Therapeutic Drug Monitoring TDM

Chapter 1: Introduction

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Today's lecture

- TDM concept and applications
- Basic concepts in pharmacokinetics and pharmacodynamics
- Linear and non-linear kinetics
- Clearance
- Volume of distribution
- Elimination
- Bioavailability
- Bioequivalence

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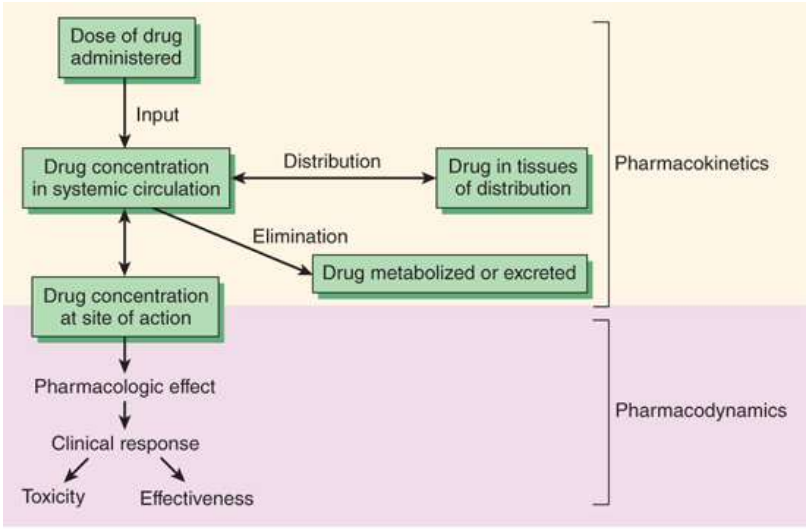
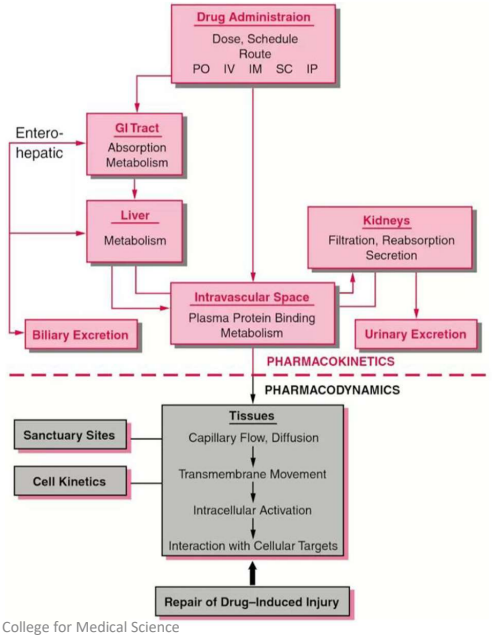
Basic definitions

- **Pharmacokinetics:** The study of drug absorption, distribution, metabolism, and excretion, figure 1.
- **Pharmacodynamics:** The relationship between drug concentration and pharmacological response, figure 1.
- **Clinical pharmacokinetics:** The application of pharmacokinetic principles to ensure safe and effective therapeutic effect of drugs in an individual patient.



Source: Bertram G. Katzung, Anthony J. Trevor: Basic & Clinical Pharmacology, 13th Ed.
www.accesspharmacy.com

Figure 1: Schematic representation of pharmacokinetics and pharmacodynamics



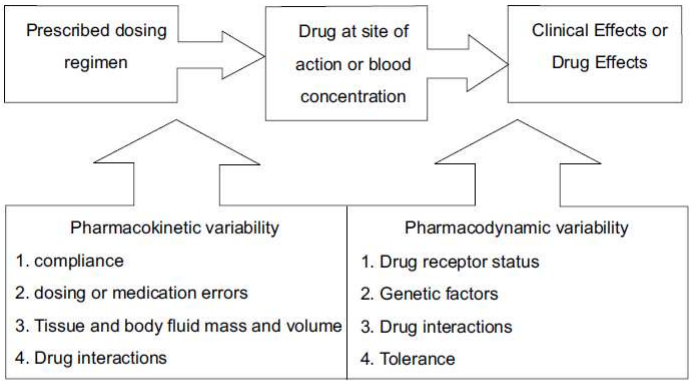


Figure 4. Relationships of pharmacokinetics and pharmacodynamics and factors that affect pharmacokinetic and phamacodynamic variability [16].

Kang JS and Lee MH. Overview of therapeutic drug monitoring, The Korean Journal of Internal Medicine Vol. 24, No. 1, March 2009

- Goals of clinical pharmacokinetics:
  - *enhancing efficacy*
  - *decreasing toxicity* of a patient's drug therapy

- Pharmacokinetic concepts have been used successfully by pharmacists to individualize patient drug therapy for about a quarter century.

- Pharmacokinetic consultant services and individual clinicians routinely provide patient-specific drug-dosing recommendations that increase the efficacy and decrease the toxicity of many medications.

Therapeutic Drug Monitoring (TDM)

- The use of assay procedures to determine drug concentration in plasma, and applying the resulting measurements to develop new, safe and effective drug regimens.

- If performed properly, TDM allows for the achievement of therapeutic concentrations of a drug more rapidly and safely than can be attained with empiric dose changes.

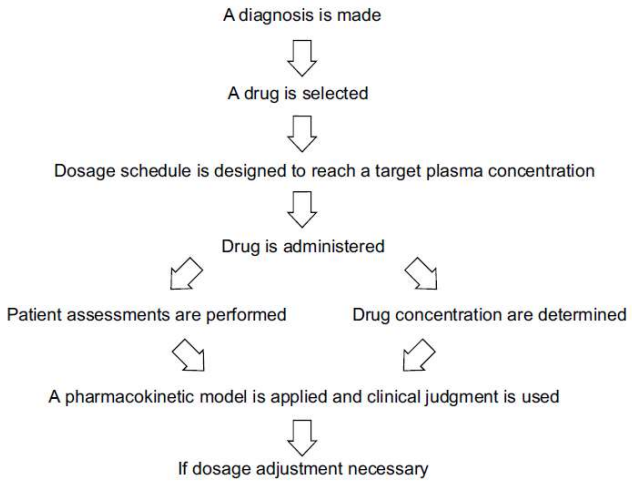


Figure 1. Process for reaching dosage decisions with therapeutic drug monitoring.

Kang JS and Lee MH. Overview of therapeutic drug monitoring, The Korean Journal of Internal Medicine Vol. 24, No. 1, March 2009

TDM is valuable when

- A good correlation exists between the pharmacologic response and plasma concentration. Over at least a limited concentration range, the intensity of pharmacologic effects should increase with plasma concentration. This relationship allows us to predict pharmacologic effects with changing plasma drug concentrations
- Wide intersubject variation in plasma drug concentrations results from a given dose.
- The drug has a narrow therapeutic index (i.e., the therapeutic concentration is close to the toxic concentration).
- The drug's desired pharmacologic effects cannot be assessed readily by other simple means (e.g., blood pressure measurement for antihypertensive), or for drug given prophylactically

- Laboratories routinely measure patient serum or plasma samples for many drugs, including
  - antibiotics (eg, aminoglycosides and vancomycin)
  - Theophylline
  - antiepileptic (eg, phenytoin, carbamazepine, valproic acid, phenobarbital, and ethosuximide)
  - Methotrexate
  - Lithium
  - antiarrhythmic (eg, lidocaine and digoxin)
  - immunosuppressants (eg, cyclosporine and tacrolimus)

- Combined with a knowledge of the disease states and conditions that influence the disposition of a particular drug, kinetic concepts can be used to modify doses to produce serum drug concentrations that result in desirable pharmacologic effects without unwanted side effects.
- This narrow range of concentrations within which the pharmacologic response is produced and adverse effects prevented in most patients is defined as the **therapeutic range of the drug**.

Applications of TDM

- TDM and pharmacokinetics are used to optimize the administration and the therapeutic effects of drugs, as well as the design and evaluation of drug dosage forms. For example:

1. Calculate loading and maintenance drug doses. The loading dose is a large initial dose given to achieve therapeutic drug levels from the beginning; a maintenance dose is then given at fixed intervals to keep drug concentrations within the therapeutic range.
2. Calculate drug dosage regimen. The dosage regimen is a systemized dosage schedule with two variables:
   a) The size of each drug dose
   b) The time between consecutive dose administrations. Dosage regimen calculations are frequently based on population pharmacokinetics and therapeutic drug monitoring.

Applications of TDM, cont'

3. Perform dosage adjustments in special cases patients, for example, renal and hepatic diseases.
4. Design of dosage form and determination of route of administration, for example, sustained-release versus immediate-release oral dosage forms, and parenteral versus oral dosage forms. The route of administration can affect drug pharmacokinetics.
5. Perform bioequivalence studies, that is, pharmacokinetic evaluations of drug formulations. Some pharmaceutical excipients can enhance or decrease drug bioavailability.
6. Predict drug-drug and drug-food interactions. Both co-administered drugs and various food products can interfere with drug absorption, distribution, metabolism, and excretion

Pharmacokinetic Models

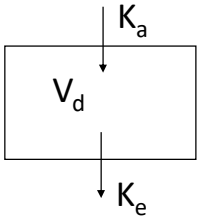
- PK models are relatively simple mathematical schemes that represent complex physiologic spaces or processes.
- Accurate PK modeling is important for precise determination of elimination rate.

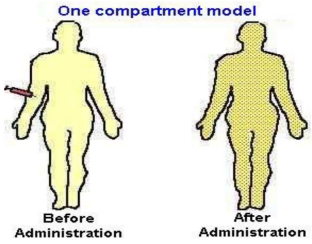
- The most commonly used pharmacokinetic models are:

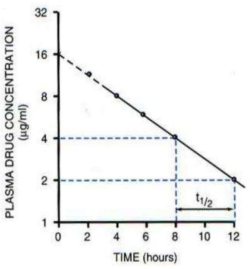
1. One compartment model
2. Two compartment model
3. Non compartment model

One compartment model

- The body is described as a *single, uniform compartment* into which the drug is administered and from which it is eliminated.





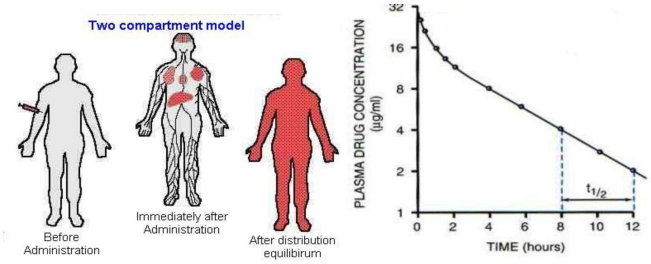


One compartment model

- A very simplistic view of the body, in which the drug enters the bloodstream and is then rapidly equilibrated with other parts of the body.
- Does not predict actual drug concentrations in the various tissues but assumes that drug tissue concentrations will be proportional to the drug plasma concentrations.
- Drug ***rapidly*** equilibrates with the tissue compartment, which uses only one volume term, the apparent volume of distribution, Vd.
- A log scale plot of the serum level decay curve of a one compartment model yields a straight line. e.g., aminoglycosides

Two compartment model

- Drugs which exhibit a ***slow*** equilibration with peripheral tissues, are best described with a two compartment model.
- A log scale plot of the serum level decay curve of a 2-compartment model yields a ***biphasic line***. e.g. vancomycin.

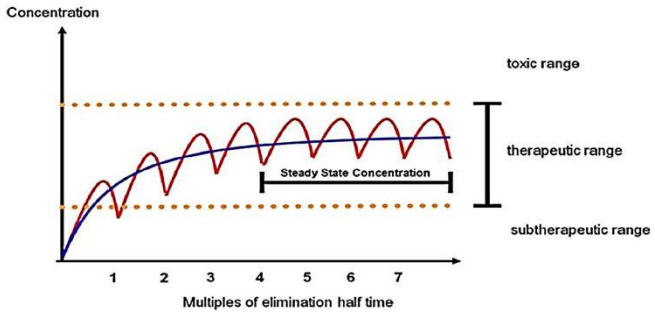


Noncompartmental analysis

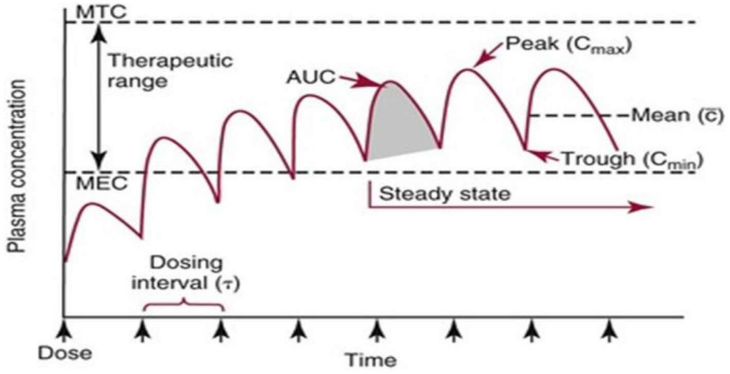
- Sometimes pharmacokinetic analysis can be conducted without specifying any mathematical models (non-compartmental methods), which is highly dependent on estimation of total drug exposure.
- Total drug exposure is most often estimated by area under the curve (AUC) methods.

Steady state condition

- In pharmacokinetics, steady state refers to the situation where the **overall intake** of a drug is fairly in *dynamic equilibrium* with **its elimination**.
- In practice, it is generally considered that steady state is reached when a time point of 3 - 5 times the half-life for a drug after regular dosing is started



Steady state condition



Linear PK Models

- The reaction proceeds at a rate that is dependent on the concentration of the drug present in the body.
- Assumes that the processes of ADME follow first-order reactions and most drugs are eliminated in this manner.
- Most drugs used in clinical practice at therapeutic dosages will show first-order rate processes; that is, the rate of elimination of most drugs will be first-order. However, there are notable exceptions, for example phenytoin and high-dose salicylates.

Characteristics of Drugs with Linear Pharmacokinetics

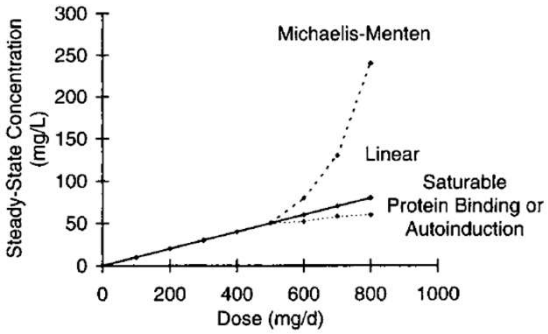
1. Half-life is **in**dependent of concentration

   The instantaneous rate of change in drug concentration depends only on the current concentration. The half-life will remain constant, no matter how high the concentration.

2. Clearance is **in**dependent of schedule

Characteristics of Drugs with Linear Pharmacokinetics

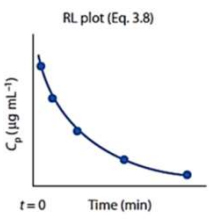
3. Drug exposure (AUC) is not affected by changes in drug schedule. For example, the AUC after a 60 mg/m^2 bolus dose of doxorubicin equals the total AUC for 3 daily (or weekly) bolus doses of 20 mg/m^2, which equals the AUC for the same dose administered as a 96-hour infusion.
4. The AUC is proportional to the dose. Thus, if one measures the AUC for a 60 mg/m^2 dose, one can estimate the AUC for a 90 mg/m^2 dose in the same patient as being 50% greater.

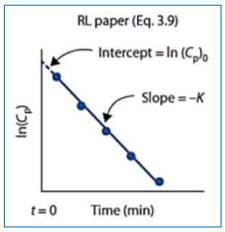


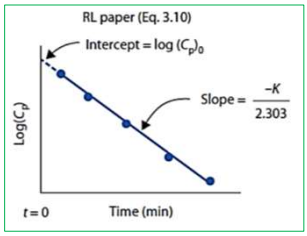
when doses are increased for most drugs, steady-state concentrations increase in a proportional fashion leading to linear pharmacokinetics **(solid line).** However, in some cases proportional increases in steady-state concentrations do not occur after a dosage increase. When steady-state concentrations increase *more than expected* after a dosage increase (upper dashed line), Michaelis-Menten pharmacokinetics may be taking place. If steady-state concentrations increase less than expected after a dosage increase (lower dashed line), saturable plasma protein binding or auto induction are likely explanations

Linear Pharmacokinetic Model

Semi-log plot







By applying a straight line equation

$$Y = intercept + (X * slope)$$

$$lnC_p = ln(C_p)_0 - K_t \qquad \log C_p = \log(C_p)_0 - {}^{K_t}/_{2.303}$$

$$\boldsymbol{C_p = (C_p)_0 e^{-Kt}}$$

Nonlinear Pharmacokinetic Models

- Kinetics resulting from saturable drug transfer, or auto induction leading to variation of the standard kinetic parameters with drug concentration

- Linear kinetics: ↑ or ↓dose → **proportional** ↑ or ↓Css
- Nonlinear kinetics: ↑ or ↓dose → ***dis*proportional** ↑ or ↓Css → problems when adjusting doses

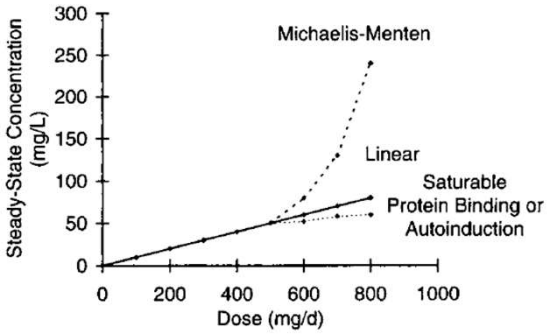
Factors leading to nonlinear kinetics

1. saturation occurring in one of the pharmacokinetic mechanisms:
   a) protein binding
   b) hepatic metabolism
   c) drug absorption
2. auto induction
3. active renal transport of the drug.

Saturable PK mechanisms

1. Elimination:
   C_p increase beyond certain level → $R_e = R_e^{MAX}$
2. drug protein binding or drug reabsorption in kidney tubules
   C_p increase beyond certain level → maximal capacity is reached, e.g. vitamins
3. Absorption
   $C_{at\ absorption\ site}$ increase beyond certain level → $\downarrow R_{absorption}$ and possibly bioavailability

Nonlinear kinetics



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Saturable PK mechanisms , clinical implications

- Changing dose and dosing regimen is difficult and unpredictable for drugs with saturable elimination and may result in toxicity, e.g. phenytoin

- Evaluating the efficiency of a drug dosage regimen: Changing dosage for drugs with saturable absorption or tubular reabsorption, may lead to a less than optimal plasma concentration.

Nonlinear PK models, clinical implications

- Imply that some aspect of the pharmacokinetic behavior of the drug is saturable.

- The principles are very relevant to several anticancer agents. However, alteration of the administration schedule of drugs that display nonlinear kinetics may markedly affect the AUC and potentially alter clinical effects.

Clearance (Cl):

- Clearance: the volume of serum or blood completely cleared of the drug per unit time

  Dimension:

  volume per unit time (**L/h** or **mL/min)**

- Liver is most often the organ responsible for drug metabolism

Clearance (CL):

- Clearance is a descriptive term used to evaluate efficiency of drug removal from the body.

- Clearance is **not** an indicator of how much drug is being removed; it only represents the theoretical volume of blood which is totally cleared of drug per unit time.

- clearance is a first-order process →

  the amount of drug removed depends on the concentration.

- Clearance can be thought of as the proportionality constant that makes the average steady-state drug level equal to the rate of drug administration.

maintenance dose (rate in) = Cl (rate out) X average steady-state concentration

Cl= MD / Css

- Clearance is the most important pharmacokinetic parameter **because** it determines the maintenance dose (MD) that is required to obtain a given steady-state serum concentration (Css)

MD =Css · Cl

- Ex: theophylline therapeutic range is 10–20 µg/mL for the treatment of asthma with concentrations of 8–12 µg/mL considered as a reasonable starting point. If theophylline clearance for a patient = 3 L/h and desired Css = 10 µg/mL:

theophylline maintenance dose = ?

MD = Css · Cl
= 10 µg/mL X 3 L/h
= 10 mg/L X 3 L/h
= 30 mg/h

- Since the concentration of the chemical in its volume of distribution is most commonly sampled by analysis of blood or plasma, clearances are most commonly described as the “plasma clearance” or” blood clearance” of a substance.

- Clearance of an organ depends on:

1. Blood flow to the organ
2. Ability of the organ to eliminate the drug (by metabolism or excretion), which is measured by extraction ration, ER

ER: the fraction of drug removed by the organ

$$ER = (C_{in} - C_{out})/C_{in}$$

$$Cl = BF \cdot ER$$

BF: blood flow

- **Hepatic Clearance:** depend on

1. Intrinsic clearance
2. Blood flow
3. Fraction of free drug in the blood

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

- Where LBF is liver blood flow

f_B: fraction of unbound drug in the blood

Cl'_{int} intrinsic clearance

For drugs with a low hepatic extraction ratio (≤ 0.3)

$$Cl_H = f_B \times Cl'_{int}$$

- drug interactions that displace drug molecules bound to proteins will increase the fraction of unbound drug in the blood (↑f) →
- more unbound drug molecules will be able to leave the vascular system (drug-protein complexes are far too big to exit the vascular system) and enter hepatocytes →
- additional unbound drug will be metabolized and hepatic drug clearance will increase.

For drugs with a **low hepatic extraction** ratio:

$$Cl_H = f_B \times Cl'_{int}$$

- Drug interactions that inhibit or induce the cytochrome P- 450 enzyme system (↓or↑Cl'_{in}) → change hepatic clearance.

- The hepatic clearance of drugs with low extraction ratios does not change much when liver blood flow decreases secondary to liver or cardiac disease. Examples of drugs with low hepatic extraction ratios are valproic acid, phenytoin, and warfarin.

- For drugs with **high hepatic extraction** ratios,

Cl_H = LBF

The rate limiting step for drug metabolism in this case is how much drug can be delivered to the liver(which depends on LBF) because the capacity to metabolize drug is very large →

Hepatic clearance is very sensitive to changes in liver blood flow due to congestive heart failure or liver disease.

protein binding displacement
enzyme induction or inhibition
} does not affect hepatic clearance

Examples of drugs with high hepatic extraction ratios are lidocaine, morphine, and most tricyclic antidepressants.

Renal Clearance

- Physiological determinants of renal clearance:

1. GFR: glomerular filtration rate
2. F : free fraction of drug in the blood or serum
3. Cl_{sec} clearance of drug via renal tubular secretion
4. FR: fraction of drug reabsorbed in the kidney

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

Cl_{sec}

Volume of distribution

- Volume of distribution (apparent volume of distribution, V): a term that relate the measured concentration (Cp) at a time to the mass of drug (Dose) at that time.
- Dimensions: volume units, such as L or mL.
- At any given time after drug has been absorbed from extravascular sites and the serum and tissue drug concentrations are in equilibrium, the serum concentration for a drug (C) is

$$\mathbf{C = A_B/V}$$

- ↑ V: drug distributes extensively into body tissues and fluids (non-polar drugs), e.g: digoxin V = 500 L

- ↓ V: limited drug distribution (polar drugs), drug is primarily contained in the blood (warfarin V = 5–7 L)

V determines the loading dose (LD) that is required to achieve a particular steady-state drug concentration immediately after the dose is administered:

$$\mathbf{LD = Css \cdot V}$$

Physiologic determinates of V

$$V = V_B + \frac{f_B}{f_T} V_T$$

1. actual volume of blood **(V_B)**
2. size (measured as a volume) of the various tissues and organs of the body **(V_T)**

→ larger person, such as a 160-kg football player, would be expected to have a larger volume of distribution for a drug than a smaller person, such as a 40-kg grand- mother.

Physiologic determinates of V, cont'

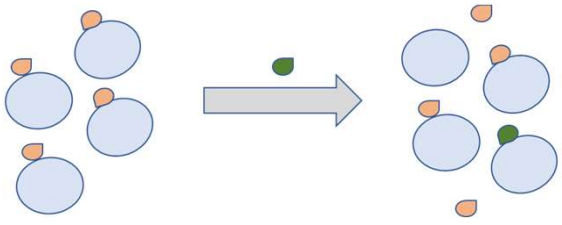
3. Drug binding to blood proteins compared to the binding in tissues

- Warfarin V = 5–7 L: drug is highly bound to serum albumin → $\mathbf{f_B}$ is very small.
- Digoxin V = 500 L: drug is highly bound to tissues (primarily muscle) → f_T is very small

- $\mathbf{f_T}$ = unbound drug concentration in the tissue/total tissue drug concentration).

$$V = V_B + \frac{f_B}{f_T} V_T$$

- This equation can help clinicians understand why a drug has a large or small volume of distribution, or why the volume of distribution might change under various circumstances.
- For example: drug interactions that affect plasma protein binding



$$\uparrow V = V_B + (\uparrow f_B / f_T) V_T$$

Elimination

- Drugs are cleared primarily by the liver and kidneys.
- Excretion into the urine is a major route of elimination for metabolites and unchanged drug.
- Most drugs are eliminated by a first-order process.
  - The amount of drug eliminated is directly proportional to the serum drug concentration (SDC, Cp).
  - At a certain point in therapy, the amount of drug administered during a dosing interval exactly replaces the amount of drug excreted →

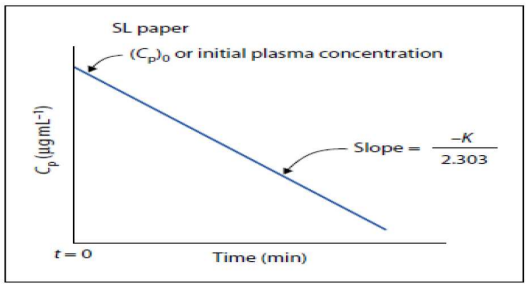
  rate in = rate out → steady-state is reached

Elimination rate constant (K_e)

- K_e : the fraction of drug eliminated per unit time
- Dimension: h^{-1}, min^{-1}
- With first-order elimination,

  rate of elimination ∝ Cp →

linear relationship between rate of eliminations and Cp → amount of drug eliminated changes with concentration, but the **fraction** of a drug eliminated remains **constant**



Since $C_p = (C_p)_0 e^{-Kt}$ ➡

$\ln C_p = \ln(C_p)_0 - Kt$ ➡

$$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2).$$

Note: ↑ Ke → ↑ rate (rate of absorption or excretion)

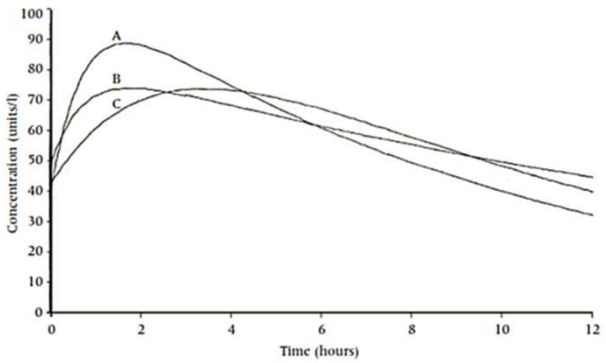


Figure 6. Oral steady state concentration–time profiles illustrating the influence of absorption and elimination rate.
Key:
***A* = absorption rate constant 1.5/h, elimination rate constant 0.1/h. *B* = absorption rate constant 1.5/h, elimination rate constant 0.05 /h. *C* = absorption rate constant 0.4/h, elimination rate constant 0.1/h.**

Half-life ($t_{½}$)

- The half-life is the time necessary for the concentration of drug in the plasma to decrease by half.
- Both t ½ and K_e attempt to express the same idea: how quickly a drug is removed, and therefore, **how often** a dose has to be administered.
- An important relationship between $t_{½}$ and K_e can be shown as:

$$t_{½} = 0.693 / K_e$$

Relationship between K_e, V_d, and Cl

- K_e (and $t_{½}$) are dependent upon clearance and the volume of distribution (dependent variables)
- Cl and V depends only on physiological conditions: independent variables

- It is **invalid** to make any assumptions about the Vd or Cl of a drug based solely upon knowledge of its half-life.

$$K_e = Cl / V_d$$

AUC

The area under the plasma drug concentration-time curve (AUC) reflects the **actual body exposure to drug** after administration of a dose of the drug and is expressed in **mg.h/L**

- AUC depends on
    1. rate of elimination of the drug
    2. dose administered.

- The AUC is directly proportional to the dose when the drug follows linear kinetics.

$$AUC \propto dose$$

- The AUC is inversely proportional to the clearance of the drug

$$AUC \propto 1/Cl$$

- ↑clearance: ↓ time the drug spends in the systemic circulation, ↑ decline in the plasma drug concentration → body exposure to the drug and AUC ↓

Cl calculation using AUC

- Clearance = ratio of **the dose** (D) and **area under the serum concentration/time curve** (AUC)

  For IV administered drugs

  Cl = D/AUC.

  For extravascularly administered drugs

  Cl = (FD)/AUC

  F: bioavailability fraction.

  F must be included to compensate for drug that does not reach the systemic vascular system

V calculation using AUC

- Given that $K_{el} = Cl / V_d$

$$V = \frac{D}{K_e \times AUC}$$

K_e: elimination rate constant.

For doses administered extravascularly

$$V = \frac{F \times D}{K_e \times AUC}$$

Bioavailability

- ***The fraction of the administered dose that is delivered to the systemic circulation***

- Bioavailability can be defined the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action

- For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

Bioavailability calculation

$$F = AUC_{PO}/AUC_{IV}$$

AUC_{po}: area under the curve after oral administration

$AUC_{i.v}$: AUC after intravenous administration

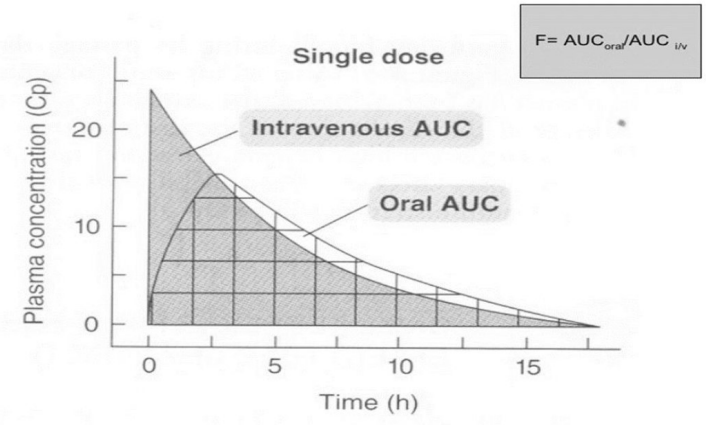
- Given that same does was given by both routs

Bioavailability calculation

$$F = AUC_{PO}/AUC_{IV}$$

- If it is not possible to administer the same dose intravenously and extravascularly due to poor absorption or presystemic metabolism resulting in serum concentrations that are too low to measure → the bioavailability calculation can be corrected to allow for different size doses for the different routes of administration.

$$F = (AUC_{PO}/AUC_{IV})(D_{IV}/D_{PO})$$



Bioequivalence

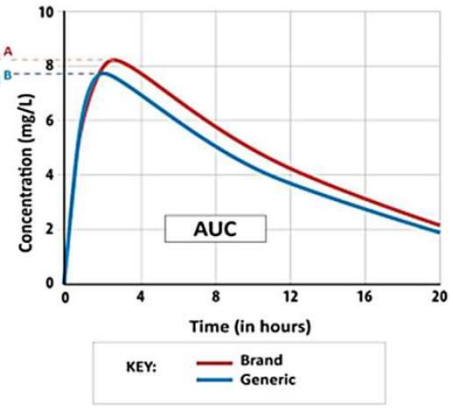
- According to The United States Food and Drug Administration (FDA), bioequivalence is defined as the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

Bioequivalence

- The ratio of the area under the serum concentration-time curves for the generic (AUC generic) and brand name (AUC) drug dosage forms is known as the **relative bioavailability ($F_{relative}$)** since the reference AUC is derived from the brand name drug dosage form

$$F_{relative} = AUC_{generic}/AUC_{brand}$$

Figure 1: Simulation of a Drug Concentration Versus Time Curve for Two Drug Products



C_{max} maximum plasma drug concentration;
AUC total area under the plasma drug concentration-time curve

Table 5-1 COMMON UNITS IN PHARMACOKINETICS

Pharmacokinetic Parameter	Abbreviation	Fundamental Units	Units Example
Area under the curve	AUC	Concentration × time	μg × hr/mL
Total body clearance	Cl_T	Volume/time	L/hr
Renal clearance	Cl_R	Volume/time	L/hr
Hepatic clearance	Cl_H	Volume/time	L/hr
Apparent volume of distribution	V_D	Volume	L
Volume of distribution at steady state	V_{ss}	Volume	L
Peak plasma drug concentration	C_{max}	Concentration	mg/L
Plasma drug concentration	C_p	Concentration	mg/L
Steady-state drug concentration	C_{ss} or C_{av}	Concentration	mg/L
Time for peak drug concentration	T_{max}	Time	hr
Dose	D_0	Mass	mg
Loading dose	D_L	Mass	mg
Maintenance dose	D_M	Mass	mg
Amount of drug in the body	D_B	Mass	mg
Rate of drug infusion	R	Mass/time	mg/hr
First-order rate constant for drug absorption	k_A	1/time	1/hr or hr^{-1}
Zero-order rate constant for drug absorption	k_0	Mass/time	mg/hr
First-order rate constant for drug elimination	k (sometimes referred to as kel)	1/time	1/hr or hr^{-1}
Elimination half-life	$t_{½}$	Time	hr
Fraction of drug absorbed	F	(no units)	Ranges from 0 to 1 (0%–100%)