Medical Committee
The University of Jordan

DATE: / /

PHARMACOLOGY

Lecture No.: 5

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Pharmacokinetics –Lecture #5-

Question: If we mistakenly overdose a patient, how do we decide if we need to acidify their urine or alkalize it? By knowing the pharmacology of the drug, knowing the pharmacology of the drug will tell us.

Question: When plasma protein concentrations are lower than the normal, the total drug concentration will be lower than expected but the free drug concentration will….???

The total is lower because the free is the part that undergoes elimination, when the free part of the drug is eliminated; it causes dissociation of the DP complex to give free drug + free protein

Here is the DP complex, when the free fraction of drug is eliminated because the protein is low, the equilibrium will shift to the left giving free drug, the ratio would be the same. The total amount of the drug goes down because the free is eliminated, but the free will remain, because the albumin or the protein is low and it is not enough to bind the drug.

✳ the free fraction of drug undergoes elimination and distribution and causes the pharmacological effects.

✳When the free fraction is distributed, it's no longer present in the plasma and so we don't measure it. So the total drug concentration is low, what we measure is what's in the blood/ plasma and not what's in the tissue.

-From the previous lecture:

Clearance: is the volume of blood that is completely cleared of drugs per unit of time. <u>It's not only elimination; it is both elimination and distribution</u>. We are talking about the disappearance of drugs from blood and this could occur by elimination from the body, or distribution from blood to tissues. In both cases the drug is not in the plasma.

-Types of Clearance:

1) Renal clearance 2) Hepatic clearance, and there are other types of clearance.

- Hepatic Clearance (CL_H) = Q *(Ci–Co)/Ci

Q: the blood flow, hepatic blood flow is constant for a particular person under normal conditions; so it does not change whether in or out -and for that we take it out as a common factor-.

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Ci: is the concentration of the drug in blood going into the liver.

Co: is the concentration of drug in blood leaving the liver.

BUT: (Ci-Co)/Ci = *E*xtraction *R*atio (ER) → **SO :** $CL_H = Q * ER$

Note: **Q=** 90 L/hour (90 liters of blood go to the liver per hour). How many liters per minute? 90/60=1.5 L of blood go to liver per minute -it is a large volume of blood-. This is in a 70 Kg man, it could increase or decrease depending on many factors.

ER is a measure of the first pass effect:

ER= CL liver/ Q …… (CL liver= CL_H)

There are 3 variables; if you know 2 you can calculate the third.
If the drug has an ER value > 0.7 then there is first pass effect, and the drug has a "high hepatic ER"
If the drug has an ER value < 0.3 then the drug has a "low hepatic ER"
If the drug has an ER value in between (0.3 < ER <0 .7) then it has an "intermediate hepatic ER"

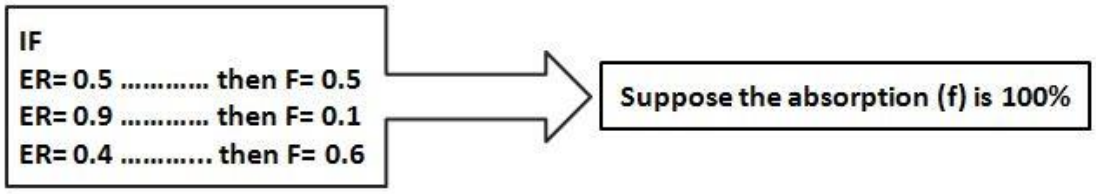
Bioavailability: it is a fraction (percentage)

- A 100% bioavailable drug means that the whole dose goes to the systemic circulation.
- A 50% bioavailable drug means that 50% of the dose goes to the systemic circulation.

How is bioavailability calculated? [From the ER and the extent of absorption (f)].

From this equation ……F = (f) * (1-ER)

F: Bioavailability f: the fraction or percentage of drug absorption.



? When we say a drug isn't completely absorbed (the dose is 90% absorbed for example), this is not first pass effect, nor hepatic metabolism or hepatic excretion, or gastrointestinal metabolism, but the drug is not absorbed completely.

Question: Suppose a drug is 90% absorbed (f= 0.9) and 70% extracted by the liver, what is the bioavailability of the drug?

Answer: F= 0.9 * (1- 0.7) → 0.9 * 0.3= 0.27

Question: A drug is 80% absorbed from the GI tract (f= 0.8) and ER= 0.67 ((about 2 thirds)) (it is for morphine), what is the bioavailability (F) of the drug?

F = 0.8 * (1- 0.67) = 0.26

Because 2/3s of what enters is extracted and so 1/3 or 0.33 remains, but only 0.8 of the 0.33 is absorbed.

-Types of Elimination:

Types of elimination: #first-order elimination.
#zero-order elimination.
} You have to know the difference.

1-**First-Order Elimination:** means that the rate of drug elimination at pharmacological doses or therapeutic concentrations is directly proportional to the amount of the drug in the body, this occurs with many drugs at therapeutic concentrations. There is no saturation of the first-order elimination process.

Example:

If the fraction eliminated= 0.3

If the patient is given 100 mg of the drug; 30 mg will be eliminated per unit time.

If 1000 mg; then 300 mg will be eliminated per time unit, If 10000 then 10,000 * 0.3= 3000 mg will be eliminated.

That fortunately occurs with most drugs at therapeutic concentrations **When we talk about 1st or zero order elimination, we consider the therapeutic concentration (which is the concentration that gives the pharmacological effect)**

In other words: Constant **fraction** "not amount" of the drug is eliminated per unit time.

Equations:

- Ab: Amount of the drug in the Body.

This is differentiation (تفاضل): $-dAb/dt \sim Ab$ [-d (amount of drug in the body)/ d (time)]... means:

The rate of change in the amount of drug in the body with time [which is the rate of elimination (-dAb /dt)] is proportional to the amount of drug in the body, as mentioned in the definition above.

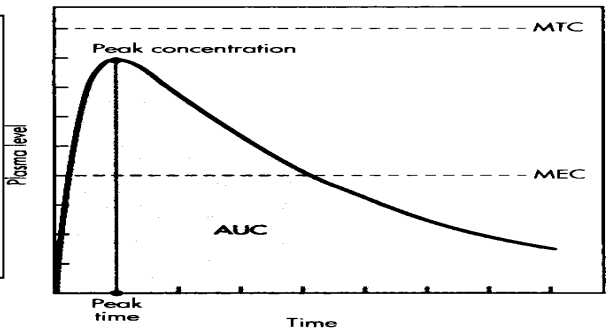
*the negative sign is to indicate that the amount of the drug in the body decreases with time (doesn't increase).

❓ To make the proportional relation an equation we use a constant (k) → - dAb/dt= K . Ab

K: first-order elimination rate constant. "NOT the elimination rate".

Remember in first-order elimination, a constant **fraction** "not amount" of the drug is eliminated per unit time. This fraction is the K and its unit is (fraction per time)

NOTICE that we are talking about elimination not absorption or any other thing, exactly when the elimination is greater than the absorption. "the left portion of the curve."



*integration of this equation (-dAb/dt = K . Ab) from time 0 to time t gives:

$$Ab^t = Ab^0 * e^{-kt}$$

Abt: amount of the drug at time t.
Ab0: amount of drug at time 0. (The bioavailable dose- for example not the 100 mg given to the patient but how much of the 100 mg reached the circulation)
e ^ -kt : an exponential term, e to the power -kt
So, if we know (K), we can calculate the amount of drug in the body circulation at any time, because 3 out of 4 variables are known (Ab^0, K, t (we determine the time we want) so we can calculate the 4th (Ab at time t).

*We need this to determine the frequency of administration (how many times the dose should be given), not only for dosing. After a certain number of hours the amount of drug in the body won't be enough to produce pharmacological effects, so the patient must be given another dose.

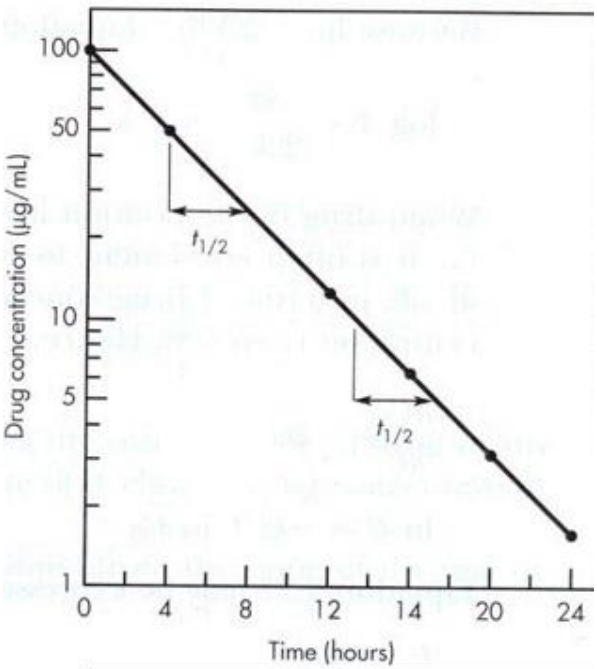
✨Dividing this equation ($Ab^t = Ab^0 * e^{-kt}$) by volume distribution of the drug (V_D) gives:

$Cp^t = Cp^0 * e^{-kt}$ ..... (amount/volume=concentration)
Cpt: concentration of the drug in the plasma at time t.
Cp0: concentration of the drug in the plasma at time zero.
NOW we work with concentrations. If we know Cp^0 and K we can calculate Cp at any time.

*After intravenous administration we will have a curve like the following:
#the time axis is normal: distances between numbers are equal units.
#the concentration axis: if it is normal the 50 should be in the place of the10, we call this: logarithmic scale.

**This plot is called semi logarithmic (Why? Because the Y axis is logarithmic while the X axis is normal), and we do that to have a straight line.

♻ Instead of calculating (logs) multiple times for each concentration, we plot the concentrations on a logarithmic scale (for simplicity) as if you calculate the (logs) for every concentration separately. Meaning the 100 and 50 took those positions on the Y axis because if we plot the logs of 100 and 50 on a normal scale they will take those positions as well, so instead of taking the logs of concentrations and plotting them to give a straight line, we plot the concentrations on a logarithmic scale and it will give a straight line. ***With first-order elimination***



*In the case of IV administration the curve will look like that, but there is no such thing as 100mg/mL concentration at time zero; at zero time from injection the concentration is zero.

❗ So! Where did the 100 come from? When a dose is given Intravenously, after 10 minutes we take a blood sample from the patient, then another sample after 30 minutes, then another after an hour and so on (this goes on for up to 48 hours) so we obtain a series of blood samples at different times and we plot them.

Extrapolation (extending the line backwards till it intersects with the Y axis) of this curve back: gives Cp0 (Cp0 is the value of the Y intercept) (this is not a real Cp0), what does this tell us? If the body is like the beaker we discussed last time, and we put the dose instantly and stir (dissolve it), with fractions of a second it'll be distributed, that concentration is equal to the concentration at time zero.

☑What is the benefit of this concentration? We need it to calculate the volume of distribution of the drug V_D; dividing the dose by the extrapolated Cp^0-NOT REAL– gives VD (also not real).

$V_D = Ab / Cp^0$

✓In brief: from a single dose (given intravenously not orally), take a series of blood samples, plot concentration with time, extrapolate the curve back to give Cp0.

Note: normally, we do not start blood sampling from zero time but after zero.

✨ How do we tell if the elimination is first-order elimination? By plotting the concentrations on a logarithmic scale vs time, if the result is a straight line then it's first-order elimination.

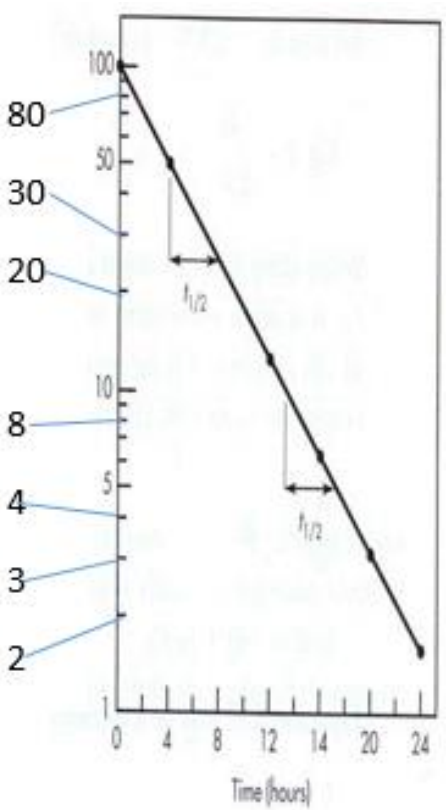
To read the Y axis of the previous curve:

Note the X axis starts from 0 but the y axis starts from 1. Note2: after 100 on the logarithmic scale comes 1000 (so this is how we read the scale 12345678910>20 30 40... 100 > 1000 2000... and so on)

❓ Straight lines are easier to work with for example we can get multiple pieces of information from this straight line:

1-<u>volume distribution</u> = dose/Cp^0 (Cp0 is the value of the Y intercept of the extrapolated line backwards)

2-<u>Half life</u>, 4 hours because it took the drug 4 hours to decrease in concentration from 100 to 50.
3- we can measure <u>K</u> from this curve (<u>the slop</u>).



4- and from V_D we can know where the drug is distributed

Remember: clearance is not only elimination

- CL (clearance) = rate of elimination /Cp (plasma concentration) → rate of elimination = CL * Cp
- $-dAb/dt = K.Ab$
- (-dAb/dt): the rate of elimination of the drug from the body.
- So: K * Ab = CL * Cp ..... assuming the elimination is first-order.
- CL = k.Ab/Cp ..... (but Ab/Cp=VD) So → $CL = K * V_D$

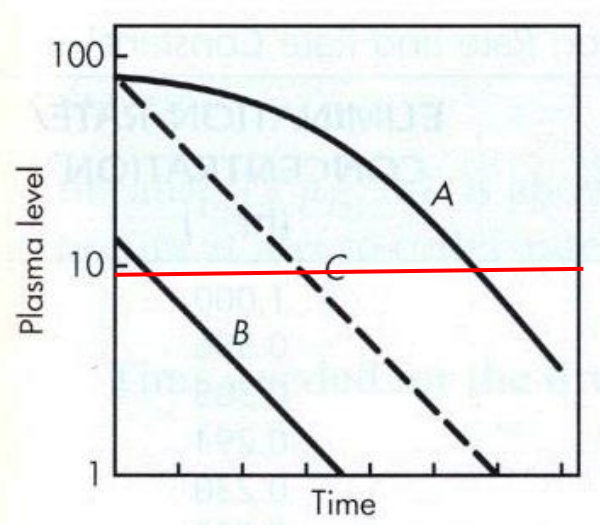
✓**We proved that:** Elimination rate + distribution both affect drug clearance in the blood.

2-Capacity-Limited Elimination: also called zero-order elimination, where a constant amount (NOT a fraction) of the drug is removed from the body per unit time.

[The plot of Log concentration Vs time is not linear]

Capacity-limited elimination is also called:
1. Zero-order elimination
2. Saturable elimination (first-order elimination is not saturable)
3. Dose -or concentration- dependent elimination
4. Non-linear elimination (first-order elimination plots are linear)
5. Michaelis-Menten elimination –related to enzyme kinetics and Michaelis-Menten constant, they apply to drugs that undergo zero-order elimination because the enzymatic reactions in the body follow zero-order kinetics.

- (B+C) → first-order elimination (straight lines indicate first-order elimination).
- (A) → zero-order elimination; it's not a straight line. Notice how at high concentrations (at the saturation level and above) (at 100 for example) the elimination is slow because a constant amount is eliminated per unit time (zero order elimination) so it takes the drug more time to be eliminated. But when the concentraion drops below the saturation level (below 10 for this example) elimination becomes (first-order).



What charactarises zero-order elimination? The change in the type of elimination as concentration decreases. So the curve isn't a straight line but multiple straight lines.

What is the problem with zero-order elimination? If the dose is large, it takes a long time to be eliminated from the body. In fisrt-order elimination, whatever the dose (100mg or a 1000mg) will be eliminated from the body after 4 half lives.

Rate of elimination of the drug in the body with time (- dAb/dt) is constant (=k0) where k0 is the zero-order elimination rate constant. The rate of elimination is not proportional to the amount of drug in the body but a constant amount is elimiated per unit time, because of saturation of the elimination process.

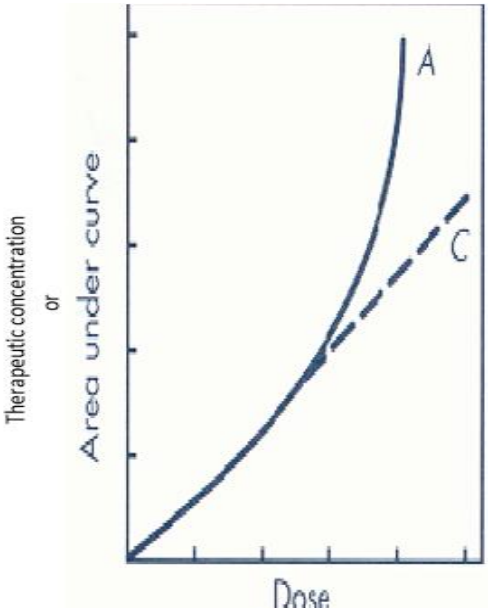
👈First-order elimination is better than zero-order elimiantion👈because it doesn't lead to prolongation of toxicity. Fortunately, few drugs undergo zero-order elimination at therapeutic concentrations (aspirin,phenytoin, alcohol and few others). Most of the drugs at therapeutic concentrations undergo first-order elimination.

**Saturation of the elimination process :suposs that the drug is actively secreted in the urine, it needs a carier, the carier can transport 2mg/hour, if you give it 50 mg it needs 25hours,100 mg need 50hours, 1000mg/500hours, it's a constant fraction.

- Michaelis-Menten equation applies to zero-order elimination, but the terms CL and VD can't be used with zero-order elimination.
- Rate of elimination (V)(the rate of the enzymatic reaction)=(Vmax*C)/(Km+C)
  Vmax: the maximal velocity of the reaction. (Elimination process)
  Km: the substrate concentration at which the rate of the reaction (the elimination rate) is 50% of Vmax.

❓ if a patient is given a certain dose of drug and then we measure the therapeutic concentration and find out it's not enough, what is the change in the dose needed?
Ex: if the patient is given 100mg of the drug and the therapeutic concentration turns out to be 5 when we actually need 7.5, how much more drug should we give the patient? The patient should be given 150mg. The rate of change of the dose is proportional to the needed change in concentration. (first-order).

- Curve C is first-order elimination, so we increase the dose proportionally to the needed increase in concentration. In the previous example, if we need the therapeutic concentration to be 10, we have to give the patient 200mg.
- Curve A is zero-order elimination (the concentration is jumping so we can't change the concentration of the dose proportionally to the desired therapeutic concentration; (because this causes toxic effects). The more we increase the dose, the more the concentration will increase (out of proportion to the increase in the dose), which is bad.



Flow-Dependent Elimination in brief:

- ◆ This is especially for "high extraction ratio" drugs
- ◆ Their elimination is neither first-order nor zero-order
- ◆ It is flow dependent.
- ◆As the blood flow to the liver increases, the amount extracted by the liver increases.
- ◆Flow dependant elimination is peculiar to "High extraction ratio" drugs.
- ◆The rate of the elimination is proportional to the hepatic blood flow.

-Half-Life:

Is the time required for the amount of drug in the body to drop one ½. Or (assuming first-order elimination), it's the time needed for plasma concentration of the drug in the body to drop one ½ or by 50%.

In the case of first-order elimination:

- After 1 half life: 50% of the drug will remain in the body and 50% will be eliminated.
- By the 2ed half life: 75% of the drug will be eliminated (50% eliminated by the first half life + ½ of the 50% that remained -25%-) so 50+25=75% ((25% of the drug remains in the body))

By the 3ed half life: 75% that got eliminated by the 2ed half life+ ½ of the remaining 25% -12.5%- = 87.5% will be eliminated. And 12.5% of the drug stays in the body.

By the 4th half life: 87.5% is removed by the 3ed half life+ ½ of 12.5% remaining -6.25- = 93.75%, so about 94% of the drug will be eliminated and about 6% of the drug stays in the body.

- After 4 half lives, 94% of the dose will be eliminated and only 6% of it stays in the body which is relatively insignificant and can be neglected, so (for drugs that undergo first-order elimination) the drug will be eliminated from the body regardless of the dose whether for example 1mg or 1000mgs.

- Note: [The above doesn't apply to zero-order elimination]

- Note: elimination is highest after the first half-life but with time the amount of drug eliminated decreases (the ratio or the fraction of elimination however stays the same) Why does (the amount eliminated) decrease? Because as half lives pass, the amount of drug that remains in the body decreases and since elimination is proportional to the amount of drug in the body, it decreases as well.

- Half life is constant for drugs that undergo first-order elimination kinetics, but not for those which undergo zero-order elimination kinetics.

  - $Cp^{t} = Cp^{0} * e^{-kt}$ ..... substitute t ½ for t in the equation
  - Cpt after 1 half life = ½ Cp0 or Cp0/2
  - $(Cp^{0})/2 = Cp^{0} * e^{-kt1/2}$
  - $e^{-kt1/2} = 0.5$..... the inverse of this gives → $\underline{k*T\ ½ = 0.693}$ (for drugs that undergo first-order elimination)
  - If we know the half life, we can calculate the elimination rate constant k. and if we know K (the slope of the conc. vs time plot) we can calculate the half-life of the drug.

<u>In the case of first-order elimination:</u>

The half-life is not constant and is affected by the plasma concentration of drugs.

For example:
If the capacity is to remove 2mg/hour, and we have 100mg, we need 50 hours to remove them, but the time required to remove only half of the 100 -50mg- (the half life that is) is 25 hours, how about if there were 1000mg? We need more time to eliminate half of that; we need 250 hours (more time).

So, the half-life is not constant for drugs that undergo zero-order elimination kinetics.
The higher the concentration of the drug, the longer the half life, and vice versa.

All the previous terms (except for ½ life) can be expressed by body weight, VD/ body weight of the patient → gives VD/kilogram for this person. CL/ body weight → gives CL/kg for this patient. But this is not needed for individual patients; it's needed for populations, if we have information about the pharmacokinetics in 1000 individuals for example.

If the drug is water soluble and the patient has edema, then there are going to be more fluids in the body and thus greater volume, suppose the drug is lipid-soluble and a patient is obese, again VD is going to be large because more drug will enter their body due to more fat (lipid).
If the drug goes to fat then we divide by the actual body mass, if the drug doesn't go to fat then we divide by the lean body mass.

"من عمل على غير فهم كان ما يفسده أكثر مما يصلحه" عمر بن عبد العزيز