GEORGIA CAMPUS

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PHAR 227G Pharmacokinetics:

Drug Absorption, Distribution, Protein Binding, Clearance and Elimination

Xinyu (Eric) Wang, PhD

Associate Professor of Pharmaceutical Sciences

PCOM - School of Pharmacy

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Outlines

Drug Absorption, Bioavailability and Salt Factor

Drug Distribution

Volume of Distribution

Loading Dose

Protein Binding

Drug Clearance

Elimination Rate Constant

Elimination Half-life

Learning objectives

After completing this lecture, students should be able to:

1. Explain Bioavailability (F) and salt factor (S) and calculate amount of drug absorbed with consideration of F and S.
2. Describe the process of drug distribution and list factors that affect drug distribution.
3. Describe drug distribution in various tissues.
4. Define the term, Volume of Distribution.
5. List factors that affect Volume of Distribution.
6. Describe the utility of loading dose and calculate loading dose to achieve a certain concentration of drug.

Learning objectives

After completing this lecture, students should be able to:

7. Describe the impact of drug – protein binding.
8. List major proteins for binding drugs.
9. List factors that affect drug – protein binding.
10. Define drug clearance.
11. List factors that affect clearance of drugs.
12. Define steady state.

Learning objectives

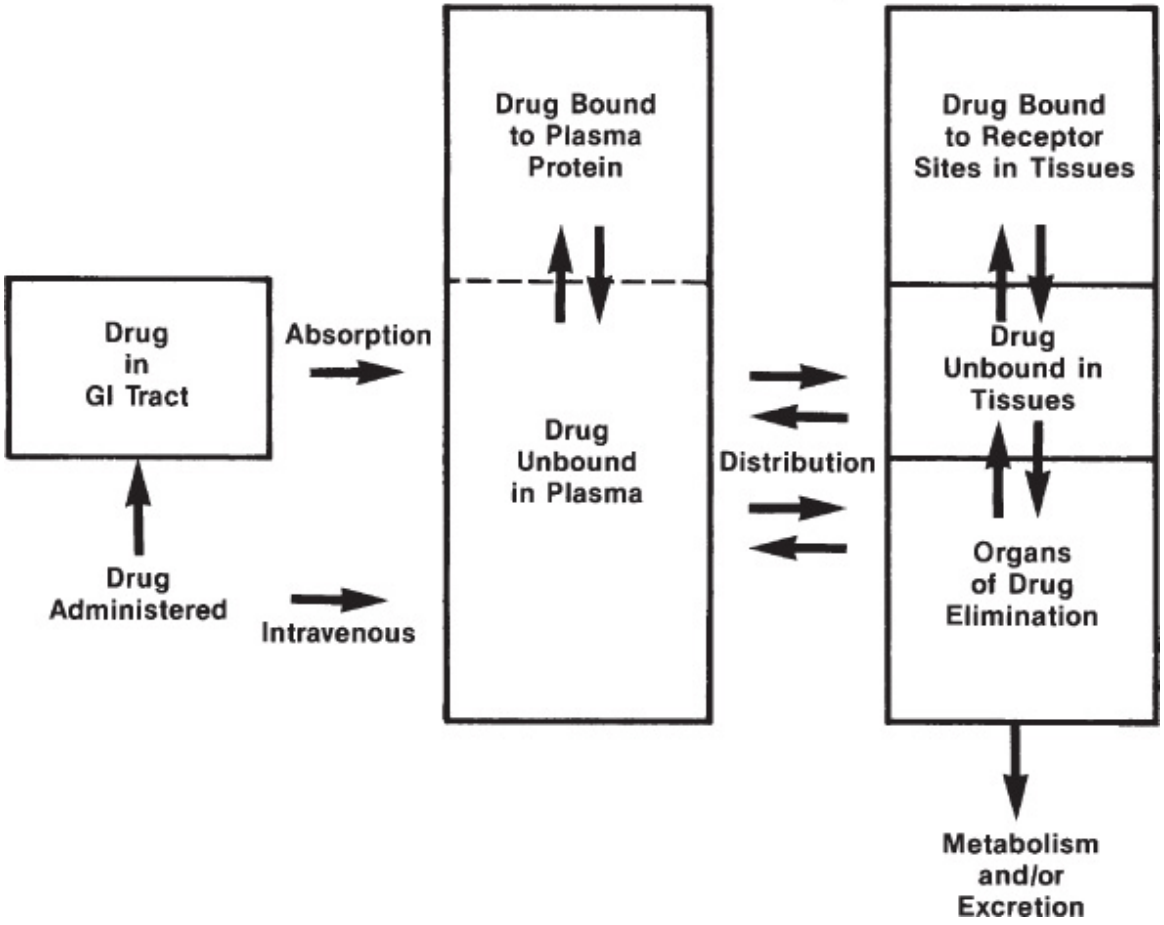
After completing this lecture, students should be able to:

13. Calculate drug clearance, administration rate (R_a), and steady-state concentration of drugs (C_{ss}).
14. Define and describe the application of elimination rate constant.
15. Calculate elimination rate constant.
16. Define and describe the application of elimination half-life.
17. Describe how elimination half-life affects the time to reach C_{ss}.
18. Describe how elimination half-life facilitates prediction of drug concentration following iv infusion and repetitive dosing.

Introduction

Pharmacokinetics:

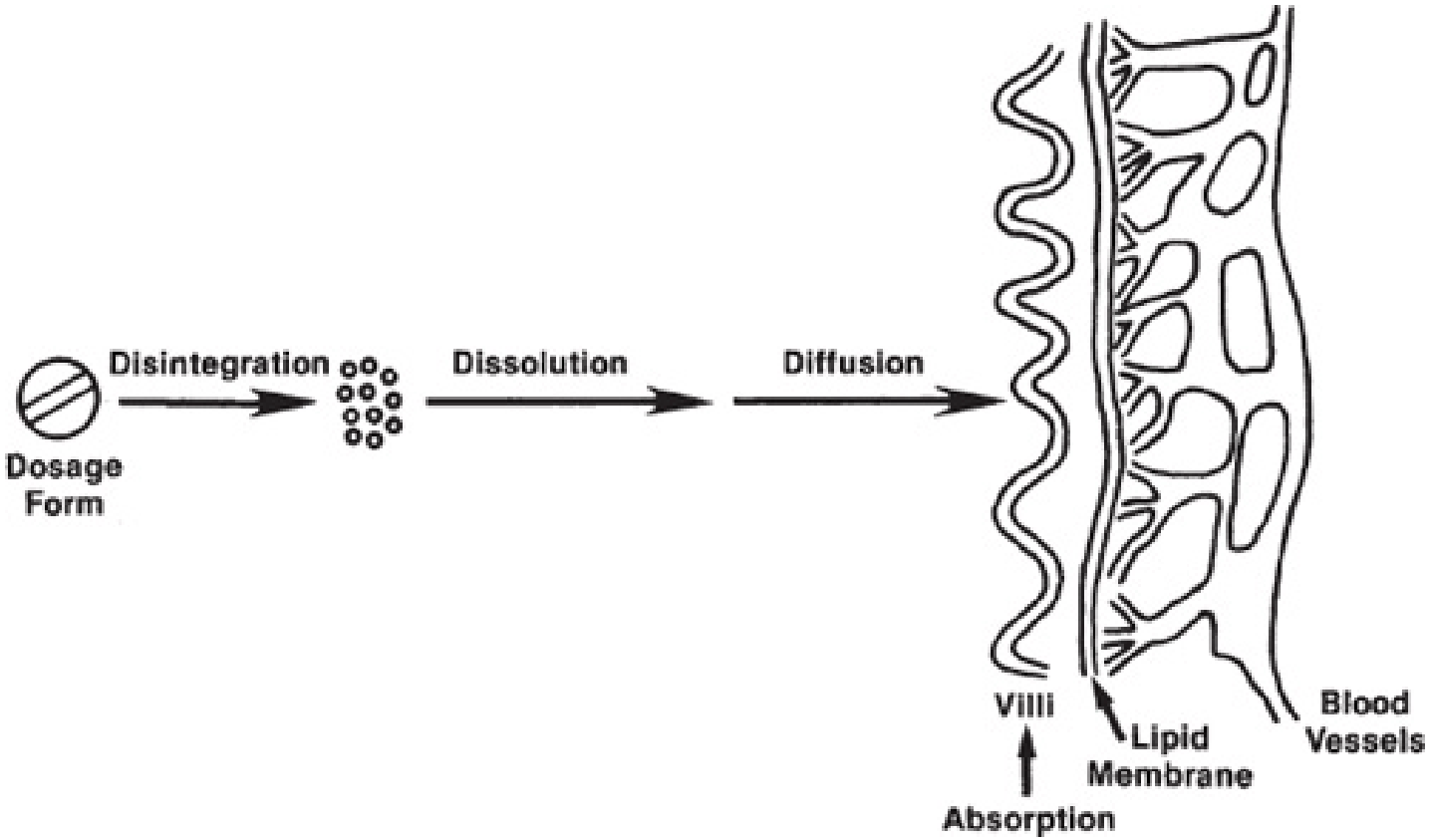
--- The study of the kinetics of drug absorption, distribution, metabolism, and excretion.



Drug Absorption

Oral drug absorption:

--- Processes involved in absorption of a drug from a tablet dosage form.



Drug Absorption

Oral drug absorption: factors

--- Dissolution of the drug in the GI tract: drug particle size, drug solubility

--- Lipophilicity of the drug

--- Molecular size of the drug

--- Charge state of drug molecule (pH partition hypothesis)

--- Dosage forms: tablet, capsule, suspension, solution

--- Stability of the drug in the GI tract

Drug Absorption

Oral drug absorption: factors

--- pH of the GI tract: stomach vs small intestine

--- Membrane of various parts along the GI tract: small intestine

--- Gastric emptying time: food, drug, emotion, exercise

--- GI motility

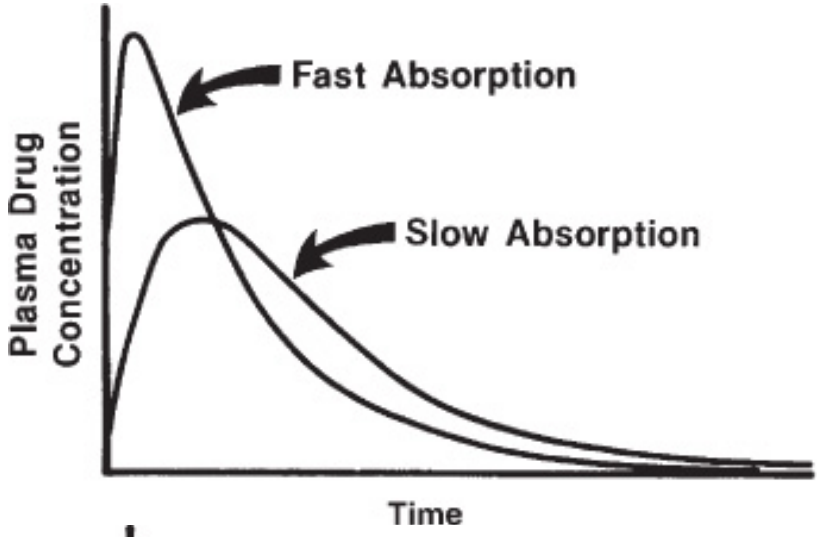
--- Food effect: double-peak phenomenon

--- Effects of disease: HIV, Congestive heart failure, Parkinson's disease

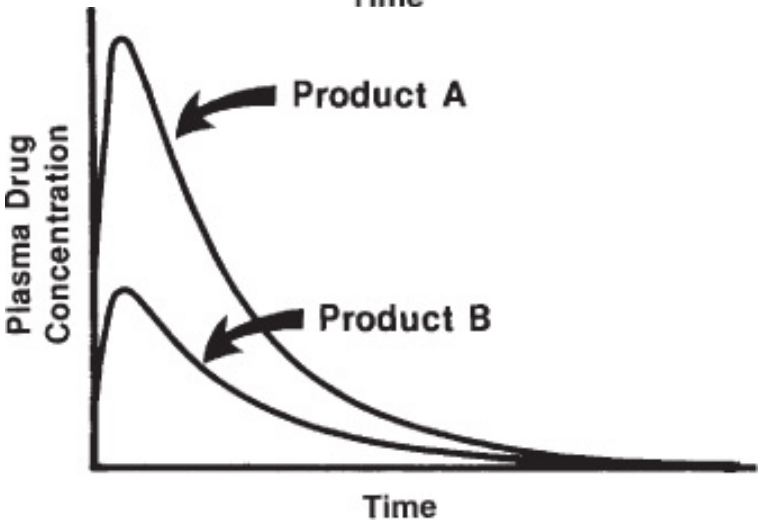
Drug Absorption

Oral drug absorption:

--- Effect of different absorption rates on plasma drug concentrations.



--- Effect of different extents of absorption on plasma drug concentrations.



Bioavailability

Bioavailability (F):

--- The percentage or fraction of the administered dose that reaches the systemic circulation of the patient.

Factors affecting drug bioavailability:

--- Chemical form of the drug (e.g. ester, salt)

--- Dosage form of the drug (e.g. tablet, capsule, suppository)

--- Route of drug administration (e.g. iv, po)

--- Stability of API in the GI tract

--- Extent of drug metabolism before reaching the systemic circulation (first-pass effect)

Bioavailability

Calculation of system-absorbed dose:

Amount of drug absorbed = **F × Dose**

Example: The bioavailability of digoxin in the dosage form of orally administered tablet is estimated to be 0.7. What is the absorbed dose of digoxin if 500 mcg of digoxin is given orally.

Impact of dosage form on F:

Example: Bioavailability of various dosage forms of Digoxin
Digoxin elixir: 0.8
Digoxin soft gelatin capsule: 1
Digoxin tablet: 0.7

Calculation of **equivalent dose**:

Dose of new dosage form (Dose 2)
= Amount of drug absorbed from current dosage form (F1×Dose 1) / F of new dosage form (F2)

Or Simply, **F1×Dose 1 = F2×Dose 2**

Example: A patient has been receiving digoxin 0.25 mg in the dosage form of orally administered tablet with a F of 0.7. What is the equivalent dose of digoxin in the dosage form of the elixir if this patient is switched to Digoxin elixir? What if the patient is switched to soft gelatin capsule of digoxin?

Impact of chemical form (S) on F:

Amount of drug absorbed = (**S**) × (**F**) × **Dose**

Dose of new dosage form
= Amount of drug absorbed from current dosage form / (S)×(F) of new dosage form

Or Simply, **S1× F1×Dose 1 = S2× F2×Dose 2**

Example:

1. Aminophylline (Ethylenediamine salt of theophylline, S = 0.8)

   100 mg Aminophylline = 20 mg Ethylenediamine (20%)+ 80 mg Theophylline (80%)

2. Phenytoin Sodium (Sodium salt of phenytoin, S = 0.92)

   100 mg Phenytoin Sodium = 92 mg Phenytoin + 8 mg Sodium

Impact of chemical form (Salt factor, S) on F:

Amount of drug absorbed = (**S**) × (**F**) × **Dose**

Example:

1. What is the amount of theophylline (S = 0.8) absorbed from a 200-mg uncoated aminophylline tablets (F=1)?

2. What is the amount of phenytoin (S = 0.92) absorbed from 300 mg of phenytoin sodium assuming complete absorption?

Drug Distribution

Drug distribution:

--- The process by which a drug reversibly leaves the blood stream and enters the interstitial fluid and/or tissue cells.

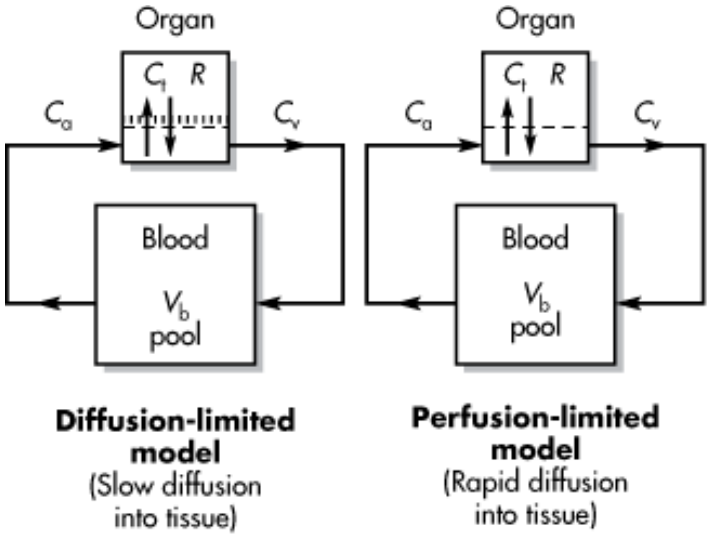
Is drug distribution homogeneous throughout the intravascular and extravascular compartments?

Are drug concentrations in tissues and fluids always the same as drug is absorbed, distributed, or eliminated?

Rate-limiting steps in drug distribution:

--- Perfusion (flow) - limited

--- Permeability (diffusion) - limited



Diffusion-limited model (Slow diffusion into tissue)

Perfusion-limited model (Rapid diffusion into tissue)

Drug Distribution

Factors affecting drug distribution:

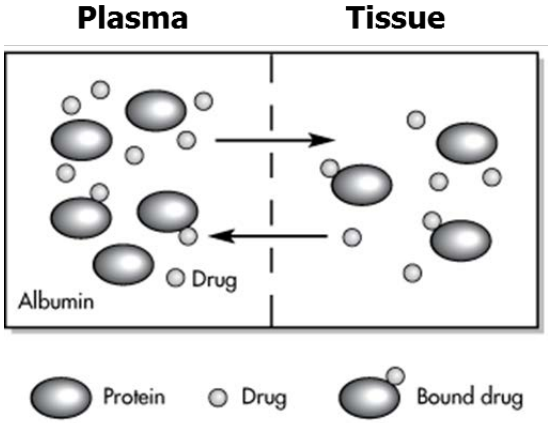
--- Rate of blood flow (heart, liver, kidney, brain, lung, bone, muscle, fat)

--- Membrane permeability (blood brain barrier, blood placenta barrier, etc)

--- Plasma protein/tissue binding

--- Transporter

--- Composition of specific tissues



Organ	Flow (ml/min/g)	
Lung	10	
Kidney	4	Highly perfused
Liver	0.8	
Brain	0.5	
Fat	0.03	Poorly perfused
Muscle	0.025	
Bone	0.02	

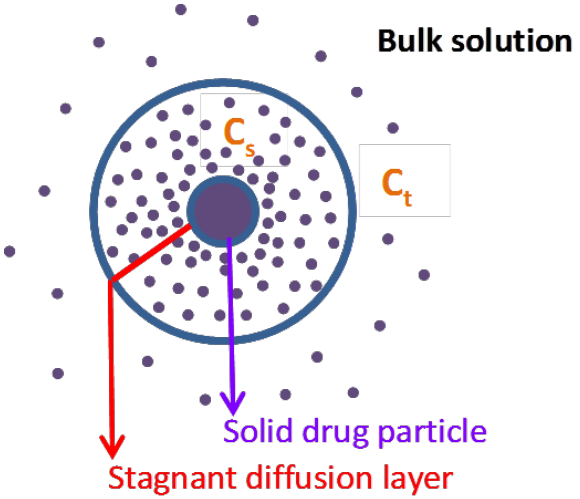
Drug Distribution

Factors affecting drug distribution:

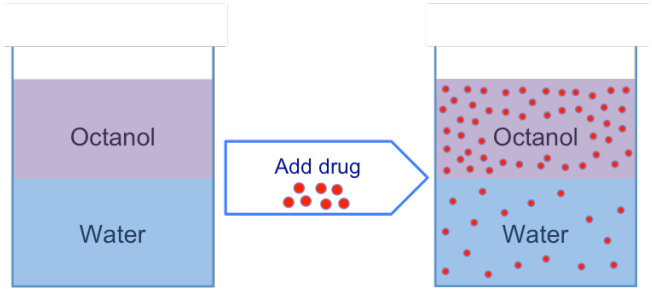
--- Organ/tissue size

--- Disease states

--- Physicochemical properties of the drug
- --- Lipophilicity
- --- Hydrophilicity
- --- Molecular size

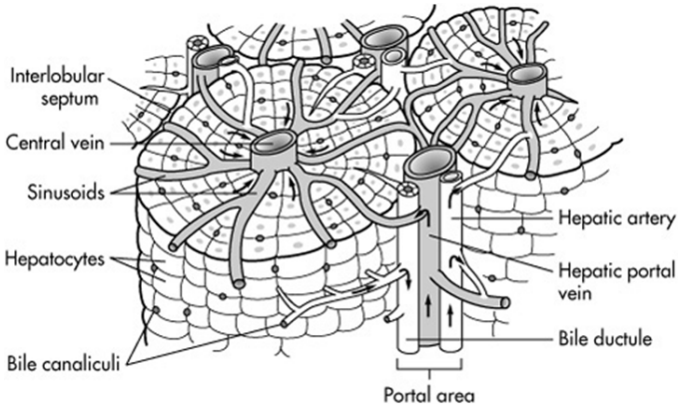


--- Reginal differences in physiologic pH



Drug Distribution

Tissue distribution of drug:



Liver:

--- Fenestrated capillaries: hepatic sinusoids.

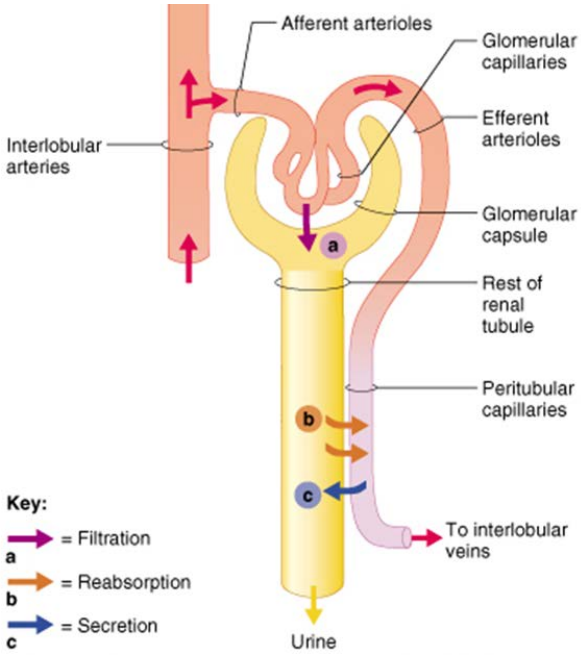
--- Drugs move in and out of liver hepatocytes easily.

Kidney:

--- Fenestrated capillaries: renal glomerulus.

--- Glomerular filtration:

1) Driving force: hydrostatic pressure.
2) Blood cells, platelets, plasma proteins, protein-bound drugs are not renally filtered at normal situation.



Drug Distribution

Tissue distribution of drug:

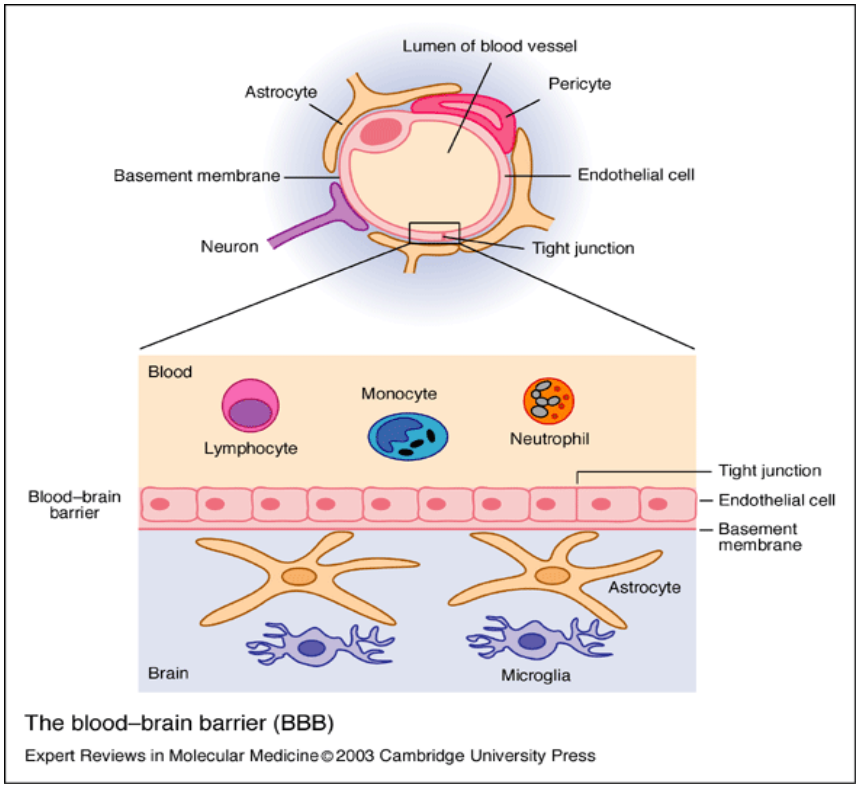
Brain:

--- Blood brain barrier:
1) endothelial cells with tight junction
2) thick basement membrane
3) astrocyte projections (astrocytic endfeet)

--- Mechanism:
1) passive diffusion (lipophilic drugs)
2) transporter-mediated process (transferrin/transferrin-receptor system)

--- Access: lipophilic drugs, small hydrophobic molecules (O_2, CO_2, hormones)

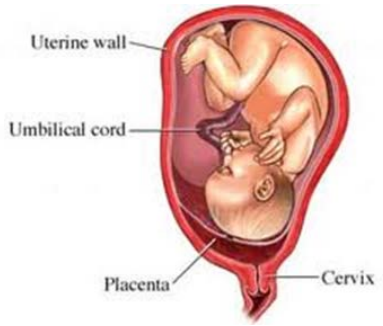
--- No access: bacteria, hydrophillic drugs, large molecules



The blood–brain barrier (BBB)

Drug Distribution

Tissue distribution of drug:



Maternal-fetal distribution:

--- lipophilic drugs vs hydrophilic drugs

--- Large (MW>1000) vs small-size drugs

Breast milk distribution:

--- Drug concentration in breast milk is based on drug concentration in maternal blood

--- Factors:

1) milk composition (amount of H_2O, lipid, protein, and pH)
2) Physicochemical properties of drug (pKa, protein binding, and lipophilicity)

Drug Distribution

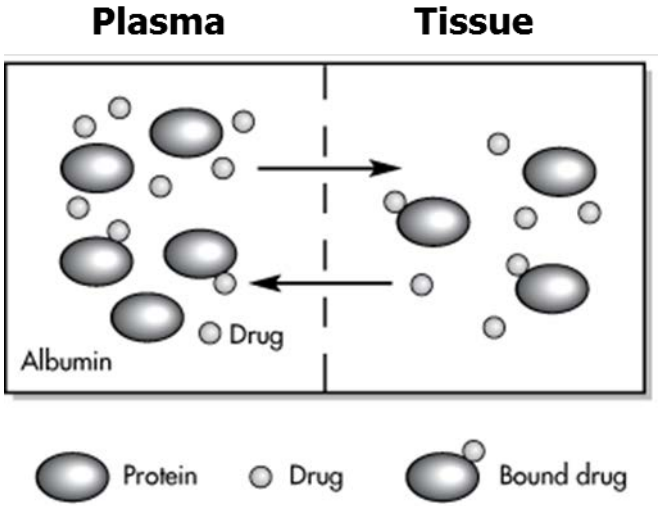
Tissue re-distribution of drug:

--- Fate of drug molecules distributed into tissues and non-plasma fluids: It can be re-distributed back into the plasma.

--- Consequence of drug molecules after tissue re-distribution back into the plasma: Drug elimination by kidney and liver.

--- Major driving force for drug molecules to move out of the cells/ tissues: concentration gradient (lower plasma concentration of drugs)

--- Factors that do not favor re-distribution of drug molecules from tissues to plasma:
1) Drugs extensively bound to tissue proteins
2) Drugs with large partition coefficient



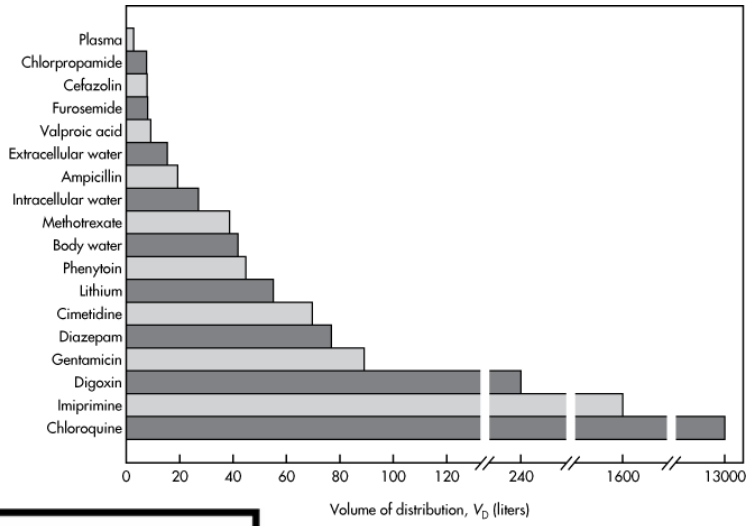
Drug Distribution

Volume of Distribution (V_d):

--- A theoretical space (apparent volume of distribution) with no physiologic meaning

--- An indicator of drug distribution patterns.

1) V_d: 3 ~ 5 L, distribution within blood plasma.
2) V_d: 30 ~ 50 L, distribution possibly through body water.
3) V_d: greater than 100% body weight, distribution in certain tissue compartments.



Factors decreasing Vd	Factors increasing Vd
Hydrophilic drugs	Lipophilic drugs
Increased plasma protein binding	Decreased plasma protein binding
Decreased tissue protein binding	Increased tissue protein binding

Drug Distribution

Volume of Distribution (V_d):

$$V_d = \frac{\text{amount of drug in body}}{\text{plasma drug concentration}}$$

$$V_d = \frac{D_B}{C_p} \qquad D_B = V_d \times C_p$$

Example: A dose of analgesic (50 mg) is administered intravenously and a blood sample is taken shortly afterwards. The concentration of this drug in the blood sample is determined to be 0.85 µg/ml. What is the volume of distribution of this analgesic in liters?

Drug Distribution

Volume of Distribution (V_d): Loading Dose

--- Vd is often used to determine loading dose.

--- Why is loading dose needed?

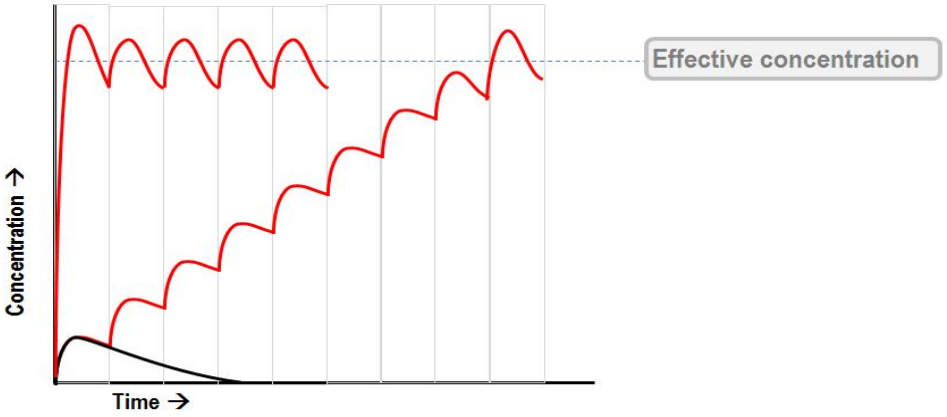
1) Suppose a drug requires a certain concentration in order to be therapeutic

2) A single dose of the drug is insufficient to achieve this therapeutic concentration

3) Multiple doses are thus required, but it may take hours or days before the therapeutic concentration is achieved

4) The patient would be sub-therapeutic during this phase

5) Loading doses are useful in achieving the desired therapeutic concentration QUICKLY



Drug Distribution

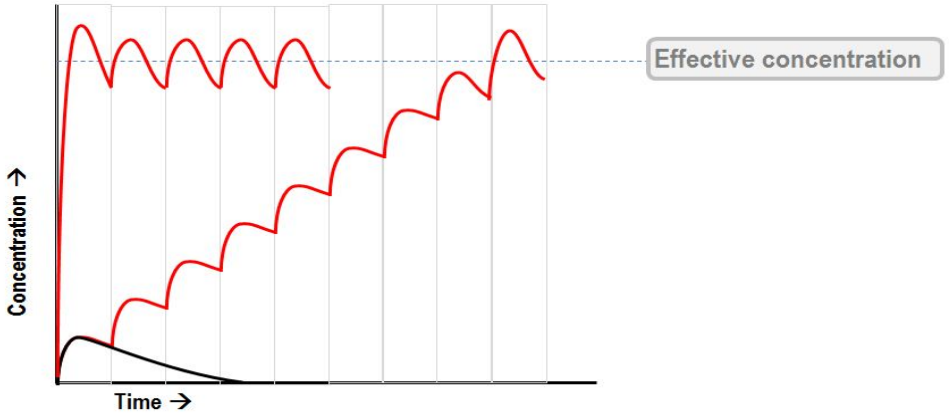
Volume of Distribution (V_d): Loading Dose

--- Loading dose is required for anesthetic drugs and drugs with long half-life or drugs whose therapeutic effect relies on its concentration at steady state.

--- Knowledge of the V_d is needed in order to achieve this therapeutic concentration.

$$\text{Loading Dose} = \frac{(V)(C)}{(S)(F)}$$

C = Desired drug concentration
V = Volume of distribution
S = Salt factor
F = Bioavailability



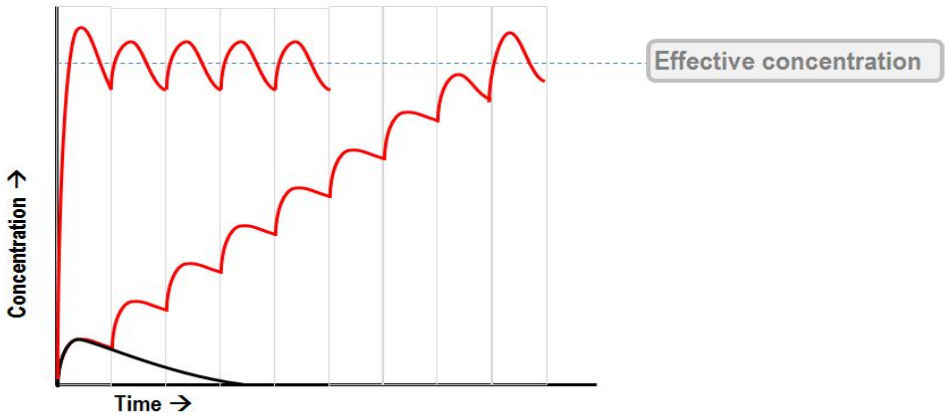
Drug Distribution

Volume of Distribution (V_d): Loading Dose

C = Desired drug concentration
V = Volume of distribution
S = Salt factor
F = Bioavailability

$$\text{Loading Dose} = \frac{(V)(C)}{(S)(F)}$$

Example: What loading dose is required to achieve a plasma drug concentration of 1.5 µg/L? Assume:
patient weight: 70 kg
V_d = 7.3 L/kg
S = 1
F = 0.7



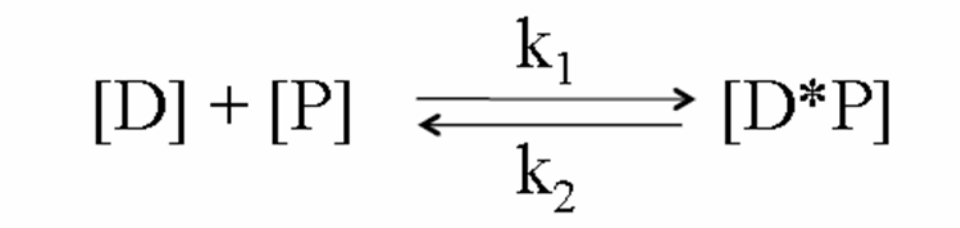
Protein Binding

Protein Binding of Drugs:

--- Binding of drugs to blood components: blood cells and plasma proteins.

--- Binding of drugs to extravascular tissues:
Tissue proteins, lipids (barbiturates), and bones (tetracycline)

--- Kinetics of Protein Binding:



[D] = Free drug concentration
[P] = Protein concentration
[D*P] = Bound drug concentration
k_1 = Rate constant for association
k_2 = Rate constant for dissociation
$k_a = k_1 / k_2$
k_a : equilibrium association constant
indicator of the affinity between the drug and the protein binding site

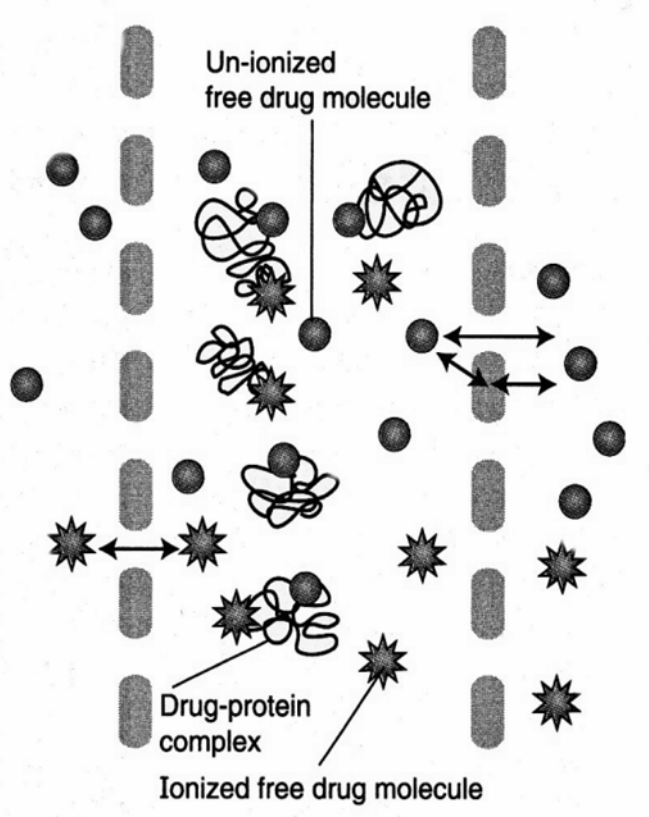
Protein Binding

Plasma protein Binding of Drugs:

--- Plasma drug concentrations reported from the laboratory include concentrations of both protein-bound drugs and free drugs.

--- **Only** free drug molecule is distributed to the site of action where it reacts with its receptor or to the elimination organs (liver and kidney) to be eliminated from the body.

--- For drugs that are highly bound to plasma proteins, the drug is typically confined to the central compartment which reduces the V_d.



Protein Binding

Plasma protein Binding of Drugs: fraction unbound (fu)

$$fu = \frac{\text{Free Drug Concentration}}{\text{Total Drug Concentration}}$$

$$fu = \frac{C\ free}{C\ bound\ +\ C\ free}$$

--- Alteration of plasma protein concentration or binding of drugs to plasma proteins affects free drug concentration and fu.

--- Increase in free drug concentration or fu for highly protein bond drugs produces greater pharmacological effect.

--- When drugs primarily bind to albumin, fraction of drug unbound (fu) dose not vary with plasma drug concentrations due to large amount of albumin available.

Protein Binding

Plasma protein Binding of Drugs: fraction unbound (fu)

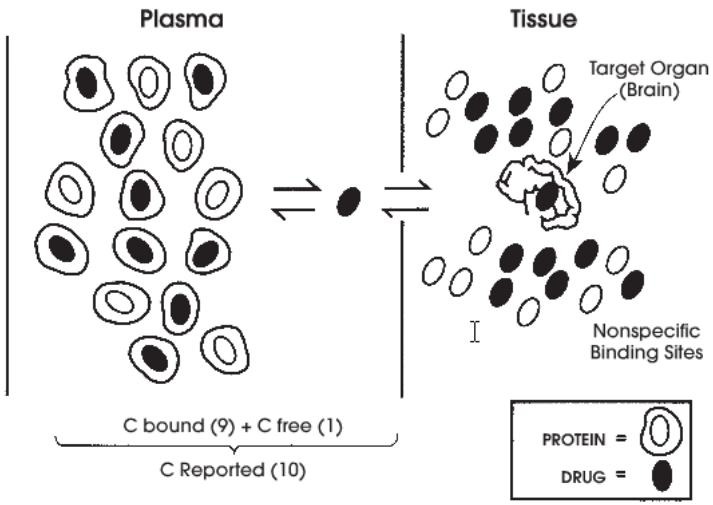
Reduced Plasma Protein Concentration:

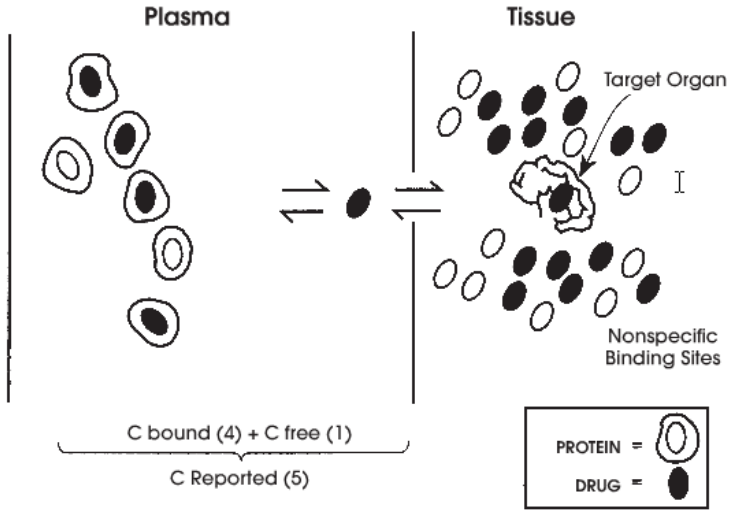
$$fu = \frac{C\ free}{C\ bound\ +\ C\ free}$$

--- It decreases *C bound*.

--- It does **NOT** affect *C free* generally.

1) nonspecific tissue binding
2) increased clearance from the body





--- Fraction of drug unbound (fu) increases as plasma protein concentrations decrease.

Protein Binding

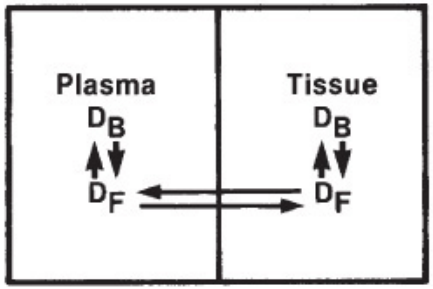
Plasma protein Binding of Drugs: fraction unbound (fu)

Elevated Plasma Protein Concentration:

$$fu = \frac{C\ free}{C\ bound\ +\ C\ free}$$

--- It increases *C bound*.

--- Little or no change in *C free* due to re-equilibration with large tissue stores.



D_B = Bound Drug
D_F = Free Drug

--- It increases total drug concentration in the plasma (C bound` + C free).

--- Fraction of drug unbound (fu) decreases as plasma protein concentrations increase.

Protein Binding

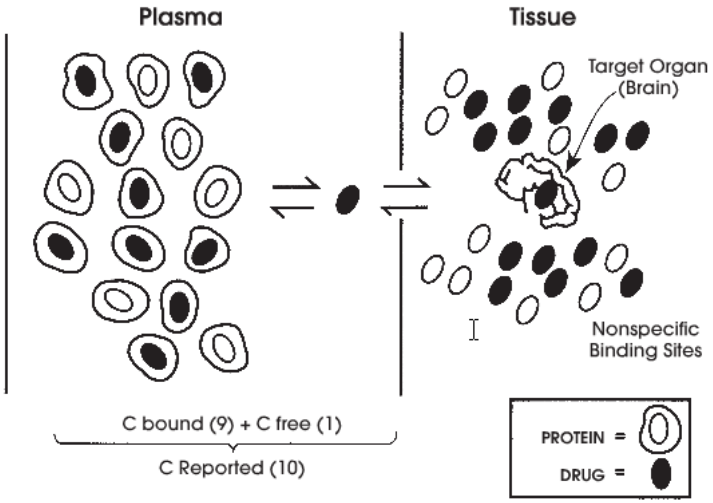
Plasma protein Binding of Drugs: fraction unbound (fu)

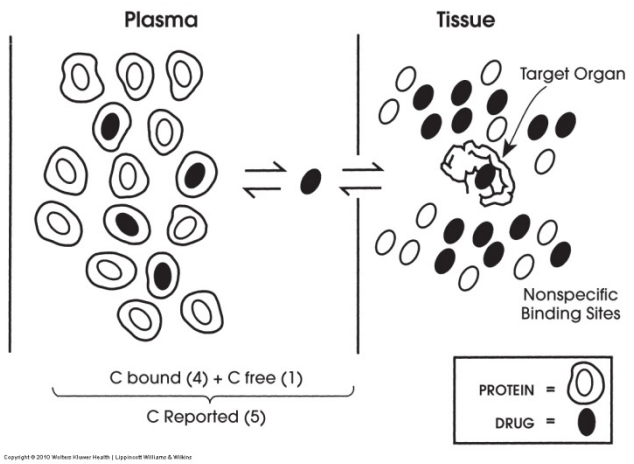
Binding affinity:

$$fu = \frac{C\ free}{C\ bound\ +\ C\ free}$$

--- It can alter fu.

--- Decrease in binding affinity increases in fu.





--- Example: Plasma proteins in patients with uremia have less affinity for phenytoin.

Protein Binding

Plasma protein Binding of Drugs: fraction unbound (fu)

$$\text{C free} = (\text{fu})(\text{C total})$$

$$\text{fu} = \frac{\text{C free}}{\text{C bound} + \text{C free}}$$

Change of drug - plasma protein binding:

--- It has greater impact on highly plasma protein bound drug.

--- It may change bound drug concentration (C bound).

--- It may result in a change of fraction of drug unbound (fu).

--- Unbound drug concentration (C free) is, in most cases, unchanged or unaffected.

--- C free depends on both fu and C total.

--- Alteration in C total (or C free) is not necessarily due to a change in plasma protein binding but probably because of a change of administered dose or drug elimination.

Protein Binding

Plasma protein Binding of Drugs: Plasma proteins

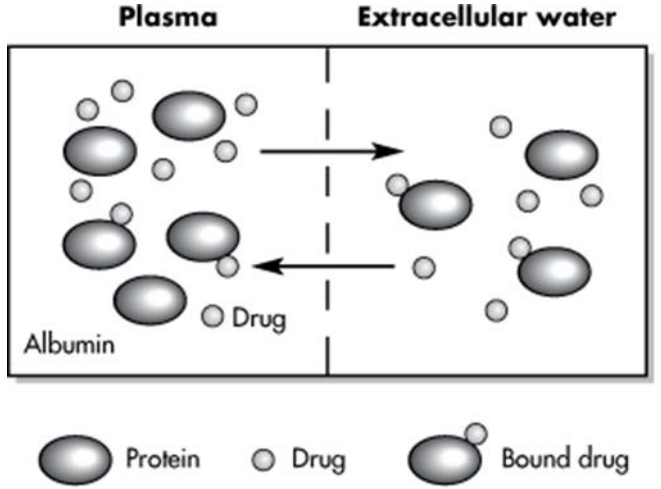
Albumin:

--- Most abundant plasma protein with great binding capacity to drugs.

--- Preferably bound to acidic and neutral drugs.

--- At least 2 main binding sites exist on albumin molecule:
Site 1: Warfarin, Sulfonamides, Phenytoin, Valproic acid
Site 2: Semi-synthetic penicillines, Probenecid

--- Alteration in albumin binding:
1) Hypoalbuminemia
2) Hyperalbuminemia
3) Altered drug affinity to albumin:
<u>Drug induced</u>
<u>Disease induced</u>
<u>Competitive displacement</u>



Protein Binding

Plasma protein Binding of Drugs: Plasma proteins

α_1-acid glycoprotein (AAG):

--- Mainly bound to basic drugs.

--- One major binding site is identified on AAG.

--- Situations of increased AAG concentration is more common than that of reduced AAG concentration.

--- Increased AAG concentrations are identified in the following situations:
Surgery, Crohn's disease, burns, trauma.

NOTE:

Generally, drugs that can bind to both albumin and AAG have a higher affinity for AAG

- Albumin: high capacity, low affinity
- AAG: low capacity, high affinity

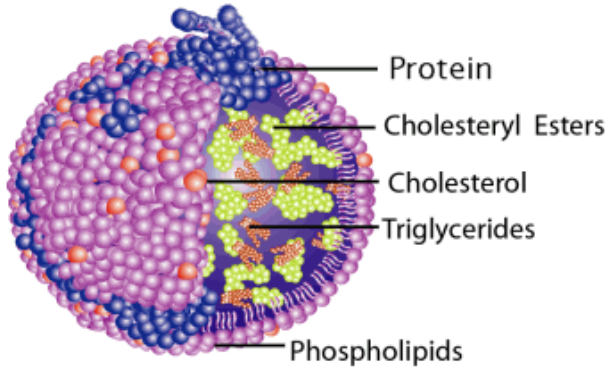
Protein Binding

Plasma protein Binding of Drugs: Plasma proteins

Lipoproteins:

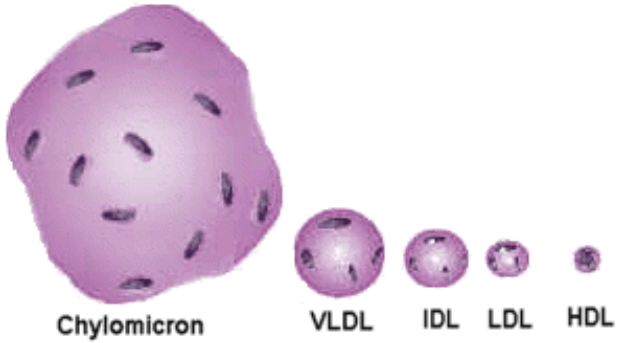
--- a heterogeneous group of proteins.

--- Spherical proteins with a lipid core surrounded by phospholipids, cholesterol, apolipoproteins.



--- Classification:

Chylomicrons
Very Low Density Lipoproteins (VLDL)
Intermediate Density Lipoproteins (IDL)
Low Density Lipoproteins (LDL)
High Density Lipoproteins (HDL)



--- Binding to neutral and basic drugs more common than acidic drugs.

--- Plasma concentrations of lipoproteins is relatively low.

--- Some drugs are thought to “bind” via a reversible liposolubilization process.

Protein Binding

Factors affecting protein Binding of Drugs:

Drug lipophilicity:

--- drug lipophilicity is proportional to the extend of drug protein binding.
example: slower absorption of cloxacillin than ampicillin after IM injection

Ethnicity:

--- Different ethnic patients taking certain drugs may result in different fu.
example: Higher fu found in Chinese patients than Caucasian patients after taking lidocaine and propranolol

Extremes of age:

--- Plasma protein binding of drugs may be lower in neonates than adults

--- Modest decreases in albumin may lead to lower plasma protein binding of drugs in the elderly.

Protein Binding

Factors affecting protein Binding of Drugs:

Pregnancy:

--- Decreased plasma protein binding of drugs has been observed in pregnant woman.

--- The increase in fu of drugs is found higher in the 3rd trimester.

Disease:

Disease	Influence on plasma protein	Influence on protein drug binding
Renal failure (uremia)	albumin content ↓	Decreased binding of acidic drug, basic drug are unaffected
Hepatic failure	albumin synthesis ↓	Decrease binding of acidic drug ,binding of basic drug is normal or reduced depending on AAG level.
Inflammatory state	AAG levels ↑	Increase binding of basic drug, neutral and acidic drug unaffected.

Protein Binding

Factors affecting protein Binding of Drugs:

Summary:

	Conditions	Change in concentration
Albumin	hepatic cirrhosis	↘
	burns	↘
	nephritic syndrome	↘
	pregnancy	↘
α-glycoprotein	myocardial infarcts	↗
	surgery	↗
	trauma	↗
	rheumatoid arthritis	↗

Drug Clearance & Elimination

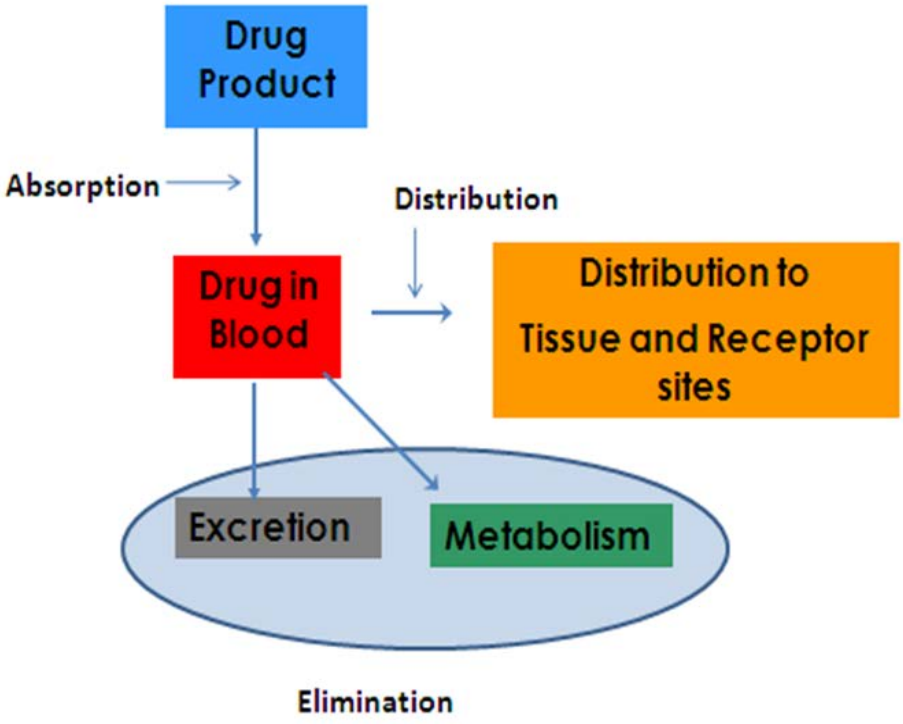
Drug Elimination:

--- Irreversible removal of drug from the body.

Metabolism:
--- Elimination of the drug by chemical transformation.
--- Phase I and Phase II metabolism.
--- Liver, kidney, intestine, blood

Renal Excretion:
--- Elimination of the drug in the urine.
--- Glomerular filtration,
Active tubular secretion,
Tubular reabsorption

Other excretion routes?



Drug Clearance & Elimination

Drug Clearance:

--- The apparent volume of reference fluid (plasma or blood) cleared of drug per unit time.

--- A proportionality factor between the rate of elimination of a drug from the entire body (systemic clearance) or an organ (organ clearance) and its concentration at the site of measurement (plasma or blood).

$$\mathbf{CL = \frac{Rate\ of\ elimination\ of\ drug}{Plasma\ drug\ concentration}}$$

$$\mathbf{(Units = volume\ per\ unit\ time)}$$

Note:

- Clearance is **NOT** an indication of how much of a drug is being eliminated per unit time, but rather how much apparent volume of reference fluid is cleared of a drug per unit of time.
- The amount of drug that is actually removed from the body depends on:
  --- The concentration of the drug in the blood plasma
  --- Drug clearance

Drug Clearance & Elimination

Drug Clearance:

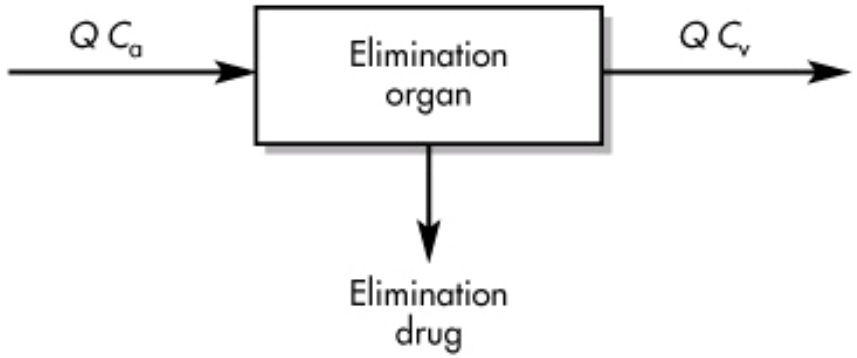
Total body clearance (systemic clearance) of a drug:
--- A measure of the ability of the entire body to eliminate the drug.

$$\textbf{Total Body Clearance} = CL_{liver} + CL_{kidney} + CL_{lungs} + CL_x$$

Organ clearance:
--- A measure of the ability of a particular organ to eliminate the drug.

$$\textbf{Organ clearance} = Q \times E$$

$$E = \frac{C_a - C_v}{C_a}$$



Note:

Drug clearance is the pharmacokinetic term used to determine a maintenance dose.

Drug Clearance & Elimination

Drug Clearance: Single dose

Application of a single dose:

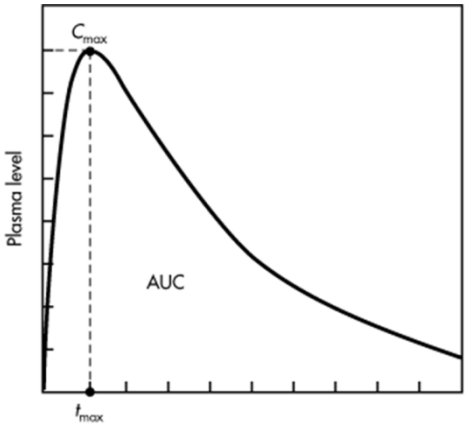
--- The drug will reach a maximal concentration (C_{max}) at some time (T_{max}).

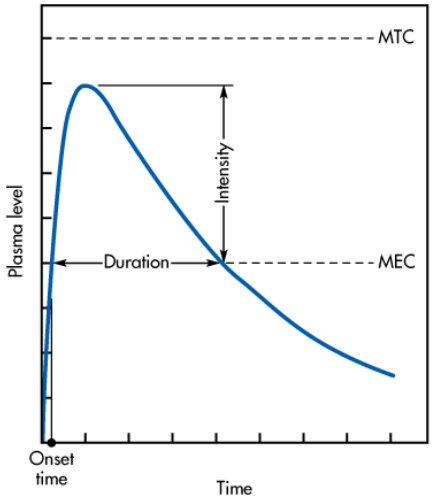
--- The drug will be cleared from the volume of distribution.

--- For almost all drugs, the concentration of drug will reach zero at some time point.

--- A single dose is usually not sufficient to achieve the therapeutic purpose.
(Exception: Single dose of certain antibiotic drugs is curative)

--- Multiple doses are thus required.





Source: Shargel L, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics, 6th Edition*: www.accesspharmacy.com

Drug Clearance & Elimination

Drug Clearance: Multiple doses

Steady state:

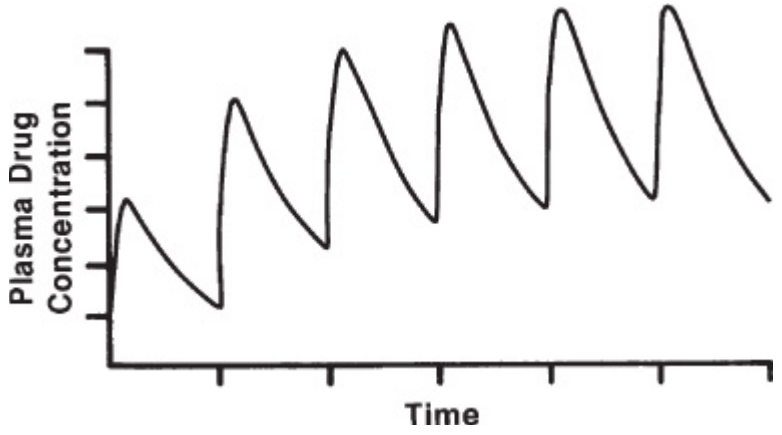
--- Rate of drug administration (R_A)

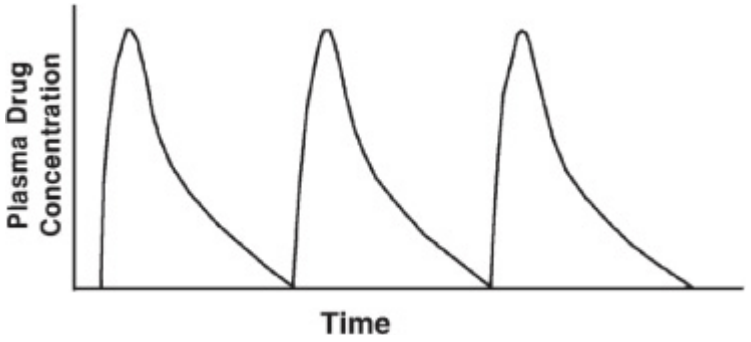
--- Rate of drug elimination (R_E)

--- If $R_A > R_E$, drug accumulation occurs.
Drug concentration increases over time.

--- If $R_A = R_E$, steady state is reached.

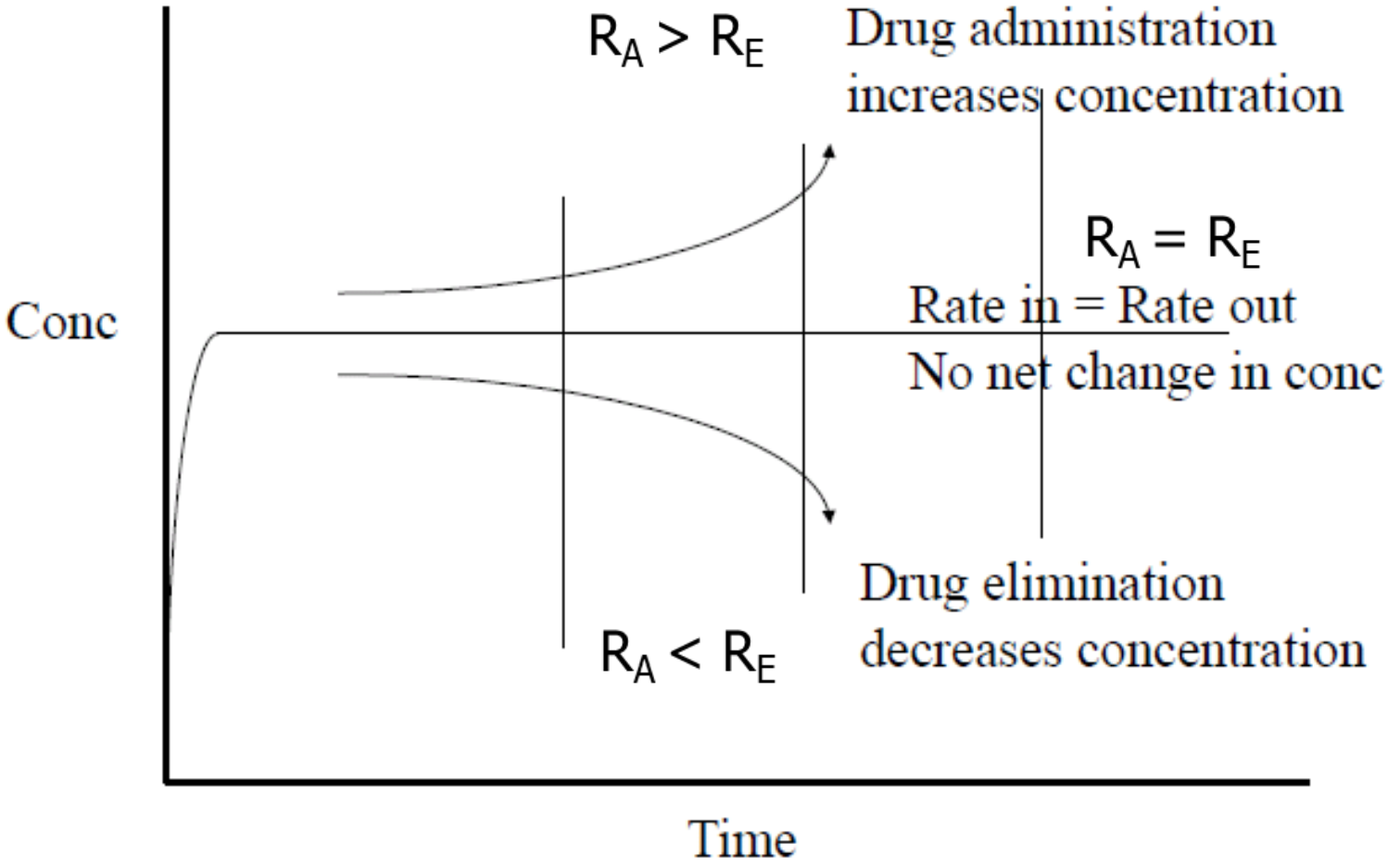
--- If $R_A < R_E$, no drug accumulation.
Drug concentration reaches a point of zero.





Drug Clearance & Elimination

Drug Clearance: Steady state



Drug Clearance & Elimination

Drug Clearance: Calculation

Steady state: $R_A = R_E$

$$R_a = \frac{\text{Dose}}{\tau} \qquad R_a = \frac{Cl \cdot C_{ss}}{S \cdot F}$$

$$Cl = \frac{S \cdot F \cdot \text{Dose} / \tau}{C_{ss}}$$

Note: Drug concentration must be at steady state.

F = bioavailability
τ = dosing interval
Css = steady state concentration of a drug
S = salt factor

Drug Clearance & Elimination

Drug Clearance: Calculation

1. Lidocaine is infused at a rate of 120 mg/hr and the steady-state concentration is given as 3 mg/L. What is the clearance in this case?

$$Cl = \frac{S \cdot F \cdot Dose / \tau}{C_{ss}}$$

2. Calculate aminophylline infusion rate to achieve Css = 15 mg/L of theophylline. Given S = 0.8 and Cl = 2.5 L/hr in this case.

$$R_a = \frac{Cl \cdot C_{ss}}{S \cdot F}$$

Drug Clearance & Elimination

Drug Clearance: Factors

- Body weight/ Body Surface Area (BSA)
- Cardiac output (CO)
- Drug-drug interactions
- Extraction ratio
- Hepatic & Renal function
- Plasma protein binding
- Genetics

Drug Clearance & Elimination

Drug Clearance: Factors

- Body weight/ Body Surface Area (BSA)

--- Consideration of a patient's body mass or BSA can be used to adjust clearance factors

--- Average body weight and BSA: 70 kg, 1.73 m^2

--- Attempt to normalize Cl values to 70 kg or 1.73 m^2

$$\text{BSA in } m^2 = \left(\frac{\text{Patient's Weight in kg}}{70\,\text{kg}}\right)^{0.7} (1.73\,m^2)$$

--- Body mass or BSA may relate to different size or function of organs associated with clearance

--- Increased body mass or BSA is also associated with an increased V_d

Drug Clearance & Elimination

Drug Clearance: Factors

- Cardiac output (CO)

--- Since the heart provides the CO to all the major organs, changes in CO result in changes in blood flow to Liver and Kidneys.

--- Reduced blood flow can result in reduced clearance from each of these organs. (congestive heart failure)

- Drug-drug interactions

--- Drugs that inhibit liver metabolism of drugs, e.g. Cimetidine, erythromycin

--- Drugs that induce liver metabolism enzymes, e.g. Phenobarbital, rifampin

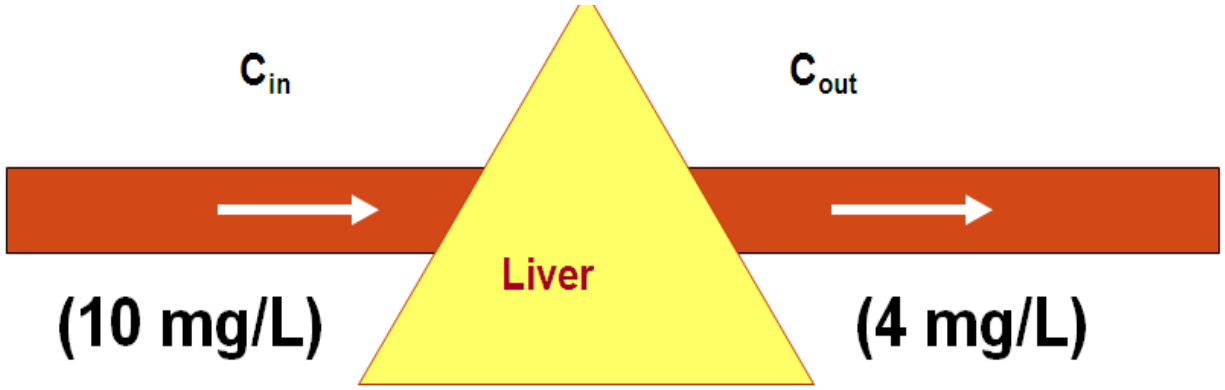
Drug Clearance & Elimination

Drug Clearance: Factors

- Extraction ratio

--- The extraction ratio refers to the proportion of drug removed by a single pass through a clearance organ (e.g. liver)

--- Drugs with high extraction ratio vs drugs with low extraction ratio



Drug Clearance & Elimination

Drug Clearance: Factors

- Hepatic & Renal function

--- The liver and the kidneys represent the organs with the greatest capacity to clear drugs from the Vd

$$Cl_T = Cl_H + Cl_R$$

--- Note that usually renal clearance and hepatic clearance are independent of each other

--- Example: a drug with 33% hepatic clearance and 67% renal clearance

-- situation 1: liver failure occurs resulting in 0% hepatic clearance

-- situation 2: kidney failure occurs resulting in 0% renal clearance

Drug Clearance & Elimination

Drug Clearance: Factors

- Hepatic & Renal function

$$Cl_T = Cl_H + Cl_R$$

--- Hepatic function is usually more difficult to quantitate than renal function

--- Cl_T is most commonly adjusted when there is decreased renal function.

$$Cl_{adjusted} = Cl_H + Cl_R \times (\text{fraction of normal renal function remaining})$$

Dose Rate Adjustment Factor =

[Fraction Eliminated Metabolically] + [Fraction Eliminated Renally] [Fraction of Normal renal Function Remaining]

Ex) A drug is 25% metabolized and 75% renally cleared and normally administered as 100 mg per 12 hours. If this drug were to be given to a patient who has only 33% of normal renal function. What the dosing rate adjustment factor be? How should administer the drug?

Drug Clearance & Elimination

Drug Clearance: Factors

- Plasma protein binding

Considering a case of hypoalbuminemia

$$fu\uparrow = \frac{C_{p,\,free}}{C_{p,\,bound}\downarrow + C_{p,\,free}}$$

--- Fraction of free drug (fu) increases
--- Drug clearance (CL) increases
--- Drug concentration at steady state (C_{ss}) decreases
--- Concentration of free drug remains similar
--- Pharmacologic effect achieved remains similar

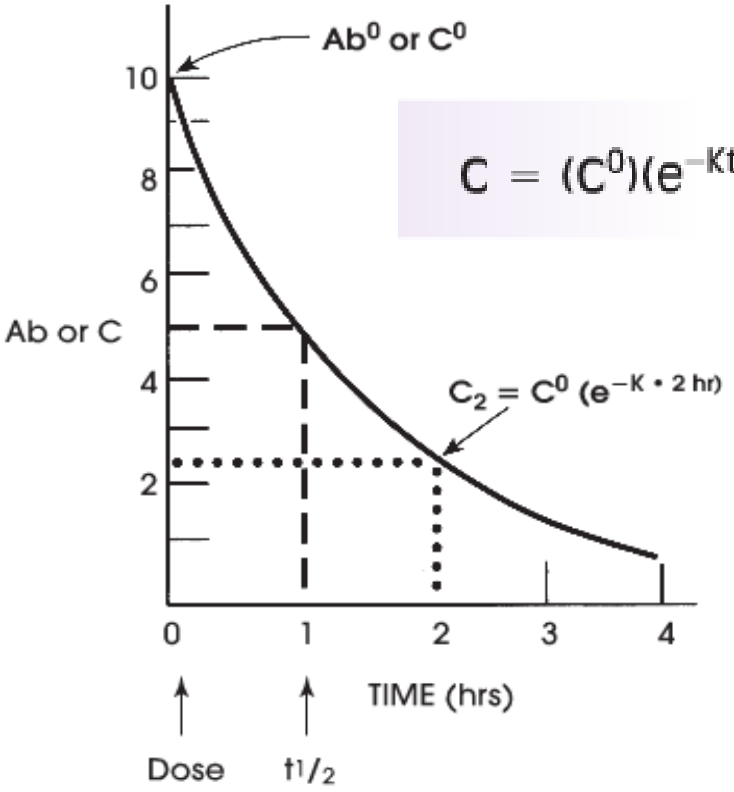
- Genetics

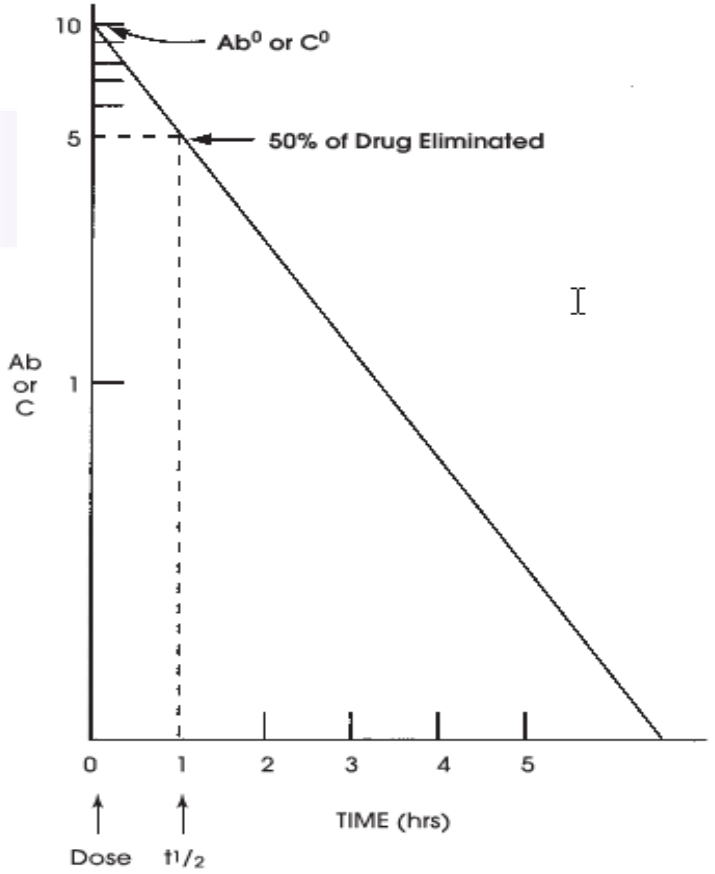
--- Difference in genetic makeup of individuals results in different rate of drug metabolism and thus different clearance of the drug.

Example: fast vs slow acetylators who take isoniazid

Drug Clearance & Elimination

Elimination Rate Constant (K): First order pharmacokinetics





Ab^0: Initial amount of drug

C^0: Initial plasma concentration of drug

C: Plasma concentration of drug at time t

e^{-kt}: Fraction of drug remaining at time t

Drug Clearance & Elimination

Elimination Rate Constant (K):

--- The fraction or percentage of the total amount of drug in the body removed per unit of time.

--- Independent of drug dose or concentration.

--- The fraction of the volume of distribution that will be cleared of drug per unit of time.

$$K = \frac{Cl}{V}$$

Example: Calculate the elimination rate constant of a drug with a clearance of 10 L/day and a V of 100 L.

Drug Clearance & Elimination

Elimination Rate Constant (K):

--- K can be calculated using two points (plasma concentrations) measured during the elimination phase.

--- The time interval between this two points should be at least one half-life.

$$C_2 = (C_1)(e^{-Kt})$$

$$\frac{C_2}{C_1} = e^{-Kt}$$

$$\ln\left(\frac{C_2}{C_1}\right) = -Kt$$

$$\ln\left(\frac{C_1}{C_2}\right) = Kt$$

$$\frac{\ln\left(\frac{C_1}{C_2}\right)}{t} = K$$

$$K = \frac{\ln\left(\frac{C_1}{C_2}\right)}{t}$$

t: time interval between C_1 and C_2.

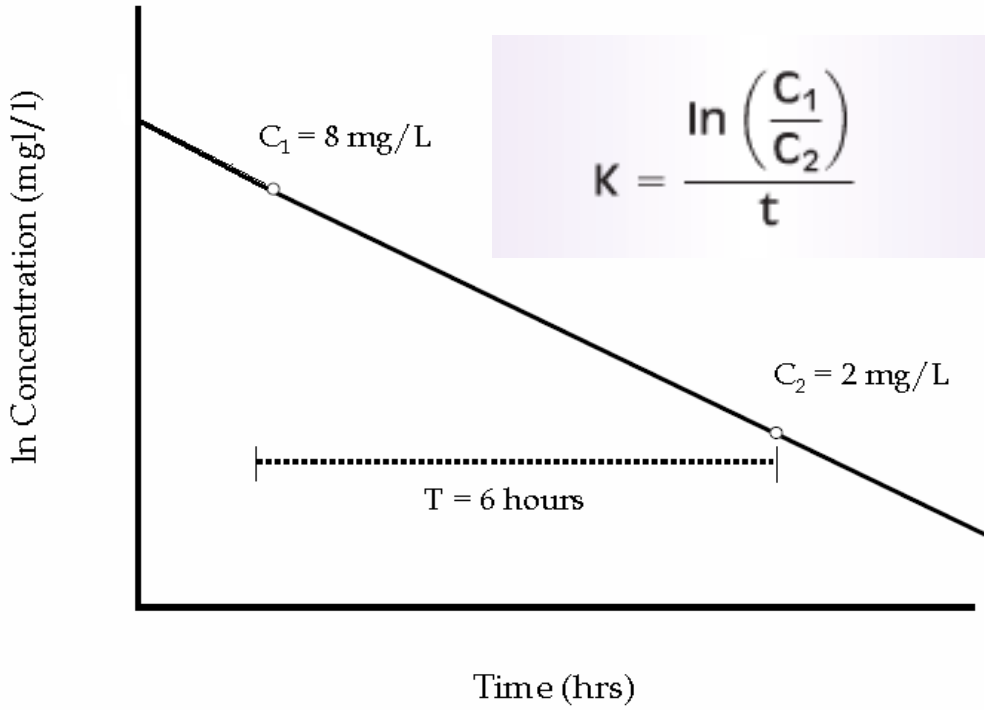
Drug Clearance & Elimination

Elimination Rate Constant (K):

--- K can be calculated using two points (plasma concentrations) measured during the elimination phase.

--- The time interval between this two points should be at least one half-life.

Example:
Calculate K.



$$K = \frac{\ln\left(\frac{C_1}{C_2}\right)}{t}$$

Drug Clearance & Elimination

Elimination Half-life ($t_{1/2}$) and K:

--- The K is often expressed in terms of a drug's half-life.

--- $t_{1/2}$: The time required for the total amount of drug in the body or C_p to decrease by one-half.

$$t_{1/2} = 0.693/k$$

--- It depends on drug clearance and volume of distribution.

- $t_{1/2}$ is proportional to V_d
- $t_{1/2}$ is inversely proportional to CL

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

$$(\text{Units} = \text{time})$$

Drug Clearance & Elimination

Elimination Half-life ($t_{1/2}$) and K: Clinical applications

--- Estimating the time to reach Css after initiation or change in the maintenance dose.

--- Estimating the time required to eliminate all or a portion of the drug from the body once dosing is discontinued.

--- Predicting a Css level from a non-Css level obtained at a specific time following the initiation of an infusion.

--- Predicting non-Css levels following the discontinuation of an infusion.

--- Determining the appropriate dosing interval to achieve desired Cmax and Cmin.

Drug Clearance & Elimination

Elimination $t_{1/2}$ and K: Clinical applications

1. Determining time to reach Css:

--- Steady state: $R_A = R_E$

--- The time it takes for a drug to reach steady-state is determined by the elimination half-life of the drug.

--- After each half-life passes, the drug proceeds to a level of steady-state:

- 1 $t_{1/2}$ = 50% of steady state
- 2 $t_{1/2}$ = 75% of steady state
- 3 $t_{1/2}$ = 87.5% of steady state
- 4 $t_{1/2}$ = 93.75% of steady state
- 5 $t_{1/2}$ = 96.875% of steady state

--- It takes about 4 to 5 half-lives for a drug to achieve steady state.

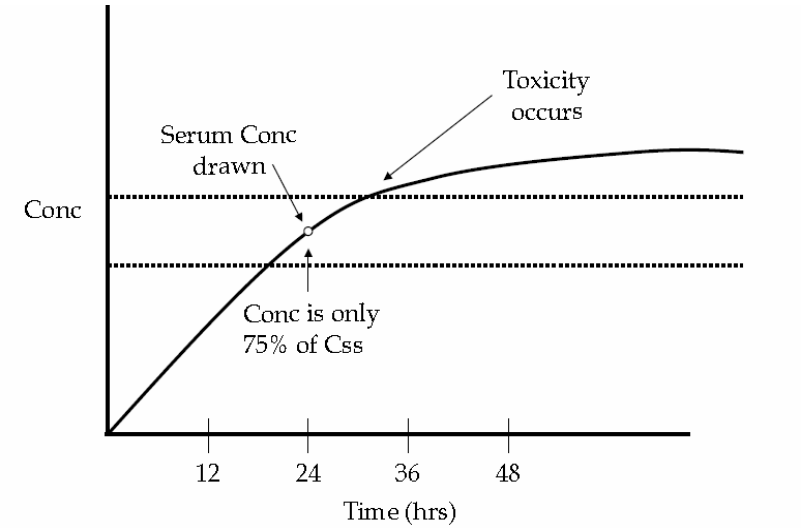
Drug Clearance & Elimination

Elimination $t_{1/2}$ and K: Clinical applications

1. Determining time to reach Css:

Example:
Assume that the half-life of a drug is 12 hours for a drug with a narrow therapeutic window:

- The first dose of the drug is given, and then a maintenance IV dose is started
- A serum concentration is drawn after 24 hours.
- Assume the serum concentration is within the therapeutic range.



*Is it **safe** when concentrations of the drug reach steady-state?*

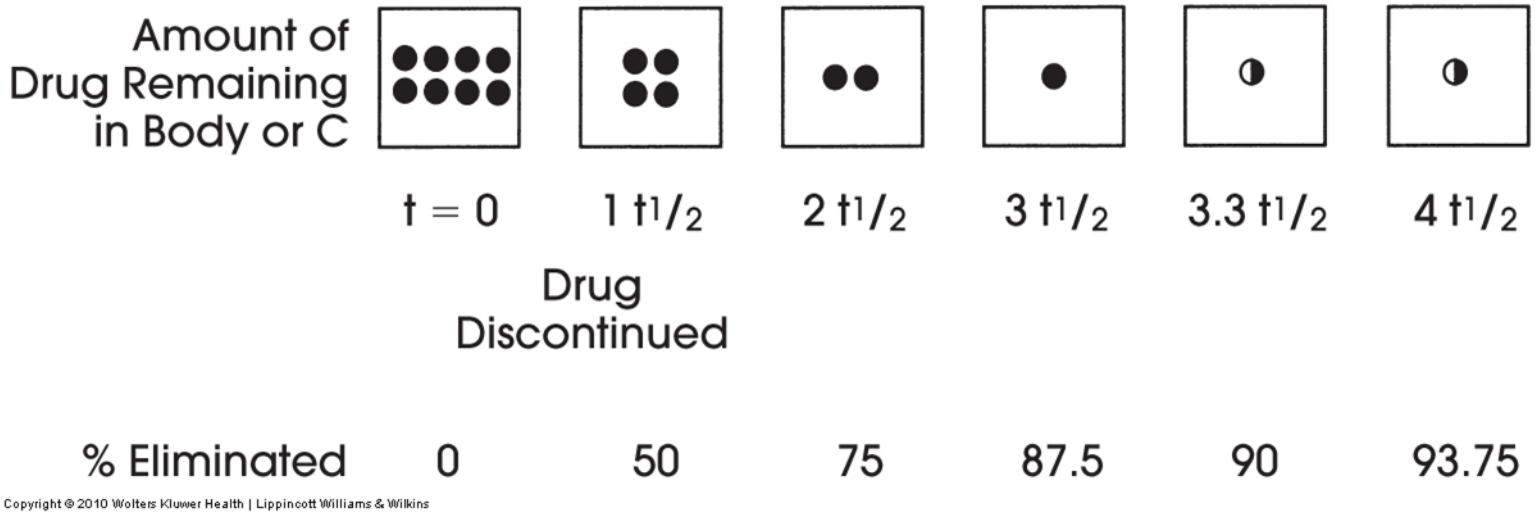
Drug Clearance & Elimination

Elimination $t_{1/2}$ and K: Clinical applications

2. Determining time for drug elimination:

--- The same principle holds true for drug elimination.

--- After each half-life passes, the drug concentration halves from previous Cp:

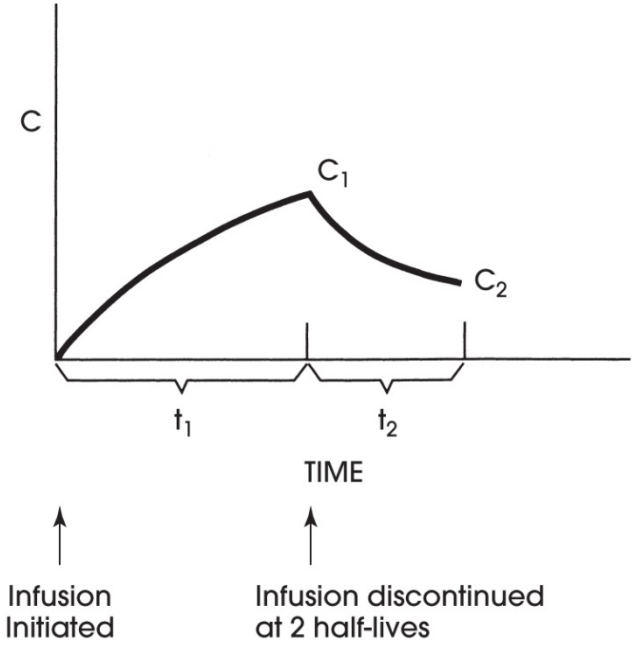


--- It takes about 4 to 5 half-lives for a drug to be effectively eliminated from the body in most clinical situations.

Drug Clearance & Elimination

Elimination $t_{1/2}$ and K: Clinical applications

3. Predicting C_p following initiation of an infusion:



--- Fraction of steady state achieved:

$$\text{Fraction of Steady State Achieved at time } t_1 = 1 - e^{-Kt_1}$$

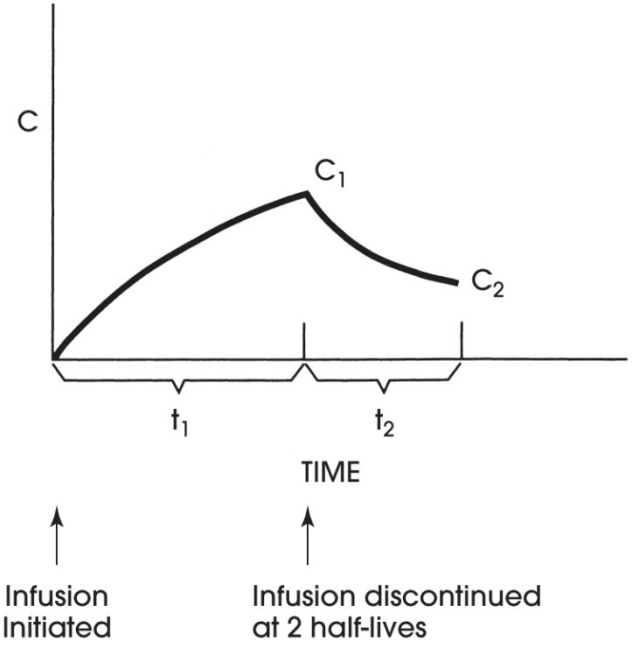
--- Average plasma concentration at steady state $C_{ss\ ave}$:

$$Cl = \frac{(S)(F)(Dose/\tau)}{Css\ ave} \Rightarrow Css\ ave = \frac{(S)(F)(Dose/\tau)}{Cl}$$

Drug Clearance & Elimination

Elimination $t_{1/2}$ and K: Clinical applications

3. Predicting C_p following initiation of an infusion:



--- Expected C_1 at a specific time t_1 after initiation of an infusion:

$$C_1 = (\text{Css ave})\left(\text{Fraction of Steady State Achieved at } t_1\right)$$

$$\text{Css ave} = \frac{(S)(F)(\text{Dose}/\tau)}{Cl}$$

$$\text{Fraction of Steady State Achieved at time } t_1 = 1 - e^{-Kt_1}$$

$$C_1 = \frac{(S)(F)(\text{Dose}/\tau)}{Cl}(1 - e^{-Kt_1})$$

$$\text{Css ave} = \frac{C_1}{1 - e^{-Kt_1}}$$

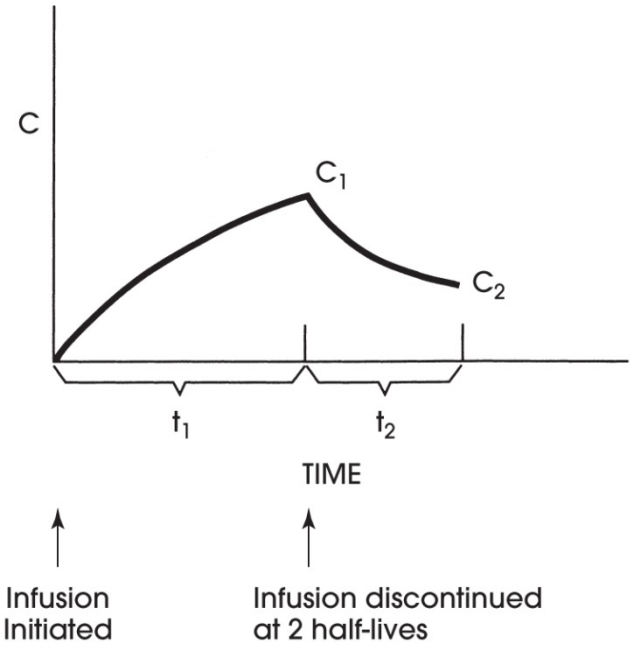
Drug Clearance & Elimination

Elimination $t_{1/2}$ and K: Clinical applications

4. Predicting C_p following discontinuation of an infusion:

--- Fraction of drug remaining at t_2: e^{-kt_2}

$$C_2 = (C_1)(e^{-kt_2})$$



Recall,

$$C_1 = \frac{(S)(F)(Dose/\tau)}{Cl}(1 - e^{-Kt_1})$$

$$C_2 = \frac{(S)(F)(Dose/\tau)}{Cl}(1 - e^{-Kt_1})(e^{-Kt_2})$$

Drug Clearance & Elimination

Elimination $t_{1/2}$ and K: Clinical applications

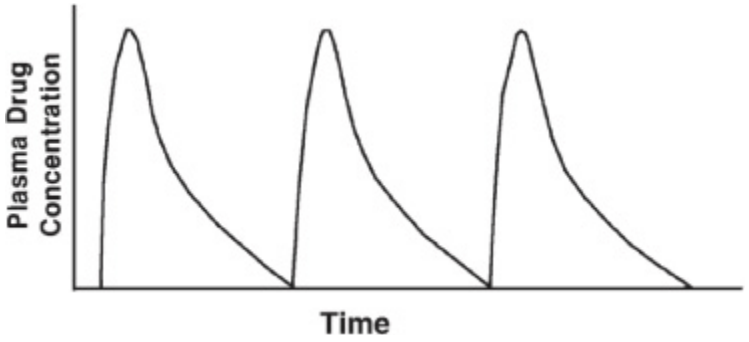
5. Determining dosing interval (τ):

--- The $t_{1/2}$ can be used to estimate dosing interval for maintenance therapy.

$$\text{Maintenance Dose} = \frac{(Cl)(Css\,ave)(\tau)}{(S)(F)}$$

--- If τ is equal to $t_{1/2}$, the degree of fluctuation between peak ($C_{ss,max}$) and trough ($C_{ss,min}$) concentration during one τ is equal to 50%.

--- If τ is much longer than $t_{1/2}$,
each new dose is a new loading dose,
and each new $C_{ss,max}$ is determined by V_d.

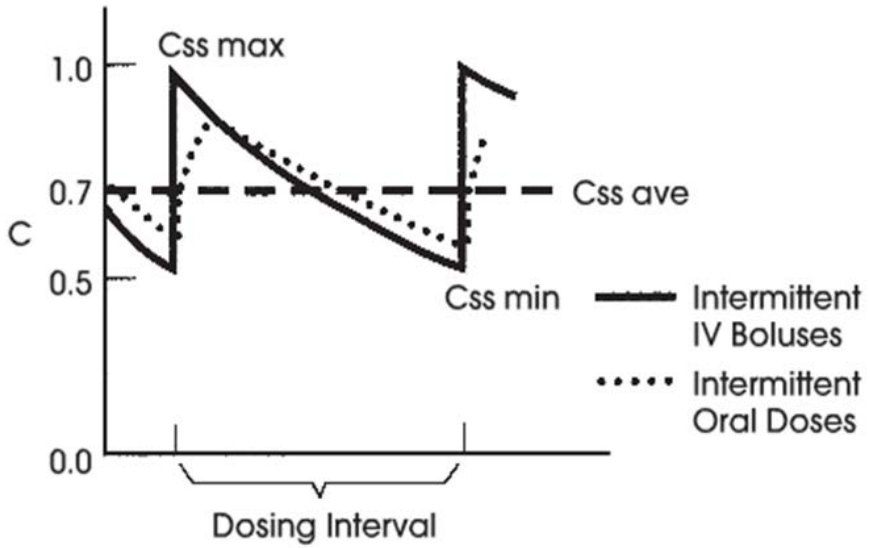


--- If τ is much shorter than $t_{1/2}$,
drug plasma level is determined primarily by clearance.

Drug Clearance & Elimination

Elimination $t_{1/2}$ and K: Clinical applications

5. Determining dosing interval (τ):



$$\text{Css ave} = \frac{(S)(F)(\text{Dose}/\tau)}{Cl}$$

$$\text{Css max} = \frac{\dfrac{(S)(F)(\text{Dose})}{V}}{1 - e^{-K\tau}}$$

$$\text{Css min} = \frac{\dfrac{(S)(F)(\text{Dose})}{V}}{1 - e^{-K\tau}} e^{-K\tau}$$

$$\text{Css}_1 = \frac{\dfrac{(S)(F)(\text{Dose})}{V}}{1 - e^{-K\tau}} e^{-Kt_1}$$

Reference

1. Winter's Basic Clinical Pharmacokinetics, 6th Edition (2018), Beringer, PM.

2. Concepts in Clinical Pharmacokinetics, 6th Edition (2014), DiPiro, JT, *et al*.

3. Applied Biopharmaceutics and Pharmacokinetics, 7th Edition (2016), Shargel, L, *et al*.

PHAR 227G Pharmacokinetics:

Drug Absorption, Distribution, Protein Binding, Clearance and Elimination

The End

Xinyu (Eric) Wang, PhD

Associate Professor of Pharmaceutical Sciences

PCOM-School of Pharmacy