Pharmacokinetic Principles

Dr Asia Abdullah

asia_abdullah65@yahoo.com

ADME

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

Elimination

Drugs can be eliminated by the following mechanisms:

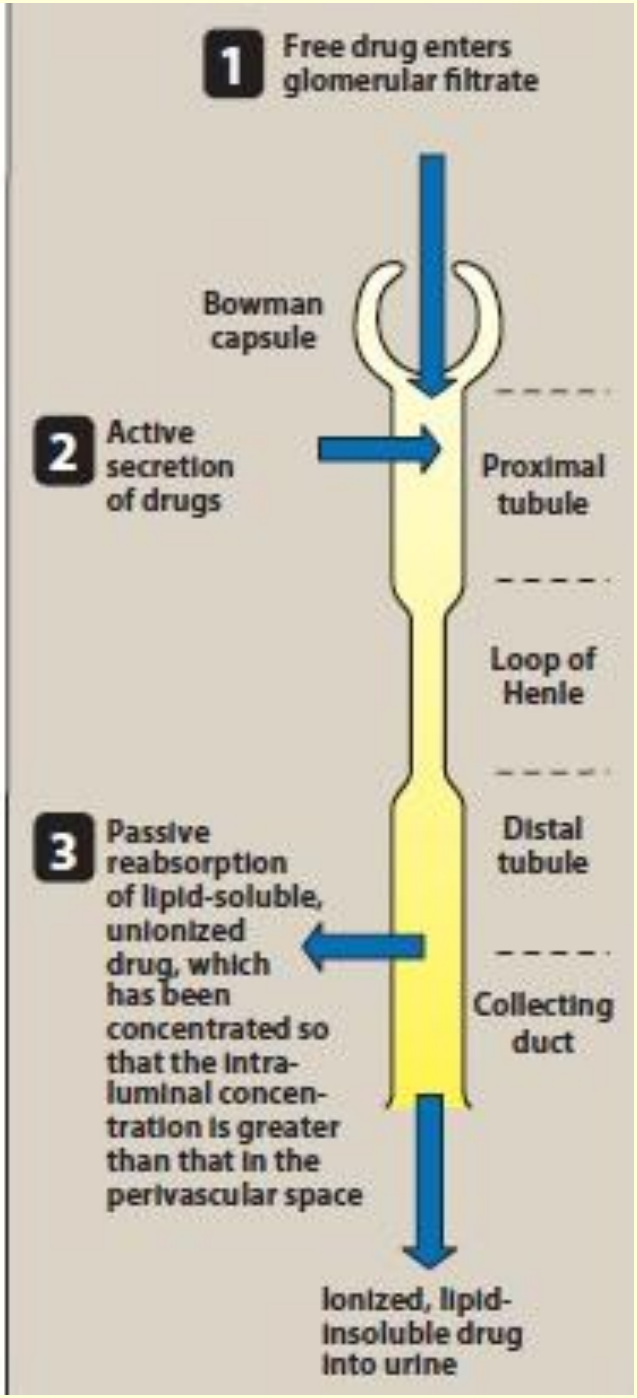
1. Metabolism
2. Storage e.g. Highly lipid soluble drugs in fat, heavy metals in bone, phenothiazines and chloroquine in melanin-containing tissues
3. Excretion

Excretion

Renal excretion: is the most important route of excretion if the drug is water soluble and of low molecular weight.

Three mechanisms for Excretion:

1. Glomerular Filtration
2. Active tubular secretion
3. Tubular reabsorption



DRUG CLEARANCE BY THE KIDNEY

1. Glomerular filtration:

Drugs enter the kidney through renal arteries, which divide to form a glomerular capillary plexus. Free drug (not bound to albumin) flows through the capillary slits into the Bowman space as part of the glomerular filtrate.

DRUG CLEARANCE BY THE KIDNEY

2. Proximal tubular secretion:

Drugs that were not transferred into the glomerular filtrate leave the glomeruli through efferent arterioles, which divide to form a capillary plexus surrounding the nephric lumen in the proximal tubule. Secretion primarily occurs in the proximal tubules by two energy-requiring active transport systems: one for anions and one for cations. Thus, competition between drugs for these carriers can occur within each transport system.

DRUG CLEARANCE BY THE KIDNEY

3. Distal tubular reabsorption:

As a drug moves toward the distal convoluted tubule, its concentration increases. The drug, if uncharged, may diffuse out of the nephric lumen, back into the systemic circulation. Manipulating the urine pH to increase the fraction of ionized drug in the lumen may be done to minimize the amount of back diffusion and increase the clearance of an undesirable drug. Weak acids can be eliminated by alkalinization of the urine, whereas elimination of weak bases may be increased by acidification of the urine. This process is called “ion trapping.”

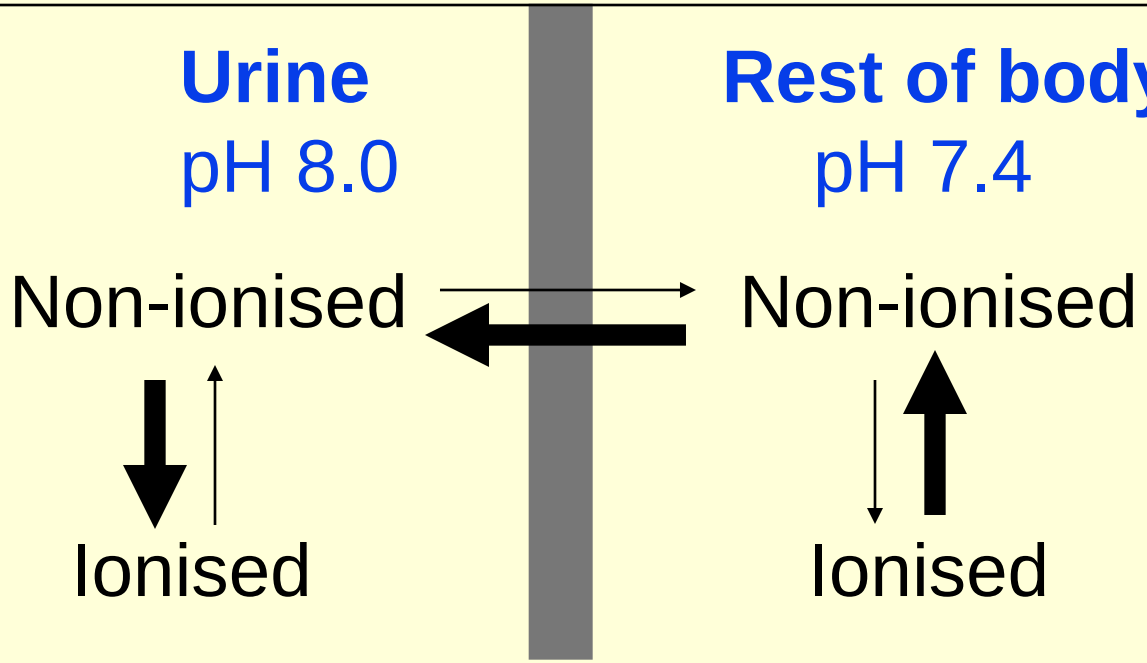
Renal Elimination

- **weak acids**
  - increased rate of excretion in alkaline urine
  - decreased rate of excretion in acid urine
- **weak bases**
  - increased rate of excretion in acid urine
  - decreased rate of excretion in alkaline urine

Can you explain why?

Ion trapping

Urine pH varies (4.5 - 8.0). Consider a barbiturate overdose. Sodium bicarbonate may be given to make the urine alkaline



Barbiturate moves into urine - eliminated from body

Drug Elemination

Drugs can be eliminated by the following routes:

1. Renal excretion (many drugs)
2. Elimination in milk, e.g. Chloramphenicol.
3. Pulmonary elimination, e.g. volatile anesthetics
4. Fecal elimination, either the drug is not absorbed, passive diffusion or Biliary elimination

CONCEPT OF ELIMINATION HALF-LIFE ($t_{1/2}$):

DEFINITION of $t_{1/2}$

Time required for drug elimination processes to decrease the amount of drug in the body half

Half-life ($t_{1/2}$) and Elimination rate constant (K_e)

The inverse relationship

between K_e and $t_{1/2}$

$$K_e = \frac{0.693}{t_{½}} \qquad t_{½} = \frac{0.693}{K_e}$$

CONCEPT OF ELIMINATION HALF-LIFE: DETERMINANTS OF $t_{1/2}$

$$t_{1/2} = \frac{0.693 \times V_d}{Cl}$$

Note that if:

- **Cl increases, $t_{1/2}$ decreases**
- **Cl decreases, $t_{1/2}$ increases**
- **V_d increases, $t_{1/2}$ increases**
- **V_d decreases, $t_{1/2}$ decreases**

Creatinine clearance

Creatinine is a waste product formed continuously by muscle.

- Filtered by kidneys
- Almost no active secretion
- Almost no reabsorption

→ Creatinine clearance approximately equals filtration rate (G.F.R.)

Creatinine clearance used as an estimate of G.F.R.

Why are creatinine clearance and GFR important in ADME?

- The clearances of many renally excreted drugs are closely linked to GFR.
- The clearance of gentamicin approximately equals GFR and therefore also approximates to creatinine clearance.
- When calculating a dosage regime we can assume that gentamicin clearance will equal creatinine clearance

Factors influencing serum creatinine concentration

1) Creatinine **production** rate depends upon muscle mass, which in turn depends upon:

- Body weight
- Age (% muscle declines with age)
- Gender (men have higher % muscle than women)

2) Creatinine **clearance** rate

Total body clearance

- The total body (systemic) clearance, CL_{total}, is the sum of all clearances from the drug-metabolizing and drug-eliminating organs.
- The kidney is often the major organ of elimination.
- The liver also contributes to drug clearance through metabolism and/or excretion into the bile.
- Total clearance is calculated using this equation:

$$CL_{total} = CL_{renal} + CL_{hepatic} + CL_{pulmonary} + CL_{other}$$

Clinical situations resulting in changes in drug half-life

Patients who may have an increase in drug half-life include:

1. diminished renal or hepatic blood flow, e.g. in cardiogenic shock, heart failure, or hemorrhage.

2. decreased ability to extract drug from plasma, e.g. in renal disease.

3. decreased metabolism, e.g. when a concomitant drug inhibits metabolism or in hepatic insufficiency, as with cirrhosis.

These patients may require a decrease in dosage or less frequent dosing intervals.

Clinical situations resulting in changes in drug half-life

In contrast, the half-life of a drug may be decreased by:

1. increased hepatic blood flow
2. decreased protein binding
3. increased drug metabolism.

This may necessitate higher doses or more frequent dosing intervals.

DESIGN AND OPTIMIZATION OF DOSAGE REGIMEN

To initiate drug therapy, the clinician must select the appropriate route of administration, dosage, and dosing interval. Selection of a regimen depends on various patient and drug factors, including **how rapidly therapeutic levels of a drug must be achieved.**

The regimen is then further refined, or optimized, to maximize benefit and minimize adverse effects.

DESIGN AND OPTIMIZATION OF DOSAGE REGIMEN

A. Continuous infusion regimens

More commonly, drugs are continually administered, either as an IV infusion or in oral fixed-dose/ fixed-time interval regimens (for example, “one tablet every 4 hours”).

Continuous or repeated administration results in accumulation of the drug until a steady state occurs. Steady-state is reached when the rate of drug elimination is equal to the rate of drug administration, such that the plasma and tissue levels remain relatively constant.

DESIGN AND OPTIMIZATION OF DOSAGE REGIMEN

B. Fixed-dose/fixed-time regimens

Administration of a drug by fixed doses rather than by continuous infusion is often more convenient. However, fixed doses of IV or oral medications given at fixed intervals result in time-dependent fluctuations in the circulating level of drug, which contrasts with the smooth ascent of drug concentration observed with continuous infusion.

DESIGN AND OPTIMIZATION OF DOSAGE REGIMEN

1. Multiple IV injections:

When a drug is given repeatedly at regular intervals, the plasma concentration increases until a steady state is reached.

2. Multiple oral administrations:

In contrast to IV injection, orally administered drugs may be absorbed slowly, and the plasma concentration of the drug is influenced by both the rate of absorption and the rate of elimination. Oral medications taken at a specific dose one, two, or three times daily.

Bioavailability (F)

Systemic availability:

The percentage of the administered dose that reaches the systemic circulation in a chemically unaltered form.

or how much of the drug dose is available to produce a biological effect

Fractional availability = F

Quote as percentage or decimal e.g. 25% or 0.25. Has no units.

OPTIMIZATION OF DOSAGE REGIMEN

1. **Maintenance dose:** Drugs are generally administered to maintain steady-state concentration (Css) within the therapeutic window. It takes four to five half-lives for a drug to achieve Css.

$$\text{Dosing rate} = \frac{(\text{Target } C_{plasma})(CL)}{F}$$

The target concentration in plasma= Target C plasma

Clearance= CL

Fractional availability = F

OPTIMIZATION OF DOSAGE REGIMEN

2. **Loading dose:** a “loading dose” of drug is administered to achieve the desired plasma level rapidly, followed by a maintenance dose to maintain the steady state.

Loading dose = (Vd) × (desired steady-state plasma concentration)/F

For IV infusion, the bioavailability is 100%, and the equation Becomes:

Loading dose = (Vd) × (desired steady-state plasma concentration)