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Pharmacology
Med

Pharmacokinetics IV

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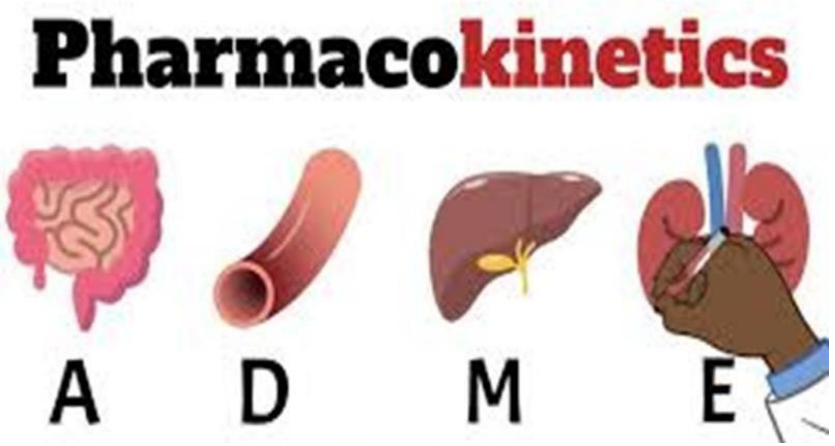
Original Slides for Dr. Heba Hassan

Pharmacokinetics



What the body does to the drug?

- Absorption
- Distribution
- Metabolism
- **Excretion**

Excretion Of Drugs

Kidney: most important organ for excretion

Excretion occurs through:

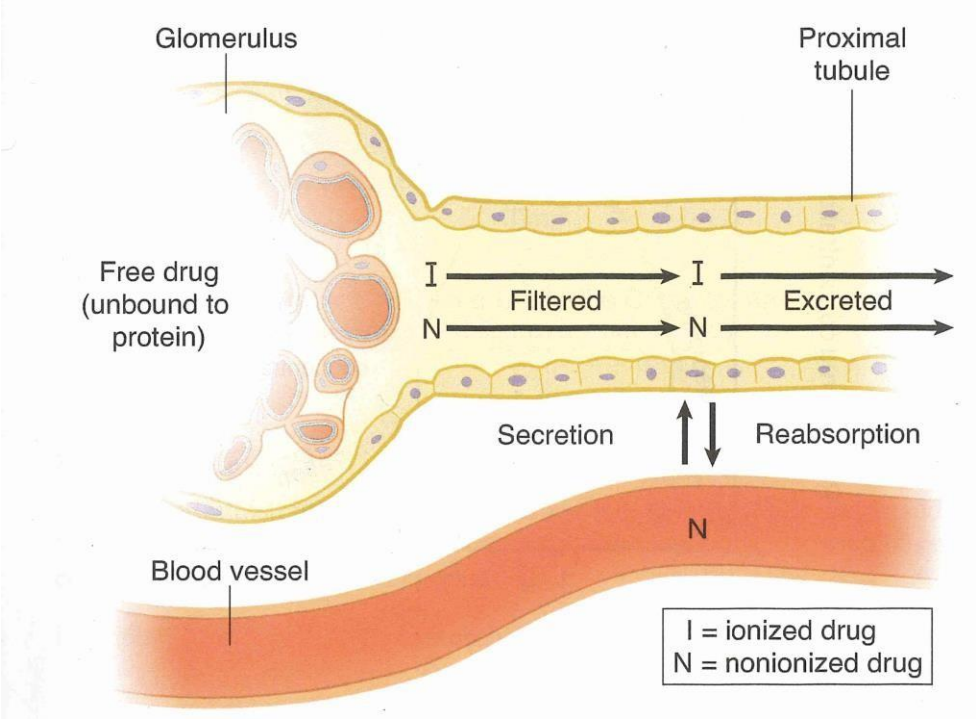
1. **Glomerular filtration**
2. **Proximal convoluted tubules (PCT)**
3. **Distal convoluted tubules (DCT)**

Ionization increases renal elimination (clearance) of drugs

EXTRA

- Only the free, non-protein bound fraction of drug is filtered out by the glomerulus
- Although both ionised and nonionised forms are filtered, only ionised form is ”trapped” in filtrate and excreted in urine
- Only non-ionised form is passively **secreted (by diffusion) in proximal tubule** or **passively reabsorbed usually in distal tubules**
- Active Secretion of drugs in proximal tubules can occur via non-selective anion or cation transporters

Excreted drug = Filtered + secreted - reabsorbed



1-Glomerular filtration

➢ All free drug molecules whose size is **less** than the glomerular pores are filtered into Bowman's capsule.

2- Proximal Convoluted tubules (PCT)

- Active secretion occurs either through
- ❑ Acid carrier e.g. for penicillin, probenicid, salicylic acid.
- ❑ Basic carrier for amphetamine and quinine

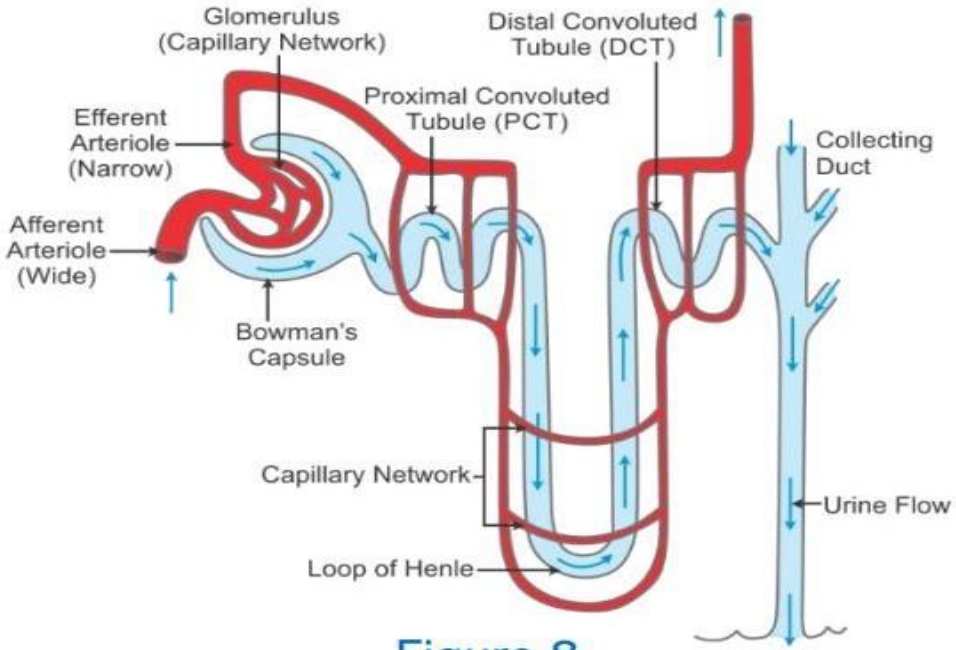


Figure 8

3- Distal Convoluted tubules (DCT)

- Lipophilic drugs may be reabsorbed back to systemic circulation.
- *Alkalinization of urine* keeps acidic drugs ionized and increases their excretion.
- *Acidification of urine* keeps basic drugs ionized and increases their excretion.
- For example, a patient comes to you overdosed with phenobarbital (weak acid drug). What do you think can be given to keep it ionized and decrease reabsorption?

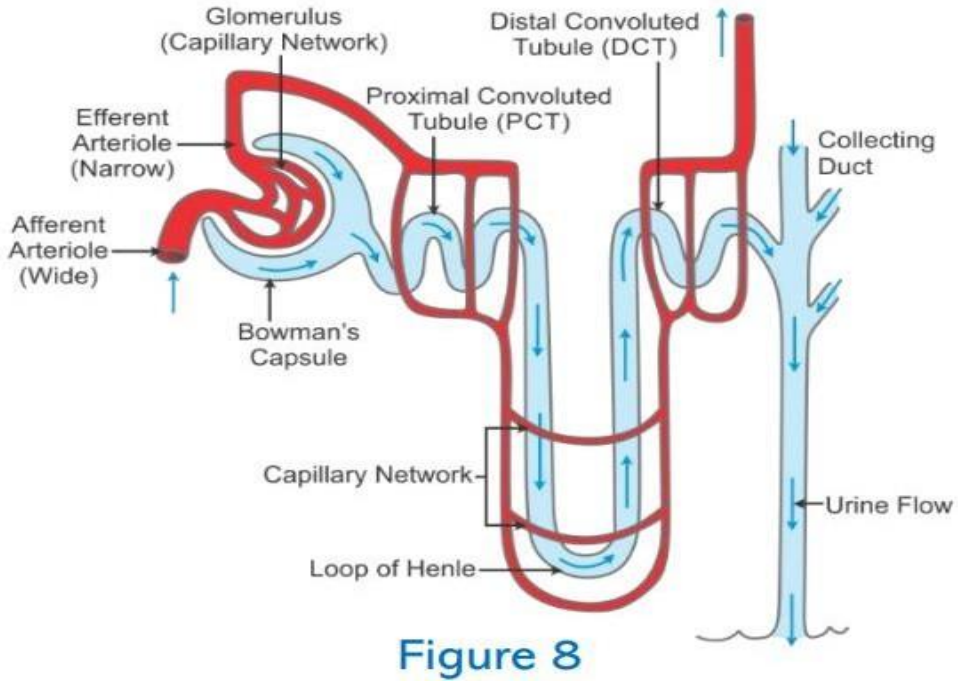
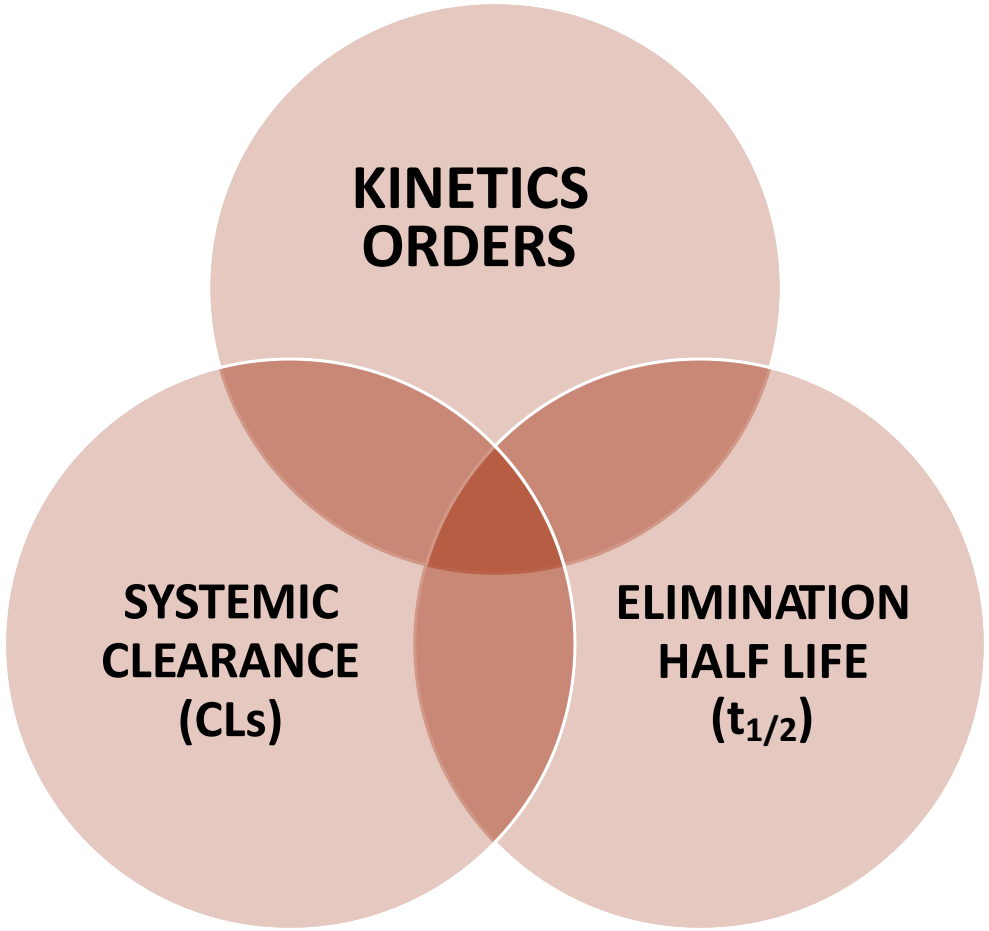


Figure 8

Other sites of excretion:

- **Bile:** e.g. Doxycycline, azithromycin.
- **Lungs** e.g. Volatile anesthetics.
- **Saliva** e.g. Iodides.
- **Sweat** e.g Rifampicin.
- **Milk**: this is important in lactating mothers.

Parameters of elimination



Kinetics Orders

- First order kinetics
- Zero order kinetics

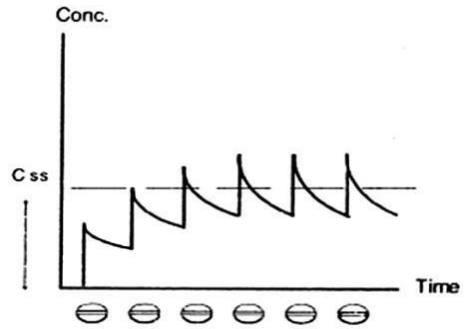
First-order kinetics (most drugs):

- Rate of elimination is directly proportionate to the blood concentration of drugs

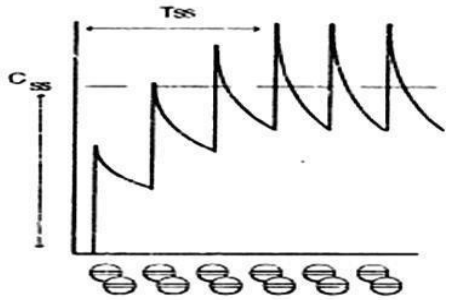
  (***constant percentage*** of the drug is eliminated per unit of time)

- **Constant "$t_{1/2}$"**

Example:



- Repeated dosing increases drug concentration and accordingly the rate of elimination increases till the rate of administration equals the rate of elimination.
- Css can be reached after 4-5 $t_{1/2}$
- Css is directly proportionate to the dose.

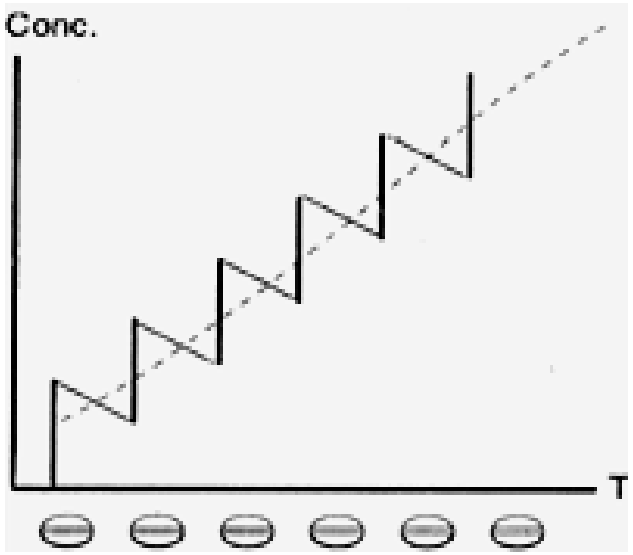


↑ dose → ↑ Css

Zero-order kinetics (Phenytion and Salicylate)

- Rate of drug elimination is constant i.e. ***constant amount*** of drug is eliminated per unit of time.
- "$t_{1/2}$" (half life) is not constant. (varies with dose e.g. $t_{1/2}$ = 3h for 60mg; but $t_{1/2}$ = 2h for 40mg dose)
- No Css is reached by repeated dosing.
- Any change of the dose may cause toxicity.

- **Some drugs follow 1st order kinetics in small dose and zero-order kinetic at large doses i.e. the elimination mechanism is said to be saturated (saturation kinetics).**



Continuous IV infusion and steady state concept

Extra

- In continuous IV infusion, the rate of drug entry into the body is constant.
- Most drugs exhibit first-order elimination, (a constant fraction of the drug is cleared per unit of time) so, the rate of drug elimination increases proportionately as the plasma concentration increases.
- Following initiation of a continuous IV infusion, the plasma concentration of a drug rises until a **steady state (rate of drug elimination equals rate of drug administration) is reached, at which point the plasma concentration of the drug remains constant.**

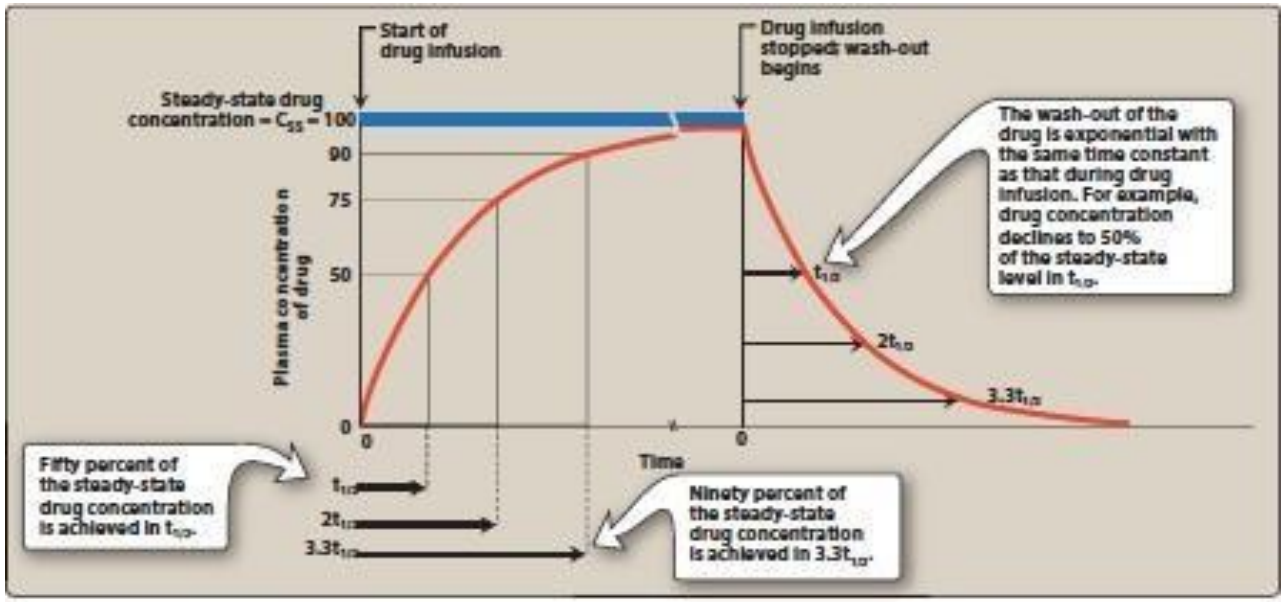


Figure 1.22
Rate of attainment of steady-state concentration of a drug in the plasma after intravenous infusion.

Elimination half life ($t_{1/2}$)

- It is the time required to reduce the plasma concentration of the drug to half the initial concentration(the time required for drug concentration to be changed by 50%).

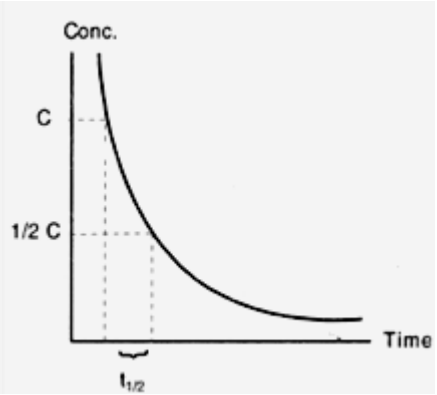
- ***$T_{1/2}$ = 0.7 V_d/CLs***

$$t_{1/2} = \frac{0.7 \times V}{CL}$$

Another definition: The elimination half-life is defined as the time for the drug concentration to reach half of its value ($t_{1/2}$).

Importance of elimination $T_{1/2}$:

- It determines the dosage interval (T).
- It indicates time required to attain Css (about 4-5 $t_{1/2}$):
- If "$t_{1/2}$"is very short (minutes), the drug should be given by IV infusion [dopamine].
- If "$t_{1/2}$"is long [digoxin], the drug should be administered in loading dose followed by maintenance dose



Factors affecting elimination "$t_{1/2}$":

- State of eliminating organs i.e. liver & kidney function.
- Delivery of drugs to the eliminating organs: affected by plasma protein binding and Vd of the drug.

SYSTEMIC CLEARANCE (CLs)

- It is the volume of fluid cleared from the drug per unit of time.
- **Systemic CLs** = Renal clearance (CL_r) + non- renal clearance (CLnr)
- **Clearance occurs mainly in kidney and liver , can also occur through intestines, bile, lungs and breast milk (Extra)**
- **Clearance important for determining half life and calculating doses needed to maintain effective or therapeutic levels of drug in blood**

Significance of clearance:

❑Calculation of the maintenance dose

1- Loading dose:

- The dose required to achieve a desired plasma concentration (desired Css) rapidly, followed by routine maintenance dose.

Loading dose = Vd ×TC

2- Maintenance dose:

- The dose given to maintain the desired Css.

Maintenance dose = CLs ×**TC**tconcentration.

Example (Extra)

Q, Suppose you have a patient who needs to achieve a desired steady-state plasma concentration (Css) of a certain medication rapidly, and then maintain it. The volume of distribution (Vd) for the drug is 40 liters, and the clearance (CLs) is 2 liters per hour. The target concentration (TC) is 15 mg/L:

Answer:

1 Loading Dose Calculation:

Loading dose = Vd × TC Loading dose
= 40 liters × 15 mg
= 600 mg

administer a loading dose of 600 mg to the patient to rapidly achieve the desired plasma concentration.

2 Maintenance Dose Calculation:

Maintenance dose (Dm) = CLs × TC
= 2 L/hr × 15 mg/L
= 30 mg/hr

administer a maintenance dose of 30 mg per hour to the patient to maintain the desired plasma concentration of 15 mg/L.

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