Pharmacokinetics (III)

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Drug elimination

- Removal of drug from body occurs via a number of routes
- The most important being through **kidney into the urine**
- Other routes include the **bile, intestine, lung, or milk** in nursing mothers

A. Renal elimination of a drug

1. Glomerular filtration
2. Proximal tubular secretion (active secretion)
3. Distal tubular reabsorption (passive reabsorption)
4. Effect of drug metabolism on reabsorption in distal tubule

A. Renal elimination of a drug

1. Glomerular filtration:

- Drugs enter kidney through renal arteries
- Free drug (not bound to albumin) flows into Bowman's space as part of the glomerular filtrate

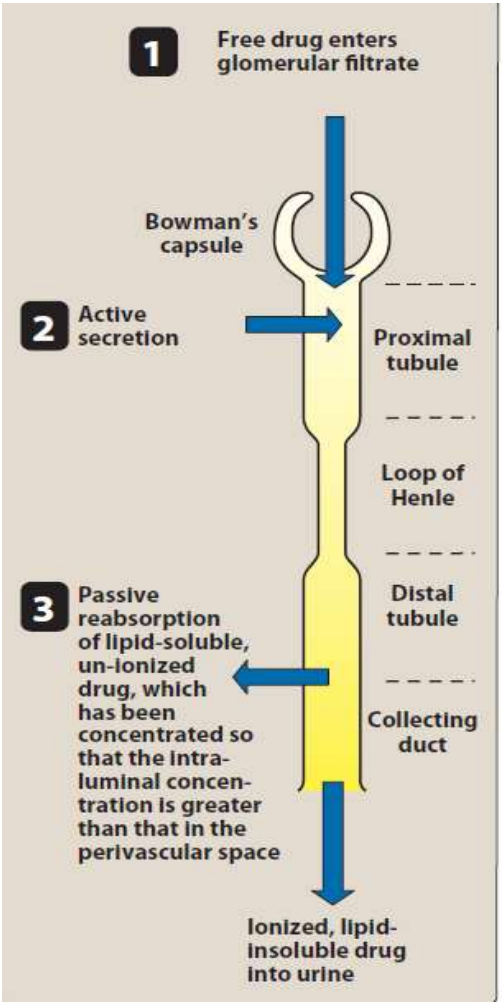
2. Proximal tubular secretion (active secretion):

- Drugs that **were not transferred into glomerular filtrate**
- Secretion occurs in proximal tubules by **active transport systems**
- **Competition** between drugs for these carriers can occur within each transport system

3. Distal tubular reabsorption (passive reabsorption):

- As drug moves toward distal tubule, its concentration increases & exceeds that of perivascular space
- Lipid-soluble drug, uncharged drug, may diffuse out of kindney's lumen, back into systemic circulation (back-diffusion)

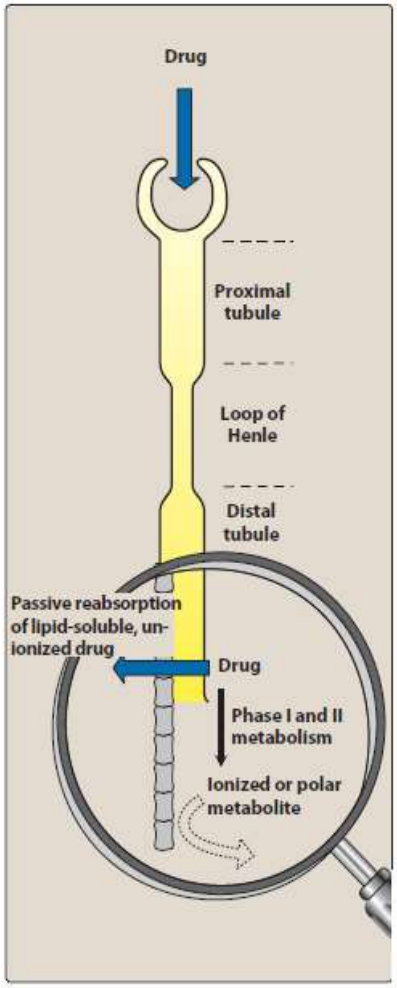
Drug elimination by kidney



Effect of drug metabolism on reabsorption in distal tubule

- Most drugs are lipid soluble & would diffuse out of kidney's lumen when drug concentration in filtrate becomes greater than that in perivascular space
- To minimize this reabsorption, drugs are modified primarily in liver into more ionized or polar substances by phase I & II reactions

Effect of drug metabolism on reabsorption in distal tubule



Manipulating pH of urine

- Manipulating pH of urine to increase ionized form of drug in lumen may be used to minimize amount of back-diffusion
- Hence, increase clearance of an undesirable drug

- As a general rule, **weak acids** can be eliminated by **alkalinization of urine**
- Whereas elimination of **weak bases** may be increased by **acidification of urine**

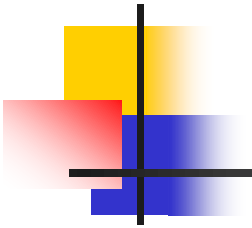
Examples

- A patient presenting with **phenobarbital (weak acid) overdose** can be given bicarbonate, which alkalinizes urine and keeps drug ionized,
- Thereby decreasing its reabsorption

Examples

- If overdose is with **a weak base**, such as **cocaine**,
- **Acidification of urine** with **NH4Cl** leads to increase in its clearance

- **Plasma clearance** is expressed as volume of plasma from which a drug is removed in a given time (mL/min)



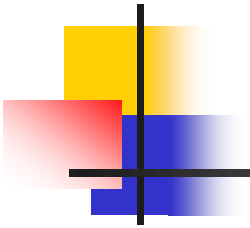
- **Extraction ratio:**
- The drugs enter kidneys at concentration C1 and exit kidneys at concentration C2

The extraction ratio = C2/C1

- **Half-life ($t_{1/2}$) of drug**: is the time required for drug concentration to change by fifty percent

- **Total body clearance:**
- CL total or CLt, is the sum of clearances from various organs

CL total = CL hepatic + CL renal + CL pulmonary + CL other



- When a patient has an abnormality that alters half-life of a drug, **adjustment in dosage is required**

Half-life of drug is increased by:

- Diminished renal plasma flow or hepatic blood (cardiogenic shock, heart failure, hemorrhage)
- Decreased extraction ratio—in renal disease
- Decreased metabolism— when another drug inhibits its biotransformation or in hepatic insufficiency, as with cirrhosis

Half-life of a drug may decrease by:

- Increased hepatic blood flow
- Increased metabolism

KINETICS OF CONTINUOUS ADMINISTRATION

- PK describes time-dependent changes of plasma drug concentration and total amount of drug in body, following drug's administration by various routes:

  A. IV infusion

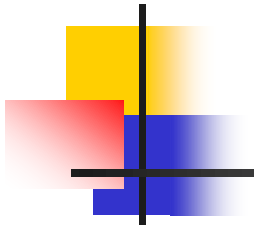
  B. Oral fixed-dose/fixed-time interval regimens (e.g one tablet every 4 hours)

A. Kinetics of IV infusion

- Rate of drug exit from body **increases proportionately as plasma concentration increases**, and at every point in time, it is proportional to plasma concentration of drug

1. Steady-state drug levels in blood:

- Following initiation of IV infusion, **plasma concentration of drug rises** until rate of drug eliminated precisely balances rate of administration
- **A steady-state** is achieved in which plasma concentration of drug remains constant



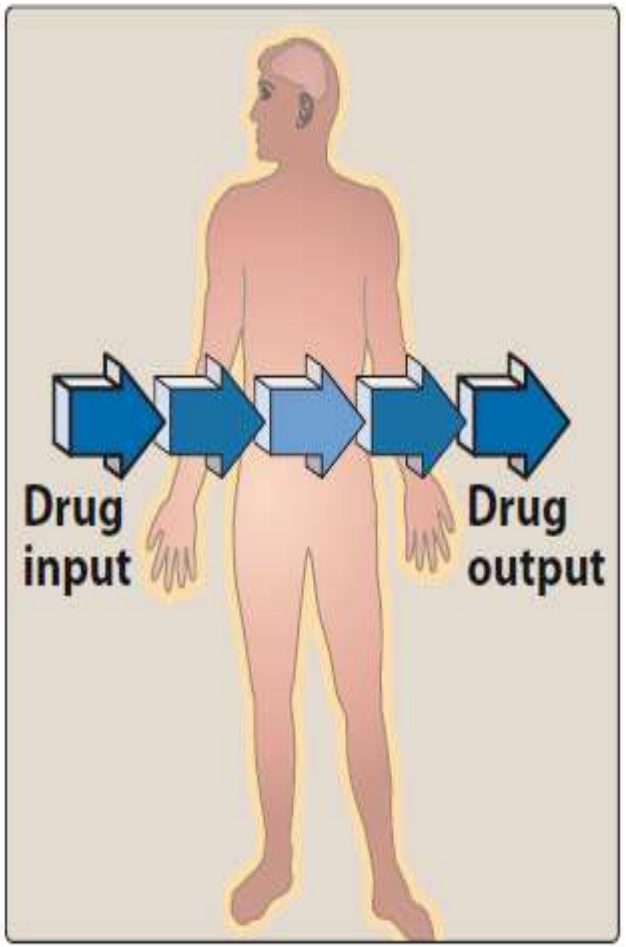
- **Rate of drug elimination from body = (CLt)(C)**
  - CLt = total body clearance
  - C = plasma concentration of drug

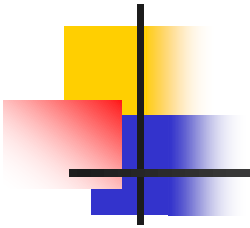
2. Influence of rate of drug infusion on steady state:

- Steady-state plasma concentration occurs when rate of drug elimination is equal to rate of administration

- **At steady state,**

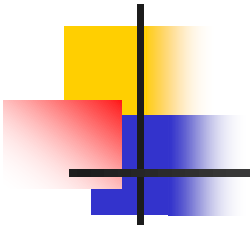
input (rate of infusion) equals output (rate of elimination)





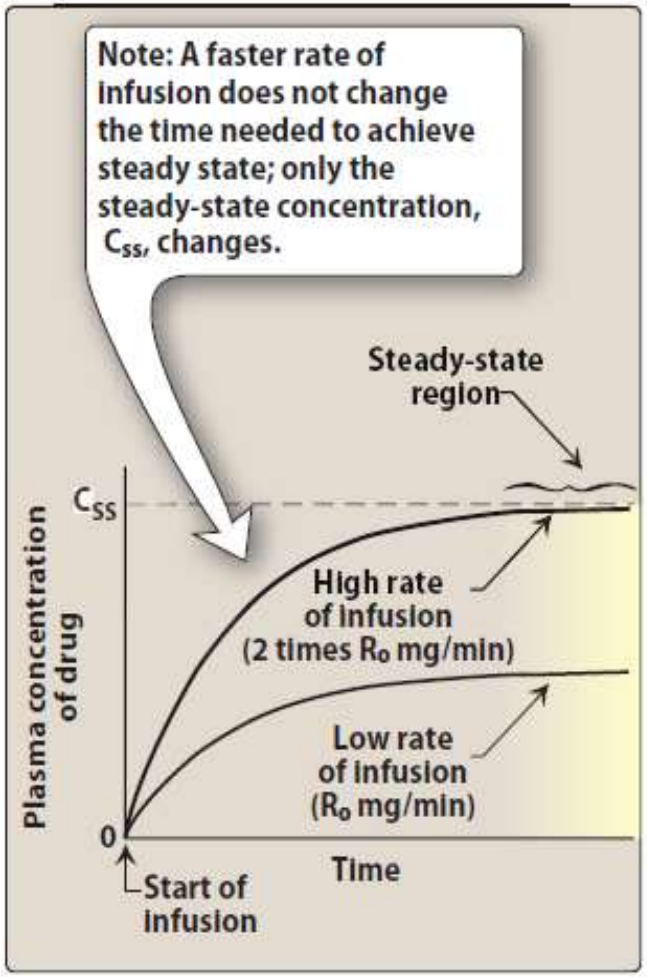
Css = Ro/keVd = Ro/CLt

- Css = steady-state concentration
- Ro = infusion rate (mg/min)
- Ke =first-order elimination rate
- Vd = volume of distribution
- Because ke, CLt & Vd are constant for most drugs showing first-order kinetics, **Css is directly proportional to Ro**



- **If infusion rate is doubled**, **plasma concentration** achieved at the steady state **is doubled**

Effect of infusion rate on steady-state concentration of drug in plasma



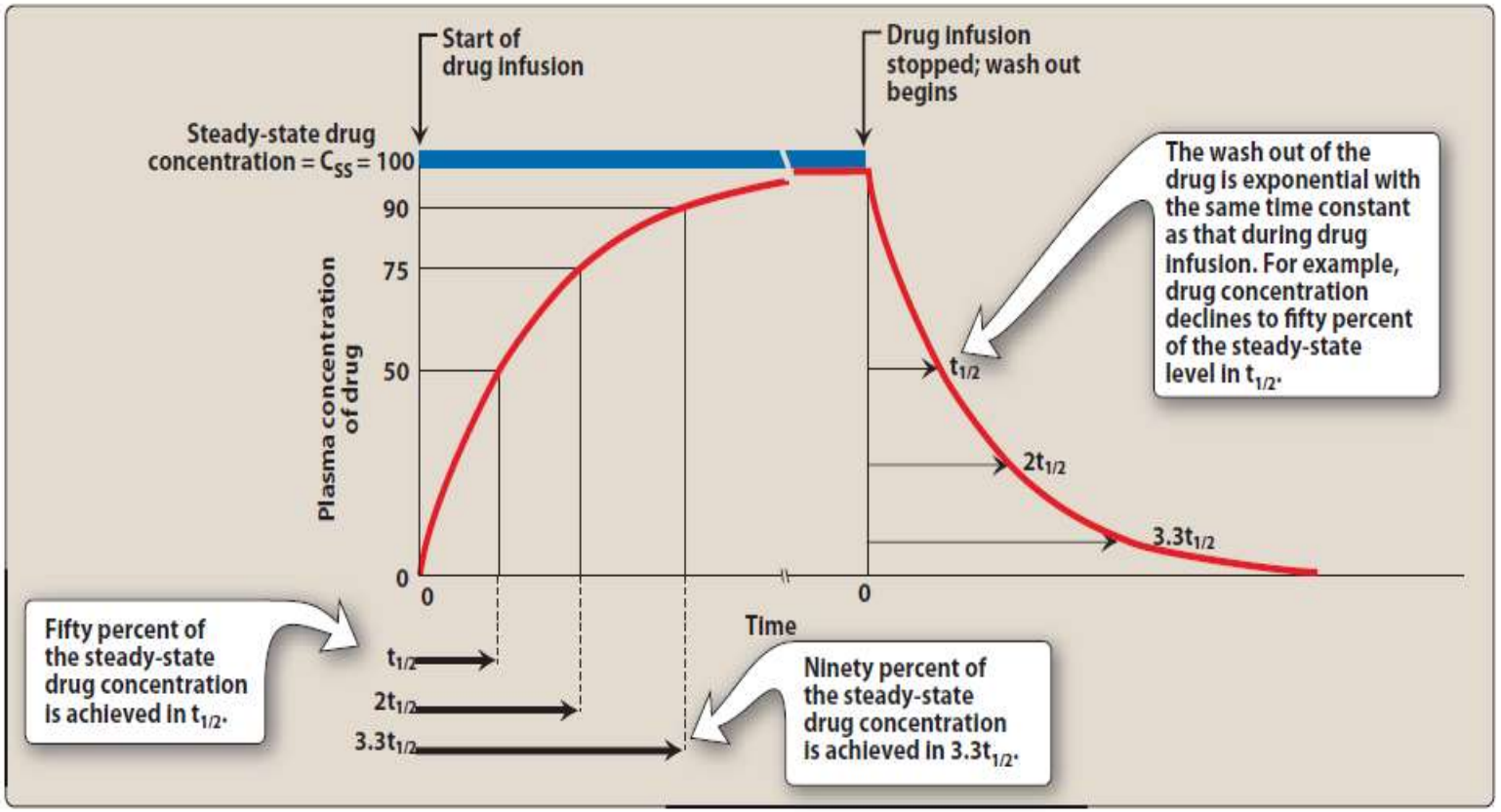
3. Time required to reach steady-state drug concentration:

- Concentration of drug rises from zero at start of infusion to its ultimate steady-state level (Css)

a. Exponential approach to steady state:

- 50% of steady state concentration of drug is achieved in the (First t1/2)
- Waiting another half-life (Second t1/2) allows drug concentration to approach 75% of Css
- 90% of steady state concentration of drug is achieved in the Third t1/2
- A drug will reach steady-state in about **Four half-lives**

Rate of attainment of steady-state concentration of drug in plasma



b. Rate of drug decline when infusion is stopped:

- **When infusion is stopped**, plasma concentration of a drug declines (washes out) to zero with same time course observed in approaching steady state

c. Loading dose:

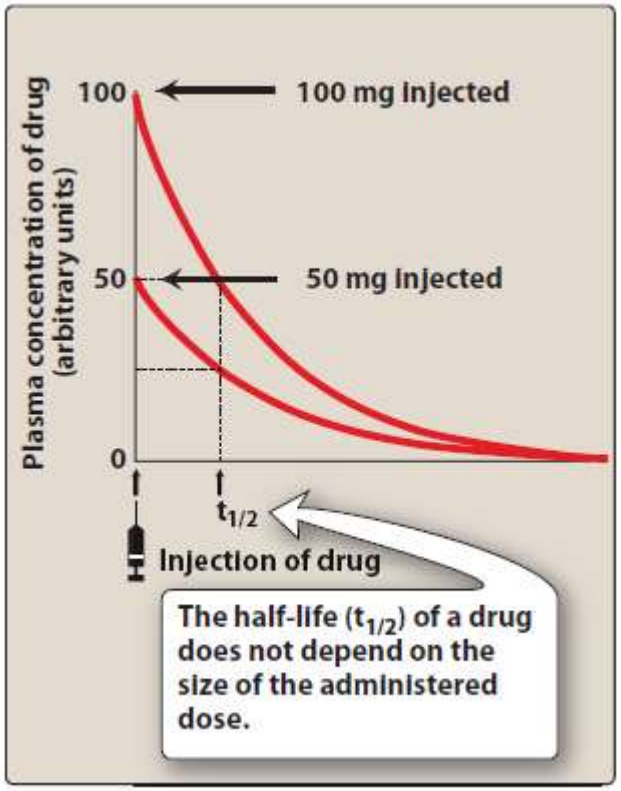
- A delay in achieving desired plasma levels of drug may be clinically unacceptable
- Therefore, **a "loading dose" of drug** can be injected as a single dose to achieve **desired plasma level** rapidly
- Followed by an infusion to maintain steady state **(maintenance dose)**

B. Kinetics of fixed-dose/fixed-time-interval regimens

- Administration of a drug by fixed doses (e.g. one tablet every 4 hrs) rather than by continuous infusion is more **convenient**
- However, fixed doses, given at fixed-time intervals, result in time-dependent fluctuations in circulating level of drug

1. Single IV injection:

- Circulating level of drug decreases exponentially with time



2. Multiple IV injections:

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

3. Orally administered drugs:

- Plasma concentration of orally administered drugs is influenced by both the rate of absorption and the rate of drug elimination