Therapeutic Drug Monitoring

Lecture 1
Dr Atheer Zgair

Therapeutic drug monitoring (TDM) refers to the individualisation of dosage by maintaining plasma or blood drug concentrations within a target range (therapeutic range, therapeutic window).

Major sources of variability between individual patients in drug response

1. **Pharmacodynamic variability:** drug concentration at the receptor and the response.

   This type of variability includes

   - Genetic Variability in Receptors such variability in *μ-opioid receptor, $ß_2$-andrenergic receptor, dopamine receptors, and serotonin receptors*

- Non-genetic variability includes psychological factors - The placebo effect is a phenomenon that a patient's symptoms can be alleviated by giving a placebo drug.

2. **Pharmacokinetic variability:** dose and plasma concentration.

   Major sources of pharmacokinetic variability

1. Compliance
2. Age - neonates, children, elderly
3. Physiology - gender, pregnancy
4. Disease - hepatic, renal, cardiovascular, respiratory.
5. Drug interactions
6. Environmental influences on drug metabolism - diet, alcohol, and tobacco.
7. Genetic polymorphisms of drug metabolism - the less effective Butyrylcholinesterase (Atypical BuCHE, type A) on succinylcholine.

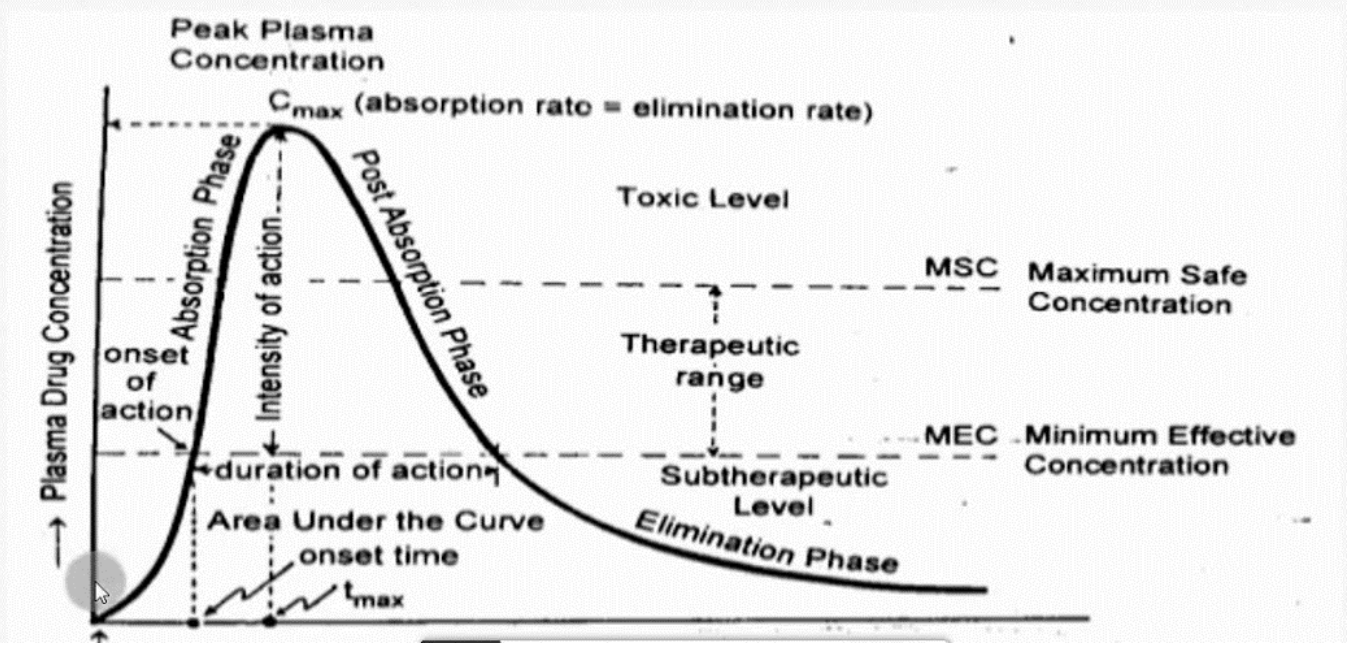
   For which drugs is monitoring helpful?

- Marked pharmacokinetic variability
- Concentration related therapeutic and adverse effects
- Narrow therapeutic index
- Defined therapeutic (target) concentration range
- Desired therapeutic effect difficult to monitor

Pharmacokinetics is the study of the time course of drug absorption, distribution, metabolism, and excretion.

Clinical Pharmacokinetics is the application of pharmacokinetic principles to the *safe* and *effective* therapeutic management of drugs in an individual patient.

➢ Absorption and Disposition kinetics



Anatomic and physiologic considerations for drug measurement in the body

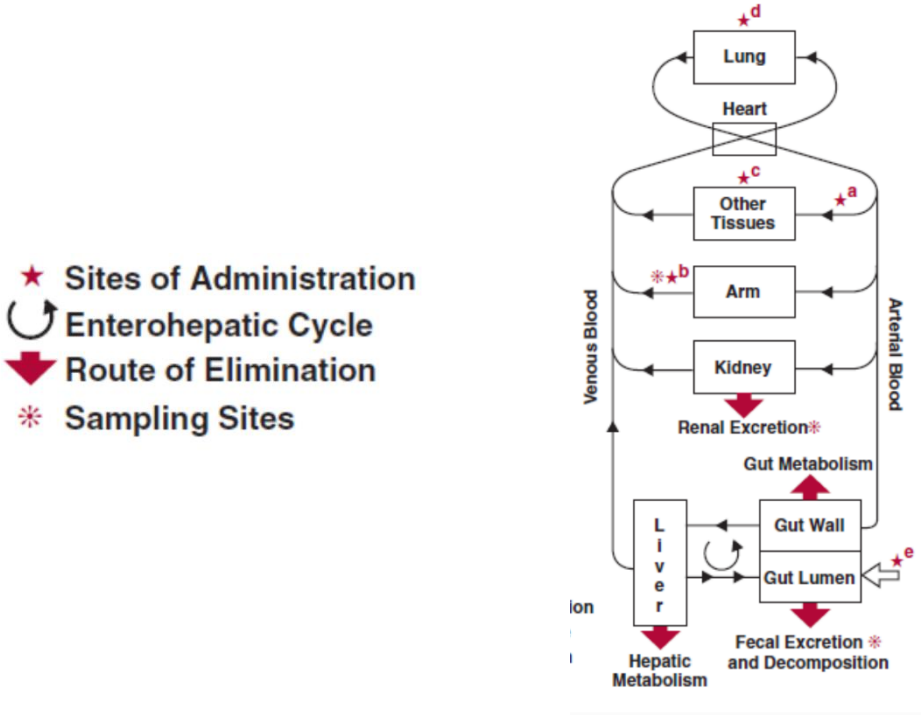
Blood is the most logical site for measurement of drug in the body. Blood receives drug from the site of administration and carries it to all the organs, including those in which the drug acts and those in which it is eliminated

Sites of Administration

There are several sites at which drugs are commonly administered.

1. **Intravascular** administration refers to the placement of a drug directly into the blood—either intravenously or intra-arterially.
2. **Extravascular** modes of administration include the intradermal, intramuscular, oral, pulmonary (inhalation), subcutaneous (into fat under skin), rectal, and sublingual (under the tongue) routes.

   After extravascular administration, an additional step, namely, absorption, is required for drug to reach the systemic site of measurement relative to that required after intravascular administration.

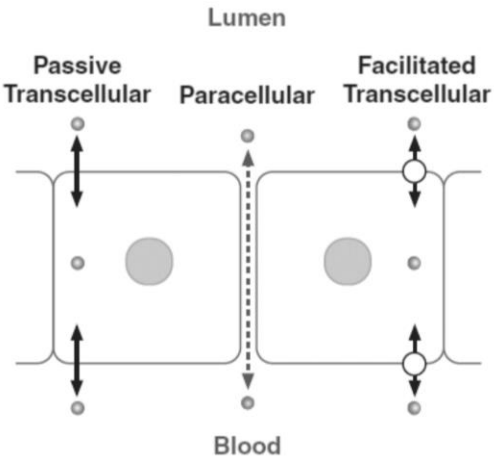


Absorption

Absorption is the process by which unchanged drug proceeds from site of administration to site of measurement within the body, usually plasma in a vein.

Drug transport across physiological membranes

Drug transport can be divided into **transcellular** and **paracellular** processes.



Factors influencing absorption

1. **Effect of pH and the extent of ionisation**

- Weak electrolytes exist in both unionised and ionised form, the ratio of the two forms varying with pH.
- The ionized form of the drug contains a charge and is water soluble and has very low lipid solubility.
- The non-ionised form of the drug is more lipid soluble and in most cases this lipid solubility is sufficient for membrane permeation.
- The extent of ionisation depends on the pKa of the drug and the pH of the medium according to ***Henderson and Hasselbalch*** **equation.**
- For weak acids, For weak bases,

$$AH \overset{Ka}{\rightleftharpoons} A^- + H^+ \qquad BH^+ \overset{Ka}{\rightleftharpoons} B + H^+$$

At a pH equals to the pK_a the drug is 50% ionised. Thus, a weakly acidic drug (e.g. aspirin) in a medium of low pH (e.g. stomach) will be mainly in its undissociated form; whereas a weakly basic drugs (e.g. amphetamines) in a medium of high pH (e.g. small intestine) will be mainly in its undissociated form.

When medium is same, drugs can cross the membrane

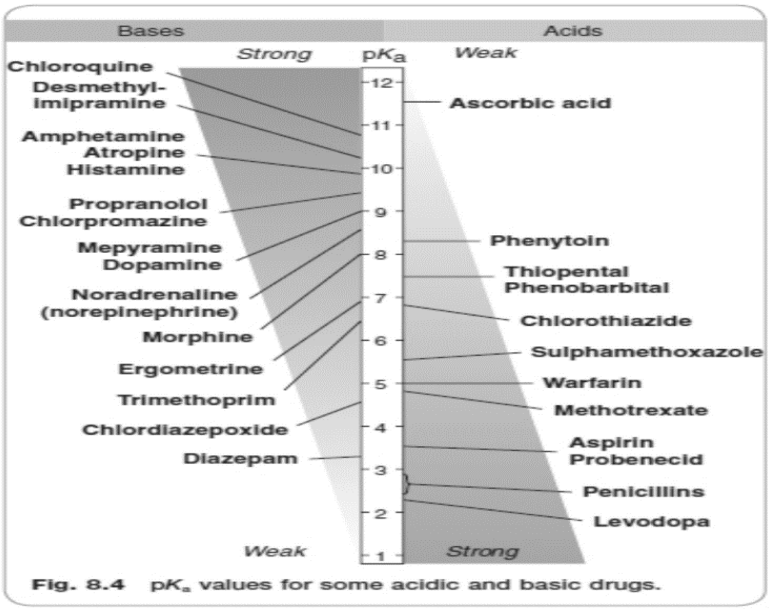
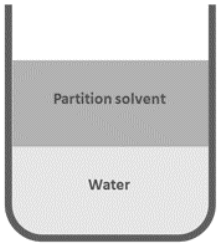


Fig. 8.4 pK_a values for some acidic and basic drugs.

Measurement of Lipid solubility - Log *P* value

$$\text{P = Partition Coefficient} = \frac{\text{Concentration dissolved in partition solvent}}{\text{Concentration dissolved in water}}$$



Conditions:
The solvents are "immiscible"
The system must be at equilibrium
All the solute must be dissolved
Temperature should be constant

Log p	-1.0	0	1.0	2.0	3.0	4.0	5.0	6.0
	Polar compounds Good aq. Solubilty Poor liquid solubility Poor adsorption and distribution.			Compound of intermediate polarity Good balance between aq. And lipid solubility. Good absorption and distribution.			Non polar compounds Poor aq. Solubility Good lipid solubility Slow excretion	

Fig:Effect of log p values on solubility absorption and distribution of drug sunstances.

2. **Blood flow to the absorption site**
3. **Total surface area available for absorption**
4. **Contact time at the absorption surface**

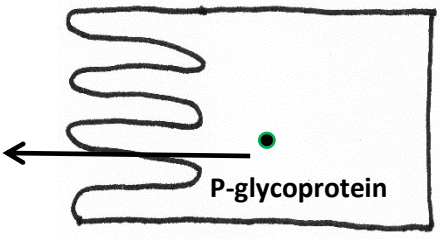
Environment in different parts of the gastrointestinal tract

The GI tract is not a uniform structure, it is composed of several regions differing in anatomy, amount of fluids, biochemical environment, pH, microbial flora, expression of transporters and absorption characteristics

Region	Length (m)	Surface Area (m^2)	pH	Residence Time	Micro-organisms
Oesophagus	0.3	0.02	6.8	>30 seconds	unknown
Stomach	0.2	0.2	1.8-2.5	1-5 hours	$\leq 10^2$
Duodenum	0.3	0.02	5-6.5	>5 minutes	$\leq 10^2$
Jejunum	3	100	6.9	1-2 hours	$\leq 10^2$
Ileum	4	100	7.6	2-3 hours	$\leq 10^7$
Colon	1.5	3	5.5-7.8	15-48 hours	$\leq 10^{11}$

5. **Efflux Transporters: P-Glycoprotein**

P-glycoprotein is an ATP-dependent transporter that is capable of transportation of an extremely wide variety of drugs OUT of the cell

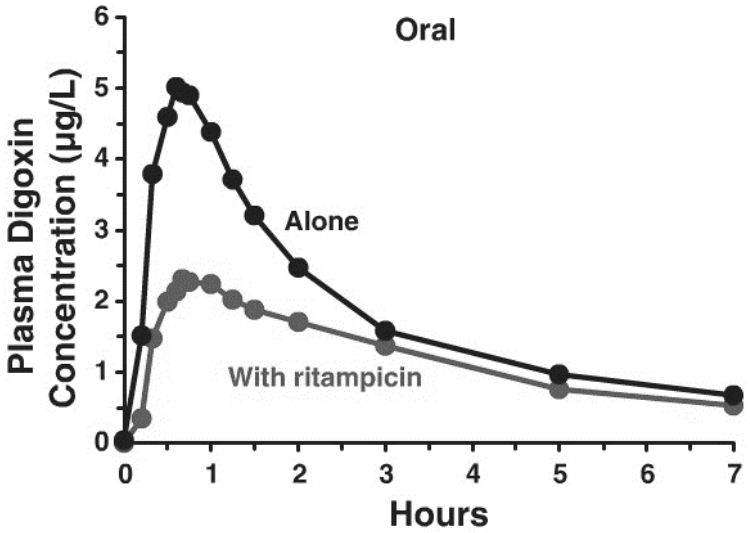


- P-glycoprotein is one of the most important barriers in intestinal absorption of drugs that are substrates to p-glycoprotein
- Most of P-glycoprotein substrates are lipophilic or amphiphilic
- P-glycoprotein is expressed not only in the intestinal epithelium, but also in liver, brain, adrenal gland and kidney
- P-glycoprotein is highly expressed by some cancer cells and is responsible for "multi-drug resistance" of cancer cells

EX Effect of induction of P-glycoprotein on absorption of digoxin

- Digoxin is used in treating heart failure and arrhythmias, and is a substrate for P-glycoprotein.
- Rifampicin is an inducer of P-glycoprotein.

Pre-treatment with rifampicin increases the efflux process from the enterocyte (intestinal epithelial cell) to the intestinal lumen and therefore ***decreases*** the absorption.

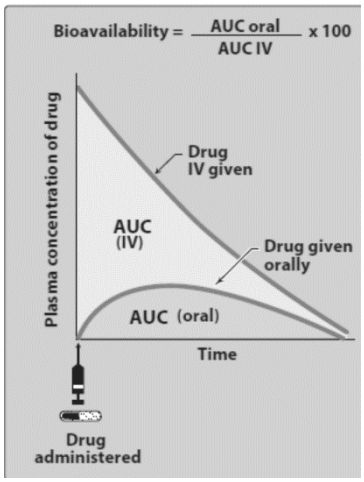


Aliases	Tissue	Drug Substrate	Inhibitor	Inducer
P-gp, MDR1	Intestine, liver, kidney, brain, placenta, adrenal, testes	Digoxin, fexofenadine, indinavir, vincristine, colchicine, topotecan, paclitaxel	Ritonavir, cyclosporine, verapamil, erythromycin, ketocoanzole, itraconazole, quinidine, elacridar (GF120918) LY335979 valspodar (PSC833)	Rifampin, St John's wort

Bioavailability (F)

- ***Bioavailability*** is the rate and extent to which an intact administered drug reaches the systemic circulation
- The fraction of the dose which reaches the systemic circulation as intact drug
- In most cases bioavailability is going to be less than 100%

Determination of bioavailability



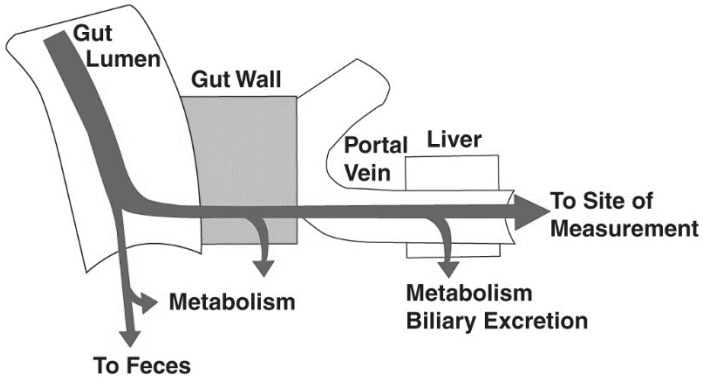
Factors that influence bioavailability

1. **First-pass hepatic metabolism**

Ex More than 90% of *nitroglycerin* is cleared during first-pass metabolism

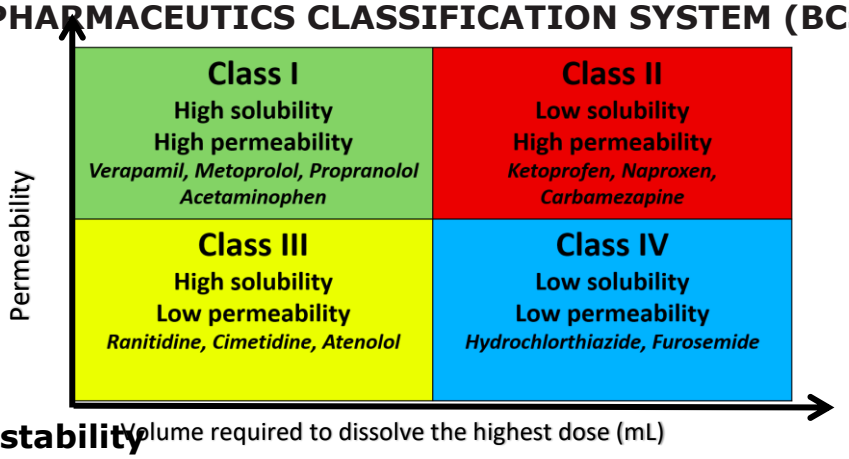
Drugs with High First pass Metabolism

Nitrates	-	Nitrates
Have	-	Hydrocortisone
Large	-	Lignocaine
Pre	-	Propanolol
Systemic	-	Salbutamol
Metabolism	-	Morphine



2. **Solubility of the drug**

THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)



3. **Chemical instability**

Penicillin G -------- unstable in the pH of the gastric contents

Insulin ---------- destroyed in the GI tract by degradative enzymes

4. **Nature of the drug formulation**

- Particle size
- Salt form
- Crystal polymorphism
- Enteric Coatings
- Excipients (such as binders and dispersing agents)

Disposition

Disposition may be defined as all the kinetic processes that occur to a drug subsequent to its systemic absorption. The components of disposition are **distribution** and **elimination**.

Distribution

- Distribution is the process of reversible transfer of a drug to and from the site of measurement and the peripheral tissues. An example is distribution between blood and muscle.
- The pathway for return of drug might not be the same as that leaving the circulation. An example is the **enterohepatic circulation**

The volume of distribution

The volume of distribution (V_D) is a hypothetical volume that relates drug plasma concentrations to the amount of drug in the body.

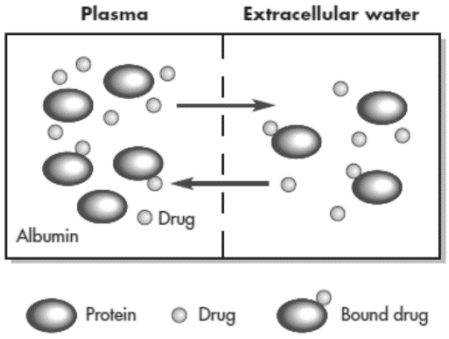
V_D in a pharmacokinetic model, is used to estimate the extent of drug distribution in the body.

$$\mathbf{Vd} = \frac{\mathbf{Amount\ of\ drug\ in\ body\ (D)}}{\mathbf{Concentration\ in\ Plasma (Cp)}}$$

PROTEIN BINDING OF DRUGS

Many drugs interact with plasma or tissue proteins to form a drug–protein *complex*. Drug–protein binding may be

1. Reversible (most common)
2. Irreversible



The protein-bound drug is a large complex that cannot easily transverse the capillary wall and therefore has a restricted distribution

TABLE 11-6 Major Proteins to Which Drugs Bind in Plasma

Protein	Molecular Weight (Da)	Normal Range of Concentrations (g/L)	Normal Range of Concentrations (mol/L)
Albumin	65,000	35–50	$5–7.5 \times 10^{-4}$
α_1-Acid glycoprotein	44,000	0.4–1.0	$0.9–2.2 \times 10^{-5}$
Lipoproteins	200,000–3,400,000	Variable	

Effect of protein binding on the apparent volume of distribution

- Displacement of drugs from plasma proteins can affect the pharmacokinetics of a drug in several ways:

1. Directly increase the free (unbound) drug concentration as a result of reduced binding in the blood;
2. Increase the free drug concentration that reaches the receptor sites directly, causing a more intense pharmacodynamic (or toxic) response;
3. Increase the free drug concentration, causing a transient increase in V_D and decreasing partly some of the increase in free plasma drug concentration;
4. Increase the free drug concentration, resulting in more drug diffusion into tissues of eliminating organs, particularly the liver and kidney, resulting in a transient increase in drug elimination.

Drugs with high plasma protein binding
- Benzodiazepines
  - *Diazepam*
  - *Chlordiazepoxide*
  - *Midazolam*
- Chlorpropamide
- Tolbutamide
- Cyclosporine
- Fluoxetine
- Imipramine
- Verapamil
- Warfarin

Elimination

- Elimination is the irreversible loss of drug from the site of measurement. Elimination occurs by two processes: excretion and metabolism.
- **Excretion** is the irreversible loss of chemically unchanged drug.
- **Metabolism** is the conversion of one chemical species to another.

➢ DRUG CLEARANCE

Drug clearance is a pharmacokinetic term for describing drug elimination from the body without identifying the mechanism of the process.

Drug clearance is the fixed volume of fluid (containing the drug) removed from the drug per unit of time.

The total body CL of a compound is a summation of the CL contributions of various organs.

$$Cl_T = Cl_{renal} + Cl_{hepatic} + Cl_{other}$$

Renal Drug Excretion

- **Glomerular filtration** is a unidirectional process that occurs for most small molecules (MW < 500), including undissociated (nonionized) and dissociated (ionized) drugs. Protein-bound drugs behave as large molecules and do not get filtered at the glomerulus.
- **Active tubular secretion** is an active transport process. As such, active renal secretion is a carrier-mediated system that requires energy input, because the drug is transported against a concentration gradient. The carrier system is capacity limited and may be saturated. Drugs with similar structures may compete for the same carrier system.
- **Tubular reabsorption** occurs after the drug is filtered through the glomerulus and can be an active or a passive process involving transporting back into the plasma.

Hepatic clearance

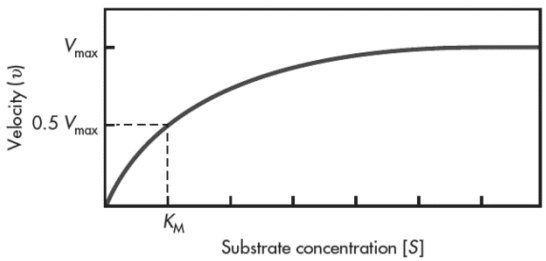
- *Hepatic clearance* may be defined as the volume of blood that perfuse the liver which is cleared of drug per unit of time.

$Cl_T = Cl_{nr} + Cl_r$

$Cl_h = Cl_T - Cl_R$

Metabolism kinetics—michaelis– menten equation

- *biotransformation* or *metabolism* is the enzymatic conversion of a drug to a metabolite.
- the metabolic enzyme concentration is constant at a given site, and the drug (substrate) concentration may vary.
- When the drug concentration is low relative to the enzyme concentration, the rate of metabolism is a first-order process.
- At high plasma drug concentration the rate process then becomes a zero-order process
- The *maximum reaction rate* is known as V_{max}
- The drug concentration at which the reaction occurs at half the maximum rate corresponds to a composite parameter K_M (*Michaelis constant)*.



The relationship between V_{max} and K_M is given by *Michaelis–Menten equation*

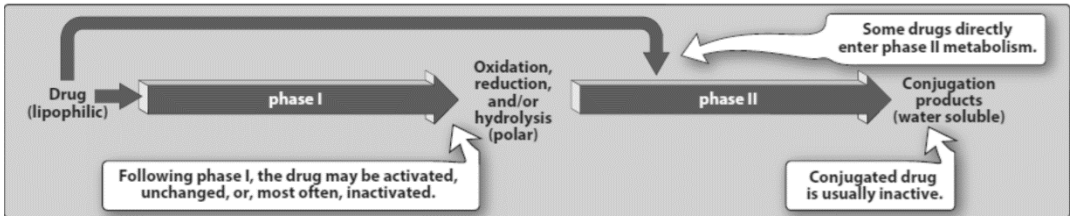
- **1. First-order kinetics**

$$v = \text{Rate of drug metabolism} = \frac{V_{max}[C]}{K_m}$$

2. Zero-order kinetics

$$v = \text{Rate of drug metabolism} = \frac{V_{max}[C]}{[C]} = V_{max}$$

Reactions of Drug Metabolism



Some examples of CP450 enzymes, their substrates, inducers, and inhibotors

CYP	Substrate	Inducer	Inhibitor
3A4 (Metabolizes 50% of drugs, most common)	• Astemizole • Cisapride • Terfenadine • Cyclosporine • Tacrolimus • Calcium channel blockers • Protease inhibitors • Estrogens	Barbiturates Rifampicin Phenytion Carbamazepine St. John's wort	Erythromycin Ketoconazole Fluconazole Grapefruit juice Ritonavir
2D6 (Metabolizes 20% drugs)	• Most antidepressants – TCA – SSRI – MAO inhibitors • Most beta blockers • Most antiarrhythmics	No known inducer	Quinidine Paroxetine
2 C 19	• Omeprazole • Clopidogrel	Rifampicin Barbiturates	Fluconazole
2 C 9	• Phenytion • Tolbutamide • Warfarin	Rifampicin Barbiturates	Erythromycin Cimetidine
1 A 2	• Theophylline warfarin	Smoking Rifampicin	Ciprofloxacin
2 E 1	• Acetaminophen • Enflurane • Halothane	Ethanol	Disulfiram

Pharmacokinetic Modelling

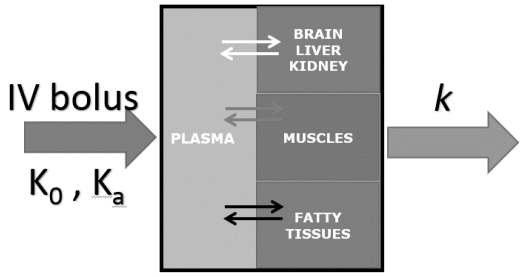
Pharmacokinetic models are mathematical schemes that represent complex physiologic spaces or processes. There are three approaches that have been suggested for pharmacokinetic modelling, compartmental, physiological and model-independent (non-compartmental).

Compartmental models

The most commonly employed approach to the pharmacokinetic characterization of a drug is to represent the body as a system of compartments, even though these compartments usually have no physiologic or anatomic reality, and to assume that the rate of transfer between compartments and the rate of drug elimination from compartments follow first-order or linear kinetics.

- **One-compartment model**

The one-compartment open model assumes that the body can be described as a single, uniform compartment (ie, one compartment), and that drugs can enter and leave the body (ie, open model).



One-compartment model - IV bolus administration

Following IV bolus administration, it assumes that the drug is administered instantly into the body, it is instantaneously and rapidly distributed throughout the body.

$$\mathbf{C} = C^0 \cdot e^{-kt} \qquad \textbf{Since} \quad C^0 = \frac{D}{V_D} \qquad \textbf{then} \quad \mathbf{C} = \frac{D}{V_D} \cdot e^{-kt}$$

Where **C** is the plasma concentration at time **t, C^0** plasma concentration at time 0, **D** amount of the drug in the body (i.e. dose administered by iv bolus), ***K*** elimination rate constant, and **V_D** apparent volume of distribution.

Note: - For most IV bolus administration is not convenient as it might induce adverse effect. Instead, a short infusion time can avoid these types of adverse effects. If the intravenous infusion time is very short compared to the half-life of the drug so that a large amount of drug is not eliminated during the infusion time, intravenous bolus equations can still be used.

Therapeutic Drug Monitoring

Lecture 2
Dr Atheer Zgair

Example 1: a patient is given a theophylline loading dose of 400 mg **intravenously over 20 minutes**. It is known that the volume of distribution is 30 L, the elimination rate constant equals 0.116 h^{-1}. Compute the expected theophylline concentration 4 hours after the dose was given. Theophylline follows one-compartment model PK.

Solution:

$t_{1/2} = \frac{0.693}{k} = \frac{0.693}{0.116} = 6$ h »» The intravenous infusion time is very short compared to the half-life. Therefore, IV bolus equations can be used.

$\boldsymbol{C = \frac{D}{VD} . e^{-kt}}$

$C = \frac{400}{30} . e^{-0.116x\,4}$

C = 8.38 mg/L

Note: - If the expected concentration needs to be calculated at a time within the infusion + distribution time (i.e. within 2 h in the case of the following example), we can't apply IV bolus equations as the drug is not at homogenous state in all compartments at this time. However, following a short infusion + distribution time, plasma concentrations can be calculated using one-compartment model equations.

Example 2: a patient is given an intravenous dose of vancomycin 1000 mg over a period of 1 h. It is known that vancomycin takes ½ - 1 h to distribute to tissues (i.e. two compartment model of PK).

If you know that $\mathbf{V_D}$ equals 50 L and **k** is 0.077 h^{-1}, calculate the expected plasma concentration of vancomycin 12 h following the administration.

Solution:

$t_{1/2} = \frac{0.693}{k} = \frac{0.693}{0.077} = 9$ h The intravenous infusion time + distribution time is very short compared to the half-life. Therefore, IV bolus equations can be used.

- $\boldsymbol{C = \frac{D}{VD} . e^{-kt}}$
- $C = \frac{1000}{50} . e^{-0.077x\,12}$, C = 7.9 mg/L

Calculation of PK parameters from plasma-concentration time curve

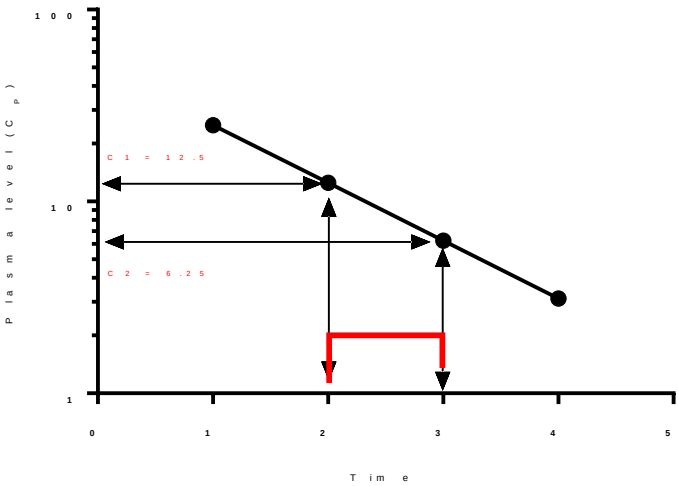
If two or more serum concentrations are obtained after an intravenous bolus dose, the elimination rate constant, half-life, and volume of distribution can be calculated by two methods:

A. Plotting the plasma-concentration time data on a semilogarithmic paper

This method includes the following steps

1. Determination of $t_{1/2}$ using the plot; choose a concentration (C_1) and then determine $C_1/2$ on the plot. The time interval between the two points on the x-axis represents the $t_{1/2}$.

$$K = \frac{0.693}{t_{1/2}}$$



2. Extrapolating the linear line of plasma concentration to t=0 and determine C_P^0 (plasma concentration at time zero).

$$V_D = \frac{D}{C^0}$$

B. Calculations without plotting the concentrations

1. Calculation of K by determining the Slope

$$\text{Slope} = \frac{\text{change in y value}}{\text{change in y value}} = \frac{(y2-y1)}{(x2-x1)}$$

Slope = $\frac{-k}{2.3}$ (if Y values are in log) or Slope = -K (if y values are Ln)

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

2. Calculation of C^0 using rearrangement of $C = C^0 . e^{-kt}$

$$C^0 = \frac{C}{e^{-kt}}$$

Note; for the calculation of the slope, the Y values (i.e. concentration values) should be either in log or Ln

Example: - a patient was given an intravenous loading dose of phenobarbital 600 mg over a period of about an hour. One day and four days after the dose was administered, phenobarbital serum concentrations were 12.6 mg/L and 7.5 mg/L, respectively. Calculate K, $t_{1/2}$, and V_D by plotting data and by calculations (without plotting).

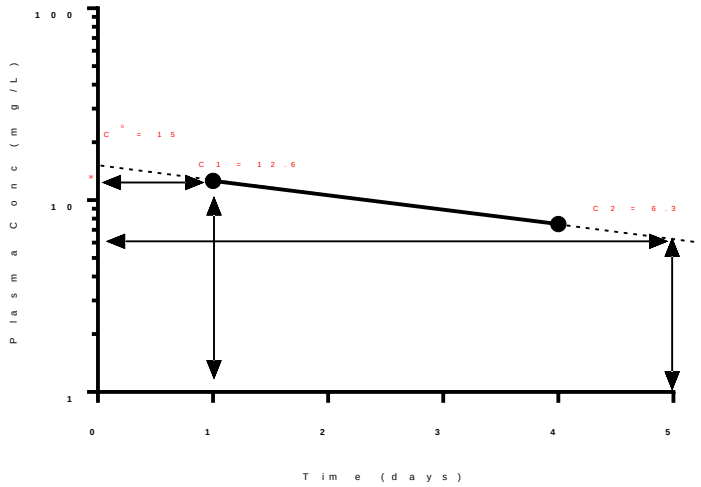
Solution;

$t_{1/2}$ = 4 days

$K = \frac{0.693}{t_{1/2}} = 0.173\ d^{-1}$

$VD = \frac{D}{C0} = = \frac{600}{15} = 40\ L$

H.W: Calculate the parameters without plotting. In addition, calculate the expected conc 7 days following administration.



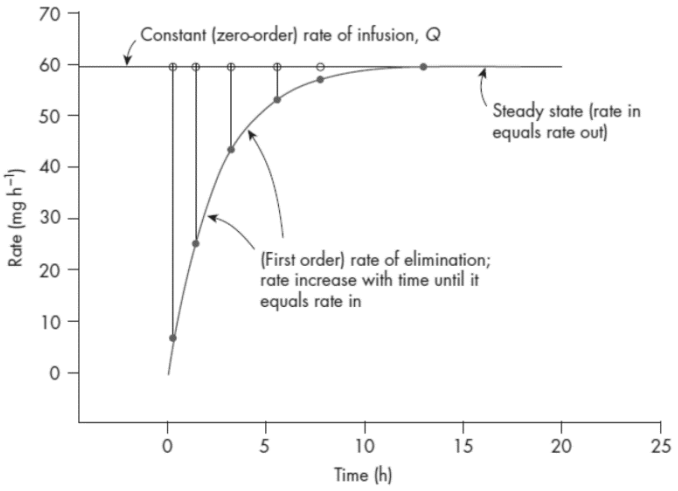
One-compartment model - Continuous Intravenous Infusion

It is common practice, in the hospital setting to infuse a drug at a constant rate (constant rate input or zero-order input). This method permits precise and readily controlled drug administration.

The infusion rate of a drug is controlled by:

1. Flow rate (e.g. mL/h).
2. Concentration (mg/mL, % w/v, etc.) of the drug in solution.

Initially, the rate at which drug enters the body, though constant, is greater than the rate at which drug is eliminated; this allows the drug to reach a certain amount and concentration in the body. As time increases, the rate at which the drug is being administered equals the rate of elimination. Hence, there is no change in mass (amount) of drug or plasma concentration of drug with time as long as the chosen constant rate (zero-order) input is maintained.



Monitoring drug in the blood (plasma/serum) in case of IV infusion

Following IV infusion, drug is monitored in blood under two conditions:

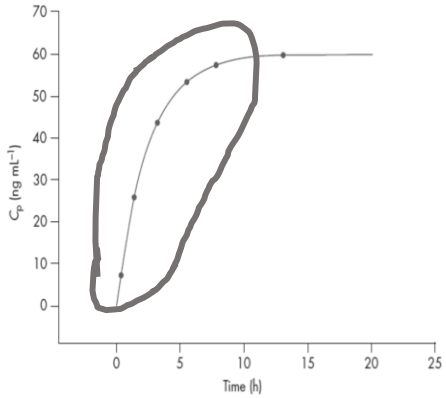
1. During infusion (while the drug is being infused)
2. The post-infusion period (following the cessation of infusion).

- **During infusion – before reaching steady-state concentration**

The concentration of the drug in the blood is determined by the following equation:

$C = \frac{K_0}{Cl} \cdot (1 - e^{-kt})$ or $C = \frac{K_0}{K \cdot V_D} \cdot (1 - e^{-kt})$

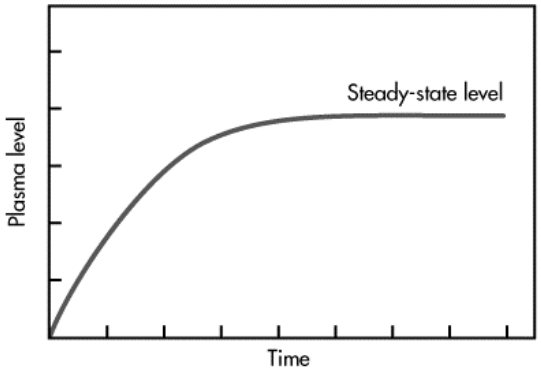
Where k_0 is the drug infusion rate (in amount per unit time, such as mg/h or µg/min)



- **During infusion – at steady-state concentration**

$C_{ss} = \frac{K_0}{Cl}$ or $C_{ss} = \frac{K_0}{K \cdot V_D}$

((steady-state condition refers to the condition when the rate of elimination and the rate of infusion become equal))

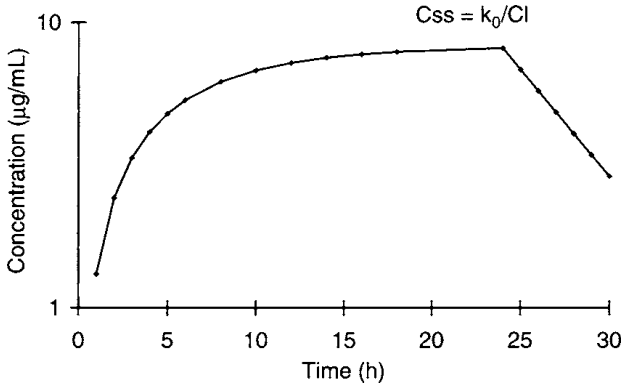


- **Post-infusion period**

$$\mathbf{C_{postinfusion}} = C_{end} \cdot e^{-kt_{postinfusion}}$$

Where $t_{postinfusion}$ is the postinfusion time ($t_{postinfusion}$ = 0 at the end of infusion and increases from that point).

If the infusion is discontinued the serum concentration/time profile decreases in a straight line when graphed on a semilogarithmic axes. In this case, a one compartment model intravenous bolus equation can be used to compute concentrations.



Example: - a patient is administered 60 mg/h of theophylline. The pharmacokinetic parameters for theophylline are: V_D = 40 L and k_e = 0.139 h^{-1}. Calculate the plasma concentration of theophylline in this patient after receiving the drug for 8 hours and at steady state. In addition, calculate theophylline plasma concentration 6 hours after the infusion being stopped.

Solution:

During infusion (8 h), $C = \frac{K_0}{K \,.\, V_D} \,.\, (1 - e^{-kt})$

$C = \frac{60}{0.139\, x\, 40} \,.\, (1 - e^{-0.139\, x\, 8})$ = 7.24 mg/L

Steady state, $C_{ss} = \frac{K_0}{K \,.\, V_D} = \frac{60}{0.139\, x\, 40}$ = 10.8 mg/L

6 h after stoppage of infusion, $\mathbf{C_{postinfusion} = C_{end} \,.\, e^{-kt_{postinfusion}}}$

$\mathbf{C_{postinfusion} = 10.8 \,.\, e^{-0.139\, x\, 6} = 4.7\ mg/L}$

Effect of infusion and distribution times on the calculations of plasma concentrations

For drugs that exhibit a short distribution phase after the drug infusion has ended, it is still possible to use one compartment model intravenous infusion equations for the drug without a large amount of error.

For example, gentamicin, tobramycin, and amikacin are usually infused over one-half hour. When administered this way, these aminoglycoside antibiotics have distribution phases that last about one-half hour. In such cases, following the infuse of the medication, wait for the distribution phase to be over before measuring plasma drug concentrations in the patient.

Note: If aminoglycosides are infused over 1 hour, the distribution phase is very short and superimposed with the infusion time. Therefore, plasma concentrations can be obtained immediately.

Example: a patient is given an intravenous infusion of gentamicin 100 mg over 60 minutes. The volume of distribution is 20 L, the elimination rate constant equals 0.231 h^{-1}, and the half-life equals 3 h. Calculate gentamicin plasma concentration at the end of the infusion.

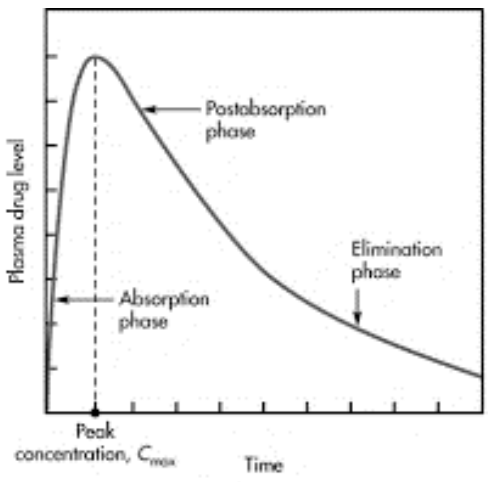
Solution:

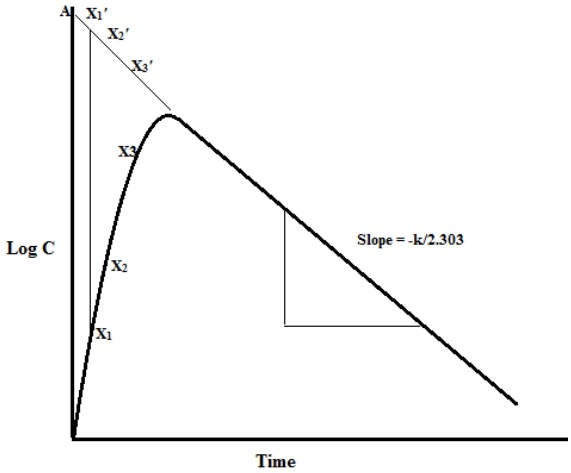
$$C = \frac{K_0}{K_0 V_D} \cdot (1 - e^{-kt})$$

$$C = \frac{100}{0.232\ x\ 20} \cdot (1 - e^{-0.231\ x\ 1}) = 4.5 \text{ mg/L}$$

Extravascular Equation

When a drug is administered extravascularly (e.g., orally, intramuscularly, subcutaneously, transdermally, etc.), absorption into the systemic vascular system must take place. If plasma concentrations decrease in a straight line when plotted on semilogarithmic axes after drug absorption is complete, a one compartment model extravascular equation can be used to describe the plasma concentration-time cure.





$$\mathbf{C} = \frac{F K_a D}{V_D(k_a - k)} \left(e^{-kt} - e^{-k_a t}\right)$$

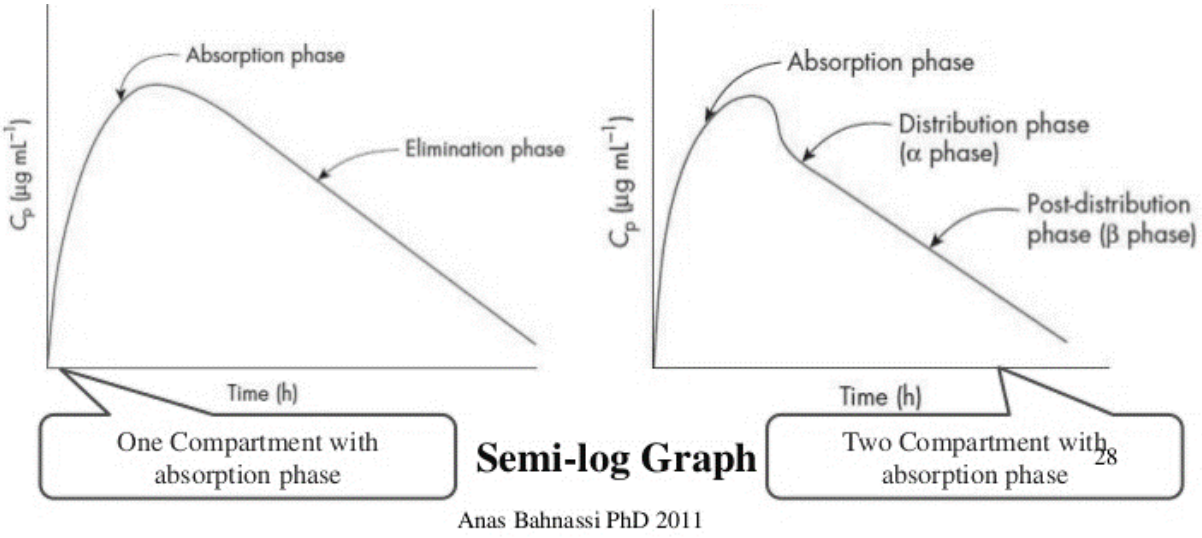
Where t is the time after the extravascular dose was given, C is the concentration at time = t, F is the bioavailability fraction, k_a is the absorption rate constant, D is the dose, V is the volume of distribution, and k is the elimination rate constant

Example: a patient was administered 500 mg of oral procainamide as a capsule. If you know that $t_{1/2}$ is 4 hours, K = 0.173 h^{-1}, V_D is 175 L, Ka is 2 h^{-1}, and an oral bioavailability fraction is 0.85. Calculate procainamide plasma concentration 4 h following a single oral dose.

$$\mathbf{C_P} = \frac{F K_a D}{V_D(k_a - k)} \left(e^{-kt} - e^{-k_a t}\right)$$

$$\mathbf{C_P} = \frac{0.85 \; x \; 2 \; x \; 500}{175 \; (2 - 0.173)} \left(e^{-0.173 \; x \; 4} - e^{-2 \; x \; 4}\right) = \mathbf{1.3 \; mg/L}$$

Note: If the plasma concentration-time curve displays a distribution phase, it is still possible to use one compartment model equations after an extravascular dose is administered. In order to do this, plasma concentrations are obtained only in the postdistribution phase.



Note: The absorption rate constant is hard to measure in patients. Therefore, when only postabsorption, postdistribution serum concentrations are obtained for a drug that is administered extravascularly, plasma concentrations can be calculated by the following simplified equation:

$$\boldsymbol{C} = \frac{FD}{V_D} . \; e^{-kt}$$

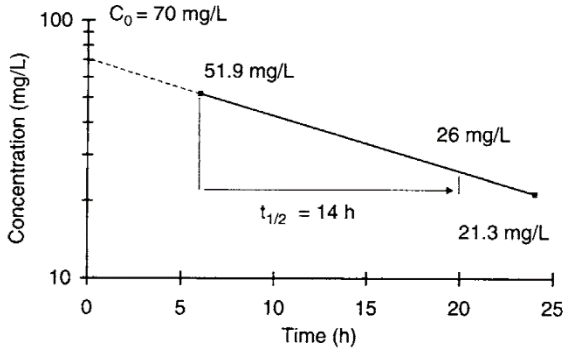
Example: a patient receiving 24 mEq of lithium ion as lithium carbonate capsules. It is known that the patient has a volume of distribution of 60 L and K of 0.058 h^{-1}. The bioavailability of the capsule is known to be 0.90. Calculate plasma concentration of lithium 12 hours after a single dose.

$$\boldsymbol{C = \frac{FD}{V_D}.\ e^{-kt}\ = \frac{0.9\ x\ 24}{60}.\ e^{-0.058\ x\ 12}\ = 0.18\ mEq/L}$$

Note: If two or more postabsorption and postdistribution serum concentrations are obtained after an extravascular dose, V_D, K, and $t_{1/2}$ can be calculated by plotting and without plotting as previously described for IV bolus injection. One exception is that the V_D/F (hybrid parameter) is calculated instead of the absolute values of V_D and F.

Example: a patient is given an oral dose of valproic acid 750 mg as capsules. Six and twenty-four hours after the dose, the valproic acid plasma concentrations are 51.9 mg/L and 21.3 mg/L. calculate V_D, K, and $t_{1/2}$.

- By plotting



$t_{1/2}$ = 14 h, $\quad k = \frac{0.693}{t_{1/2}} = 0.05\ h^{-1}$

From the extrapolation, C_0 = 70 mg/L

$$\frac{V_D}{F} = \frac{D}{C_0} = \frac{750}{70} = 10.7\ L$$

- Without plotting

$$\text{Slope} = \frac{(y2\text{-}y1)}{(x2\text{-}x1)} = \frac{\log 21.3 - \log 51.9}{24 - 6} = -0.0215,\ k = -\text{slope} \times 2.3 = 0.05\ h^{-1}$$

$$\boldsymbol{C = \frac{FD}{V_D}.\ e^{-kt}},$$

$$\boldsymbol{\frac{V_D}{F} = \frac{D}{C}.\ e^{-kt} = \frac{750}{51.9}.\ e^{-0.05\ x\ 6} = 10.7\ L}$$

Multiple-Dose and Steady-State Equations

In most cases, medications are administered to patients as multiple doses, and drug plasma concentrations for therapeutic drug monitoring are not obtained until steady state is achieved. For these reasons, multiple dose equations that reflect steady-state conditions are usually more useful in clinical settings than single dose equations.

Therapeutic Drug Monitoring

The following table summarizes the equations used for the calculation of plasma concentrations following single and multiple doses as well as at steady state concentrations.

ROUTE OF ADMINISTRATION	SINGLE DOSE	MULTIPLE DOSE	STEADY STATE
Intravenous bolus	$C = \frac{D}{V_D} . e^{-kt}$	$C = \frac{D}{V_D} . e^{-kt} \left(\frac{1 - e^{-nk\tau}}{1 - e^{-k\tau}} \right)$	$C = \frac{D}{V_D} . \left(\frac{e^{-kt}}{1 - e^{-k\tau}} \right)$
Continuous intravenous infusion	$C = \frac{K_0}{K V_D} . (1 - e^{-kt})$	**N/A**	$C_{ss} = \frac{K_0}{Cl} = \frac{K_0}{K V_D}$
Intermittent intravenous infusion	$C = \frac{K_0}{K V_D} . (1 - e^{-kt'})$	$C = \frac{K_0}{K V_D} . (1 - e^{-kt'}) \left(\frac{1 - e^{-nk\tau}}{1 - e^{-k\tau}} \right)$	$C = \frac{K_0}{K V_D} \left(\frac{1 - e^{-kt'}}{1 - e^{-k\tau}} \right)$
Extravascular (postabsorption, postdistribution)	$C = \frac{FD}{V_D} . e^{-kt}$	$C = \frac{FD}{V_D} . e^{-kt} \left(\frac{1 - e^{-nk\tau}}{1 - e^{-k\tau}} \right)$	$C = \frac{FD}{V_D} . \left(\frac{e^{-kt}}{1 - e^{-k\tau}} \right)$
Average steady-state concentration (any route of administration)	**N/A**	**N/A**	$C_{ss} = \frac{[F (\frac{D}{\tau})]}{Cl}$

C is drug plasma concentration at time = t, D is dose, V_D is volume of distribution, k is the elimination rate constant, n is the number of administered doses, τ is the dosage interval, k_0 is the infusion rate, Cl is clearance, t' is infusion time.

Therapeutic Drug Monitoring

Single-Dose, Multiple-Dose, and Steady-State Pharmacokinetic Constant Computations Utilizing a One Compartment Model

ROUTE OF ADMINISTRATION	SINGLE DOSE	MULTIPLE DOSE	STEADY STATE
Intravenous bolus	$K = -\frac{\log C2 - \log C1}{t2 - t1} \times 2.3$ $t_{1/2} = \frac{0.693}{k}$ $V_D = \frac{D}{C_0}$ $Cl = k \cdot V_D$	$K = -\frac{\log C2 - \log C1}{t2 - t1} \times 2.3$ $t_{1/2} = \frac{0.693}{k}$ $V_D = \frac{D}{(C_0 - C_{predose})}$ $Cl = k \cdot V_D$	$K = -\frac{\log C2 - \log C1}{t2 - t1} \times 2.3$ $t_{1/2} = \frac{0.693}{k}$ $V_D = \frac{D}{(C_0 - C_{predose})}$ $Cl = k \cdot V_D$
Continuous intravenous infusion	**N/A**	**N/A**	$Cl = \frac{k_0}{C_{ss}}$
Intermittent intravenous infusion	$K = -\frac{\log C2 - \log C1}{t2 - t1} \times 2.3$ $t_{1/2} = \frac{0.693}{k}$ $V_D = \frac{k_0\,(1 - e^{-kt'})}{k\,[\,C_{max} - (C_{predose} \cdot e^{-kt'})}$ $Cl = k \cdot V_D$	$K = -\frac{\log C2 - \log C1}{t2 - t1} \times 2.3$ $t_{1/2} = \frac{0.693}{k}$ $V_D = \frac{k_0\,(1 - e^{-kt'})}{k\,[\,C_{max} - (C_{predose} \cdot e^{-kt'})}$ $Cl = k \cdot V_D$	$K = -\frac{\log C2 - \log C1}{t2 - t1} \times 2.3$ $t_{1/2} = \frac{0.693}{k}$ $V_D = \frac{k_0\,(1 - e^{-kt'})}{k\,[\,C_{max} - (C_{predose} \cdot e^{-kt'})}$ $Cl = k \cdot V_D$
Extravascular (postabsorption, postdistribution)	$K = -\frac{\log C2 - \log C1}{t2 - t1} \times 2.3$ $t_{1/2} = \frac{0.693}{k}$ $\frac{V_D}{F} = \frac{D}{C_0}$ $\frac{Cl}{F} = k \cdot \frac{V_D}{F}$	$K = -\frac{\log C2 - \log C1}{t2 - t1} \times 2.3$ $t_{1/2} = \frac{0.693}{k}$ $\frac{V_D}{F} = \frac{D}{(C_0 - C_{predose})}$ $\frac{Cl}{F} = k \cdot \frac{V_D}{F}$	$K = -\frac{\log C2 - \log C1}{t2 - t1} \times 2.3$ $t_{1/2} = \frac{0.693}{k}$ $\frac{V_D}{F} = \frac{D}{(C_0 - C_{predose})}$ $\frac{Cl}{F} = k \cdot \frac{V_D}{F}$
Average steady-state concentration (any route of administration)	**N/A**	**N/A**	$\frac{Cl}{F} = \frac{(\frac{D}{\tau})}{C_{ss}}$

C_1 is drug serum concentration at time = t_1, C_2 is drug serum concentration at time = t_2, k is the elimination rate constant, $t_{1/2}$ is the half-life, V_D is the volume of distribution, k_0 is the continuous infusion rate, t_2 is the infusion time, V_D/F is the hybrid constant volume of distribution/bioavailability fraction, D is dose, C_0 is the concentration at time = 0, Cl is drug clearance, Cl/F is the hybrid constant clearance/bioavailability fraction, $C_{predose}$ is the predose concentration, Css is the steady-state concentration, N/A is not applicable.

Designing Individualized Dosage Regimens Using One Compartment Model Equations

The goal of therapeutic drug monitoring is to customize medication doses that provide the optimal drug efficacy without adverse reactions. One compartment model equations can be used to calculate initial drug doses employing population pharmacokinetic parameters that estimate the constants for a patient. The patient's own, unique pharmacokinetic parameters can be computed once doses have been administered and drug serum concentrations measured. At that time, individualized dosage regimens at steady state can be designed for a patient.

To design an individualized dosage regimen, it is important to know the therapeutic range or the effective concentration for the drug.

One compartment model equations can be used to calculate dosage interval (τ), maintenance dose, and loading dose (LD) as follow:

Rout of administration	**Dosage interval (τ), maintenance dose, and loading dose equations**
Intravenous bolus	$\tau = \frac{ln\ Css_{max} - ln\ Css_{min}}{k}$ $D = Css_{max}\ V_D\ (1 - e^{-k\tau})$ $LD = Css_{max}\ V_D$
Continuous intravenous infusion	$K_0 = Css\ Cl = Css\ k\ V_D$ $LD = Css\ V_D$
Intermittent intravenous infusion	$\tau = \frac{ln\ Css_{max} - ln\ Css_{min}}{k} + t'$ $K_0 = Css_{max}\ k\ V_D\ (\frac{1 - e^{-k\tau}}{1 - e^{-kt'}})$ $LD = \frac{k_0}{1 - e^{-k\tau}}$
Extravascular (postabsorption, postdistribution)	$\tau = \frac{ln\ Css_{max} - ln\ Css_{min}}{k} + T_{max}$ $D = \frac{Css_{max}\ V_D}{F}\ (\frac{1 - e^{-k\tau}}{e^{-kTmax}})$ $LD = \frac{Css\ V_D}{F}$
Average steady-state concentration (any route of administration)	$D = \frac{Css\ Cl\tau}{F} = \frac{Css\ k\ V_D\ \tau}{F}$ $LD = \frac{Css\ V_D}{F}$

Css_{max} and Css_{min} are the maximum and minimum steady-state concentrations, k is the elimination rate constant, V_D is the volume of distribution, Css is the steady-state concentration, k_0 is the continuous infusion rate, t_2 is the infusion time, T_{max} is the time that Css_{max} occurs, F is the bioavailability fraction.

MULTICOMPARTMENT MODELS

The multicompartment model assumes that the body composed of more than one-compartment, usually a **central compartment** and **peripheral compartment(s)**.

A two-compartment model is the simplest of the multicompartment models. The drug that shows biexponential plasma-concentration time curve is said to follow the two-compartment model.

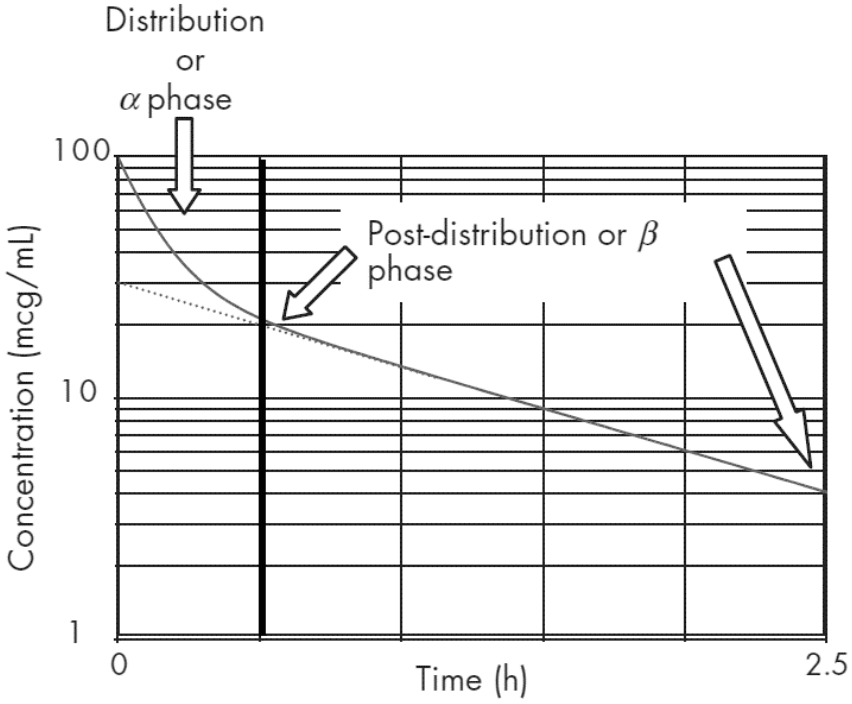


Figure: plasma concentration time profile of a drug that follows two-compartment model

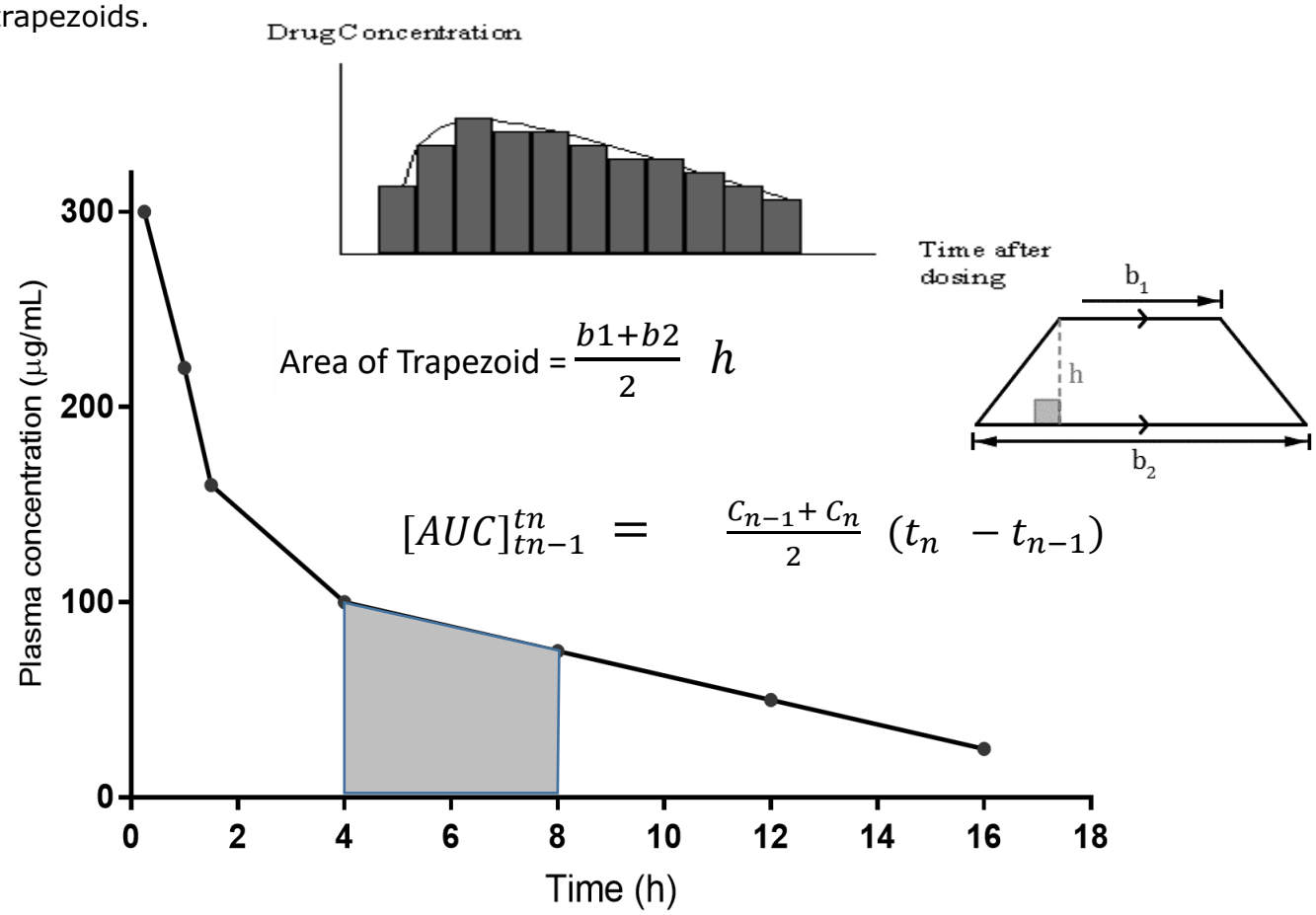
Multicompartment models are rarely used in patient care situations. If a drug follows multicompartment pharmacokinetics, plasma concentrations are usually not drawn for clinical use until the distribution phase is over and the elimination phase has been established. In these cases, it is possible to use simpler one compartment model equations to compute doses with an acceptable degree of accuracy.

Non-compartmental Analysis

Non-compartmental analysis (NCA) is the most commonly used technique of pharmacokinetic data analysis directly from plasma-concentration data without the need to assume that drug disposition follows compartmental model. This approach can be used to calculate AUC, Cl, and $t_{1/2}$.

- **The area under the concentration time curve (AUC)**

AUC is the PK parameter reflecting the exposure of the drug. It can be calculated by **trapezoidal rule** by assuming the area under the curve is the sum of several small trapezoids.



$$[\mathrm{AUC}]_{tn-1}^{tn} = \frac{C_{n-1} + C_n}{2}(t_n - t_{n-1})$$

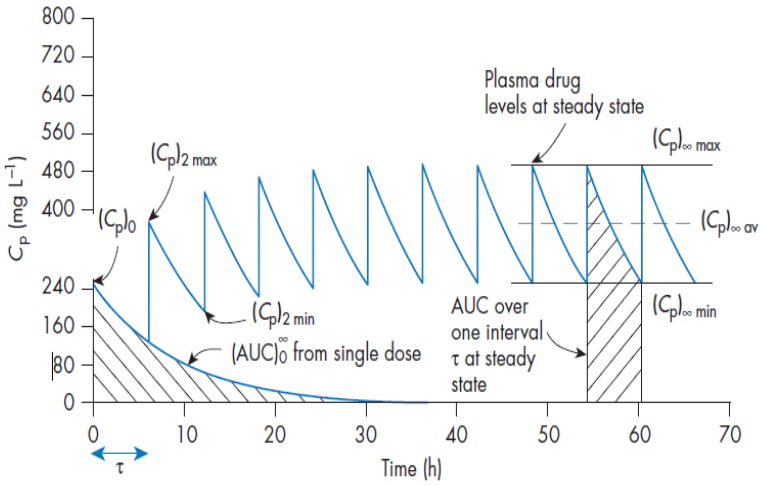
To calculate AUC from t =0 to the last observed point t = n, we sum all the calculated trapezoid areas.

$$[\mathrm{AUC}]_{t0}^{tn} = \sum[\mathrm{AUC}]_{tn-1}^{tn}$$

The calculation of AUC from t = 0 to t = ∞, we have to calculate the residual area from last time point to t = ∞. $[\mathrm{AUC}]_{tn}^{t\infty} = \frac{C_{pn}}{k}$

Where C_{pn} = last observed plasma concentration at t_n and ***k* = - slope x 2.3** obtained from the terminal portion of the curve.

Note: AUC can also be calculated following multiple doses by taking 10-15 plasma concentration time points during a dosage interval after reaching steady state, which is equal to the AUC obtained from singe administration of the same dose.



- **Calculation of Clearance**

Clearance can be determined directly from the plasma drug concentration–time curve by

$$Cl_T = \frac{D_0}{[AUC]_0^{\infty}}$$

Clearance can be calculation based on AUC without the need for the assumption of compartmental models.

- **Volume of distribution (V_D)**

For IV injections $V_D = \frac{D}{K\,.\,AUC}$

For doses administered extravascularly $V_D = \frac{F\,D}{K\,.\,AUC}$

- **Half-life ($t_{1/2}$)**

The half-life of elimination (t½) can be determined directly by plotting actual concentrations on semilog graph paper. Other method for the calculation of $t_{1/2}$ is through the estimation of the slope in the plasma-concentration time curve using the following equation:

K = - slope x 2.3

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

The selection of the time points from the plasma-concentration time curve for the calculation of the slope is crucial in the determination of elimination $t_{1/2}$. The last few points of the curve represent the elimination phase. Therefore, the slope should be determined using plasma concentration-time points at the elimination phase.

Michaelis-Menten Equations For Saturable Pharmacokinetics

When the dose of a drug is increased and steady-state serum concentrations do not increase in a proportional fashion, but instead increase more than expected, Michaelis-Menten or saturable pharmacokinetics may be taking place. This situation occurs when the serum concentration of the drug approaches or exceeds the Km value for the enzyme system that is responsible for its metabolism.

$D = \frac{Vmax\ Css}{Km\ Css}$ ….. Michaelis-Menten expression

when the plasma concentration of the drug approaches or exceeds the Km value (Michaelis-Menten constant) for the enzyme system that is responsible for its metabolism, saturable pharmacokinetics may be taking place.

The calculation of V_{max} and Km are important to estimate the dose required to give a desired Css without approaching saturation.

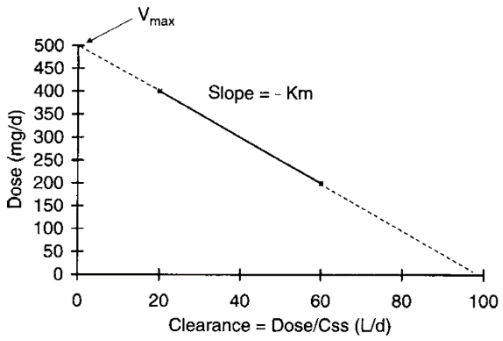
Method of calculating Michaelis-Menten constants

The Michaelis-Menten equation is rearranged to the following formula: $D = V_{max} - km\ (\frac{D}{Css})$ which similar to the formula of straight line ((y = intercept + (Slope) X)).

For the calculation of V_{max} and Km a patient is placed on an initial dose (D1) of the medication, a steady-state concentration is obtained (Css1), and the dose/steady-state concentration ratio determined (D1/Css1). The dose of the medication is changed (D2), a second steady-state concentration is measured (Css2), and the new dose/steady-state concentration ratio is computed (D2/Css2). The values of Dose vs dose/Css are plotted as follow:

the slope of the straight line = - Km and the intercept of the line with the y axis = V_{max}.

The V_{max} and Km values obtained by this method can be used to calculate a new dose that would not reach saturable PK.



Practice problems

Q1: A patient with tonic-clonic seizures is given phenobarbital 100 mg intravenously daily until steady-state occurs. Pharmacokinetic constants for phenobarbital in the patient are: k = 0.116 d^{-1}, V_D = 75 L. Calculate the steady-state concentration 23 hours after the last dose.

Solution
The steady-state concentration following multiple IV injections can be calculated by the following equation

$$\boldsymbol{C = \frac{D}{V_D} . \left(\frac{e^{-kt}}{1 - e^{-k\tau}}\right)}$$

23 hours after the last dose = $\frac{23}{24}$ = 0.96 d

$$\boldsymbol{C = \frac{100}{75} . \left(\frac{e^{-0.116\ x\ 0.96}}{1 - e^{-0.116\ x\ 1}}\right)} = 10.9 \text{ mg/L}$$

Q2: A patient with gram-negative pneumonia is administered tobramycin 140 mg every 8 hours until steady state is achieved. Pharmacokinetic parameters for tobramycin in the patient are: V = 16 L, k = 0.30 h^{-1}. Calculate the steady-state concentration immediately after a 1-hour infusion. Note tobramycin is administered as an infusion over 1 hour.

Solution

$$C = \frac{K_0}{KV_D} \left(\frac{1-e^{-kt\prime}}{1 - e^{-k\tau}}\right)$$

$$C = \frac{140}{0.3\ x\ 16} \left(\frac{1-e^{-0.3\ x\ 1}}{1 - e^{-0.3\ x\ 8}}\right) = 8.3 \text{ mg/L}$$

Q3: A patient with an arrhythmia is administered 250 mg of quinidine orally (as 300 mg quinidine sulfate tablets) every six hours until steady state occurs. Pharmacokinetic constants for quinidine in the patient are: V = 180 L, k = 0.0693 h^{-1}, F = 0.7. Calculate the postabsorption, postdistribution steady-state concentration just before the next dose

Solution
Just before the next dose means that the time of calculating the plasma concentration is 6 hours (t = 6).

$$\boldsymbol{C = \frac{FD}{V_D} . \left(\frac{e^{-kt}}{1 - e^{-k\tau}}\right)}$$

$$\boldsymbol{C = \frac{0.7\ 300}{180} . \left(\frac{e^{-0.0693\ x\ 6}}{1 - e^{-0.0693\ x\ 6}}\right)} = 1.9 \text{ mg/L}$$

Q4: A patient receiving theophylline 300 mg intravenously every 6 hours has a predose concentration equal to 2.5 mg/L and postdose concentrations of 9.2 mg/L one hour and 4.5 mg/L five hours after the second dose is given. Calculate k and V_D.
Solution

$$K = - \frac{\log C2 - \log C1}{t2 - t1} \times 2.3$$

$$K = - \frac{\log 4.5 - \log 9.2}{5 - 1} \times 2.3 = 0.179^{-1} \text{ h.}$$

$$V_D = \frac{D}{(C_0 - C_{predose})}$$

C_0 can be calculated from following equation

$$\boldsymbol{C = C_0 . e^{-kt}}$$

$$\boldsymbol{4.5 = C_0 . e^{-0.179 \, x \, 5}}$$

$$\boldsymbol{C_0 =} \text{ 11 mg/L}$$

$$V_D = \frac{300}{11 - 2.5} = 35.3 \text{ L}$$

Q5: a patient is prescribed gentamicin 100 mg infused over 60 minutes every 12 hours. A predose steady-state concentration ($C_{predose}$) is drawn and equals 2.5 mg/L. After the 1-hour infusion, a steady-state maximum concentration (C_{max}) is obtained and equals 7.9 mg/L. Calculate k and V_D

Solution
Since the patient is at steady state, it can be assumed that all predose steady-state concentrations are equal. Because of this the predose steady-state concentration 12 hours after the dose can also be considered equal to 2.5 mg/L and used to compute the elimination rate constant (k) of gentamicin for the patient:

$$K = - \frac{\log C2 - \log C1}{t2 - t1} \times 2.3$$

$$K = - \frac{\log 2.5 - \log 7.9}{12 - 1} \times 2.3 = 0.105^{-1} \text{ h.}$$

$$V_D = \frac{k_0 \, (1 - e^{-kt\prime})}{k \, [\, C_{max} - (C_{predose} \, . \, e^{-kt\prime})}$$

$$VD = \frac{100 \, mg/1h \, (1 - e^{-0.105 \, x \, 1})}{0.105 \, [\, 7.9 - (2.5 \, . \, e^{-0.105 \, x \, 1})} = 16.8 \text{ L}$$

Q6: A patient is given procainamide capsules 750 mg every 6 hours. The following concentrations are obtained before and after the second dose: $C_{predose}$ = 1.1 mg/L, concentrations 2 hours and 6 hours postdose equal 4.6 mg/L and 2.9 mg/L. Calculate K and V_D.

The two concentration time points (postdose) can be used to calculate the K as follow

$K = - \frac{\log C2 - \log C1}{t2 - t1} \times 2.3$

$K = - \frac{\log 2.9 - \log 4.6}{6-2} \times 2.3 = 0.115\ h^{-1}$.

Procainamide was administered orally. However, the bioavailability is unknown. Therefore, the absolute value of V_D can't be calculated. Instead, the hybrid constant of V_D/F can be calculated as follow:

$$\frac{VD}{F} = \frac{D}{(C_0 - C_{predose})}$$

C_0 can be calculated from following equation

$$\boldsymbol{C = C_0 . e^{-kt}}$$

$$\boldsymbol{4.6 = C_0 . e^{-0.115\ x\ 2}}$$

$\boldsymbol{C_0}$ = 5.8 mg/L

$$\frac{VD}{F} = \frac{300}{5.8 - 1.1} = 160\ L$$

Q7: A patient is administered 250 µg of digoxin tablets daily for heart failure until steady state. The pharmacokinetic constants for digoxin in the patient are: F = 0.7, Cl = 120 L/d. Calculate he average steady-state concentration.

$$C_{ss} = \frac{[F(\frac{D}{\tau})]}{Cl}$$

$$C_{ss} = \frac{[0.7(\frac{250}{1})]}{120} = 1.5\ \mu g/L$$

Q8: patient is given 1500 mg of procainamide sustained release tablets every 12 hours until steady state for the treatment of an arrhythmia. The pharmacokinetic parameters for procainamide in the patient are: F = 0.85, Cl = 30 L/h. Calculate the average steady-state concentration.

$C_{ss} = \frac{[F(\frac{D}{\tau})]}{Cl}$, $C_{ss} = \frac{[0.85(\frac{1500}{12})]}{30} = 3.5$ mg/L

Q9: Calculate the dose and the dosage interval for a patient that needs to be treated for complex partial seizures with intravenous phenobarbital. The target Css_{max} and Css_{min} are 30 and 25 mg/L, respectively. The population PK parameters for phenobarbital are: k = 0.139 d^{-1} and V_D = 50 L.

Solution

$\boldsymbol{\tau} = \frac{ln\ Css_{max} - ln\ Css_{min}}{k} = \frac{ln\ 30 - ln\ 25}{0.139}$ = 1.3 day (this value is rounded to 1 day for practical use)

D = $Css_{max}\ V_D\ (1 - e^{-k\boldsymbol{\tau}})$

D = 30 x 50 $(1 - e^{-0.139\ x\ \mathbf{1}})$ = 202 mg (this dose is rounded to 200 mg for practical use).

Therefore, the calculated dose of phenobarbital would be IV injection of 200 mg every day.

Q10: A patient receiving tobramycin for the treatment of intraabdominal sepsis. Using pharmacokinetic parameters (V_D = 20 L, k = 0.087 h^{-1}) calculate a tobramycin dose (infused over 1 hour) that would provide maximum (Css_{max}) and minimum (Css_{min}) steady-state concentrations of 6 mg/L and 1 mg/L, respectively.

$\boldsymbol{\tau} = \frac{ln\ Css_{max} - ln\ Css_{min}}{k}$ + t' , $\quad \boldsymbol{\tau} = \frac{ln\ 6 - ln\ 1}{0.087}$ + 1 = 22 h (round to practical dosage interval of 24 h)

$K_0 = Css_{max}\ k\ V_D\ (\frac{1 - e^{-k\boldsymbol{\tau}}}{1 - e^{-kt'}})$, $\quad K_0 = 6 \text{ x } 0.087 \text{ x } 20\ (\frac{1 - e^{-0.087\ x\ 24}}{1 - e^{-0.087\ x\ 1}})$ = 110 mg

The patient would be prescribed tobramycin 110 mg infused over 1 hour every 24 hours

Q11: a patient with simple partial seizures that needs to receive valproic acid capsules (population pharmacokinetic parameters are V = 12 L, k = 0.05 h^{-1}, T_{max} = 3 h, F = 1.0). Calculate the optimum dose and dosage interval to achieve maintain steady-state maximum (Css_{max}) and minimum (Css_{min}) concentrations of 80 mg/L and 50 mg/L, respectively.

$\boldsymbol{\tau} = \frac{ln\ Css_{max} - ln\ Css_{min}}{k} + T_{max}$, $\quad \boldsymbol{\tau} = \frac{ln\ 80 - ln\ 50}{0.05}$ + 3 = 12.4 h (round to a practical interval of 12 h)

$D = \frac{Css_{max}\ V_D}{F}\ (\frac{1 - e^{-k\boldsymbol{\tau}}}{e^{-k\boldsymbol{Tmax}}})$, $\quad D = \frac{80 \text{ x } 12}{1}\ (\frac{1 - e^{-0.05\ x\ 12}}{e^{-0.05\ x\ \mathbf{3}}})$ = 503 mg (round to practical dose of 500 mg)

The patient would be prescribed valproic acid capsules 500 mg orally every 12 hours.

Q12: a patient with an atrial arrhythmia needing treatment with procainamide sustained-release tablets (clearance equals 24 L/h; F = 0.85, $\boldsymbol{\tau}$ = 12 h for sustained-release tablet). The target average steady-state procainamide concentration is 5 mg/L. Calculate the dose of procainamide required to achieve this concentration.

D = $\frac{Css\ Cl\boldsymbol{\tau}}{F} = \frac{5\ x\ 24\ x\ \mathbf{12}}{0.85} = 1694\ mg$ (round to a practical dose of 1500 mg)

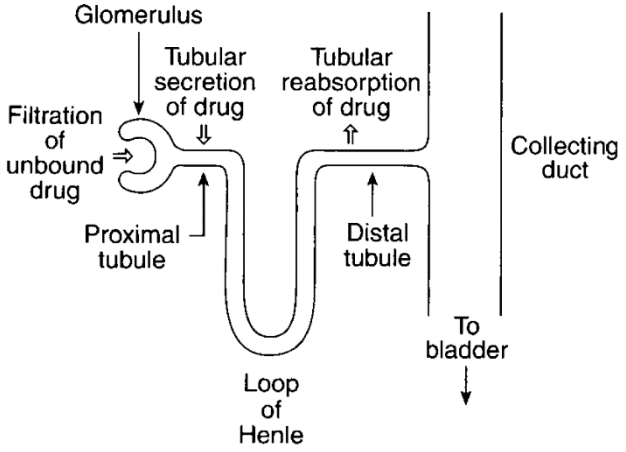
The patient would be prescribed procainamide sustained-release tablets 1500 mg orally every 12 hours.

Drug Dosing in Special Populations

Drug Dosing in Renal Disease

The kidney is the main organ responsible for drug excretion. Three processes of drug movement occur in the kidney:

- Glomerular filtration
- Active tubular secretion
- Tubular reabsorption



The equation that describes these various routes of renal elimination is:

$$Cl_R = [\ (f_B \,.\, GFR) + \frac{RBF \,.\, (f_B \,.\, Cl'_{sec})}{RBF + (f_B \,.\, Cl'_{sec})}\ ]\ (1 - FR)$$

where f_B is the free fraction of drug in the blood, GFR is glomerular filtration rate, RBF is renal blood flow, Cl'_{sec} is the intrinsic clearance for tubular secretion of unbound drug, and FR is the fraction reabsorbed.

Measurement and Estimation of Creatinine Clearance

The measurement and estimation of creatinine clearance (CrCl) is recommended by the Food and Drug Administration (FDA) and others to estimate renal function for the purposes of drug dosing as creatinine is a by-product of muscle metabolism that is primarily eliminated by glomerular filtration.

One of the commonly used equations for the estimation of CrCl is Cockcroft-Gault method which is based on serum creatinine:

$$CrCl_{est} = \frac{[(140 - age)/BW]}{72 \,.\, S_{Cr}} \quad \text{..... for males}$$

$$CrCl_{est} = \frac{[0.85\ (140 - age)/BW]}{72 \,.\, S_{Cr}} \quad \text{..... for females}$$

Where $CrCl_{est}$ is estimated creatinine clearance in mL/min, age is in years, BW is body weight in kg, and S_{Cr} is serum creatinine in mg/dL.

The Cockcroft-Gault method should only be used in

1. Patients ≥18 years old.
2. When actual weight within 30% of their ideal body weight (IBW)

   IBW_{male} (in Kg) = 50 + 2.3 (Ht – 60)
   IBW_{female} (in Kg) = 45 + 2.3 (Ht – 60)

   Where Ht is the height in inches (1 inch = 2.45 cm)
3. Stable serum creatinine concentrations.

For example, a 55-year-old, 80-kg, 5-ft 11-in male has a serum creatinine equal to 1.9 mg/dL. The estimated creatinine clearance would be

IBW_{male} (in Kg) = 50 + 2.3 (Ht – 60)

Note that 1 foot = 12 inches

IBW_{male} (in Kg) = 50 + 2.3 (71 – 60) = 75.3 kg

Therefore, BW (80 kg) is within 30% of IBW (75.3 kg) so that Cockcroft-Gault method can be used to calculate $CrCl_{est}$

$$CrCl_{est} = \frac{[(140-\text{age})/\text{BW}]}{72 \,.\, S_{Cr}} = \frac{[(140-55)/80]}{72 \,.\, 1.9} = 50 \text{ mL/min}$$

Note: in obese patients where Cockcroft-Gault method can't be used alternative equations can be applied:

$$CrCl_{est} = \frac{(137-age)[(0.285 \,.\, Wt)+(12.1 \,.\, Ht^2)]}{51 \,.\, S_{Cr}} \quad \text{.....} \quad \text{for males}$$

$$CrCl_{est} = \frac{(146-age)[(0.287 \,.\, Wt)+(9.74 \,.\, Ht^2)]}{60 \,.\, S_{Cr}} \quad \text{.....} \quad \text{for females}$$

Therapeutic Drug Monitoring

Lecture 4
Dr Atheer Zgair

Estimation of Drug Dosing and Pharmacokinetic Parameters Using Creatinine Clearance

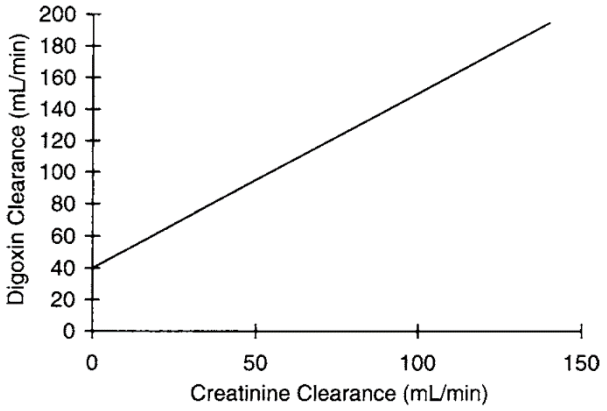
It is widely accepted that dosage adjustment is required when patient is treated with a medication that eliminated by the kidney. One of three methods is commonly used for dose adjust. These are:

1. Decrease the drug dose and retain the usual dosage interval.
2. Retain the usual dose and increase the dosage interval.
3. Simultaneously decrease the dosage and prolong the dosage interval.

For drugs with narrow therapeutic indexes, measured or estimated creatinine clearance may be used to estimate pharmacokinetic parameters for a patient based on prior studies conducted in other patients with renal dysfunction.
For example, for digoxin, an equation that describes the relationship between digoxin clearance (Cl) and creatinine clearance (CrCl in mL/min) is:

$Cl\ (in\ mL/min) = 1.303 \cdot CrCl + Cl_{NR}$

where Cl_{NR} is nonrenal clearance and equals 20 mL/min in patients with moderate-severe heart failure and 40 mL/min in patients with no or mild heart failure. This equation is derived from the linear relationship between digoxin Cl and CrCl



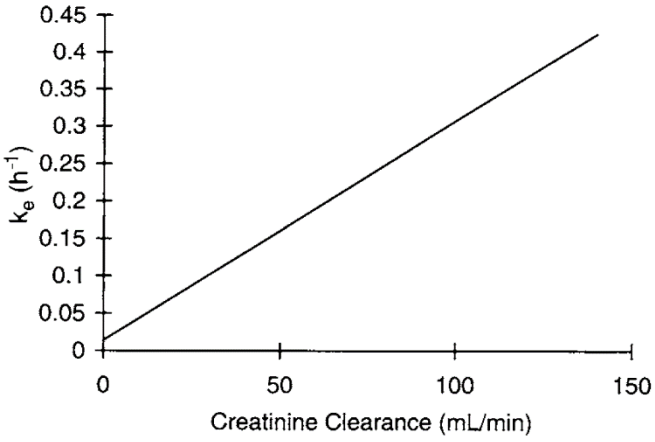
Digoxin volume of distribution decreases in patients with decreased renal function according to the following equation:

$V_D\ (in\ L) = 226 + [(298 \cdot CrCl)/(29.1 + CrCl)]$

where CrCl is in mL/min. The decline in volume of distribution presumably occurs because of displacement of tissue-bound digoxin.

For the aminoglycoside antibiotics, an equation that represents the relationship between aminoglycoside antibiotic elimination rate constant (k) and creatinine clearance (CrCl in mL/min) is:

$k\ (in\ h^{-1}) = 0.00293 \cdot CrCl + 0.014$



Hepatic Disease

The equation that describes hepatic drug metabolism is

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{LBF + (f_B \cdot Cl'_{int})}$$

Where LBF is liver blood flow, f_B is the fraction of unbound drug in the blood, and Cl'_{int} is intrinsic clearance.

- Hepatic metabolism of drugs is not completely developed in neonates (~40-weeks gestational age) and continues to increase so that by age 3–6 months it is stable. In premature infants (<35 weeks), hepatic metabolism may take even longer to develop in the postpartum period.

- On a per kilogram basis, drug metabolism is more rapid in children until puberty and then metabolic rate gradually decreases to adult values.

- Elderly individuals have decreased liver mass, and it appears that hepatocytes which are still present have decreased ability to metabolize drugs.

There are two major types of liver disease: hepatitis and cirrhosis. These diseases cause the following:

1. Decrease the number of functional hepatocytes and therefore decrease hepatic clearance.
2. Liver blood flow decreases in patients with cirrhosis results in less drug delivery to still-functioning hepatocytes and depresses hepatic drug clearance even further.
3. In patients with cirrhosis, the production of biding proteins (albumin and a1-acid glycoprotein) decline which causes the free fraction of drugs in the blood increases because of a lack of binding proteins.
4. High concentrations of endogenous substances in the blood that are normally eliminated by the liver, such as bilirubin, can displace drugs from plasma protein binding sites causing an increase in V_D.

As a result of decreased clearance and increased V_D in hepatic disease the K is increased.
$K = Cl/V_D$

Child-Pugh Scores

The Child-Pugh score for a patient is used to estimate the ability of the liver to metabolize drug as described in the following table.

Child-Pugh Scores for Patients with Liver Disease

TEST/SYMPTOM	SCORE 1 POINT	SCORE 2 POINTS	SCORE 3 POINTS
Total bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds prolonged over control)	<4	4–6	>6
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy	None	Moderate	Severe

- The Child-Pugh score for a patient with normal liver function is 5.
- A Child-Pugh score equal to 8–9 is grounds for a moderate decrease (~ 25%) in initial daily drug dose for agents that are primarily (≥60%) hepatically metabolized.
- A score of 10 or greater indicates that a significant decrease in initial daily dose (~ 50%) is required for drugs that are mostly liver metabolized.

For example, the usual dose of a medication that is 95% liver metabolized is 500 mg every 6 hours, and the total daily dose is 2000 mg/d. For a hepatic cirrhosis patient with a Child-Pugh score of 12, an appropriate initial dose would be 50% of the usual dose or 1000 mg/d. The drug could be prescribed to the patient as 250 mg every 6 hours or 500 mg every 12 hours.

The method used to reduce the dose for patients with liver dysfunction will depend on the route of administration and the available dosage forms. For example, if the medication is only available as an oral capsule, it is likely that the usual dose will be given to a patient with liver disease but the dosage interval will be prolonged. However, if the drug is given parenterally, it may be possible to simultaneously modify the dose and dosage interval to attain the same maximum and minimum steady-state concentrations in patients with hepatic dysfunction as those encountered in patients with normal liver function.

Heart Failure

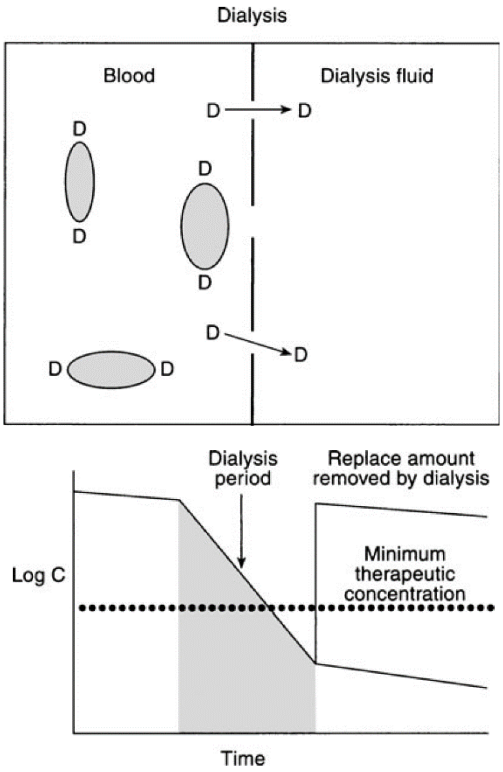
Heart failure is accompanied by a decrease in cardiac output which results in lower liver and renal blood flow. The most common consequences of heart failure on drug kinetics are:

1. Decrease in hepatic clearance, especially for compounds with moderate-to-high hepatic extraction ratios.
2. Decreased drug bioavailability due to the collection of edema fluid in the gastrointestinal tract which makes absorption of drug molecules more difficult and decreased blood flow to the gastrointestinal tract.
3. Decrease in the volume of distribution.

Dialysis

Dialysis is a process whereby substances move via a concentration gradient across a semipermeable membrane as described in the figure below.

Synthetic semipermeable membranes are used in **artificial kidneys** to remove waste products from the blood. Also, **physiologic membranes**, such as those present in the peritoneal cavity in the lower abdomen, can be used with **peritoneal dialysis** as an endogenous semipermeable membrane.



Substances that are small enough to pass through the pores in the semipermeable membrane will pass out of the blood into the dialysis fluid. Once in the dialysis fluid, waste products and other compounds can be removed from the body.

Dialysis is usually used for the removal of toxic waste products that would usually be eliminated by the kidney. Drug molecules are also removed from the blood coincidental to the removal of toxic waste products. In some cases, dialysis is used to remove drugs from the bodies of patients that have taken drug overdoses or are experiencing severe adverse effects from the drug. In both cases, dialysis will cause a decline in the plasma concentration of drug that are significantly removed by dialysis. This might cause a decline in the plasma concentration below the minimum therapeutic concentration and replacement dose will be required.

In a renal failure patient, the only clearance mechanism available to remove drugs from the body are nonrenal ($Cl = Cl_{NR}$, where Cl is total clearance and Cl_{NR} is nonrenal clearance).
In case of dialysis; $Cl = Cl_{NR} + Cl_D$, where Cl_D is dialysis clearance.

If dialysis clearance is ≥30% of total clearance then a replacement dose is required.

Drug Characteristics that Effect Dialysis Removal

1. Molecular Size

The semipermeable membranes used in dialysis are either

a. Low-flux filter; permit the permeation of small drug molecules (molecular weight <500 Da, such as theophylline, lidocaine, procainamide). Drug molecules with moderate molecular weights (molecular weight 500–1000 Da, such as aminoglycoside antibiotics [~400–500 Da] and digoxin) may have sufficient dialysis clearances to require postdialysis replacement doses.
b. High-flux filters; permit the removal of large drug molecules such as vancomycin.

2. Water/Lipid Solubility

Drugs that have a high degree of water solubility will tend to partition into the water-based dialysis fluid, while lipid-soluble drugs tend to remain in the blood.

3. Plasma Protein Binding

Only unbound drug molecules are able to pass through the pores in the semipermeable membrane.

4. Volume of Distribution

Compounds with small volumes of distribution (<1 L/kg, such as the aminoglycoside antibiotics and theophylline) usually demonstrate high dialysis clearance rates. Drugs with moderate volumes of distribution (1–2 L/kg) have intermediate dialysis clearance values, while agents with large volumes of distribution (>2 L/kg, such as digoxin and tricyclic antidepressants) have poor dialysis characteristics.

Hemodialysis

During hemodialysis, blood is pumped out of the patient at the rate of 300–400 mL/min and through one side of the semipermeable membrane of the artificial kidney by the hemodialysis machine. Dialysis fluid is pumped through the artificial kidney at a rate of 400–600 mL/min on the other side of the semipermeable membrane.

Computation of Initial Doses and Modification of Doses Using Drug Serum Concentrations

The calculation of initial doses and replacement doses for a drug that is significantly cleared by hemodialysis requires the knowledge of the PK parameters of the drug before dialysis and during dialysis.

For example, a patient is a 62-year-old, 5-ft 8-in male who weighs 65 kg, has chronic renal failure, and receives hemodialysis three times weekly (3 h in each session). Calculate loading dose that gives peak concentrations of 6–7 mg/L and replacement dose for tobramycin during the dialysis sessions. The patient is expected to have hemodialysis two-days after having the loading dose.

From population PK studies, the V_D of aminoglycosides is 0.26 L/kg.

The loading dose required to achieve peak plasma concentration of 6 mg/L is

$LD = C \cdot V_D$

$LD = 6 \times (0.26 \times 65) = 101$ mg (rounded to 100 mg).

After receiving this loading dose, tobramycin plasma concentration is expected to reach plasma level of 6 mg/L.

Before dialysis, tobramycin concentration is eleminated by the patient's own mechanisms. To note, the patient is in a case of renal failure which means that CrCl is zero. Therefore, the elimination rate constant (k) in this case is calculated as follow:

k (in h^{-1}) = 0.00293 · CrCl + 0.014

k (in h^{-1}) = 0.00293 x 0 + 0.014 = 0.014 h^{-1}

In the above example the patient receives hemodialysis three times weekly. We need to calculate plasma concentration just before hemodialysis (i.e. calculation of the decline in concentration from the time of administration of loading dose to the time of hemodialysis).
The above patient has received the loading dose two days (48 h) before hemodialysis.

$$C = C_0 . e^{-kt}$$

$$C = 6 . e^{-0.014 \, x \, 48} = 3.06 \text{ mg/L}$$

While the patient is receiving hemodialysis, tobramycin is eliminated by the patient's own mechanisms plus dialysis clearance. During hemodialysis, the average half-life for **aminoglycosides is 4 hours.**

$$k = \frac{0.693}{t_{1/2}} = 0.1732 \ h^{-1}$$

Dialysis session is 3 h, therefore

$$C = C_0 . e^{-kt}$$

$$C = 3.06 . e^{-0.173 \, x \, 3} = 1.82 \text{ mg/L}$$

After the dialysis, a postdialysis replacement dose could be given to increase the maximum concentration to its original value of 6 mg/L.

Replacement dose = (C_{max} – $C_{baseline}$) x V_D

Replacement dose = (6 – 1.82) x (0.26 x 65) = 70.6 mg (rounded to 70 mg).
For the calculation of the decline in plasma concentration of tobramycin during the time until the second hemodialysis session, keep in mind that K = **0.014 h^{-1}** as elemination is by the patient's own mechanisms only.

Peritoneal Dialysis

Peritoneal dialysis involves the surgical insertion of a catheter in the lower abdomen into the peritoneal cavity. The peritoneal membrane covering the internal organs is highly vascularized, so when dialysis fluid (1–3 L) is introduced into the peritoneal cavity using the catheter, waste products move from the blood vessels of the peritoneal membrane (a semipermeable membrane) into the dialysis fluid along a concentration gradient. The dialysis fluid is periodically removed from the peritoneal cavity and discarded.
Compared to hemodialysis, peritoneal dialysis removes drug much less efficiently. So, it is less likely that replacement drug doses will need to be given during intermittent peritoneal dialysis.

Obesity

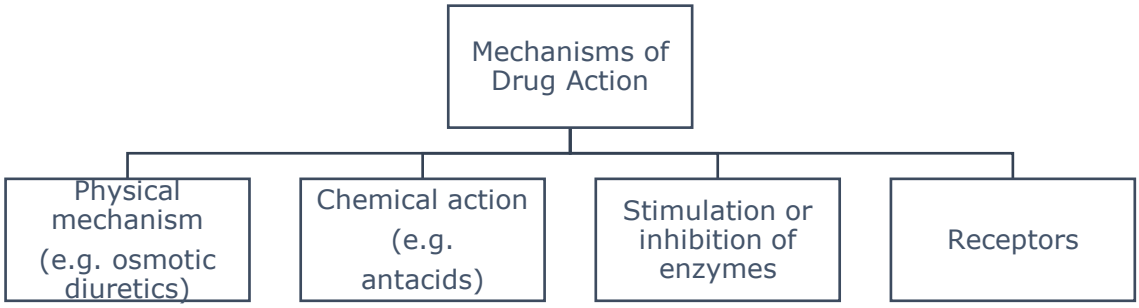
The presence of excessive adipose tissue can alter the pharmacokinetics of drugs by changing the volume of distribution.
Medications that have high lipid solubility tend to partition into adipose tissue, and the volume of distribution in obese patients for these drugs can be larger than in normal weight patients such as in the case of diazepam, carbamazepine, and trazodone.
Hydrophilic drugs tend to not distribute into adipose tissue so that the volume of distribution for many water-soluble drugs is not significantly different in obese and normal weight patients.

In addition to adipose cells, there are additional supportive tissues, extracellular fluid, and blood present in adipose tissue. For hydrophilic drugs with small volumes of distribution like aminoglycosides, the addition of just a few liters of extracellular fluid can alter the pharmacokinetics of these antibiotics and cases larger volume of distribution in overweight patients. For drugs with large and intermediate V_D, the effect of extra volume is not significant.

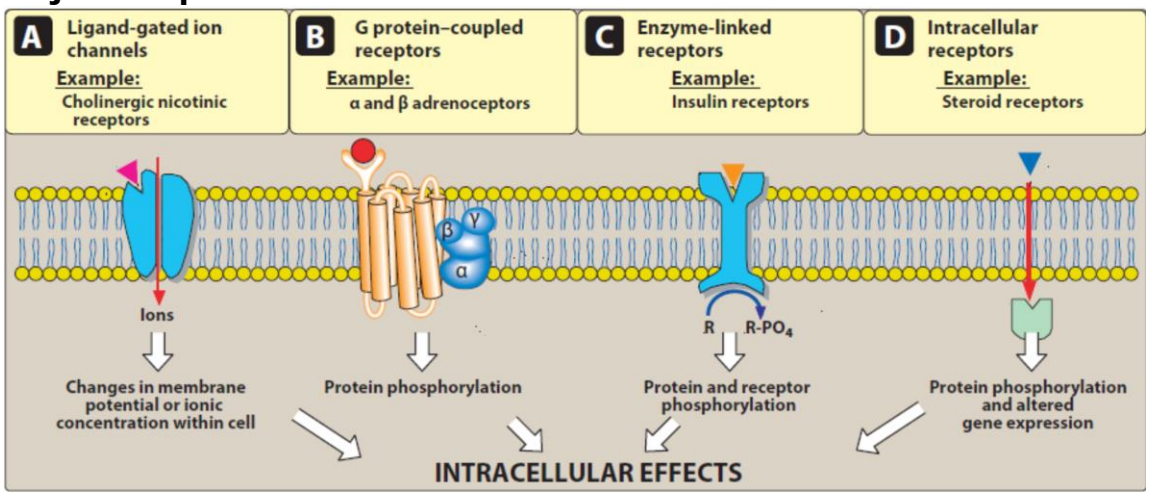
Another change that is found in obese individuals is increased glomerular filtration rates. This alteration affects hydrophilic drug compounds that are renally eliminated and will increase the renal clearance of the agent such as vancomycin, aminoglycosides, and cimetidine.

Obesity has variable effects on the metabolism of drugs. Hepatic clearance increases as with diazepam or decreases as with methylprednisolone.

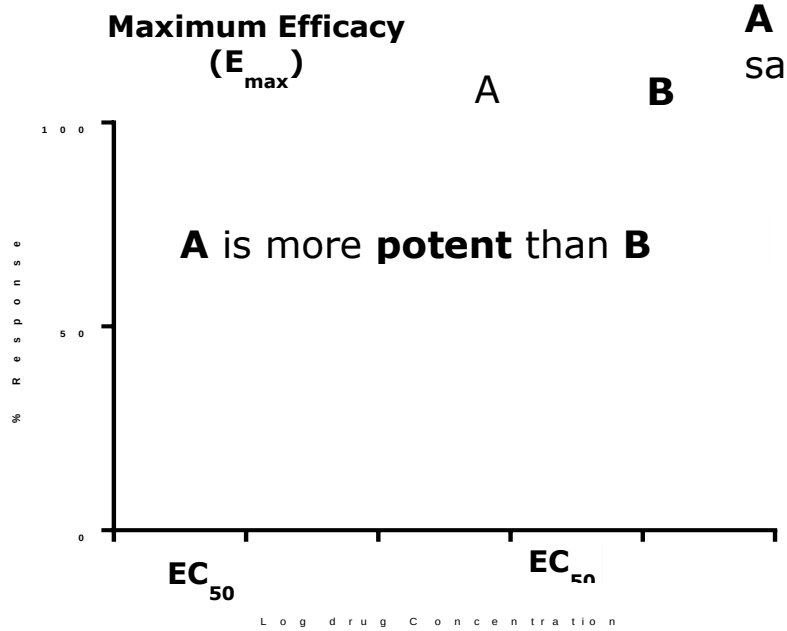
Basic Pharmacodynamics



Major receptor families



GRADED DOSE–RESPONSE RELATIONS

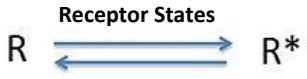


A and **B** have the same **Efficacy**

A is more **potent** than **B**

Intrinsic Activity

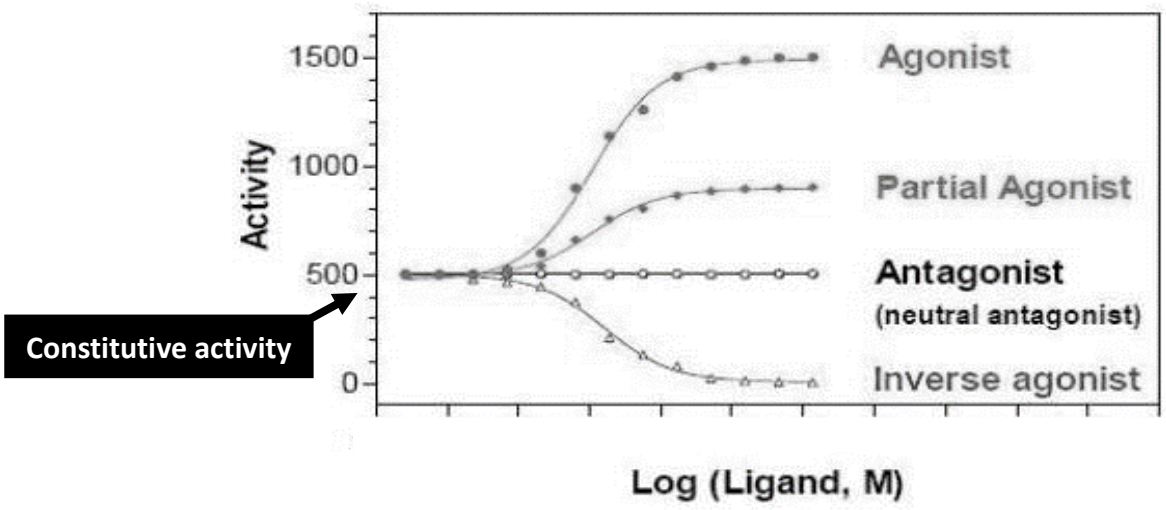
The intrinsic activity of a drug determines its ability to fully or partially activate the receptors.



Full agonist: drug binds to a receptor and produces a maximal biologic response. It stabilizes the receptor in its active state and is said to have an intrinsic activity of one.

Partial agonist: a drug binds to a receptor and does not produce a maximal biological response. It said to have an intrinsic activity > zero and < one.

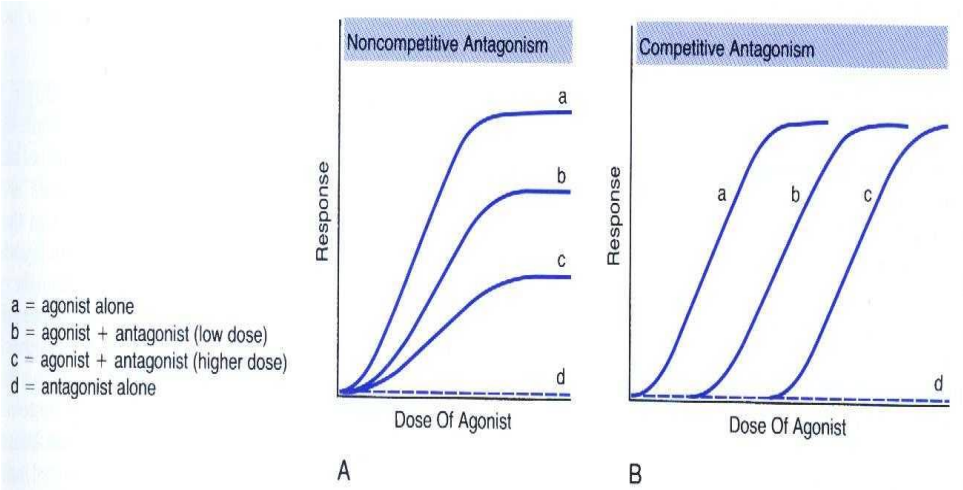
Inverse agonist: bind to receptor and reduce the effect. intrinsic activity less than zero



Types of Antagonists

1. **Pharmacologic Antagonists**

- **Competitive antagonists:** The competitive antagonist prevents an agonist from binding to its receptor.
- **Irreversible antagonists:** Irreversible antagonists bind covalently to the active site of the receptor, thereby reducing the number of receptors available to the agonist.
- **Allosteric antagonists:** This type of antagonist binds to a site ("allosteric site") other than the agonist-binding site and prevents the receptor from being activated by the agonist.



re 6–6. Dose-response curves in the presence of competitive and noncompetitive antagonists.

2. Physiologic antagonists

The antagonist is a different agonist that acts on the same tissue as the agonist, but combine with different receptors (from those of the agonist) to produce effects on the tissue that are opposite to those of the agonist.

Adrenaline antagonises the effect of endogenous histamine on blood vessels and bronchial smooth muscle when used in the treatment of anaphylactic shock.

3. Chemical Antagonists

A chemical antagonist interacts directly with the drug being antagonized to remove it or to prevent it from binding to its target

Examples; Dimercaprol, a chelator of lead and some other toxic metals, and pralidoxime, which combines avidly with the phosphorus in organophosphate cholinesterase inhibitors.

QUANTAL DOSE–RESPONSE RELATIONSHIPS

- Quantal dose–response curves are useful for determining doses to which most of the population responds.