◉ Sheet ○ Slides

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A case to study… continued from last lecture

(Remember that $t_{1/2}$ =3.6 hours …. Vd = 25 liters)

- **What is the first-order elimination rate constant of the drug (K)?**

$K \times t_{1/2} = 0.693$ → $K = 0.693/t_{1/2}$ → $K = 0.693/3.6 = 0.1925\ hour^{-1}$

K= 0.1925/hour (this means the 19% of the drug in the body at any time is removed per hour)

- **Calculate the clearance**

K = CL/ Vd → CL = K × Vd → 0.1925 × 25 = 4.8 L/hour

So, Cl is approximately 5 liters per hour

- **What is the maintenance dose every 24 hours if the steady-state therapeutic concentration of the drug is 10 mg/L?**

MD (maintenance dose) = CL × Css (steady-state concentration)

MD = 5 L/hour × 10 mg/L = 50 mg/hour

*Note that the answer gives you the dose that is required per hour, but the question asks about the dose required per 24 hours so we multiply the answer by 24.

→ MD = 24 × 50 = 1200 mg per 24 hours

- **Does this drug require a loading dose?**

We calculate the time required to reach the steady-state concentration without using a loading dose, which equals four to five) half-lives of the drug, so the time needed is approximately 14.4 hours (4 × 3.6).

14.4 hours is relatively a short time so we don't need a loading dose except if the case is critical and we can't wait for 14.4 hours so we need a maintenance dose. but if someone has a headache (not critical) then a loading dose is not required (he may even get better before reaching the steady-state, but we get maximum effect when reaching the steady-state)

If we want to give a loading dose:
LD = Vd × Css = 25 × 10 = 250 mg

*notice that this loading dose is small (250 mg) so it isn't dangerous and won't cause toxicity.
But in other cases, if the loading dose was large, then we can reach a toxic effect because when you give this loading dose as one bolus, you will immediately reach the toxic concentration.

A student's question: why would we reach the toxic concentration if this dose was calculated to reach the target therapeutic concentration?
We reach the toxic concentration immediately after that high dose because it is not distributed yet to the whole Vd, so at the site where you injected the drug we may reach a toxic concentration until it is distributed (so this toxicity will be in the distribution phase, before the elimination phase).

-how to overcome this?

1) Divide the dose.
Divide it into portions and give it one at a time or give it slowly by IV infusion**.**

*example: if the loading dose was 2000 mg then we can give it as 500mg per hour (so that each one hour is enough for each peak generated after each 500 mg to descend, so if you give the next 500mg then the peak won't be as high as it would be if we give the two portions combined as 1000 mg)

0:00-10:00

2) Give it by another route of administration (not IV)

If we give the loading dose orally then the peak concentration in blood won't be as high as if we give it IV. Why? Because the absorption is slow over two hours for most drugs (some drugs take more than two hours and others may take less).

Routes of drug administration

•You should know what are the advantages and disadvantages of each route and when to use it.

There are three major groups of routes:

1-Enteral: to put the drug inside the GI tract (either through mouth or rectum)

2-Parenteral: (*not inside the GI tract),* like subcutaneous, intramuscular, etc.

3- Others: they are special routes of administration not commonly used / they are used for specific indications.

……

1. Enteral Routes

1. Oral route (PO) (*from the Latin "per os", by mouth*)

• The drug should be swallowed (so, sublingual (under the tongue) route is not considered oral)

• Most commonly used route (most drugs are given by mouth and swallowed).

• Duodenum is the major site for absorption, but other parts of GI tract may be involved.

Why is Duodenum the major site of absorption?

1) Large surface area for absorption (because it has folds which have villi with microvilli).

2) High blood supply: so anything absorbed will be washed very soon.

◘ Advantages:

- The Safest (we don't get very high concentration after the dose because distribution will occur during absorption.
- The most convenient (Example: it is more convenient than infusion because infusion is intrusion which means it may let bacteria enter the circulation or may result in air embolism (if the amount of air entered to circulation is very large, it may occlude vessels resulting in heart infarction, brain infarction, …) so infusion is not safe).
- The most economical (oral tablets or capsules which are the cheapest but that doesn't mean they are cheap).

◘ Disadvantages:

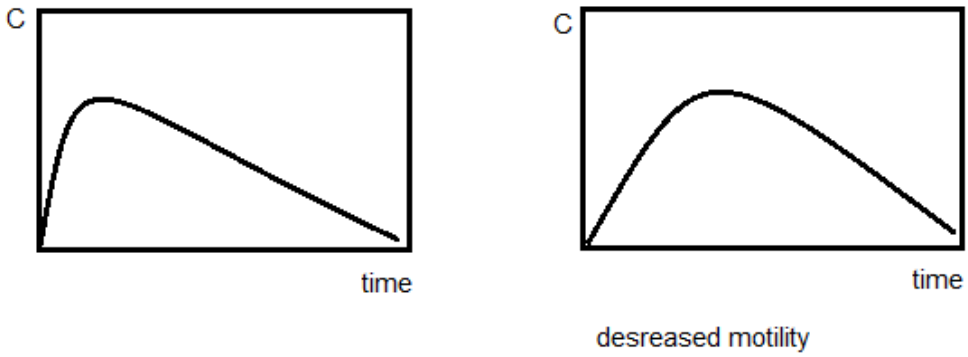
a) This route depends on the compliance of the patient so the patient must be cooperative (compliant); if the patient doesn't follow the instructions of administration (for example: if he doesn't take the drug in the administered intervals or if he doesn't even take the drug) then the treatment won't be accurate. So he must be conscious to how much his disease is severe or dangerous in order to be careful to follow the instructions properly.

b) Absorption is variable because of several factors affecting the rate and extent of absorption:

** Alteration in intestinal motility may affect absorption. (for example: if the patient was administered a drug which increases the intestinal motility, then the contact time of the drug with the absorption site within the GI tract will be shorter, so there will be a portion that won't be absorbed and vice versa but this depends on where the drug is absorbed.
(Let us consider two situations):

1-If we decrease the motility in the GI tract and the absorption site is in the intestines then the absorption will be slower because the drug will leave the stomach slowly to reach the intestines.

(Note that the plot will be shifted to right because the rate is decreased)



2- If we decrease the motility in the GIT and the absorption site is in the stomach then absorption will increase because we increase the contact time of the drug with the absorption site.

*Note: some drugs are absorbed in the duodenum , others are absorbed in the terminal ileum, etc. But the absorption in the colon is very rare because the colon's function is not absorption but it is concentrating fecal material and it just absorbs water and so it doesn't contain enough water to dissolve the tablet).

10:00-20:00

*Note: if a patient is suffering from vomiting then any drug that you give orally will be vomited too. So we have to use another route of administration.

*Can we administer the drug orally to an unconscious patient? No, because the unconscious person may vomit the drug and it enters the lung, causing pulmonary aspiration (the entry of secretions or foreign material into the trachea and lungs).

c) <u>It is affected by **disintegration and dissolution**</u> which are the most important steps in absorption because they are the first and the rate limiting steps in absorption. (Disintegration means the breakup of the dose into small granules). So if there is no disintegration, there is no absorption; if there is no complete dissolution, the absorption is very low (this is because the tablet is a mixture of the drug and other materials, so this <u>solid</u> tablet has to <u>disintegrate</u> in order for

the drug to escape the binders (the other materials in the tablet) and then it dissolute in the aqueous media of body fluids to reach the membranes).

d) First-pass effect: if the first-pass effect of a certain drug is large, either I have to use a large dose or I use another route of administration; it depends on the degree of first pass effect. How? For example if the first-pass effect is 50% then I can double the dose; but if the first-pass effect is 99% then I will definitely use another route of administration.

e) Drug may be destroyed by gastric acid or by intestinal flora. EX: Penicillin (which is the first discovered antibiotic and is still useful until today for certain infections), if you take it orally it will be damaged by gastric acids, so it has to be injected).

*Intestinal flora: is a type of bacteria that live in the intestines and can metabolize the drug. 10% of the population contain bacteria that can metabolize digoxin and if the patient (who normally metabolize digoxin by intestinal flora) was administered an antibiotic, then this will reduce the metabolism of digoxin, resulting in digoxin toxicity.

f) Food may delay absorption (but we said "it may …" because some types of food may increase absorption). EX: very high lipid soluble drugs are more absorbed with fatty meals (but remember that fatty meals are harmful for health so it is not usually administered to take drugs with these meals). Otherwise, food decreases absorption because it affects gastric emptying (and the larger the food particles, the more the delay in the gastric emptying, so the drug won't reach the intestines fast (site of absorption) and the absorption will be slow . so you have to chew the food very well before swallowing it).

*so we usually administer the drug either an hour before the meal (so that the stomach is empty and a large proportion of the drug is absorbed) or two hours after the meal (because on average, food stays in the stomach for two hours , so after two hours the stomach will be nearly empty).

*some drugs cause irritation to the stomach (Ex: iron, which is usually administered for pregnant women) are taken during the meal (not after meal) in order not to cause irritation of the stomach.

g) Absorption may be affected by splanchnic blood flow. (High blood flow washes the drug rapidly, keeping the drug concentration in the blood always low compared to the drug concentration in the site of absorption, maintaining a high concentration gradient all the time. If the blood flow decreases, absorption will be low).

**Note: as it is clear for you now that the oral route has blood flow variations (blood flow to GT tract is not always the same) , so you should notice that it is not just the absorption process that will be affected and have variations, also the elimination process will be affected and will have variations if the drug has flow dependent elimination . (Ex: if the elimination of a certain drug is flow dependent and the blood flow to the GI tract was too high, then even the elimination rate will be very high and you shouldn't administer the drug orally).

2. Sublingual route (SL):

Drug is placed under the tongue.

- **Advantages:**

- Avoids first-pass effect because it is absorbed directly from the mouth.

- Disintegration, dissolution and absorption to the systemic circulation occur directly because there are a lot of blood vessels and saliva (fluid) under the tongue. So it is used when a rapid onset is required like if it's an emergency case away from the hospital and the patient can't wait until reaching the hospital- such as angina pectoris (chest pain due to coronary heart disease). So, uses are limited).

- It is self-administered**.** (The patient can take it by himself).

3. Rectal route (PR) (*per rectum*):

◘ **Advantage:** useful for unconscious patients (comatose patients), vomiting patients or children who reject taking the drug orally (so they are given it as a suppository تحميلة).

◘ **Disadvantages:**

- Doesn't completely avoid the first-pass effect. The rectum is supplied by three arteries and drained by three veins, two of these go to the portal circulation and one goes to the systemic circulation directly. So, it may partially avoid first -pass effect (~50%).

- Absorption is often irregular, incomplete and unpredictable**.** The rectum is short and it isn't originally a site of absorption (it functions as a storage site for feces) so the absorption there is erratic and variable (sometimes it's high, sometimes it's low).

**Note: Can be used for a local effect (ex: patients with a disease in the rectum).

--Refer to the tables in the slides--

2. Parenteral Routes

• Used for drugs that are poorly absorbed from GIT, unstable in the GIT, having a high first-pass effect or having flow dependent elimination.

• Used for rapid effect (Emergency cases).

• Aseptic technique is required because injection is intrusion. For example in IV injections you put a needle (foreign body) in the circulation, so it has to be 100% sterile or it may cause bacteremia and septicemia (blood infection). This applies also to intramuscular and subcutaneous injections.

1. Intravenous route (IV):

• Could be as a **Bolus** (you put the entire dose within the circulation once within few seconds) or **infusion** (slow "drip" of medication into the vein over a period of time after dissolving the drug in a fluid (like Saline)); But be aware that you have to change the place of the needle every less than 24 hours because bacteria will accumulate. But it is not necessarily given over a long period of time; it can be a short infusion (eg; 30 minutes).

• Only aqueous solutions may be injected IV. Even though blood is colloidal (because it contains RBCs, lipids …) it is considered aqueous.

Example: insulin is prepared either as clean or turbid (cloudy) insulin bottles. Turbid insulin shouldn't be given IV because it is a suspension not a solution. Generally (not always) turbid drugs shouldn't be given IV because they contain large particles.

Also, gel and oily vehicles are not dissolved in water (in aqueous solutions) so they shouldn't be given IV. Cyclosporine (used in organ transplant as an immunosuppressant) is put usually in oil, so we don't give it IV.

**Exception: oily vehicles can be given IV if they are nutrition (not drugs).

*vehicles those precipitate blood constituents should not be given IV.

- **Advantages**:

-Rapid onset of action (once it is injected).

-No first-pass effect. The drug goes to the systemic circulation directly without passing through the liver as a first station (first to the right side of the heart, the lung, the left side of the heart, then to the systemic circulation).

◘ **Disadvantages:**

-Produce high initial concentration of the drug which might be toxic. Here we are talking about the therapeutic dose so if you increased the dose by mistake to an already toxic dose it will be very dangerous.

**Note: in order to write a good prescription to avoid giving toxic dose, never write 1.0 or 100.0 …, instead you should write 1 or 100...

- you can do nothing if you give an overdose because once injected, the drug will be in the circulation (if the overdose was given orally, you can perform gastric lavage غسل المعدة but you can't perform IV lavage in IV injections; however, we can remove the drug after injections by dialysis; but if the drug is not dialyzable then it will stay in the circulation and the patient may die).

2. Intramuscular route (IM):

• The drug is injected within muscle fibers of **Deltoid, Gluteus Maximus** (upper outer quarter of it) or **Vastus Lateralis** (on the anterior part of the thigh).Because in these sites we can avoid nerves. (Never use a forth muscle).

**Note: in neonates (newborn), we never inject in Deltoid or in Vastus Lateralis because they are still small. So we just inject in gluteus Maximus.

• Absorption of drug depends on blood supply to the muscle (slowest for Gluteus Maximus).

• Absorption is reduced in circulatory failure (heart failure or shock) as the blood flow is reduced so in these cases we give it IV.

• To be injected IM, the drug must be nonirritating to tissues**.**

**Note: IM irritation is manifested as pain but IV irritation is thrombosis which results in vein occlusion.

• Can utilize:
a. Aqueous solutions for fast absorption and rapid action.

b. Depot preparations and suspensions for slow or sustained absorption (oily vehicles/ethylene glycol/ solid particles/ crystals). Or even we can put a pellet and it may work for several months.

30:00-40:00

• Can accommodate large volumes. This has two applications:

a) When we make an IM injection, we can put a large volume of the drug (eg; 10 ml) because the drug can accumulate in spaces between muscle fibers and in the fascia surrounding the muscle, and after the drug is washed away the muscle will come together again.*But note that in IV route even larger volumes of the drug can be infused (up to Liters).

b) The anticoagulant heparin shouldn't be given IM .WHY? If it is given IM and bleeding occurs as a side effect, so large volumes of blood will accumulate in the spaces between the muscle fibers and in the fascia but the patient may not notice the bleeding until he lose about 0.5 to 1 liter of blood because swelling won't be very visible as the muscle is able to accommodate large volumes of blood and that one liter of blood lost is significant); so you give heparin as IV or SC (subcutaneous) injections, because bleeding will be manifested immediately as a change in the skin color (skin will have blue to red spots) and the patient will notice the bleeding.

Just irrelevant notes mentioned in the lecture:

-Heparin is an anticoagulant drug, so it is main side effect is bleeding
-Antidiabetic drugs cause hypoglycemia as a main side effect.

You should read the rest of the topic from the slides :")