUG/DOSE.

[1] **Glomerular filtration rate** is a test uses **creatinine** clearance to check how well the kidneys are working. Specifically, it estimates how much blood passes through the glomeruli each minute. It's used to take decisions regarding the dose of drugs.