Doctor 021

PHARMACOLOGY

Sheet no. 4

Writer :Malak Khalid Zubied

Corrector :Shahed Al Abadleh

Doctor :Yacoub Irshaid

In this sheet you will find what's written in the Slides is Blue and any other notes (whether those of doctor or me (additional) in black.

Enjoy the sheet dears!

ENTEROHEPATIC CYCLING OF DRUGS

- **After oral administration and absorption, a drug can be excreted in bile before reaching the systemic circulation, go back to gut lumen, and then reabsorbed again.**
- **This is called enterohepatic cycling of the drug.**
- **It reduces drug bioavailability and prolongs its half-life of elimination.**

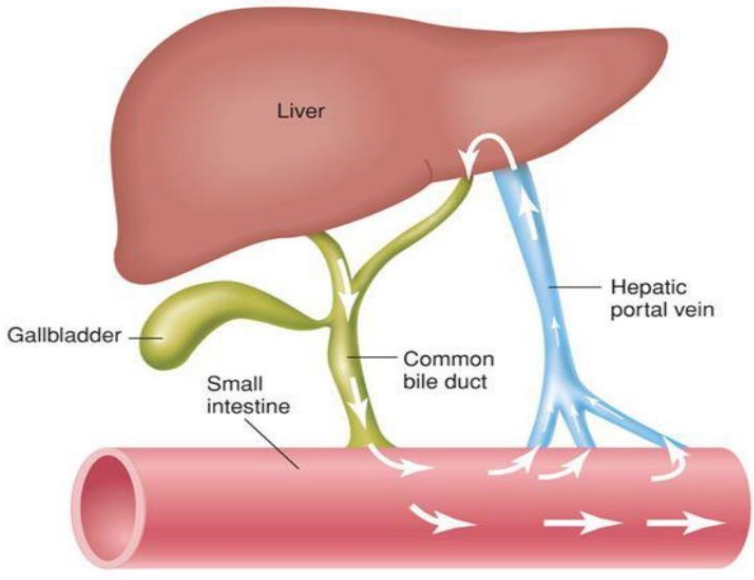
Firstly, enterohepatic means involving the intestine (entero) and the liver (hepatic) and the mean of cycling is really obvious it is the coming back to the start point. The route of the drug in this cycling is: intestine →portal vein→ liver→ biliary excretion →coming back to the lumen of the intestines and reabsorbed again.

*In case of overdose of any drug we put binders in the intestine to prevent its reabsorption, so we use activated charcoal as binders.

Additional: about last point, reducing bioavailability by preventing the drug from reaching the site of action for some time and the prolonged half-life is referred to keeping the drug for longer times before being eliminated in other tissues or renal ways.

Enterohepatic Circulation

- Is recirculation of compounds between liver and intestine
- Many compounds are released in bile, reabsorbed in SI, and returned to liver to be recycled
- Liver excretes drug metabolites into bile to pass out in feces



Additional note: as a conclusion the liver does excretion to the drug itself (unchanged form) or drug metabolites into bile and each one has a certain route. The unchanged drug will be reabsorbed by intestines while metabolites pass out in feces as written before.

ENTEROHEPATIC CYCLING OF DRUGS

APPLICATION:

- **This phenomenon can be taken advantage of in cases of drug overdose.** by using certain substances.
- **Activated charcoal can adsorb may drugs and chemicals (except ionized ones) into its surface.**
- **If we give activated charcoal in cases of drug overdose, and the drug undergoes enterohepatic cycling, then the portion of the drug that is excreted into the gut through bile can be trapped and prevented from reabsorption back into the systemic circulation. Enterohepatic Cycling of Drugs**
- **This will accelerate drug elimination from the body and reduces its half-life of elimination.**

VOLUME OF DISTRIBUTION (V_D)

- **It is the size of body fluid that would be required if the drug molecules were to be homogeneously distributed through all parts of the body.** In fact, there is no drug can be homogenously distributed all over the body as some organs take higher concentrations of that drug than others.
- **It reflects the apparent space available for the drug in the tissues of distribution.**
- **It does NOT represent a real volume**

The doctor gave this example: if we had a water bucket and we added for it 100 mg of a drug then we measured the concentration of the drug in that solution (drug and water) and the concentration was 1 mg per liter, we should know that the volume of the liquid in this bucket was 100 liters.

VOLUME OF DISTRIBUTION (VD)

- **In a normal 70 Kg man . , the volume of**

Plasma = 2.8 L

Blood = 5.6 L

ECF = 14 L

TBW = 42 L

Fat = 14 - 25 L

- **But the volume of distribution for:**

Aspirin = 11 L

Ampicillin = 20 L

Phenobarbital = 40 L

Digoxin = 640 L

Imipramine = 1600 L

Chloroquine = 13000 L

Read the previous information in the table where those on the right column represent some drugs and the left ones are the volumes of many types of body fluids.

First of all , the table is for a man not a Man differentiate between these two words because Man with a capital M means human so some volumes would differ for example females have more fats than males and so on . then, some drugs have low volumes of distribution like aspirin, ampicillin and phenobarbital. The body fluids volume can accommodate VD (volume of distribution) of these drugs so they are distributed in the fluids of the body, but VD of digoxin is 640 !!! how can the body provide enough fluids for that large volume of distribution (total volume of fluids the man have is nearly (42 L) so logically drugs with high VDs would be distributed significantly in the tissues . for example, digoxin –> in muscles.

VD Low: high concentration of the drug in the plasma

VD large: low concentration of the drug in the plasma

- **The apparent volume of distribution will be small if the drug is restricted to plasma:**

1. Due to binding to plasma proteins. Remember from the biochemistry course that the amino acids of the outer surface of plasma proteins are polar whether charged or not so these proteins are soluble

2. When it is highly ionized at plasma pH.

- **The apparent volume of distribution will be large when the drug distributes into tissues.**

- **It relates the amount of the drug in the body (Ab), with its plasma concentration (Cp), such that: V_D = Ab/Cp**

V_D: apparent volume of distribution

Ab: amount of drug in the body and it is not the dose! why? because part of the dose will be incompletely absorbed (bioavailability is less than 100%) so it is washed out with the feces consequently we focus only on the amount of drug in the body.

Ex: what is the amount of a given drug in the body if the given dose of this drug is 100mg and the bioavailability for it = 50%?

Simply, Ab = bioavailability * the dose

= 50 mg

DRUG BINDING IN PLASMA

- **Albumin is the most important drug- binding protein.**
- **α1 - Acid-glycoprotein is also important for binding certain basic drugs.**
- **Binding to plasma proteins is mostly reversible.**

Notice that only basic drugs bind to alpha1-acid-glycoprotein (it's an acid glycoprotein so it is expected that basic ones would bind to it) but to albumin both basic and acidic drugs can bind also endogenous substances can bind to albumin take bilirubin as an example (we have discussed it in biochemistry course relating to newborn babies).

*Doctor's note: The reason why both basic and acidic drugs can bind to albumin is having different groups of basic and acidic amino acids forming it.

Alpha-1-acid glycoprotein is a positive acute phase reactant which means that its concentration increases during acute inflammation, trauma and so on.

Logically, when there's an acute inflammation the concentration of alpha one ---- would increase and its binding to basic drugs would also increase resulting in the reduction of the free fraction of the drug (free drugs causes the therapeutic effects not bound ones).

Drug + Protein ⟷ Drug-Protein complex

D + P ⟷ **DP** (during elimination equilibrium shifts to the left DP complex would dissociate)

- **The free unbound drug fraction (D) is responsible for the pharmacological action and is also available for elimination.**
- **The bound drug fraction (DP) is not so available, and it represents a reservoir for the drug.**
- **One clinical importance of plasma protein binding of drugs is to help interpretation of measured plasma drug concentration of such drugs.**
- **When plasma protein concentrations are lower than normal, then the total drug concentration will be lower than expected, but the free concentration may not be affected (why?).** As it would distribute throughout the volume of distribution, and its rate of elimination will also increase.
- **Plasma protein binding is also a site for drug-drug interactions.**
- **If a drug is displaced from plasma proteins it would increase the unbound drug concentration and increase the drug effect and, perhaps, produce toxicity.**

Decreased plasma protein binding leads to an increase in free plasma fraction causing an increase in volume of distribution and a shorter elimination half-life. The increase in the apparent volume of distribution and the shorter elimination half-life cause a decrease in total plasma concentration. The free amount in plasma and in tissue and the tissue-bound amount remain unchanged under steady state conditions. Thus, a decrease in plasma protein binding in renal disease usually does not lead to increased drug toxicity, and alteration of drug dosage is not required, although the total plasma concentration may be found to be considerably lower than normal.

Drug displaced from plasma protein will of course distribute throughout the volume of distribution, and its rate of elimination will also increase, thus, its plasma concentration will NOT increase dramatically.

DRUG CLEARANCE (CL)

- **It is the volume of blood or plasma that is completely cleared of drug per unit time.**

if the clearance is 1 L/hour, that means that after one hour, 1 litre of blood will be free from drugs

• It is a measure of the ability of the body to eliminate (and distribute) the drug.

• Clearance of a drug is the factor that predicts the rate of elimination in relation to the drug concentration: CL = rate of elimination/Cp.

Clearance (volume per time) means تصفية and it differs from elimination (amount "grams" per time) after clearance the drug is whether eliminated or distributed to the tissues. It is a measure of elimination and distribution.

Advice from the doctor (important): while solving questions about pharmacokinetics don't forget to write the unit of each number or your solution would be wrong!!!

Hepatic clearance =elimination only, Renal clearance =elimination only, Total clearance or clearance = elimination and distribution

CL= RATE OF ELIMINATION (amount per time) / DRUG PLASMA CONCENTRATION (amount per volume)

So, the unit of CL is volume per time.

• Assume that the rate of elimination of a drug is 10 mg/hour, and the plasma concentration is 1 mg/L. What is drug clearance?

• CL = [10 mg/hour] / [1 mg/L]

= 10 L/hour

• There may be more than one method of elimination, and thus the rate of elimination will be the sum of all these methods.

• Renal clearance (CLR) = Cu.V/Cp

Where Cu is concentration of drug in urine, V is urine flow rate volume per time**, and Cp is the plasma concentration of the drug.**

• Hepatic clearance (CLH) = [(blood flow. C_i)- (blood flow. C_o)]/ C_i

CLH = blood flow (C_i - C_o)/ C_i

CLH = Q.ER

Ci is drug concentration in blood going to the liver, Co is drug concentration in blood leaving the liver, Q is blood flow, ER is the extraction ratio of the drug.

We should memorize all of the equations

Now we will refer to slide 48&49 which the doctor by passed in the previous lecture.

Slide: 48 & 49

EFFECT OF FIRST-PASS EFFECT ON BIOAVAILABILITY

• The effect of first-pass hepatic elimination on bioavailability is expressed as the extraction (نسبة الخروج) ratio (ER):

• ER = Clearanceliver/ Blood flow to the liver (90 L/hour in a healthy 70 Kg man). This ratio is for memorization

ER = CL liver/Q

• Bioavailability (F) can be predicted from the extent (مدى) of absorption (f) and ER.

F = (f) . (1 - ER)

F (small letter) is the fraction if the drug is not completely absorbed

• A drug like morphine is completely absorbed but its ER is 0.67, so its bioavailability is 33%.

Completely absorbed so f extent of absorption =1

F= f(1-ER)

F=1*(1-0.67)

=0.33

• Drugs with high extraction ratio exhibit interindividual differences in bioavailability and drug concentration, because of differences among individuals in hepatic blood flow and hepatic drug metabolism.

Now let's complete with 68

FIRST-ORDER DRUG ELIMINATION

• It occurs when the rate of drug elimination is directly proportional (يتناسب طرديا) to the amount of drug in the body.

• Occurs with many drugs at therapeutic concentrations.

• A constant (التخلص بشكل ثابت) fraction of the drug is eliminated per unit time.

• The elimination rate constant is designated as k, and its units are reciprocal time (1/time) meaning fraction per unit time.

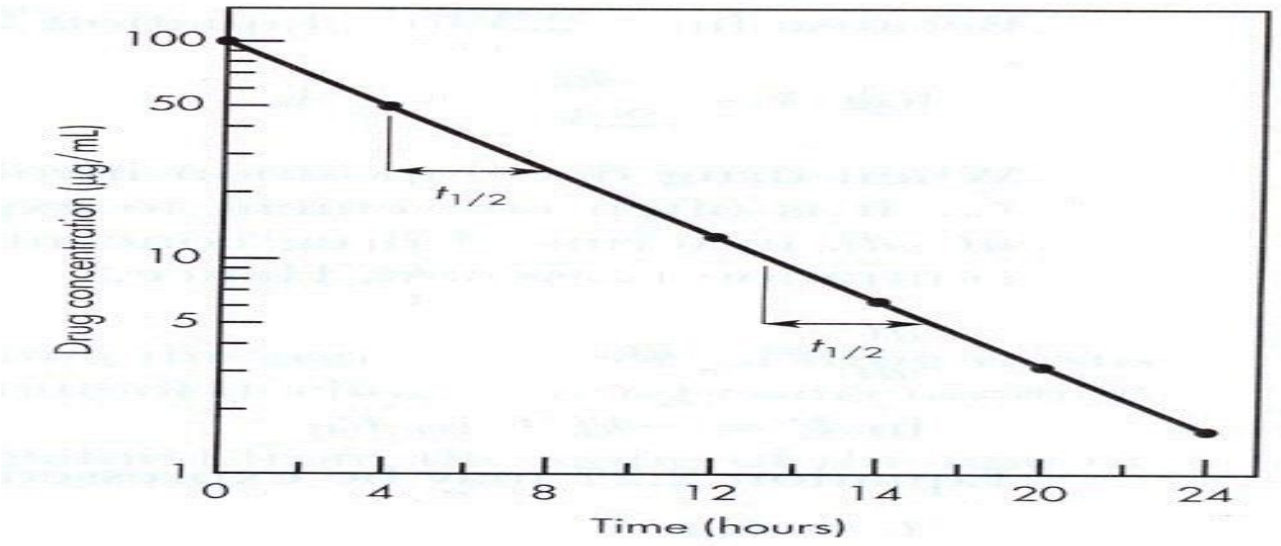
When the conc of drug increases then the rate of elimination increases.

How to judge that this reaction is a first order?

Use a semi log paper where the y axis is a log scale and the x axis is a linear scale then draw a diagram of drug conc / time. If it is linear then it is first order rxn and THE HALF-LIFE IS CONSTANT or FIXED.

T1/2 half-life the time needed to eliminate 50% of the drug from the plasma and we talk about a single dose. Note that the drug conc always become 3 % after five half-lives (يعني دائما ينتهي وجود الدواء بالجسم بعد مرور عمر النصف خمس مرات و يكون التركيز 3 % و هو قليل جدا لذلك اعتبرنا انه انتهى)

First order elimination is also called linear elimination.



ZERO-ORDER DRUG ELIMINATION

• **Also called Saturable elimination.** because the drug needs a saturable enzyme to be eliminated and it also called nonlinear elimination

• **Occurs with few drugs (aspirin, phenytoin, ethanol, ..).**

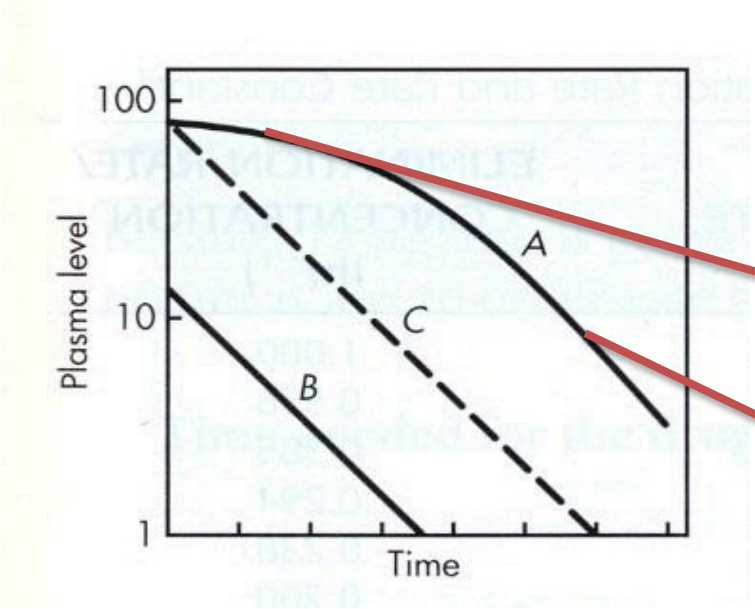
• **Elimination rate is NOT proportional to the amount of drug in the body, but a constant amount is removed per unit time, because of saturation of the elimination process.**

Here the drug has prolonged half-life (not fixed)

Zero—constant amount

First –constant fraction

When the conc of the drug is high, the elimination would be very low imagine that the dose of the drug equals 100mg and the elimination rate for this drug is 5mg per hour the drug would stay in the body for 20 hours!



Semi log paper log scale at the y axis and linear at the x axis and

A: zero order rxn

At high conc. the elimination rate is very low (in the top of the diagram) and when the conc becomes low it turns from zero to first ordered

First-Order drug elimination	Zero-Order drug elimination
Fixed ratio between the drug conc. & elimination	**ixed amount of elimination regardless the drug conc.**
Not Saturable	**Saturable**
Fixed $t_{1/2}$	**Non fixed $t_{1/2}$**
Most drugs	**Aspirin, phenytoin, ethanol**

بِقَدرِ الكدِّ تُكتَسَبُ المَعالي
وَمَن طَلَبَ العُلا سَهرَ اللَّيالي

وَمَن رامَ العُلا مِن غَيرِ كَدٍ
أضاعَ العُمرَ في طَلَبِ المُحالِ

لا تنسونا من صالح دعائكم و لكم بالمثل