

***Title of Lecture: pharmacokinetics***

***Date of Lecture: 25/9/2014***

***Sheet no: 6***

***Refer to slide no. : 28***

***Written by: Qais S. Mismar***

In this sheet I will put any extra notes that are not mentioned in the slides, so please refer to the slides while studying this sheet.

* Slide 28
* We said previously that certain drugs are excreted from the body without any help
* Some drugs need metabolism in order to be excreted, which means converting the chemical structure of the drug into water soluble, so it can be excreted easily
* Slide 29
* Now what happens in the kidneys in the process of excretion?
* The basic unit of the kidney is the nephron, which consists of Bowman's capsule, and a number of tubules (proximal, loop of Henle, distal, and the collecting duct)
* Slide 31
* There are 2 major methods drugs could be excreted from the kidneys:
1. **Filtration**: the drug reaches the tubules and remains water soluble enough to be excreted
2. **Secretion**: the nephron is surrounded by many blood vessels, the drug is actively secreted from the blood vessel into the tubule and then it is excreted
* If the drug remains lipid soluble it will be reabsorbed, we take this into consideration in our kinetics calculations
* If the drug is acidic in nature and reaches to the tubules and remains lipid soluble we alkalize it
* If it was basic we acidify it by ammonium chloride
* Excretion **reduces** drug concentration
* Metabolism **reduces** drug concentration
* Distribution **reduces** drug concentration
* The major factor that affects excretion is **kidney function**
* If there is **renal failure** (the kidney doesn’t work properly), drug concentration will **increase,** especially when we give the second dose
* People with renal failure require **lower doses** of drugs
* Slide32
* Example regarding drug excretion:
* A 6-year-old boy has tonsillitis, the drug of choice for this disease is **penicillin**, but when we give it to him he starts having nausea and vomiting, what should we do in this case?
* If we lower the dose, he will no longer have nausea and vomiting, but the drug will no longer be in the therapeutic level and hence it will no longer be effective
* Penicillin is excreted by the active secretory method, if we inhibit this secretion the concentration of the drug will increase
* **Probenecid** interferes with the secretion of penicillin at the kidney, this drug when given to a normal healthy individual it produces nothing
* When probenecid is given with penicillin it inhibits its secretion, so penicillin concentration will increase
* Giving probenecid with penicillin allows us to lower the dose while keeping the level therapeutic 🡪 no longer nausea and vomiting
* The rate of excretion of a given drug is determined by a specific constant known as **Ke** which depends on **AVD** (Apparent volume of distribution) and **clearance**
* **Clearance:** the amount of substance that is cleared (excreted) from the body per unit time
* **Ux** : concentration of urine, **V** : volume of urine or urine flow rate, **Px** : plasma concentration
* **focus on the units**
* slide 33
* **half life**: time that is required for the drug concentration to drop by 50%
* **Example**: 100ml of drug, half life is 3 hours, how much will remain after 9 hours? 🡪 **12.5**
* Rates of metabolism could be added
* **Kt**: total elimination of the drug, **Km:** part that is metabolized, **Ke**: part that is excreted by the kidney
* Slide 34
* This graph shows the change in the concentration of a drug in the blood with time from the moment we take it orally, intramuscular, or intravenous
1. **Oral**:
* we took the dose, it goes to the intestine, and is gradually absorbed, absorption increases the concentration of the blood until it reaches the maximal concentration
* How long does that take? It depends, on the half-life of the drug, on the extent of absorption…
* So we reach the maximal concentration, then the level of the blood starts to drop because the drug is metabolized and excreted
* The time needed for the maximal concentration to drop to half the amount of the maximal concentration is the half life
1. **Intramuscular (I.M):**
* Similar to oral, but more rapid action
1. **Intravenous (I.V)**
* All the dose entered the blood directly, starts getting metabolized and excreted, the level of concentration drops
* Slide 35
* This slide shows us how to determine the half-life from a graph, C0 is the maximal concentration, in this example the patient took the drug I.V, the time needed for the maximal concentration to drop to half its amount is the half-life
* Slide 36
* In this curve, we see that we give the second dose before the complete termination of the reaction, this is done especially with patients who take the drug for life
* What is happening here?
* When I give the second dose before the termination of the first dose reaction, the Cmax will increase, we keep repeating this process until we reach a point called **steady state level,** it is reached after 5 half-lives
* This is a very important and essential pharmacokinetic time
* The steady state level is within the therapeutic level
* **Reminder**: I reach the **toxic level** if there is a defect in the excretion process, I reach the **ineffective level** if there is increased excretion
* Sometimes we may face some fluctuations with the given drug, there is no way I can control it except for one way, we ask the patient who is following a certain chronic administration to visit the hospital on regular basis and take a blood sample to measure the concentration of the drug, if it reached the toxic level we lower the dose, if it reached the ineffective level we increase the dose, and so on…
* This whole process of adjusting the dose is to keep the drug in the therapeutic level
* Examples for what we took so far:
* If I have a drug with half life of 5 hours, when will I reach the steady state level? 🡪 after 25 hours
* If I have a drug with half-life of a week, when will it reach the steady state level? 🡪 theoretically, 5 weeks, but if I don’t want to wait that much, there is way we can reach a quick steady state level especially with long acting drugs by giving what is called **large loading dose**, this is conducted in hospitals, and after that we give him the normal dose
* In case of penicillin for example, we give the patient a very large dose, which is the large loading dose, then we give him 500mlg capsules every 6 hours, and this is called the **maintenance dose**, which is the dose the patient is kept on
* Slide 37 is not required
* Slide 38
* Trough and peak drug levels are very important in assessment of steady state level and controlling it
* **Peak** level is the concentration of a blood sample taken after **30 minutes** if the drug was given **I.V, 1-2 hours** if the drug was given **orally**
* **Trough level**: the level of the drug **before** giving it, **30** **minutes** before I.V, **1-2 hours** before the oral
* Slide 39
* Bioavailability-bioequivalence studies are considered **phase 1** because they are conducted on normal healthy individuals
* Bioavailability is extent of absorption
* To prove that 2 drugs are the same (bioequivalent) you must prove that they have the same **chemical structure**, **bioavailability**, **biochemical activity**, and **therapeutic effects**, and this is the purpose of these studies
* **Example** for bioequivalent drugs: panadol & revanin
* Slide 40
* To conduct the previously mentioned studies, we bring certain amount of volunteers, we divide them into 2 groups, we give 1 group a certified tested drug (panadol for example), and we give the other group the drug that we want to prove that it is bioequivalent to the tested drug
* Then I start to withdraw blood samples from the 2 groups within the next hours, I keep on taking samples every 6 or 24 hours or so, until the termination of the reaction (nothing remains in the blood)
* Then I enter the data I collected into a the computer, there are certain programs for pharmacokinetics that will give us curves like the one in this slide
* **Tlag**: initial rise in concentration, **Tmax**: time required to achieve maximal concentration, **Cmax**: maximum concentration
* The 2 drugs must have the same **AUC** (area under the curve) in order to be considered bioequivalent
* Slide 41
* In other words, **zero-order kinetics** mean: pharmacokinetic processes do not depend on the dose or the concentration
* The doctor said that these terms are not important and this slide is just for reading, don’t worry about them
* Slide 42
* In **drug tolerance**, the response for a certain drug decreases after repeated doses, so in order to get the same initial response we must increase the dose, this is noticed in the case of addicting drugs (like morphine)
* If I have a drug for hypertension, and I gave 100mlg of this drug and it decreases blood pressure, and in 2 or 3 days, 100mlg of this drug doesn’t decrease the blood pressure anymore, but if I gave 200mlg it will do the task, this drug is considered a useless drug
* **When would tolerance be useful**?
* One of the problems of morphine that is causes nausea and vomiting, it is a painkiller
* When I give morphine to the patient I tell him that it will cause nausea and vomiting, but this will disappear in 3 days, so what happened here is **that the patient developed tolerance to the bad side effects, not to the desired effect of the drug**
* Slide 43
* **Morphallaxis**: we give the drug to protect healthy individuals
* Drug interactions 🡪 explained in a previous lecture
* Slide 44
* There is no drug with no side effects
* **Important question**: what is the universal side effect of drugs? 🡪 **allergic reactions**

Good luck,

Qais S. Mismar