Pharmacokinetics

Cont..

Dr. Ahmed Faisal

Drug Metabolism

- Drugs are most often eliminated by biotransformation and/or excretion into the urine or bile.
- The process of metabolism transforms lipophilic drugs into more polar readily excretable products.
- The liver is the major site for drug metabolism, but specific drugs may undergo biotransformation in other tissues, such as the kidney and the intestines.
- Some agents are initially administered as inactive compounds (pro-drugs) and must be metabolized to their active forms.

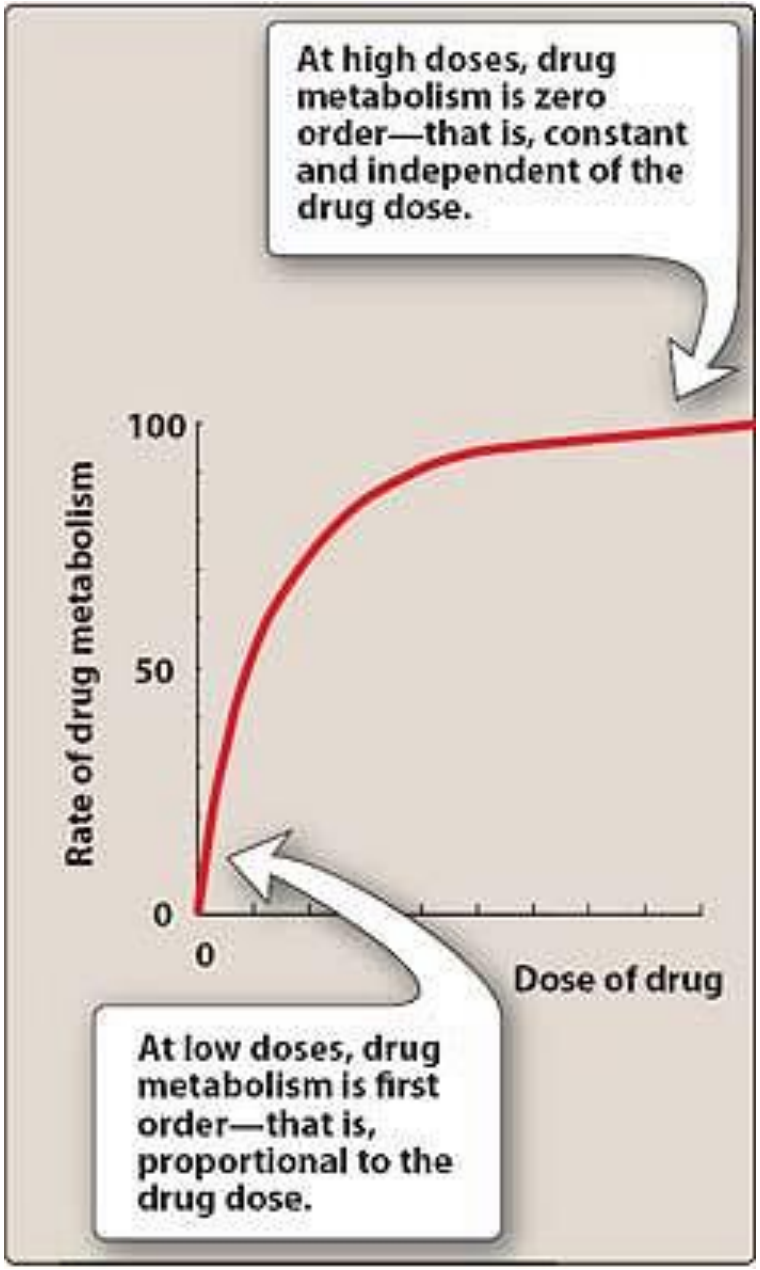
A. Kinetics of metabolism

1. First-order kinetics:

- The metabolic transformation of drugs is catalyzed by enzymes.
- The rate of drug metabolism is directly proportional to the concentration of free drug.
- This means that a constant fraction of drug is metabolized per unit of time.

2. Zero-order kinetics:

- With a few drugs when the doses are very large.
- The enzyme is saturated by a high free-drug concentration, and the rate of metabolism remains constant over time.
- A constant amount of drug is metabolized per unit of time.

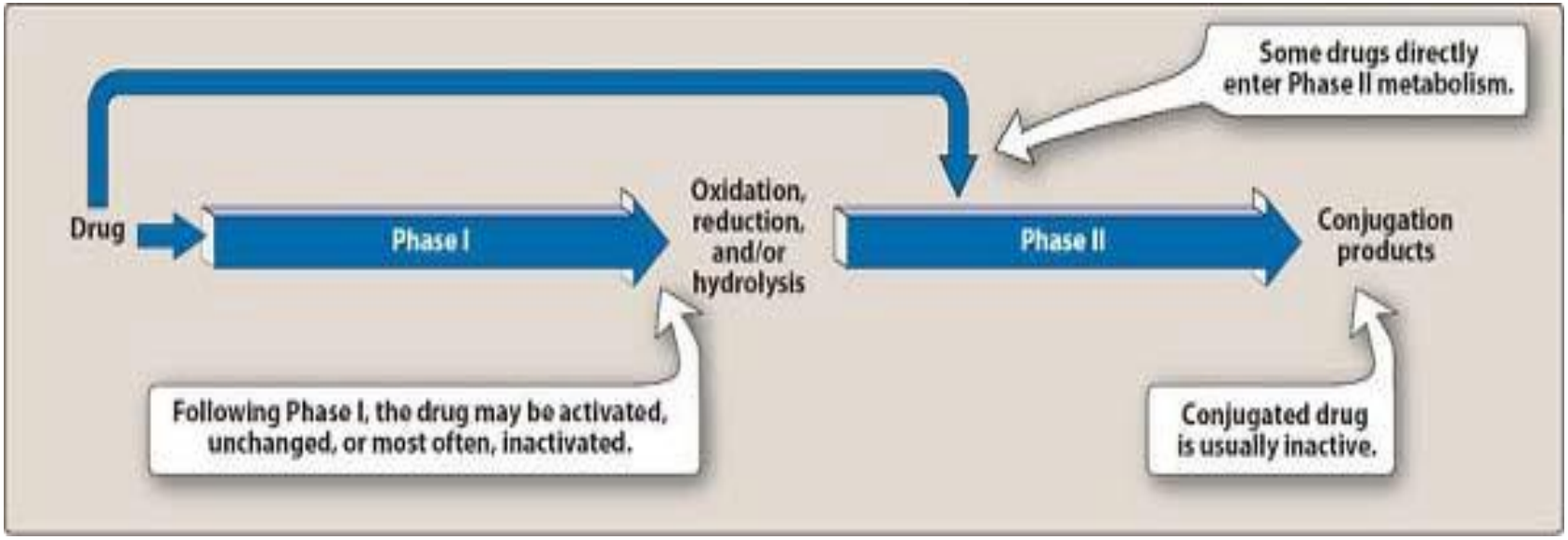


Effect of drug dose on the rate of metabolism

B. Reactions of drug metabolism

- The kidney cannot efficiently eliminate lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal tubules.

- Therefore, lipid-soluble agents must first be metabolized in the liver using two general sets of reactions, called Phase I and Phase II.



1. Phase I

- Phase I reactions function to convert lipophilic molecules into more polar molecules by introducing or unmasking a polar functional group, such as OH or NH2.

- Phase I metabolism may increase, decrease, or leave unaltered the drug's pharmacologic activity.

- Phase I reactions utilizing the P450 system: The Phase I reactions most frequently involved in drug metabolism are catalyzed by the cytochrome P450 system.

$$\text{Drug} + O_2 + \text{NADPH} + H^+ \rightarrow \text{Drug}_{\text{modified}} + H_2O + \text{NADP}^+$$

- Inducers: The cytochrome P450 dependent enzymes are an important target for pharmacokinetic drug interactions.

- One such interaction is the induction of selected CYP isozymes.

- Certain drugs, most notably *phenobarbital, rifampin*, and *carbamazepine*, are capable of increasing the synthesis of one or more CYP isozymes.

- This results in increased biotransformations of drugs and can lead to significant decreases in plasma concentrations of drugs metabolized by these CYP isozymes, with loss of pharmacologic effect.

Isozyme: CYP2C9/10

COMMON SUBSTRATES	INDUCERS
Warfarin	*Phenobarbital*
Phenytoin	*Rifampin*
Ibuprofen	
Tolbutamide	

Isozyme: CYP2D6

COMMON SUBSTRATES	INDUCERS
Desipramine	
Imipramine	
Haloperidol	
Propranolol	

Isozyme: CYP3A4/5

COMMON SUBSTRATES	INDUCERS
Carbamazepine	*Carbamazepine*
Cyclosporine	*Dexamethasone*
Erythromycin	*Phenobarbital*
Nifedipine	*Phenytoin*
Verapamil	*Rifampin*

- Consequences of increased drug metabolism include:
  - 1. Decreased plasma drug concentrations.
  - 2. Decreased drug activity if metabolite is inactive.
  - 3. Increased drug activity if metabolite is active.
  - 4. Decreased therapeutic drug effect.
- In addition to drugs, natural substances and pollutants can also induce CYP isozymes.
- Polycyclic aromatic hydrocarbons can induce CYP1A.
- This has implications for certain drugs; for example, *amitriptyline* and *warfarin* are metabolized by P4501A2.

- Inhibitors: Inhibition of CYP isozyme activity is an important source of drug interactions that leads to serious adverse events.

- The most common form of inhibition is through competition for the same isozyme.

- Numerous drugs have been shown to inhibit one or more of the CYP-dependent biotransformation pathways of *warfarin*.

- For example, *omeprazole* is a potent inhibitor of three of the CYP isozymes responsible for *warfarin* metabolism.

- If the two drugs are taken together, plasma concentrations of *warfarin* increase, which leads to greater inhibition of coagulation and risk of hemorrhage and bleeding reactions.

- The more important CYP inhibitors are *erythromycin, ketoconazole*, and *ritonavir*, because they each inhibit several CYP isozymes.

- *Cimetidine* blocks the metabolism of *theophylline, clozapine,* and *warfarin*.

- Natural substances such as grapefruit juice inhibits CYP3A4 and, thus, drugs such as *amlodipine, clarithromycin*, and *indinavir,* have greater amounts in the systemic circulation leading to higher blood levels and the potential to increase therapeutic and/or toxic effects of the drugs.

- Phase I reactions not involving the P450 system: These include amine oxidation (for example, oxidation of catecholamines or histamine), alcohol dehydrogenation (for example, ethanol oxidation), esterases (for example, metabolism of *pravastatin* in liver), and hydrolysis (for example, *procaine*).

2. Phase II

- This phase consists of conjugation reactions.
- If the metabolite from Phase I metabolism is sufficiently polar, it can be excreted by the kidneys.
- However, many Phase I metabolites are too lipophilic to be retained in the kidney tubules.
- A subsequent conjugation reaction with an endogenous substrate, such as glucuronic acid, sulfuric acid, acetic acid, or an amino acid, results in polar, usually more water-soluble compounds that are often therapeutically inactive.
- Glucuronidation is the most common and the most important conjugation reaction.

- Neonates are deficient in this conjugating system, making them particularly vulnerable to drugs such as *chloramphenicol,* which is inactivated by the addition of glucuronic acid.

- Drugs already possessing an OH, NH2, or COOH group may enter Phase II directly and become conjugated without prior Phase I metabolism.

- The highly polar drug conjugates may then be excreted by the kidney or bile.

3. Reversal of order of the phases

- Not all drugs undergo Phase I and II reactions in that order, for example, *isoniazid* is first acetylated (Phase II reaction) and then hydrolyzed to isonicotinic acid (Phase I reaction).

Drug Elimination

- Removal of a drug from the body occurs via a number of routes, the most important being through the kidney into the urine.
- Other routes include the bile, intestine, lung, or milk in nursing mothers.
- A patient in renal failure may undergo extracorporeal dialysis, which removes small molecules such as drugs.

A. Renal elimination of a drug

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 Bowman's space as part of the glomerular filtrate.
- The glomerular filtration rate (125 mL/min) is normally about twenty percent of the renal plasma flow (600 mL/min).
- Lipid solubility and pH do not influence the passage of drugs into the glomerular filtrate.

2. Proximal tubular secretion:

- Drugs that were not transferred into the glomerular filtrate leave the glomeruli through efferent arterioles, which form a capillary plexus in the proximal tubule.

- Secretion primarily occurs in the proximal tubules by two energy-requiring active transport systems, one for anions (for example, deprotonated forms of weak acids) and one for cations (for example, protonated forms of weak bases).

- Each of these transport systems shows low specificity and can transport many compounds; thus, competition between drugs for these carriers can occur.

- Premature infants and neonates have an incompletely developed tubular secretory mechanism and, thus, may retain certain drugs in the glomerular filtrate.

3. Distal tubular reabsorption:

- As a drug moves toward the distal convoluted tubule, its concentration increases, and exceeds that of the perivascular space.
- The drug, if uncharged, may diffuse out of the nephric lumen, back into the systemic circulation.
- Manipulating the pH of the urine to increase the ionized form of the drug in the lumen may be used to minimize the amount of back-diffusion, and increase the clearance of an undesirable drug.

- As a general rule, 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.

- For example, a patient presenting with *phenobarbital* (weak acid) overdose can be given bicarbonate, which alkalinizes the urine and keeps the drug ionized, thereby decreasing its reabsorption.

- If overdose is with a weak base, such as *cocaine*, acidification of the urine with NH_4Cl leads to protonation of the drug and an increase in its clearance.

4. Role of drug metabolism:

- Most drugs are lipid soluble and without chemical modification would diffuse out of the kidney's tubular lumen when the drug concentration in the filtrate becomes greater than that in the perivascular space.

- To minimize this reabsorption, drugs are modified primarily in the liver into more polar substances using the two types of reactions (Phase I and Phase II reactions).

- The conjugates are ionized, and the charged molecules cannot back-diffuse out of the kidney lumen.

B. Total body clearance

- The total body (systemic) clearance, CL_{total} or CL_t, is the sum of the clearances from the various drug-metabolizing and drug-eliminating organs.

- The kidney is often the major organ of excretion; however, the liver also contributes to drug loss through metabolism and/or excretion into the bile.

- A patient in renal failure may sometimes benefit from a drug that is excreted by this pathway, into the intestine and feces, rather than through the kidney.

- Some drugs may also be reabsorbed through the enterohepatic circulation, thus prolonging their half-life.

C. Clinical situations resulting in changes in drug half-life

- When a patient has an abnormality that alters the half-life of a drug, adjustment in dosage is required.
- It is important to be able to predict in which patients a drug is likely to have a change in half-life.
- The half-life of a drug is increased by:

    1) Diminished renal plasma flow or hepatic blood flow for example, in cardiogenic shock, heart failure, or hemorrhage.

2) Decreased excretion in renal disease.

3) Decreased metabolism for example, when another drug inhibits its biotransformation or in hepatic insufficiency, as with cirrhosis.

On the other hand, the half-life of a drug may decrease by:

1) Increased hepatic blood flow.

2) Decreased protein binding.

3) Increased metabolism.

Kinetics of Continuous Administration

- Describes the pharmacokinetic processes that determine the rates of absorption, distribution, and elimination of a drug.
- Pharmacokinetics also describes the quantitative, time-dependent changes of both the plasma drug concentration and the total amount of drug in the body, following the drug's administration by various routes.
- The two most common routes are IV infusion and oral fixed-dose/fixed-time interval regimens (for example, one tablet every 4 hours).

A. Kinetics of IV infusion

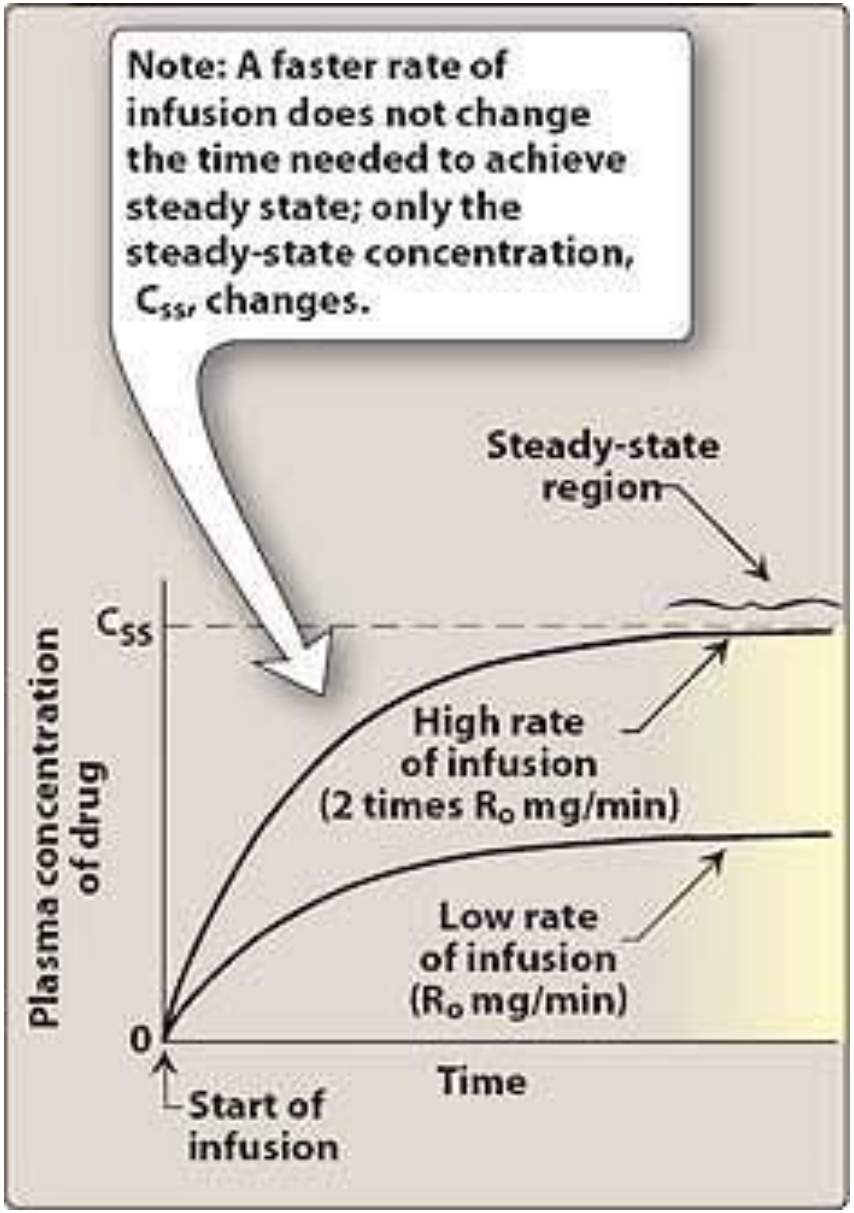
- With continuous IV infusion, the rate of drug entry into the body is constant.
- In the majority of cases, the elimination of a drug is first order; that is, a constant fraction of the agent is cleared per unit of time.
- Therefore, the rate of drug exit from the body increases proportionately as the plasma concentration increases, and at every point in time.

Steady-state drug levels in blood:

- Following the initiation of an IV infusion, the plasma concentration of drug rises until the rate of drug eliminated from the body precisely balances the input rate.
- Thus, a steady-state is achieved in which the plasma concentration of drug remains constant.
- A steady-state plasma concentration of a drug occurs when the rate of drug elimination is equal to the rate of administration.

Influence of the rate of drug infusion on the steady state:

- The steady-state plasma concentration is directly proportional to the infusion rate.
- The steady-state concentration is inversely proportional to the clearance of the drug.

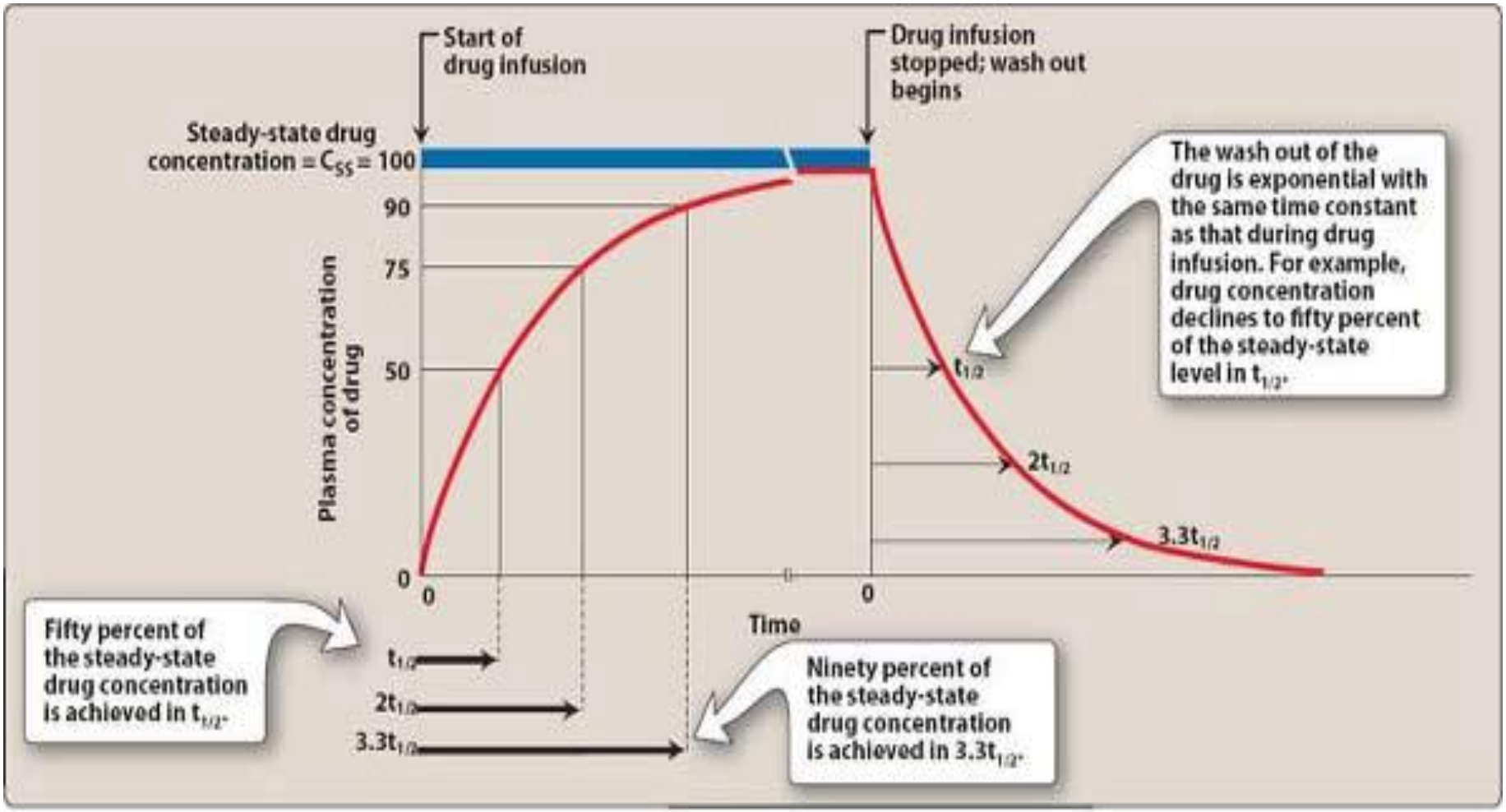


Effect of infusion rate on the steady-state concentration of drug in the plasma

Time required to reach the steady-state drug concentration:

- The concentration of drug rises from zero at the start of the infusion to its ultimate steady-state level.
- The fractional rate of approach to a steady state is achieved by a first-order process.
- The rate constant for attainment of steady state is the rate constant for total body elimination of the drug.
- Thus, fifty percent of the final steady-state concentration of drug is observed after the time elapsed since the infusion is equal to $t_{1/2}$.

- Waiting another half-life allows the drug concentration to approach 75 percent of Css.
- The drug concentration is ninety percent of the final steady-state concentration in 3.3 times $t_{1/2}$.
- Therefore, one can assume that a drug will reach steady-state in about four half-lives.



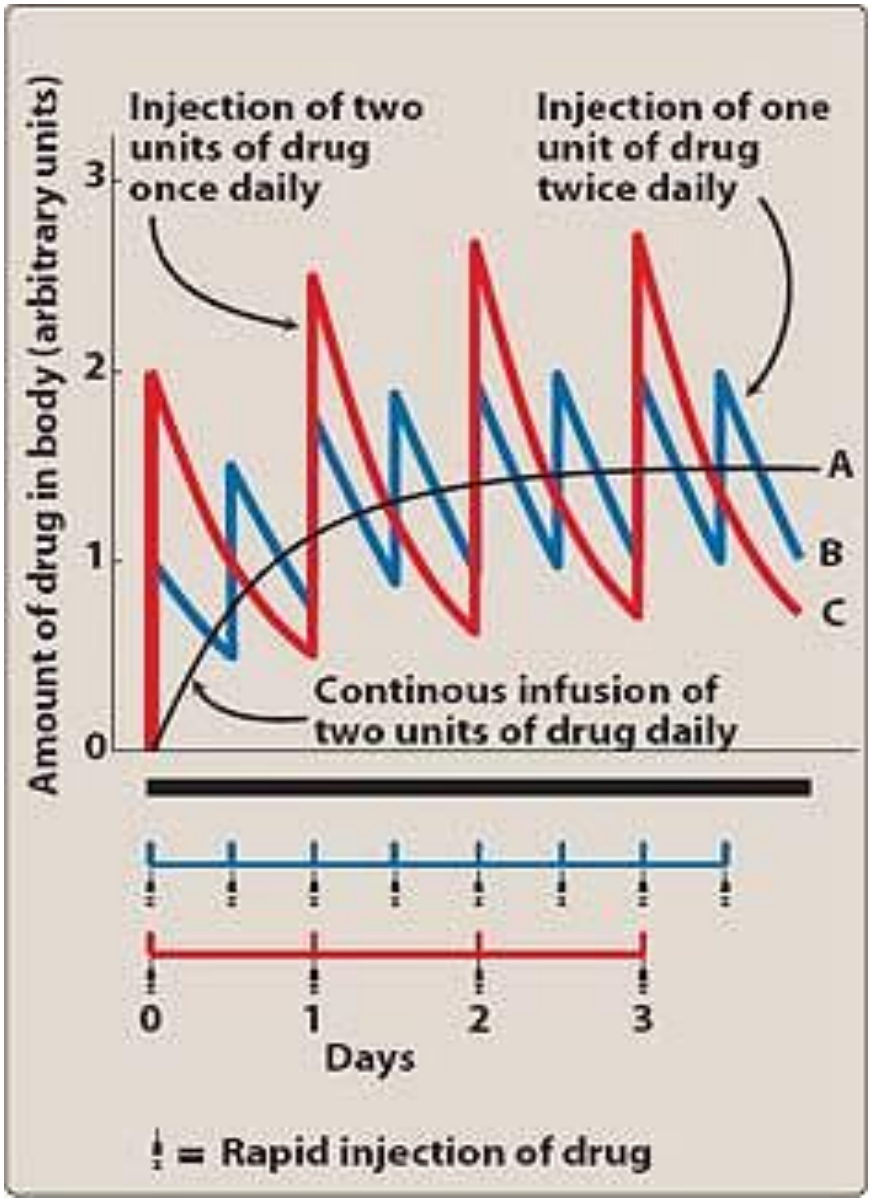
Rate of attainment of steady-state concentration of a drug in the plasma

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

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

- Because most drugs are given at intervals shorter than five half-lives and are eliminated exponentially with time, some drug from the first dose remains in the body at the time that the second dose is administered, and some from the second dose remains at the time that the third dose is given, etc.

- Therefore, the drug accumulates until the rate of drug loss exactly balances the rate of drug administration that is, until a steady state is achieved.

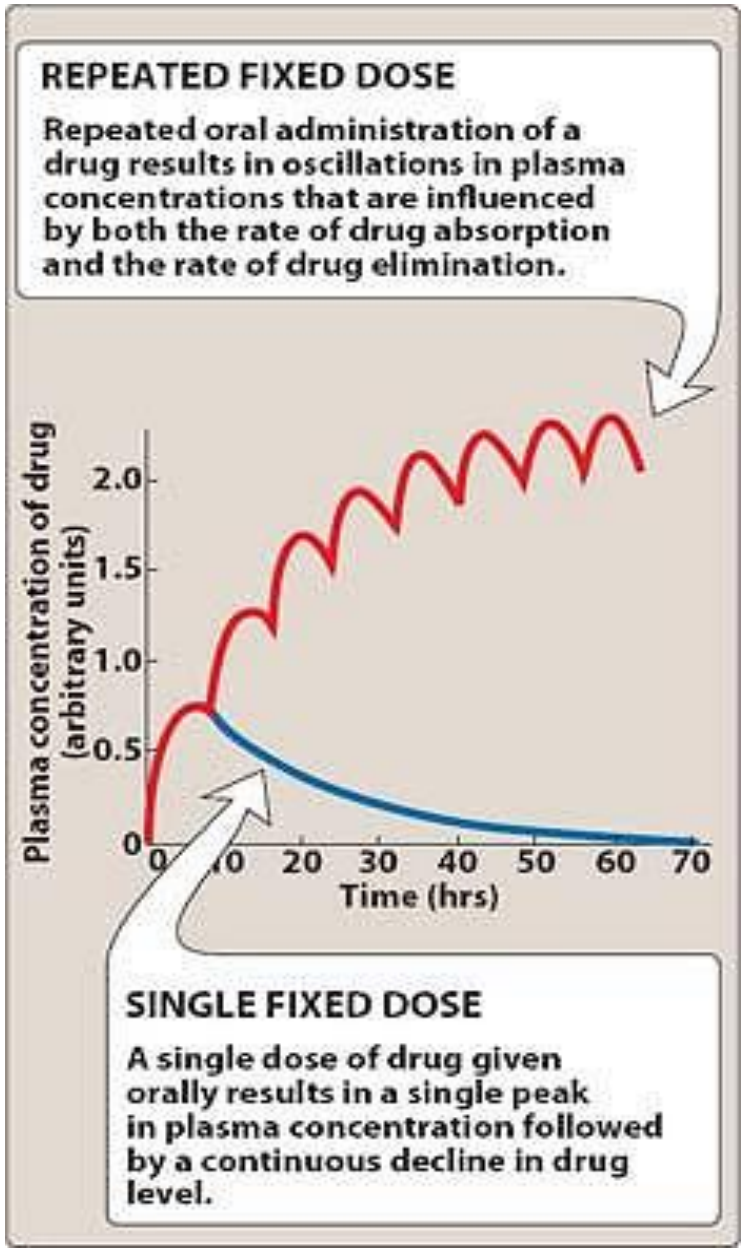


Predicted plasma concentrations of a drug given by infusion (A), twice-daily injection (B), or once-daily injection (C)

Orally administered drugs:

- Most drugs that are administered on an outpatient basis are taken orally on a fixed-dose/fixed-time-interval regimen for example, a specific dose taken one, two, or three times daily.

- 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 drug elimination.



Predicted plasma concentrations of a drug given by repeated oral administrations