GEORGIA CAMPUS PCOM

PHAR 227G Pharmacokinetics:

Pharmacokinetic models

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Outlines

Pharmacokinetic models

One compartmental models

Two compartmental models

Noncompartmental models

AUC and moment analysis

Learning objectives

After completing this lecture, students should be able to:

1. Describe compartmental and physiological pharmacokinetic models.
2. Differentiate between compartmental and physiological pharmacokinetic models.
3. List assumptions made regarding one-compartment PK models.
4. Describe one-compartment models after IV bolus and oral administration and the mathematical models applied.
5. Describe how half-life affects the time for drug elimination.
6. Calculate loading dose for one-compartment model drugs.

Learning objectives

After completing this lecture, students should be able to:

7. Describe two-compartment models after IV bolus and oral administration and mathematical models applied.
8. Describe the potential issue with calculation of a loading dose in a two-compartment model.
9. Describe non-significant and significant two-compartment models.
10. List factors that may cause a one-compartment model drug to exhibit two-compartment kinetics.
11. Describe and diagram monoexpoential and biexponential kinetic models, and explain their differences.
12. Explain the rationale for PK model selection.

Learning objectives

After completing this lecture, students should be able to:

13. Describe the application of a noncompartmental analysis.
14. List kinetic parameters estimated by a noncompartmental analysis.
15. Describe the use of moment analysis to characterize drug kinetics.
16. Define AUC, AUMC, and MRT.
17. Determine how AUC, AUMC, and MRT are estimated from moment analysis.
18. Calculate PK parameters from noncompartmental data.

Pharmacokinetic models

Pharmacokinetic models

Model

Why do modeling?

--- “Modeling is a fundamental procedure underlying scientific knowledge. The entire breadth and depth of human understanding of our perceived world is based on models.” – Westwick DT and Kearney RE (1994)

Goals of modeling:

--- Codify current facts
--- Testing competing hypotheses
--- Predicting system response under new conditions
--- Estimating inaccessible system variables

Pharmacokinetic models

Pharmacokinetic models

--- Predict plasma, tissue, and urine drug levels with any dosage regimen

--- Calculate the optimum dosage regimen for each patient individually

--- Estimate the possible accumulation of drugs and/or metabolites

--- Correlate drug concentrations with pharmacologic or toxicologic activity

--- Evaluate differences in the rate or extent of availability between formulations (bioequivalence)

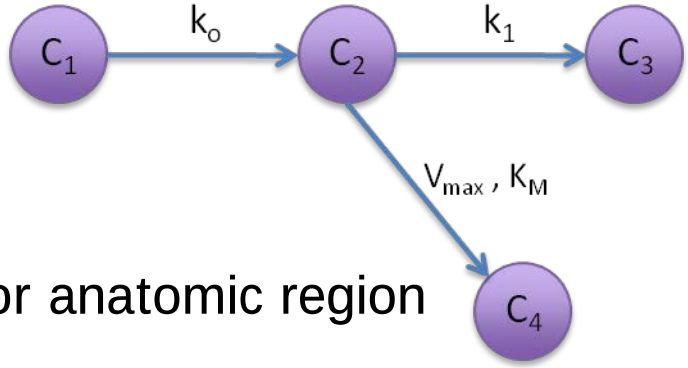
--- Describe how changes in physiology or disease affect the absorption, distribution, or elimination of the drug

--- Explain drug-drug interactions

Pharmacokinetic models

Pharmacokinetic models: Compartmental models

Concept of compartment:



--- an imaginary space, **NOT** a real physiologic or anatomic region

--- a tissue or group of tissues that have similar blood flow and drug affinity

example: central compartment (blood, heart, liver, kidney)

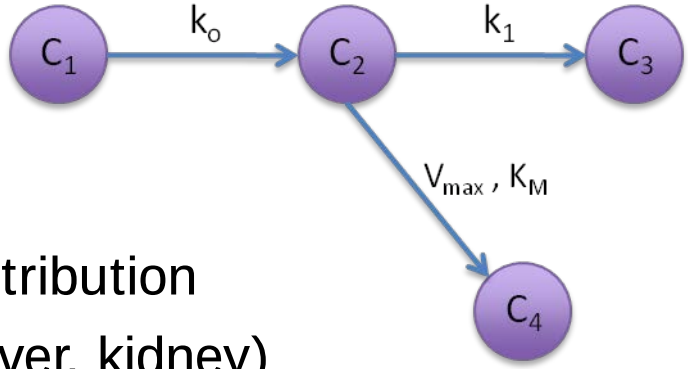
--- "well stirred", drug concentration = average concentration

--- within one compartment, rate constants represent overall rate processes

Pharmacokinetic models

Pharmacokinetic models: Compartmental models

Multiple compartments:



--- pharmacokinetically distinct components

--- central compartment: instantaneous drug distribution
highly perfused (system circulation, heart, liver, kidney)

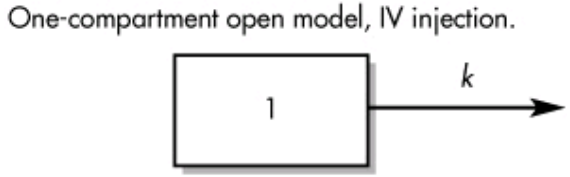
--- Peripheral or tissue compartment: Slow drug distribution
less perfused (other tissues and organs)

--- deep tissue compartment: slower drug distribution
Poorly perfused (adipose tissue, bone)

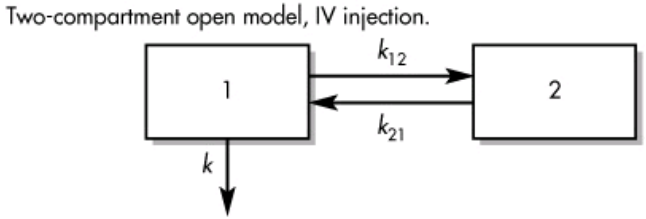
Pharmacokinetic models

Pharmacokinetic models: Compartmental models

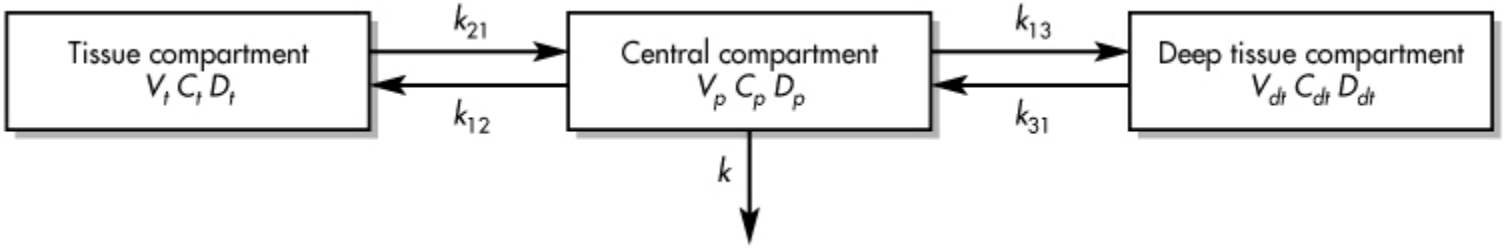
--- One-compartment model



--- Two-compartment models



--- Multi-compartment models



Pharmacokinetic models

Pharmacokinetic models: Compartmental models

--- Provide an understanding of drug distribution throughout the body (between the blood and other tissues or organs in the body)

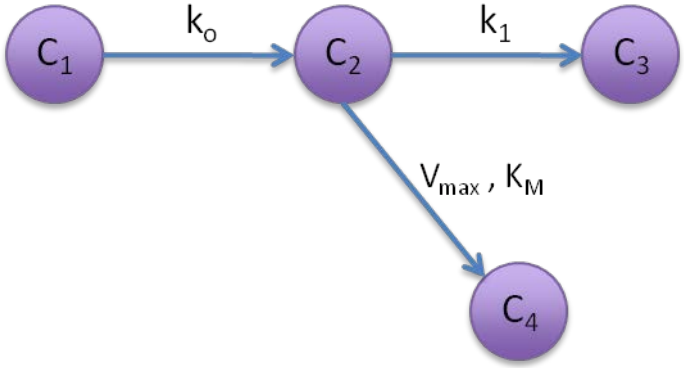
--- A visual representation of the rate processes

--- Estimate pharmacokinetic parameters (rate constants, clearance, and V_d)

Computer programs:

--- WinNonlin, WinNonMix (Pharsight)

--- NONMEM



Pharmacokinetic models

Pharmacokinetic models: Physiologic pharmacokinetic models

--- Use real anatomic and physiologic data to describe drug movement and disposition in the body.

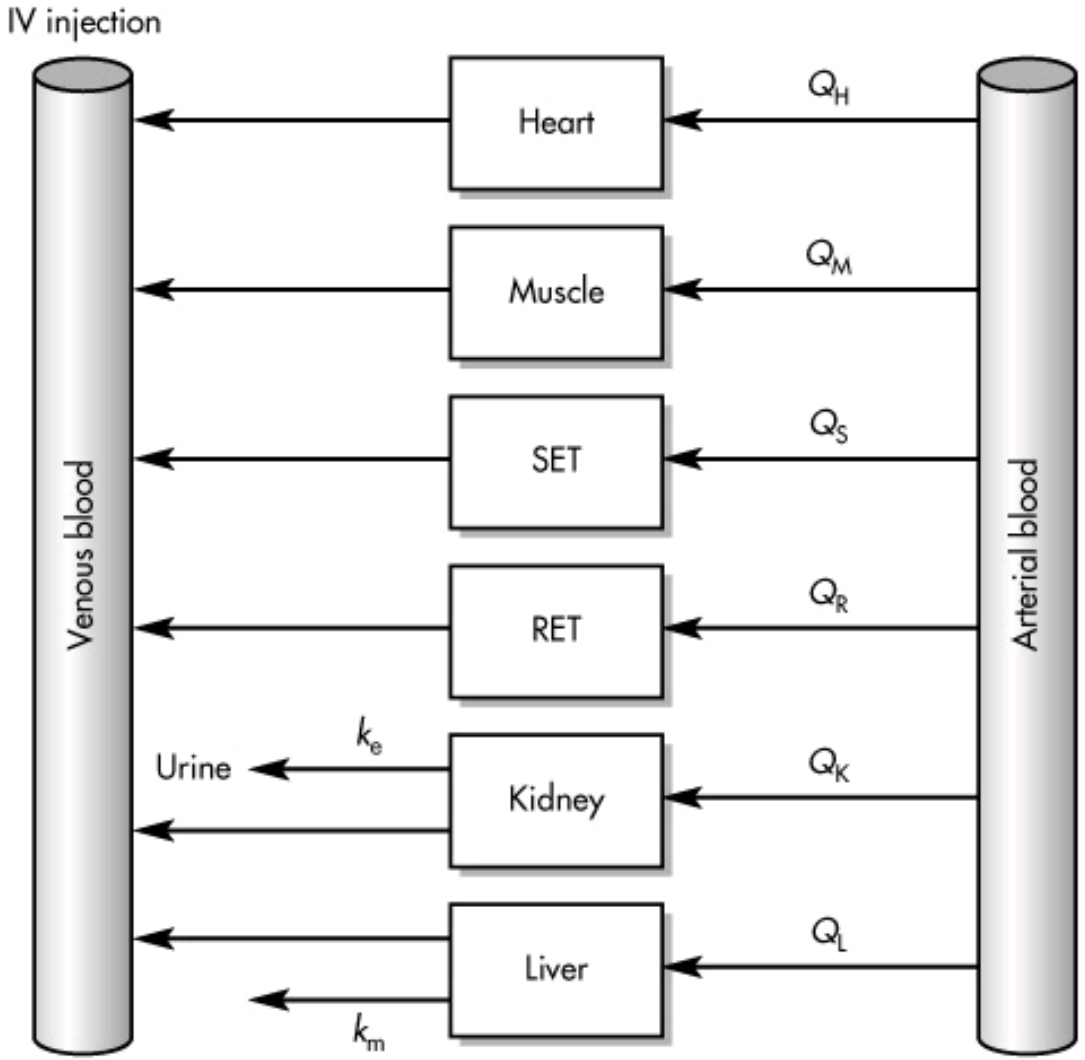
--- Flow (not membrane) limited drug distribution.

--- Predict realistic tissue drug concentrations.

--- Limitation: It's experimentally difficult to obtain the information required to adequately describe a physiological pharmacokinetic model.

Pharmacokinetic models

Pharmacokinetic models: Physiologic pharmacokinetic models



Pharmacokinetic models

Pharmacokinetic models: Physiologic pharmacokinetic models

--- Provides better insight into how physiologic factors may change drug distribution from one animal species to another.

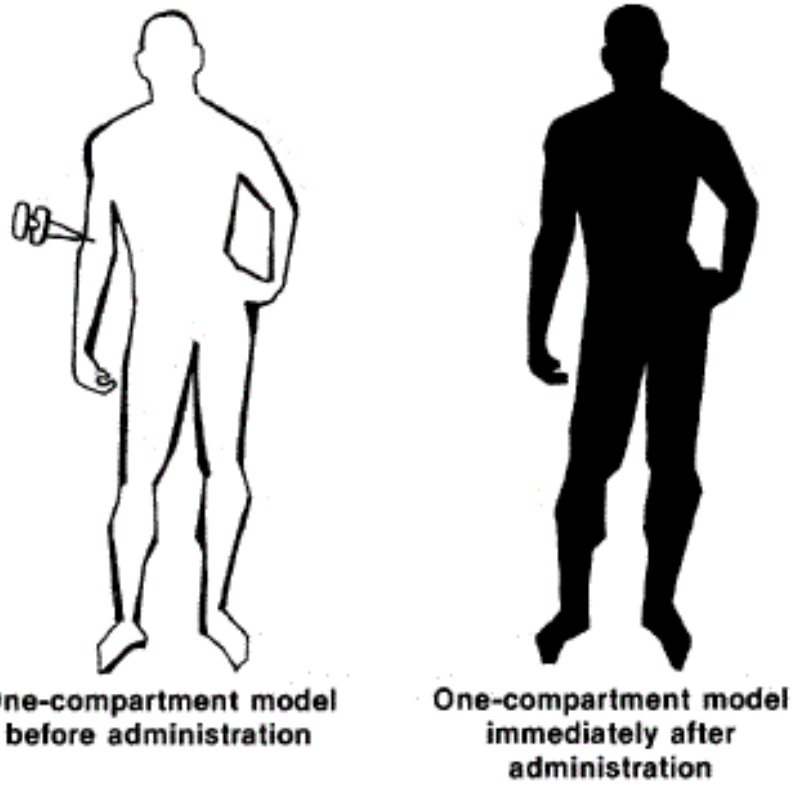
--- No data fitting is required in the perfusion model.

--- Consider the effect of variation in blood flow, tissue size, and the drug tissue-blood ratios due to certain pathophysiologic conditions.

--- Apply to several species and predict human pharmacokinetics from animal data.

Drugs described using perfusion models: Lidocaine, digoxin, thiopental

One-compartmental model

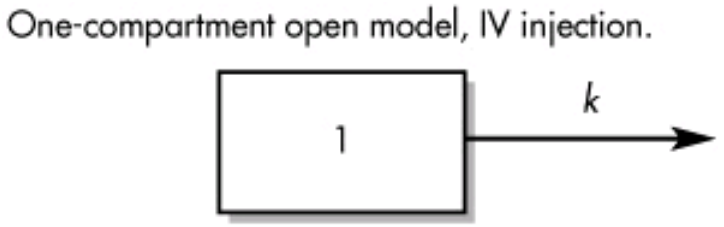


One-compartment model before administration

One-compartment model immediately after administration

One-compartmental model

Introduction:



--- Simplest compartment model.

--- Entire body viewed as a single kinetically homogeneous compartment.
(volume of distribution)

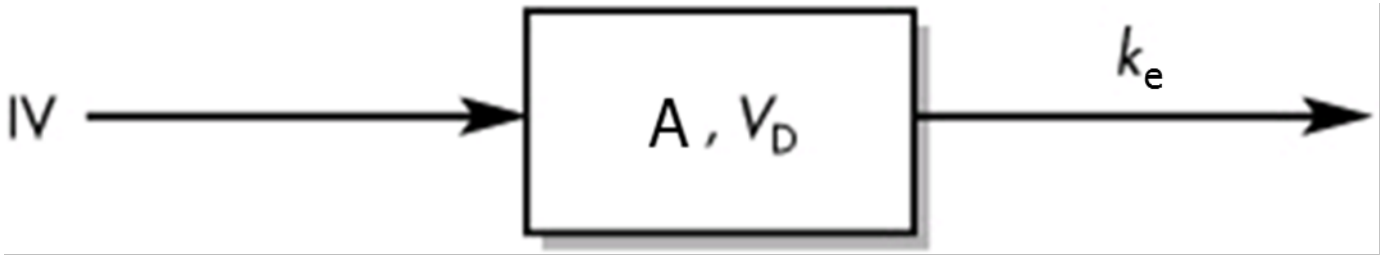
--- Drug distribution:
instantaneously and homogenously within the compartment.

--- Drug elimination:
immediately after drug enters the compartment;
first-order pharmacokinetics.

One-compartmental model

IV bolus one-compartment open model:

--- Simplest route of drug administration: a rapid intravenous injection



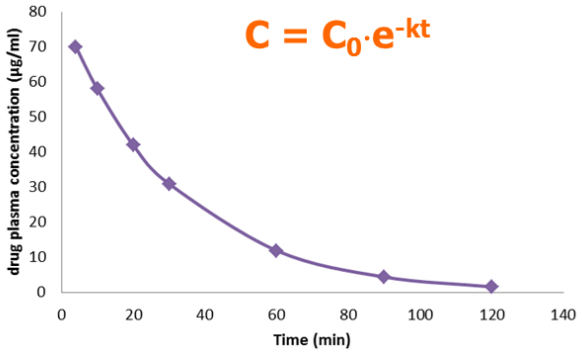
A single compartment representing the entire body

One-compartment model before administration

One-compartment model immediately after administration

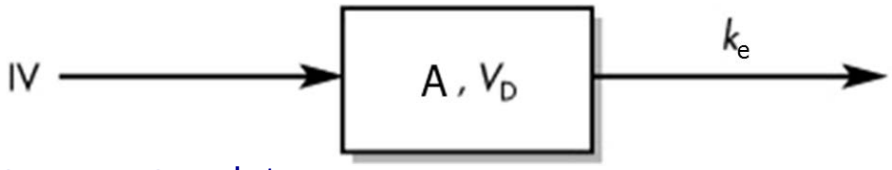
$$A_{(t)} = C_{(t)} \cdot V_d$$

$$C_{(t)} = C_0 \cdot e^{-k_e t}$$



One-compartmental model

IV bolus one-compartment open model:



$C_{(t)} = C_0 e^{-k_e t}$

Linear transformation:

$\ln C_{(t)} = \ln C_0 - k_e t$

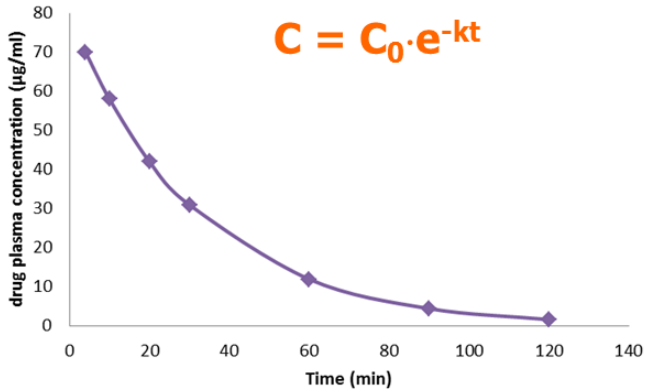
or $\log C_{(t)} = \log C_0 - k_e t/2.303$

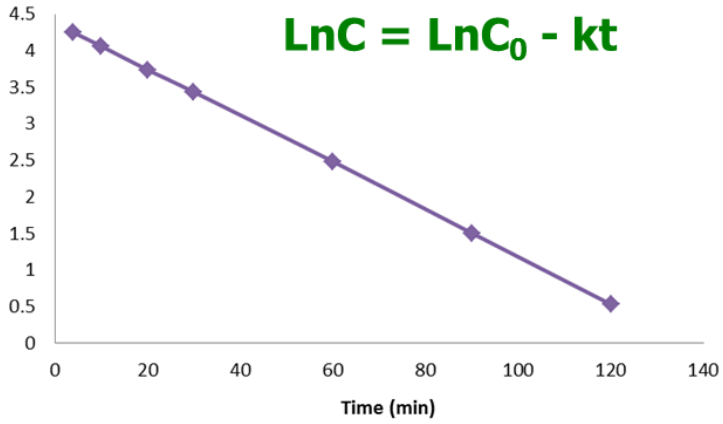
C_0: Drug plasma concentration at t = 0

$C_{(t)}$: Drug plasma concentration at time t

k_e: First-order drug elimination constant

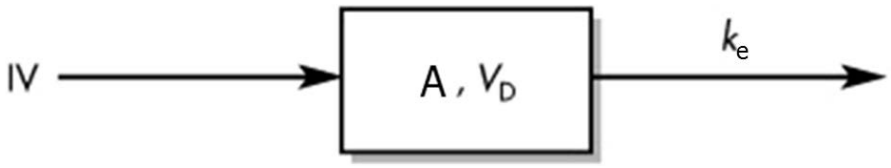
unit: $time^{-1}$





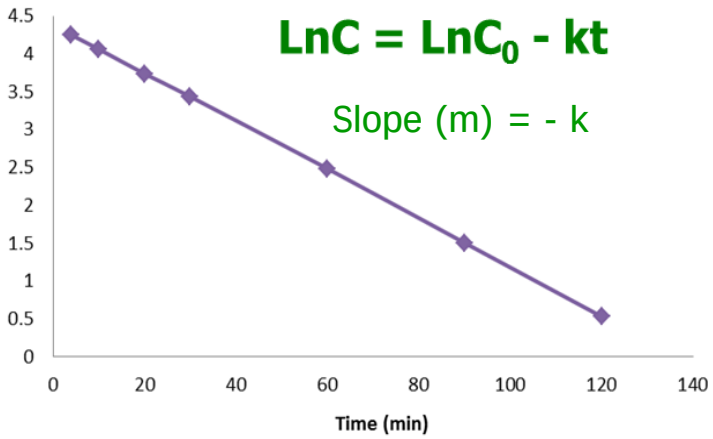
One-compartmental model

IV bolus one-compartment open model : k_e and $t_{1/2}$



$$\ln C = \ln C_0 - k_e t$$

$$k_e = (\ln C_1 - \ln C_2) / (t_2 - t_1)$$
$$= \ln(C_1 / C_2) / \Delta t$$
$$t_{1/2} = 0.693 / k_e$$



C_0: Drug plasma concentration at t = 0

C_1: Drug plasma concentration at time t_1

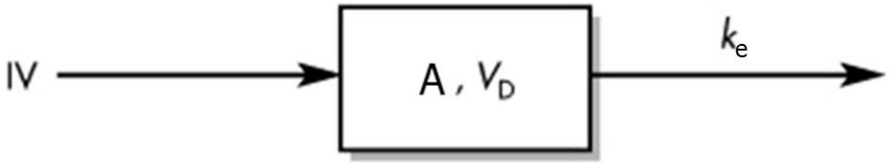
C_2: Drug plasma concentration at time t_2

k_e: First-order drug elimination constant (unit: $time^{-1}$)

$t_{1/2}$: Drug elimination half-life

One-compartmental model

IV bolus one-compartment open model: k_e and $t_{1/2}$

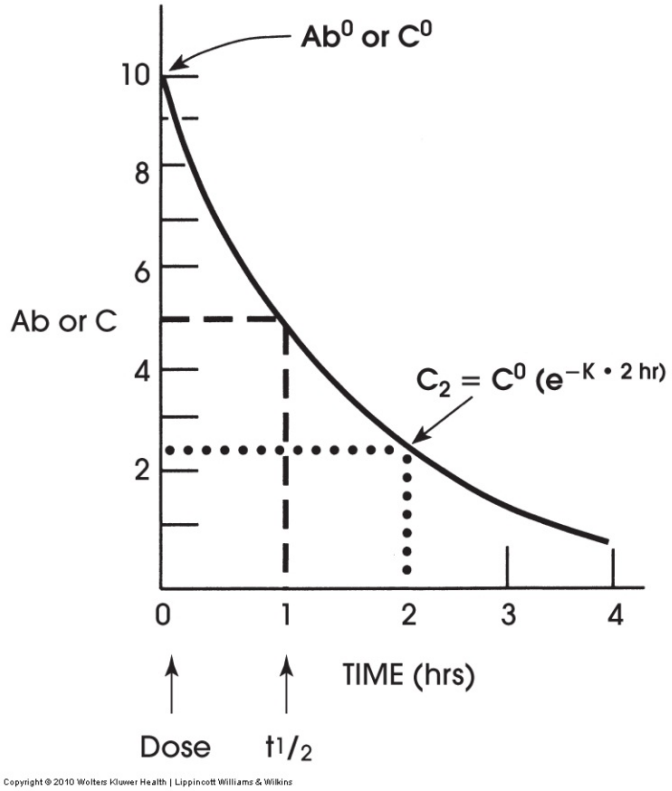


Drug elimination half-life: $t_{1/2} = 0.693 / k_e$

--- The half-life is the same for all drug concentrations.

--- If k_e is provided, $t_{1/2}$ is given and vice versa.

--- $t_{1/2}$ can be determined by visual inspection.



One-compartmental model

IV bolus one-compartment open model: **Vd** and **CL**

Apparent volume of distribution (V_d):

--- Volume of distribution extrapolated: $\mathbf{Vd_{extrap} = D_0 / C_0}$

--- Volume of distribution by area: $\mathbf{Vd_{area}}$ **or** $\mathbf{Vd_\beta = D_0 / (k_e \cdot [AUC]_0^\infty)}$

Systemic clearance (CL):

--- $\mathbf{CL = k_e \cdot Vd}$ **or** $\mathbf{CL = \dfrac{D_0}{[AUC]_0^\infty}}$

Note:

in one-compartment model, AUC can be estimated using the following equation.

$$\mathbf{[AUC]_0^\infty = C_0 / k_e}$$

One-compartmental model

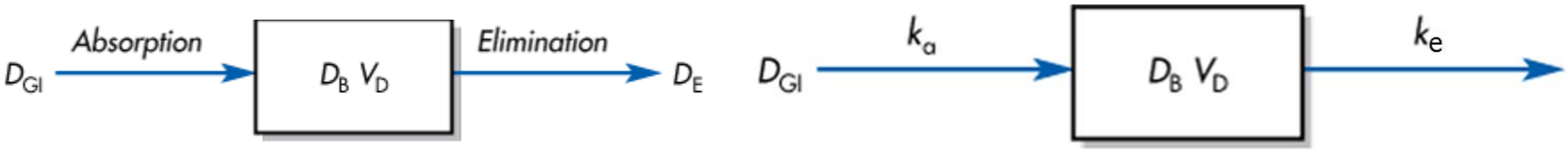
One-compartment open model : Intravenous bolus

1) A.J. is a 62 kg patient who is administered a single intravenous bolus dose of 1250 mg of Drug A. What is the peak concentration (C_0)? How long does it take after the bolus is administered for the plasma level to reach 7 mg/L? Given that V_d = 1.9 L/Kg and $t_{1/2}$ = 3.0 hour for Drug A.

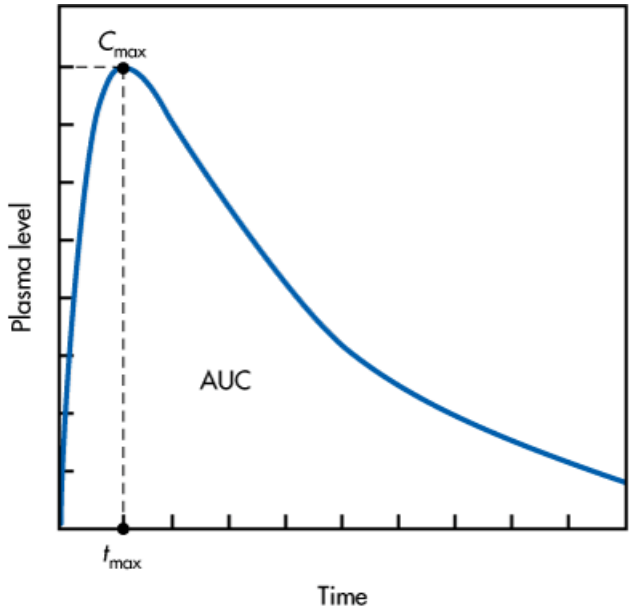
2) B.T. is an 81 kg patient administered Drug B as a single intravenous bolus. What is the dose required to reach a peak concentration (C_0) of 14 mcg/ml? What is the plasma concentration at a target time of 7 hours? Given that V_d = 0.50 L/Kg and $t_{1/2}$ = 8.0 hour for Drug B.

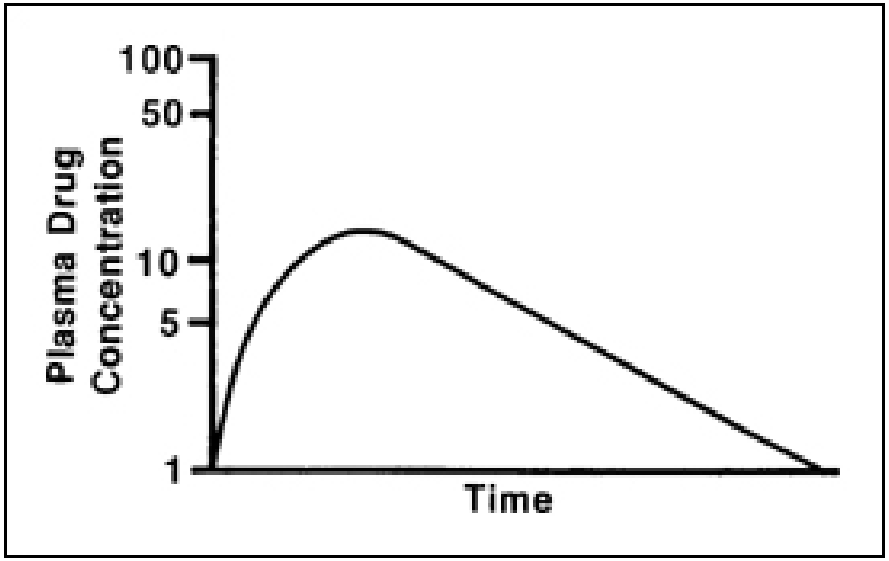
One-compartmental model

One-compartment open model: Oral administration



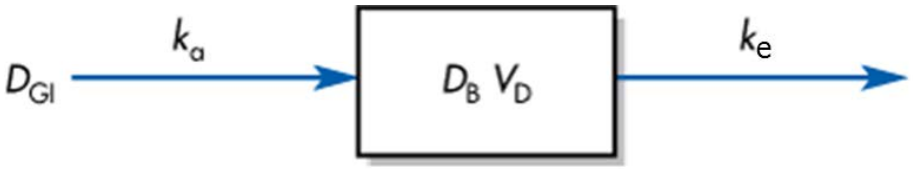
One-compartment pharmacokinetic model for first-order drug absorption and first-order elimination.



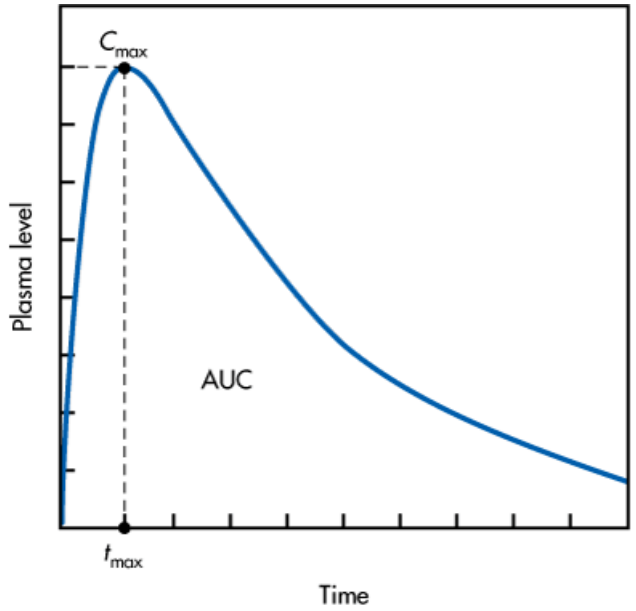


One-compartmental model

One-compartment open model: Oral administration



One-compartment pharmacokinetic model for first-order drug absorption and first-order elimination.



$$C_p = \frac{S \cdot F \cdot Dose \cdot k_a}{V_d \cdot (k_a - k_e)} \times (e^{-k_e \cdot t} - e^{-k_a \cdot t})$$

$$t_{max} = \frac{\ln (k_a/k_e)}{(k_a - k_e)}$$

C_p: Drug plasma concentration at time t

k_a: First-order absorption rate constant

k_e: First-order drug elimination constant

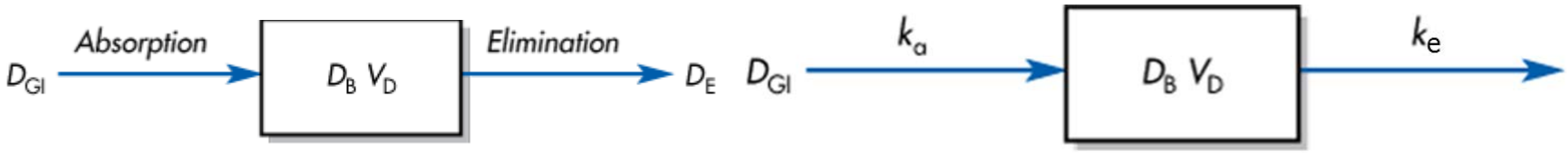
S: Salt factor

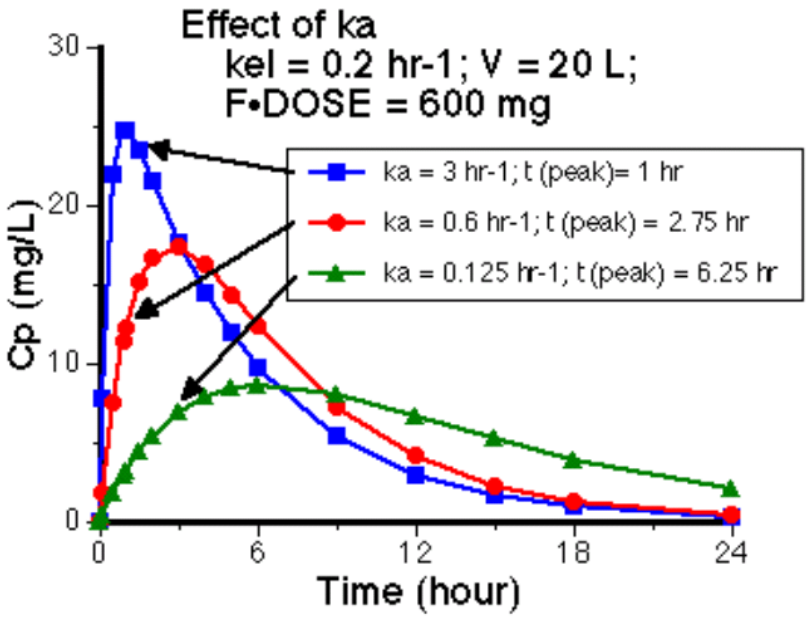
F: Bioavailability

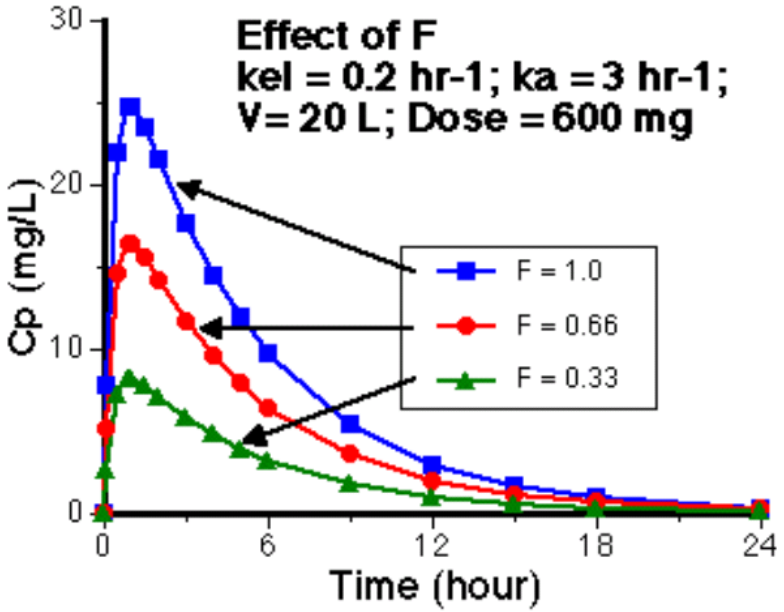
t_{max}: Time to reach peak drug concentration C_{max}

One-compartmental model

One-compartment open model: Oral administration





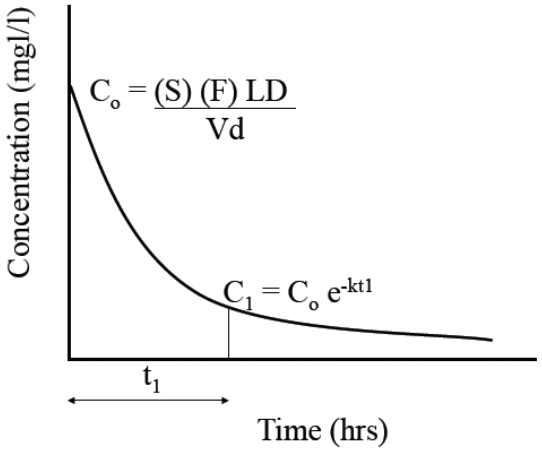


One-compartmental model

One-compartment open model : Loading Dose

Loading Dose (LD) = $V_d(C)/(S)(F)$

$C = LD(S)(F)/V_d$



C: desired plasma concentration of drug

V_d: apparent volume of distribution

S: salt factor of a drug

F: bioavailability

(S)(F): the fraction of the dose administered reaching systemic circulation

Incremental Loading Dose = $V_d(C_{desired} - C_{initial})/(S)(F)$

One-compartmental model

One-compartment open model : Loading Dose

1) Calculate an oral loading dose of drug X (i.e. using Drug X tablets) for a 70 kg man that will produce a plasma concentration of 1.5 μg/L immediately after administration. Assume that S = 1 and F = 0.7. V_d for Drug X is 7.3 L/kg.

2) If this patient had a drug X concentration of 0.5 μg/L after therapeutic drug monitoring and the desired therapeutic concentration of drug X is 1.5 μg/L, calculate the incremental loading dose to achieve the desired concentration.

Two-compartmental models

Two-compartment model before administration

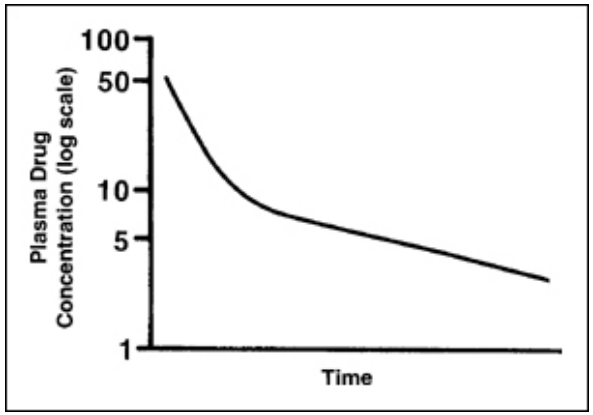
Two-compartment model immediately after administration

Two-compartment model after distributive equilibrium

Two-compartmental model

Introduction:

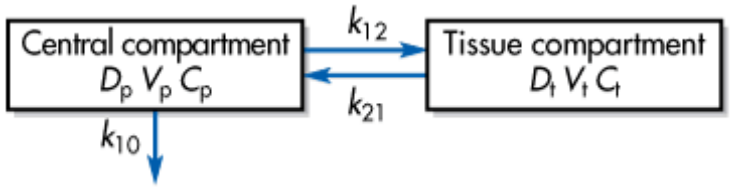
--- Distinct drug distribution process.



--- Nonlinear drug disposition.

--- Biphasic drug concentration decline.

--- Central (plasma) compartment:
blood and highly blood perfused tissue.



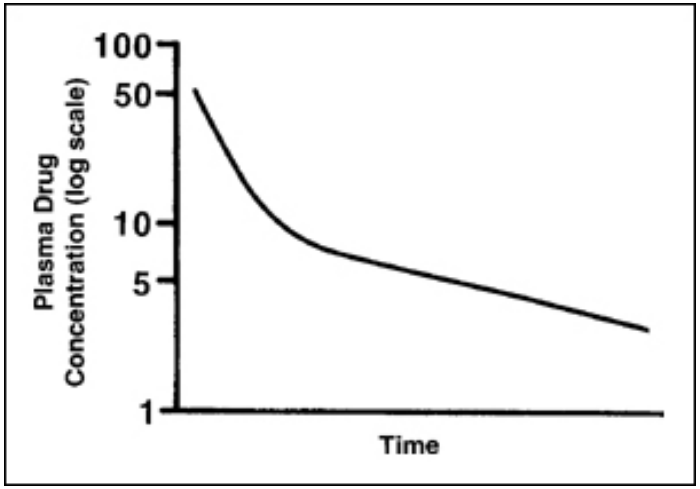
--- Peripheral (tissue) compartment:
lower blood perfusions and different affinity to the drug.

--- Assumption: first-order drug transfer rate processes.

Two-compartmental model

Introduction:

Factors resulting in nonlinear drug disposition:



--- Blood flow to the tissue.

--- Permeability of the drug into the tissues.

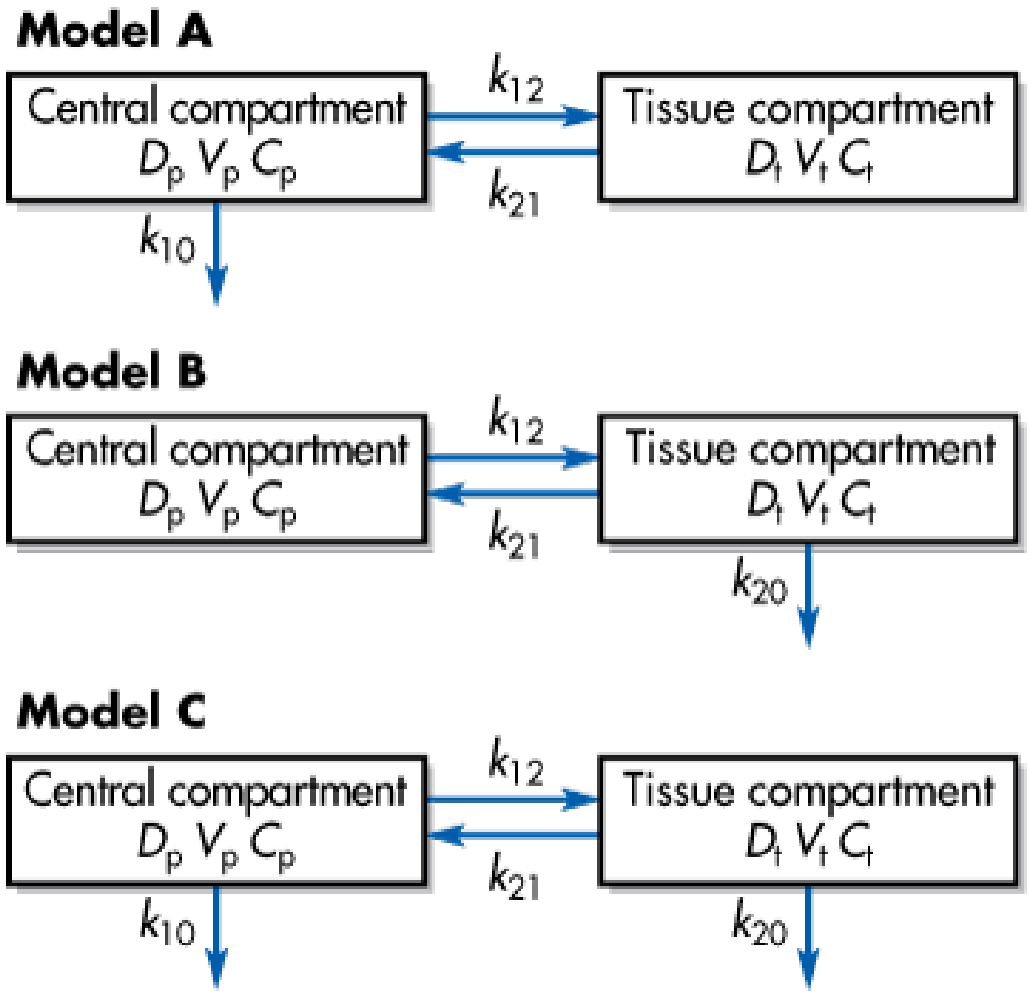
--- Capacity of the tissues to accumulate drug.

--- Effect of disease factors:

Impaired cardiac, renal, and hepatic functions.

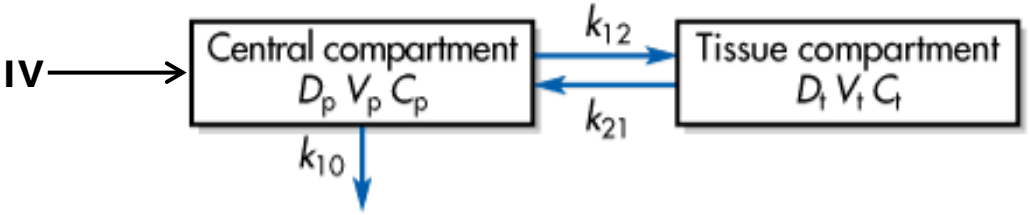
Two-compartmental model

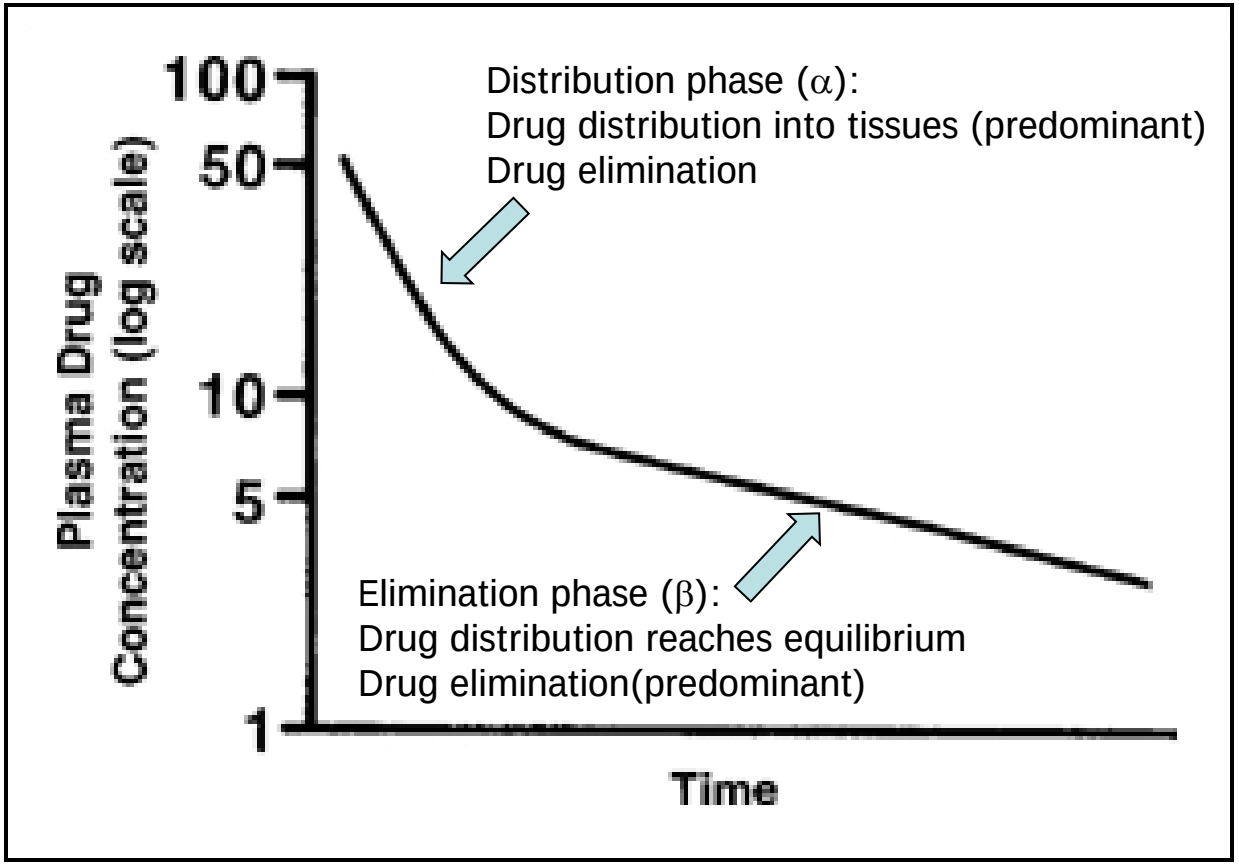
Introduction:

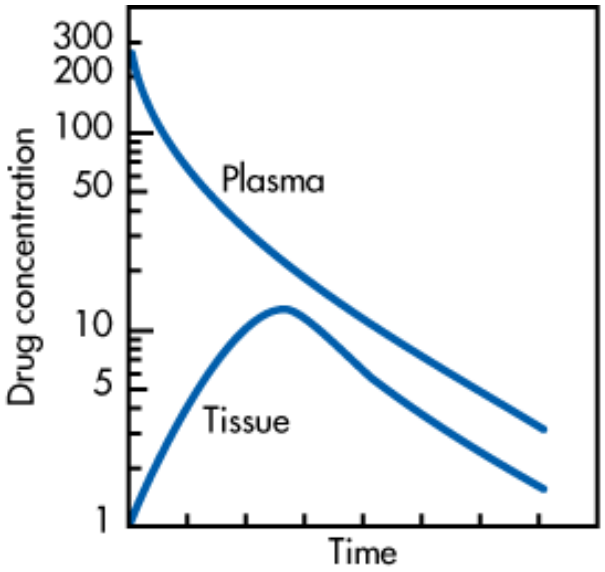


Two-compartmental model

IV bolus two-compartment open model:

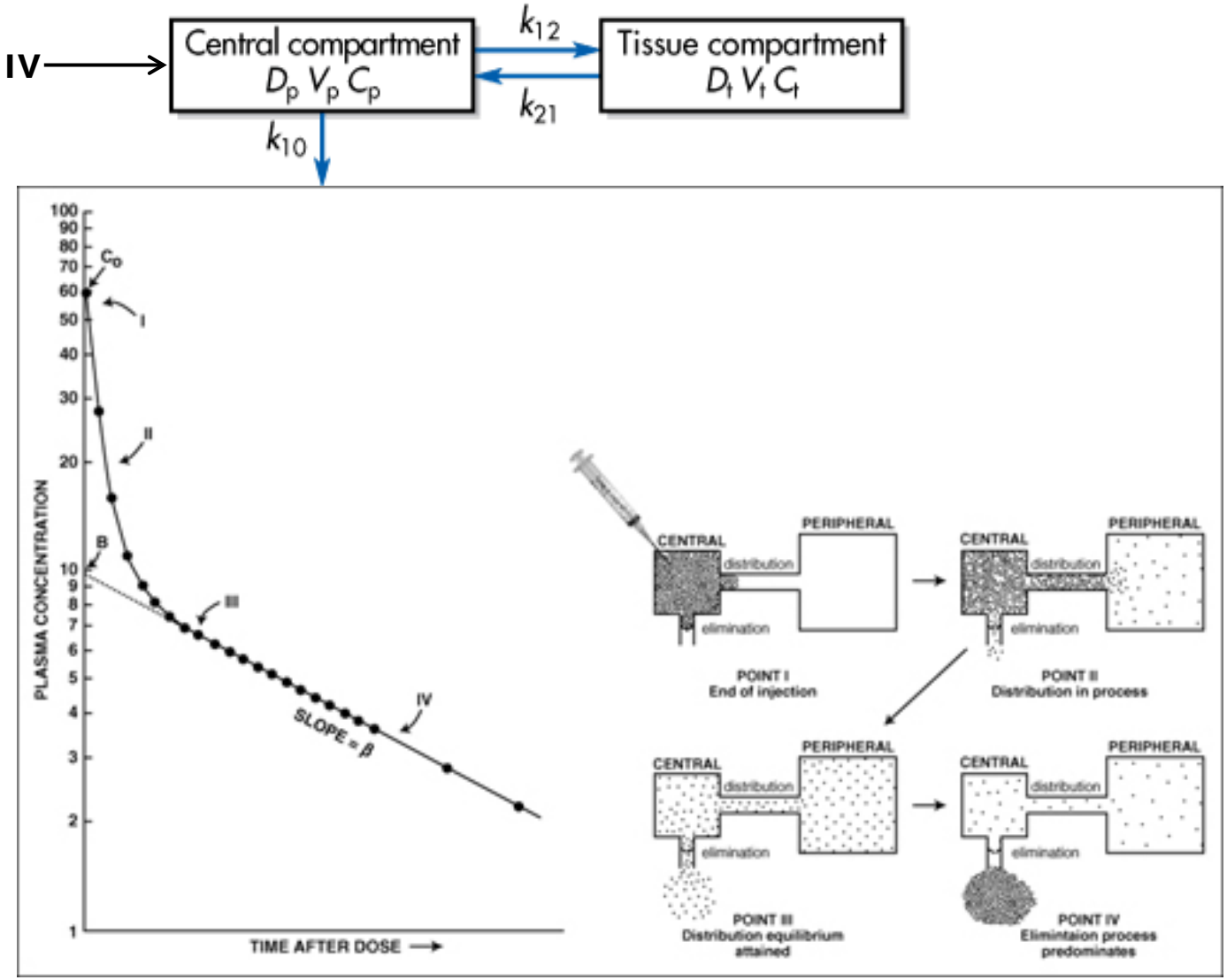






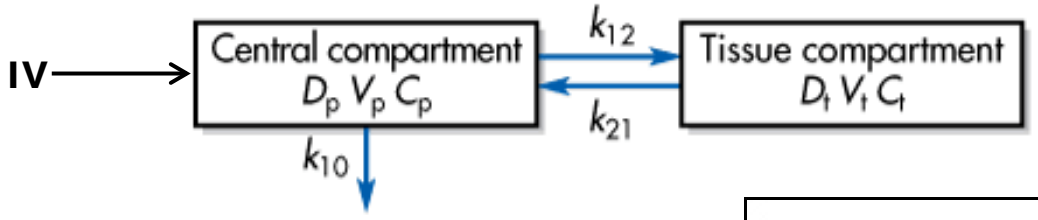
Two-compartmental model

IV bolus two-compartment open model:



Two-compartmental model

IV bolus two-compartment open model:



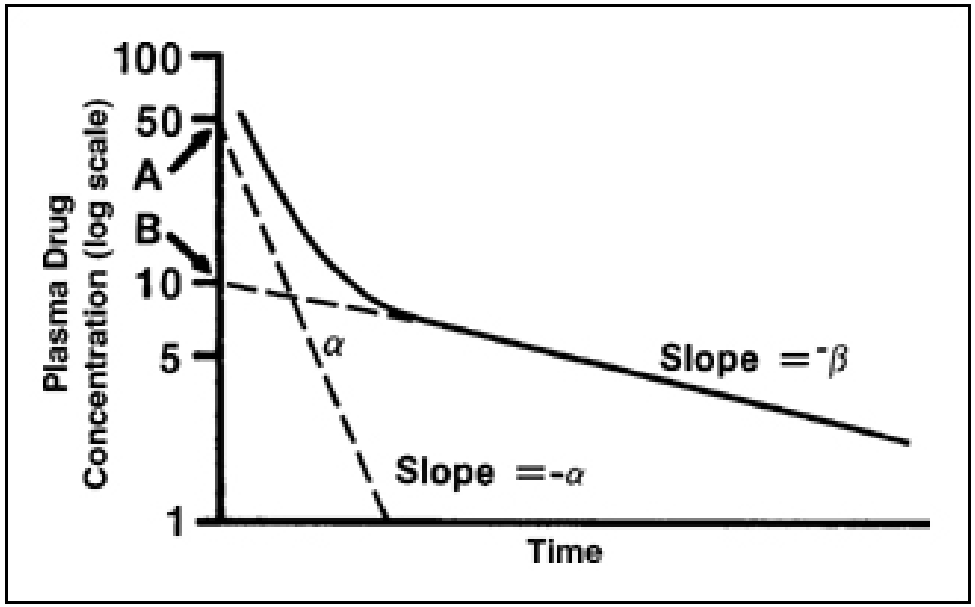
$$C_{(t)} = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}$$

α: distribution rate constant

β: elimination rate constant

A: hybrid constant

B: hybrid constant

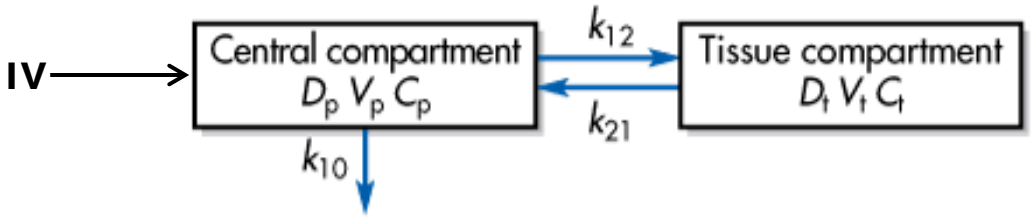


Distribution phase: initial fast decline of C_p with relatively large α

Elimination phase: slower decrease of C_p with relatively small β

Two-compartmental model

IV bolus two-compartment open model:

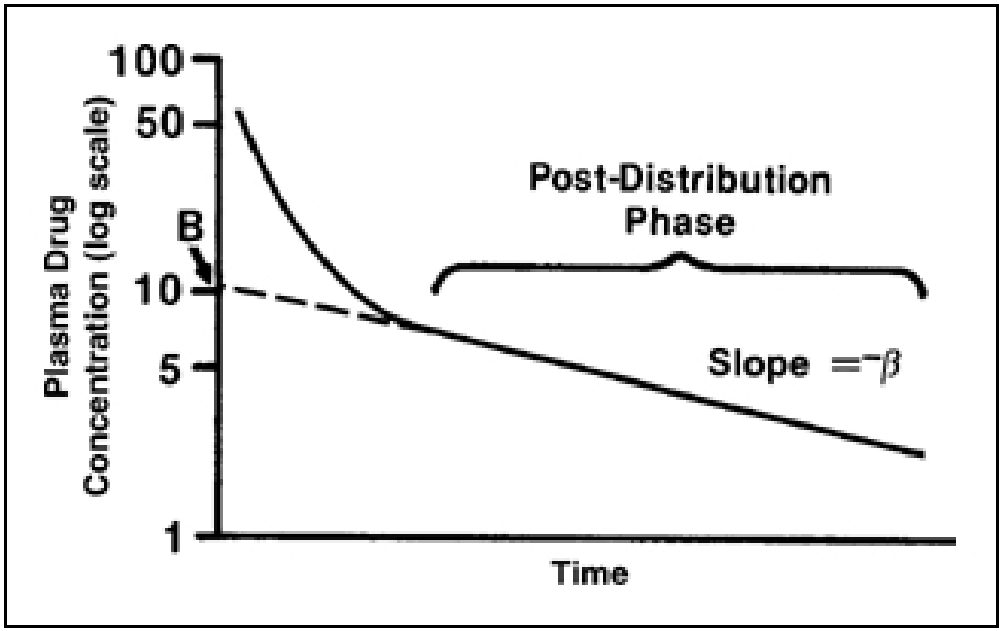


$$C_{(t)} = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}$$

Back-extrapolation: β and B.

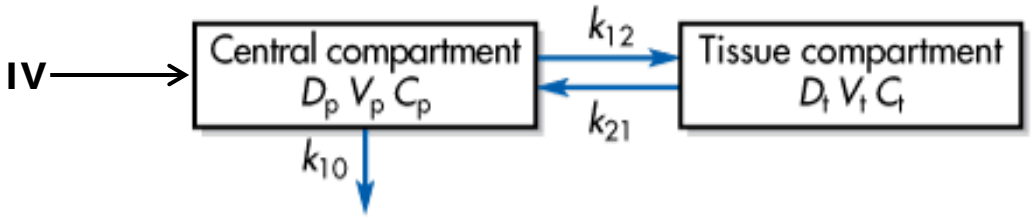
Elimination half-life:

$t_{1/2} = 0.693 / \beta$.



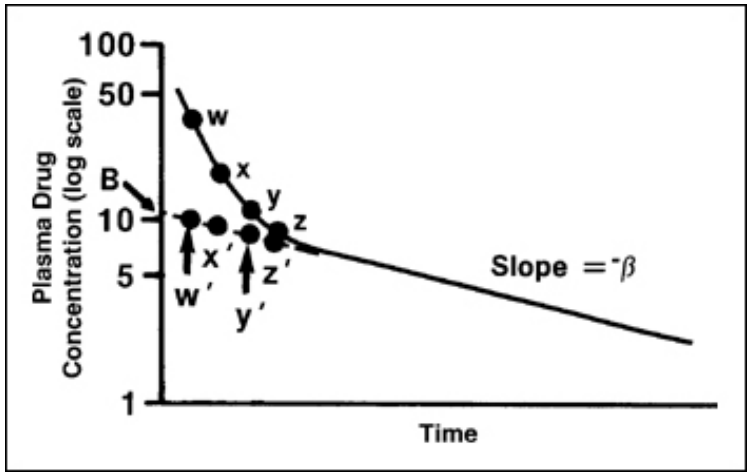
Two-compartmental model

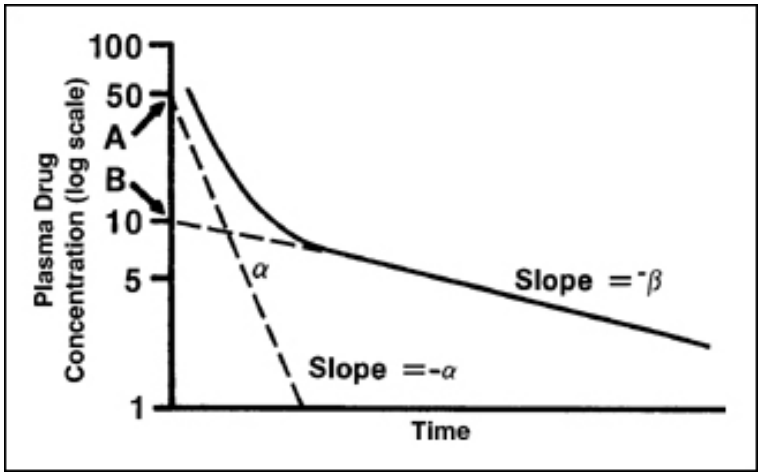
IV bolus two-compartment open model:



$$C_{(t)} = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}$$

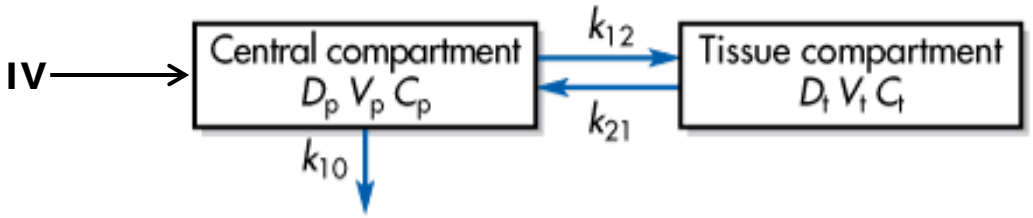
Method of residual: α and A. Distribution half-life: $t_{1/2} = 0.693 / \alpha$.





Two-compartmental model

IV bolus two-compartment open model:



$$C_{(t)} = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}$$

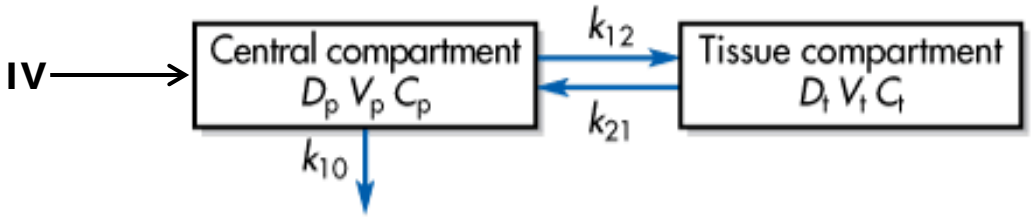
Determination of PK parameters:

K_{10}, k_{12}, k_{21} can be obtained from A, B, α, and β.

$$K_{10} = \frac{\alpha\beta\,(A + B)}{A\beta + B\alpha} \qquad k_{12} = \frac{AB\,(\beta - \alpha)^2}{(A + B)(A\beta + B\alpha)} \qquad k_{21} = \frac{A\beta + B\alpha}{A + B}$$

Two-compartmental model

IV bolus two-compartment open model:



$$C_{(t)} = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}$$

Volume of distribution:

--- Volume of central compartment (V_p or V_c):

$$V_c = \frac{dose}{A+B} = \frac{dose}{C_0}$$

--- Volume of distribution at steady state (V_{ss}):

$$V_{ss} = V_c + \frac{K_{12}}{K_{21}} V_c$$

--- Volume of distribution by area (V_{area} or V_β):

$$V_{area} = V_\beta = \frac{dose}{\beta \times AUC} = \frac{Cl}{\beta}$$

--- Volume of tissue compartment (V_t):

$$V_t = V_c \times k_{12} / k_{21}$$

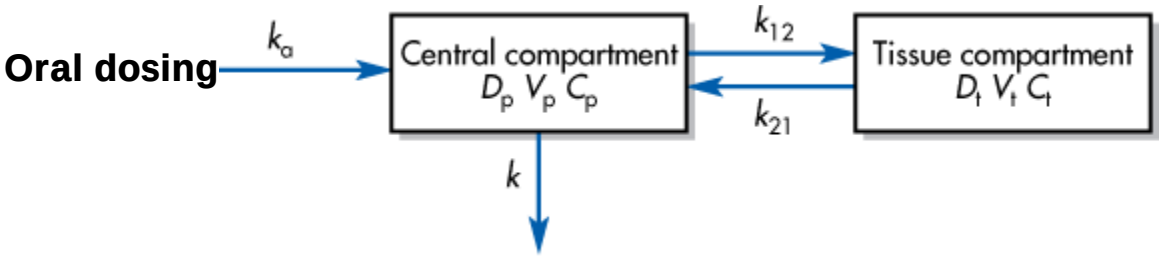
Clearance: $CL = V_\beta \cdot \beta$ **or** $CL = \frac{D_0}{[AUC]_0^\infty}$

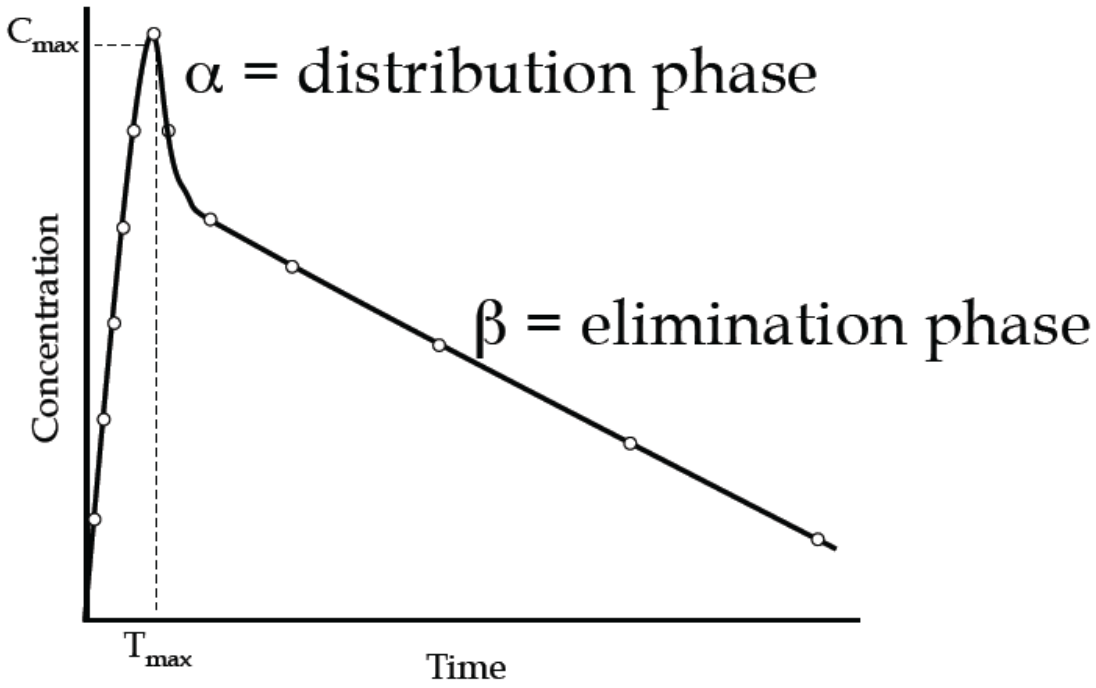
Note: $V_\beta > V_{ss} > V_c$

AUC: $[AUC]_0^\infty = A/\alpha + B/\beta$

Two-compartmental model

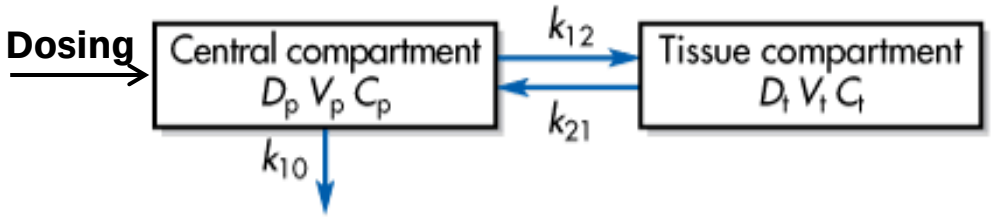
Two-compartment open model: oral administration





Two-compartmental model

Two-compartment open model: summary



--- There's a distribution time for drugs fitting two compartment model.

--- Those drugs enter central compartment first.

--- During the distribution time, some drug is eliminated from the central compartment (e.g., liver and kidney), and some drug equilibrates with the peripheral compartment.

--- Drugs have to go through central compartment in order to be eliminated or to be distribute to the tissue compartment.

Two-compartmental model

Two-compartment open model: loading dose

Potential issues:

--- A loading dose of a drug calculated based on the total V_d (V_c + V_t) may result in a toxic level of the drug.

Solution to minimize this issue:

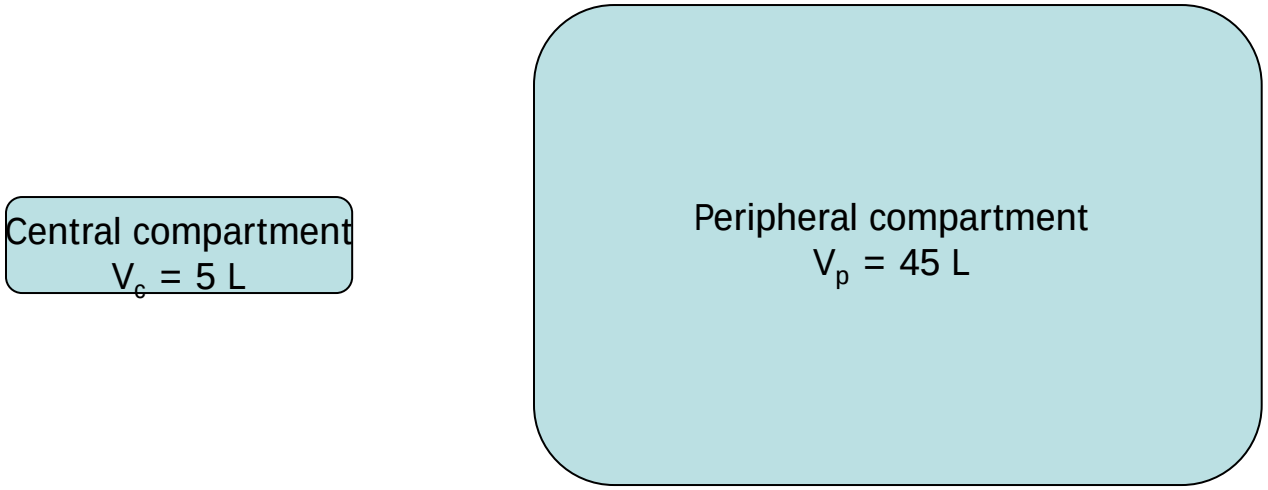
--- Calculate the loading dose based on the volume of central compartment only.

--- Calculate the loading dose based on the total V_d first, but administer the loading dose at a rate slow enough to allow for drug to transfer into tissue compartment.

--- Administer the loading dose in sufficiently small individual bolus doses.

Two-compartmental model

Two-compartment open model: loading dose



Total volume of distribution

V_d = 50 L

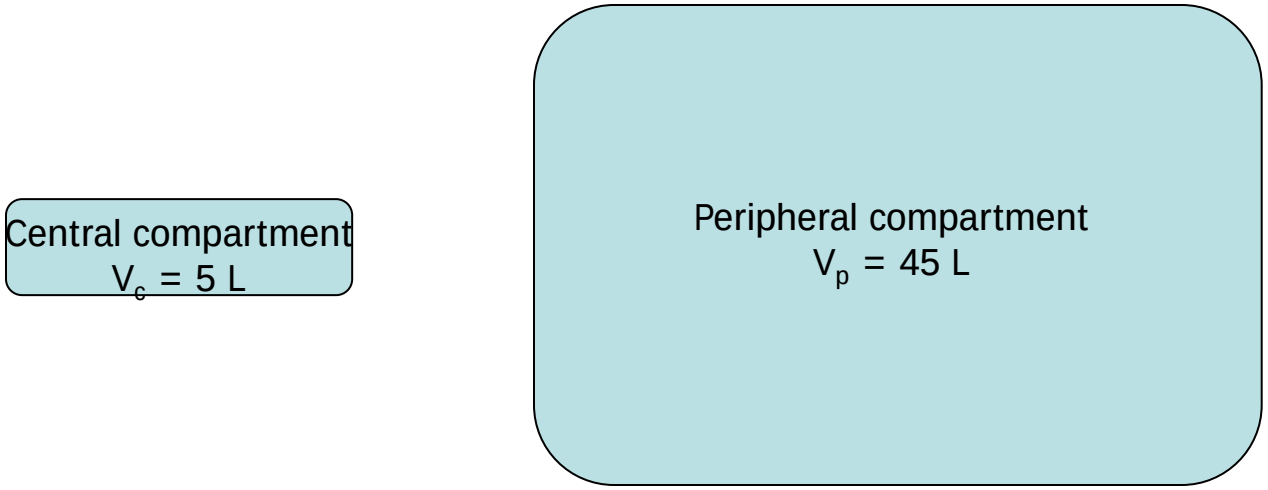
Two-compartmental model

Two-compartment open model: loading dose

A drug with a loading dose of 1000 mg is given as an iv bolus injection.

Expected C = 1000 mg / 50 L = 20 mg/L

Actual C = 1000 mg / 5 L = 200 mg/L

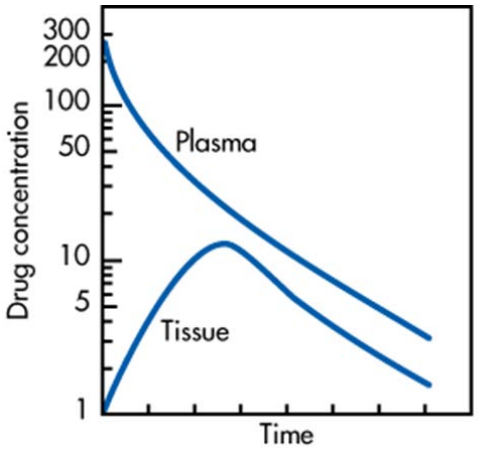


Total volume of distribution

V_d = 50 L

Two-compartmental model

Two-compartment open model: drug examples



Potassium (K):

--- It follows two compartmental models with target organ in central compartment.

--- Cardiac effects of K correlate with its plasma concentration.

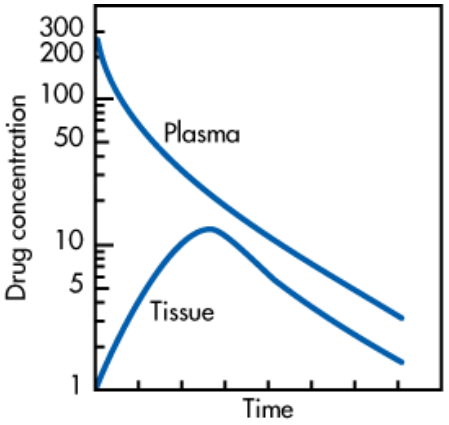
--- Slow distribution of K from plasma to tissue compartment results in slow equilibrium between plasma and tissue concentration of K.

--- If K is administered intravenously too fast, the plasma concentration of K will rise too quickly to a excessive level causing cardiac arrest because distribution of K into tissue has not occur yet.

--- Solution: Infuse K slowly to allow distribution of K into tissues, which prevents a large peak concentration happening with an iv bolus.

Two-compartmental model

Two-compartment open model: drug examples



Digoxin:

--- It follows two compartmental models with target organ in tissue compartment.

--- Increased high drug concentration in the central compartment, observed before distribution occurs, do not necessarily cause harm.

--- Plasma concentration obtained before distribution is completed does not reflect tissue concentration (target site) at equilibrium and can't be used to predict the effects of drug.

--- Assessment of digoxin effect: wait 1 to 3 hr after IV bolus administration.
Digoxin blood sampling: 4 to 6 hours after IV bolus administration.

--- **Note**: Sampling of drug concentrations during the absorption/distribution phase should be avoided.

Two-compartmental model

Two-compartment open model: Non-significant

--- Short distribution phase with predominant drug distribution from V_c to V_t.

--- Elimination of drug during the distribution (α) phase is NOT significant.

--- Drug can be modeled using one-compartment model for simplicity.
Example: aminoglycosides

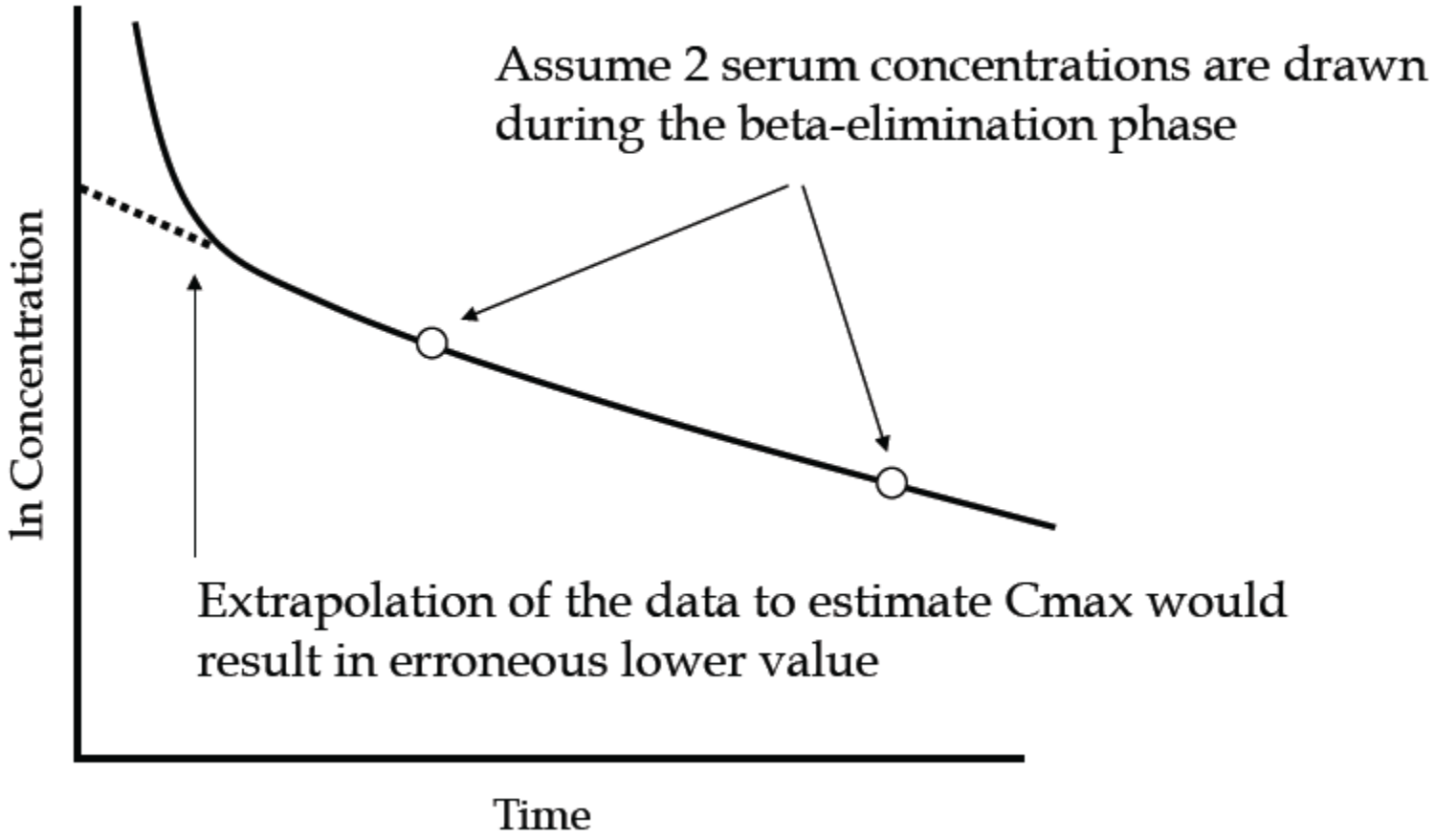
--- No drug samples are taken in the α phase.

--- PK modeling and calculations are based on C_p during the β phase only.

Attention: Some drugs may cause serious toxicity due to increased C_p in the α phase.

Two-compartmental model

Two-compartment open model: Non-significant



Two-compartmental model

Two-compartment open model: Significant

--- α phase is not simply just drug distribution.

--- Drug elimination is SIGNIFICANT during the distribution phase.

--- Technically, two compartment modeling should be applied to this kind of drugs for accuracy.

--- The use of two compartment modeling techniques and calculation is limited due to the complexity of these models and the requirement of more number of plasma samples.

--- **Note**: PK parameter calculations of two compartmental kinetics can be done with computer software (WinNonlin, etc.)

Two-compartmental model

One-compartment model drug with two-compartment model characteristics:

--- Nonlinear plasma protein binding:

a) Initial high drug concentration after IV bolus administration may saturate the number of plasma protein binding sites for the drug.

b) More free (unbound) drug is available during the early time points than that during the later time points.

c) The greater fraction of unbound drug available results in a faster clearance of the drug.

d) A more steeper decline in drug C_p at early stage due to faster clearance.

e) A slower decline in drug C_p at later stage due to more protein binding and slower clearance.

Two-compartmental model

One-compartment model drug with two-compartment model characteristics:

--- Metabolism product inhibition:

a) Metabolites of parent drugs could inhibit the elimination of parent drugs.

b) The effect of drug metabolites is not significant shortly after drug administration since few drug metabolites are formed.

c) Clearance of parent drugs can be significantly impaired at later phase due to the formation of sufficient amount of metabolites.

d) A slower decline in drug C_p at later phase due to a slower clearance of drug.

Two-compartmental model

One-compartment model drug with two-compartment model characteristics:

--- Cosubstrate depletion:

a) A cosubstrate is required for clearance (metabolism) of the drug.

b) Sufficient amount of cosubstrate is available for drug metabolism initially.

c) Depletion of cosubstrate at later stage results in slowdown of drug metabolism and a slower decline in drug C_p.

--- Enantiomers with different PK behavior:

a) Drug is administered as a racemic mixture of different enantiomers, which have different elimination rate (fast and slow clearance).

b) One enantiomer is eliminated faster, followed by the slower elimination of the other one, which results in a biphasic decline of drug profile.

Two-compartmental model

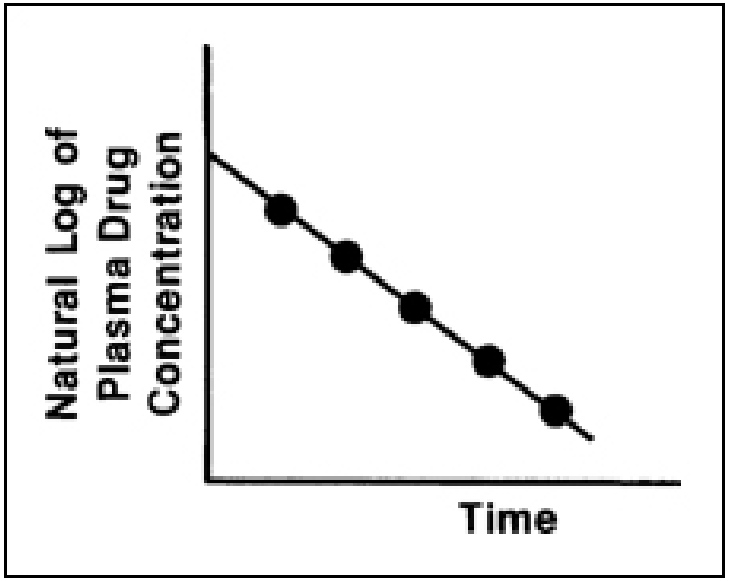
One-compartment model versus two-compartment model:

--- For one compartment model:

a) A monophasic decline in the C_p – time profile after iv bolus administration on a semilog scale indicates a one compartment model drug.

b) A monophasic decline can be described with monoexponential equation.

$$C_{(t)} = C_0 e^{-k_e t}$$



Two-compartmental model

One-compartment model versus two-compartment model:

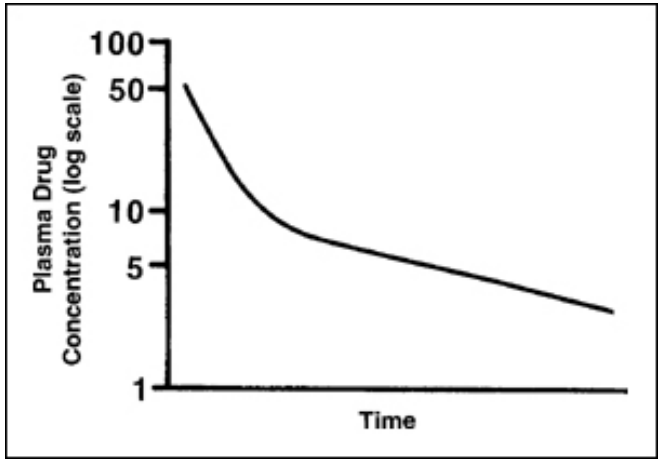
--- For two compartment model:

a) A two compartment model drug exhibits a biphasic decline in the C_p – time profile after iv bolus administration on a semilog scale.

b) A biphasic decline does NOT necessarily mean that the drug behaves as a two compartment model.

c) A biphasic decline can be described with biexponential equation.

$$C_{(t)} = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}$$



Model selection

PK model selection:

--- Physiological relevance to drug kinetic behavior.

--- Particular drug distribution patterns or elimination routes.

--- Example:

A drug shows a biphasic declining C_p time profiles after iv administration and is eliminated mainly via hepatic metabolism. What model will best fit the experimental data?

Answer: a two compartment model should be selected with elimination of the drug from the central compartment rather than from the peripheral compartment.

Model selection

PK model selection:

--- “the principle of parsimony”

--- Statistical approaches:

a) Akaike Information Criterion (AIC)

$$AIC = n \bullet \ln(WSS) + 2 \bullet m$$

n = number of data points used in the model
m = number of parameters used in the model
WSS (weighted sum of squares) = $\Sigma (Yobs - Ycalc)^2 \bullet Wi$

Wi = weighting factor ($1/Y$ or $1/Y^2$)
Yobs = observed drug concentration
Ycalc = calculated (estimated) drug concentration

Note: The model with the lowest AIC value is most appropriate.

Model selection

PK model selection:

--- “the principle of parsimony”

--- Statistical approaches:

b) Schwarz Criterion (SC)

$$SC = n \bullet \ln(WSS) + m \bullet \ln(n)$$

n = number of data points used in the model
m = number of parameters used in the model
WSS (weighted sum of squares) = $\Sigma (Yobs - Ycalc)^2 \bullet Wi$

Wi = weighting factor ($1/Y$ or $1/Y^2$)
Yobs = observed drug concentration
Ycalc = calculated (estimated) drug concentration

Note: Again, the model with the lowest SC value is most appropriate.

Noncompartmental model

Noncompartmental analysis

Noncompartmental analysis (NCA):

--- No specific compartmental model or related assumption required for the estimate of PK parameters.

--- It can be applied to virtually any PK data.

--- Often used in early drug developmental stages when little or nothing is known about its PK behavior.

--- PK parameters estimated by NCA:

area under the curve (AUC), area under the first moment curve (AUMC), systemic clearance, V_{ss}, mean residence time, bioavailability, half-life

--- noncompartmental approaches:
Moment analysis, system analysis, noncompartmental recirculatory model

Noncompartmental analysis

Moment analysis:

Statistical moment:

--- A mathematical description of a discrete distribution of data.

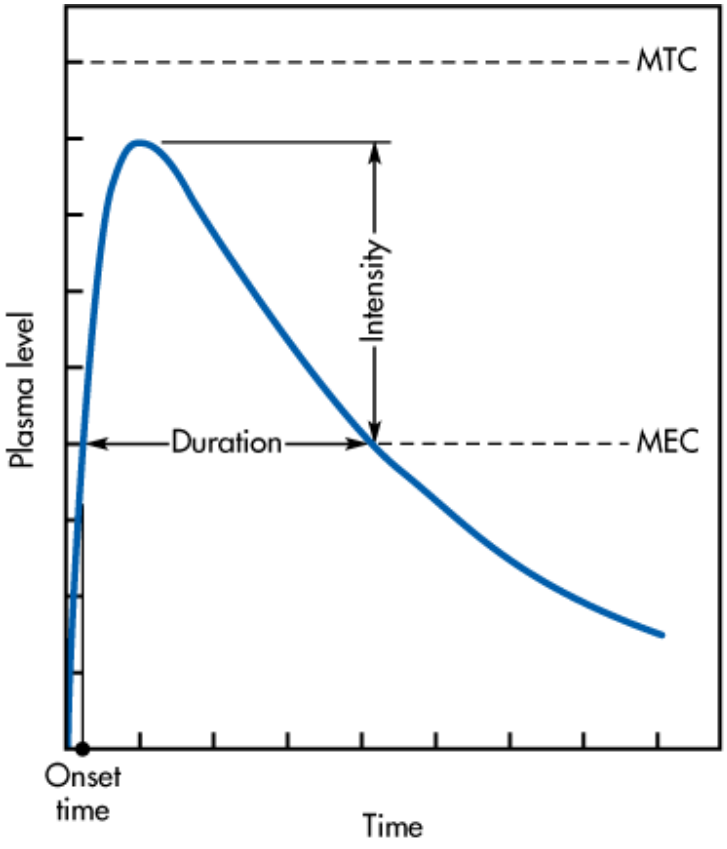
--- Pharmacokinetic application:

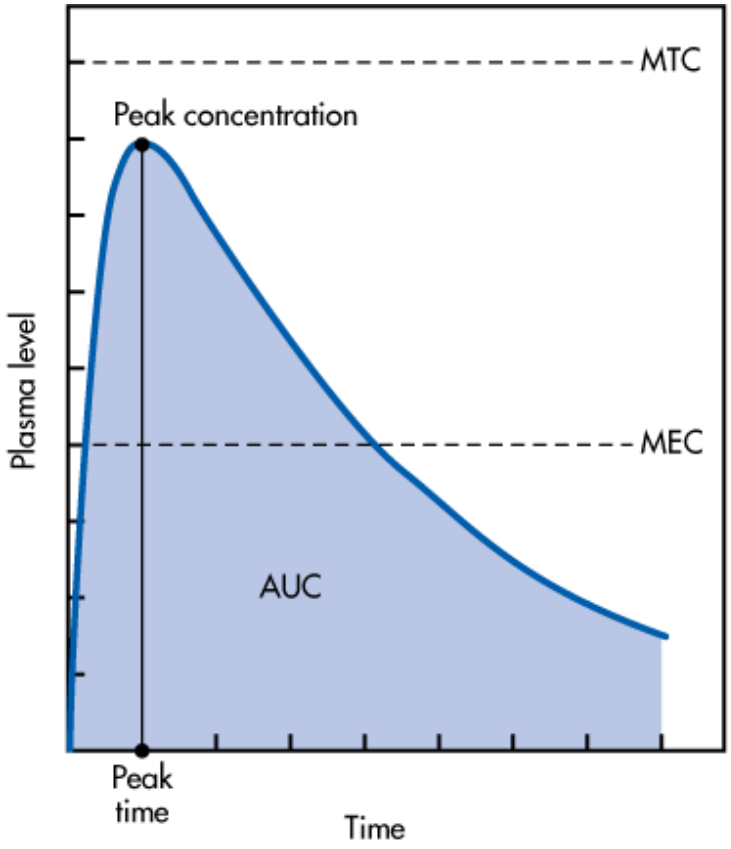
-- The plasma concentration time curve can be considered as a statistical distribution curve.
-- Statistical moment calculated represent an estimate of the true probability density function that describes the true relationship between drug concentration and time.
-- similar to the mean of a sample population represents an estimate of the true mean of the entire population.
-- **AUC**: area under the zero moment curve.
-- **AUMC**: area under the first moment curve.

Noncompartmental analysis

Moment analysis: **AUC**

--- A measure of drug exposure.



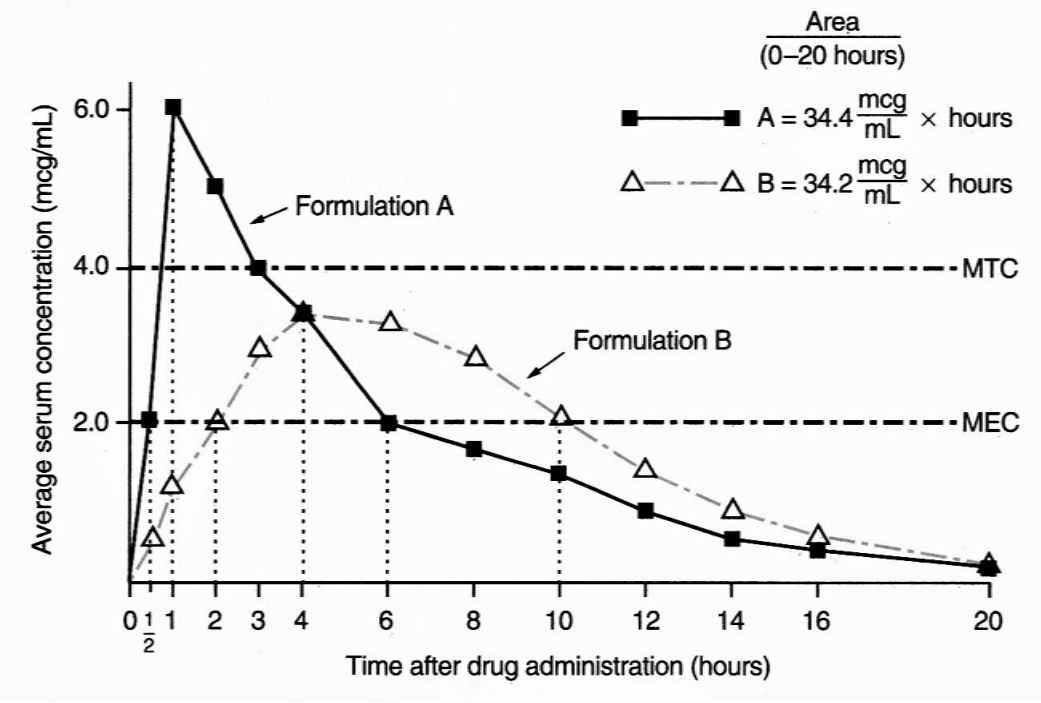


Noncompartmental analysis

Moment analysis: **AUC**

--- Application in bioavailability and bioequivalence studies.

$$\text{Absolute Bioavailability of an oral drug} = F = \frac{AUC_{po} \,/\, dose_{po}}{AUC_{iv} \,/\, dose_{iv}}$$



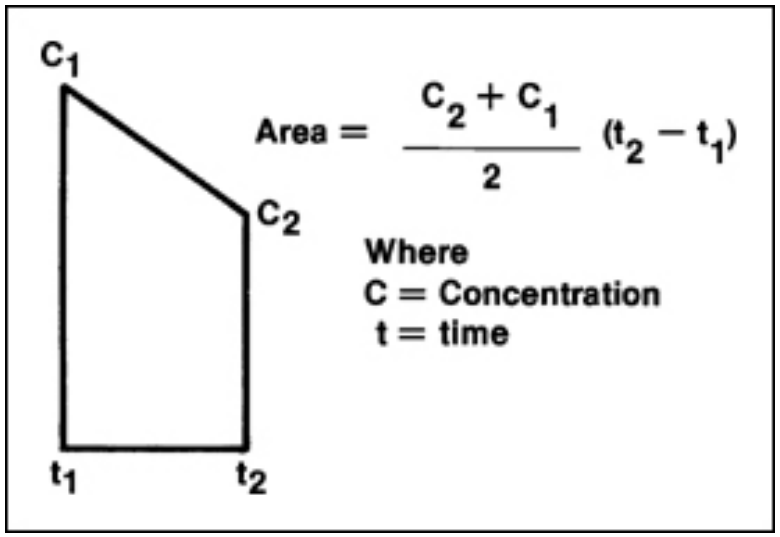
Noncompartmental analysis

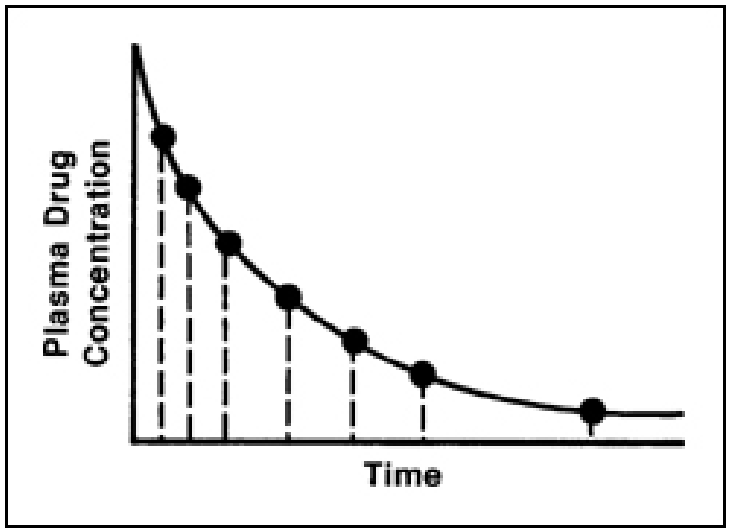
Moment analysis: **AUC**

Linear trapezoidal method:

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

$$\mathrm{AUC}_{0\sim\infty} = \int_0^{\infty} C_p(t)\cdot dt$$





Note: estimates of AUC by linear trapezoidal method must be done on a linear scale.

Noncompartmental analysis

Moment analysis: **AUC**

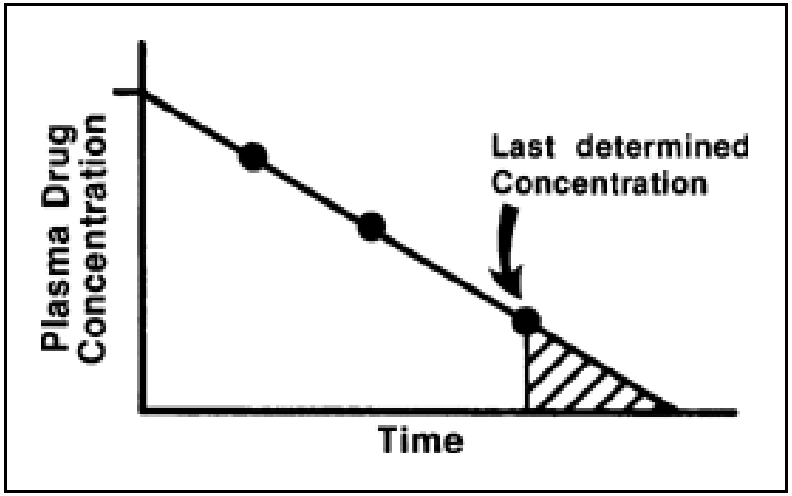
Linear trapezoidal method:

$$[AUC]_t^{\infty} = \text{terminal area} = \frac{C_{last}}{\lambda}$$

C_{last} = last plasma concentration of the drug

λ = terminal elimination rate constant

Unit: concentration $\times$ time (e.g., μg·hr/ml)



Note: C_{last} is usually estimated at the last time point from a proper linear regression using the last few (usually 3) data points.

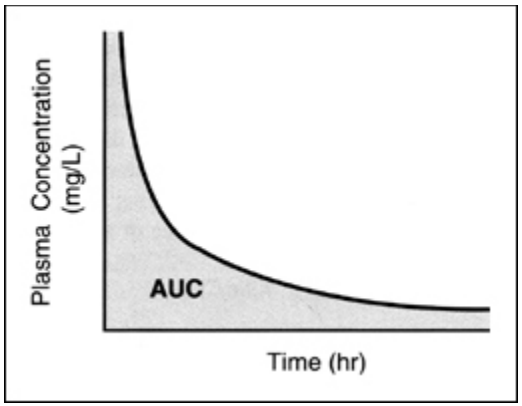
Noncompartmental analysis

Moment analysis: **AUMC**

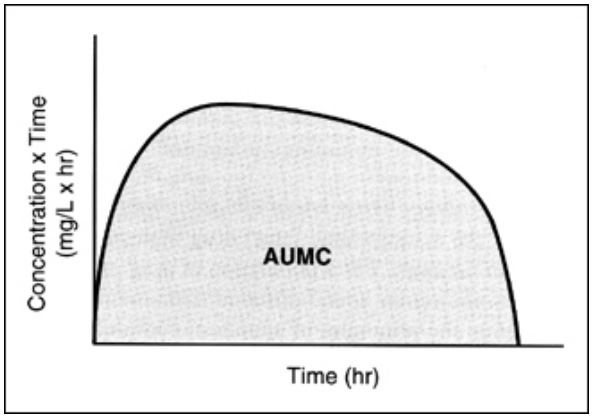
--- "area under the drug concentration versus time" versus "time" curve

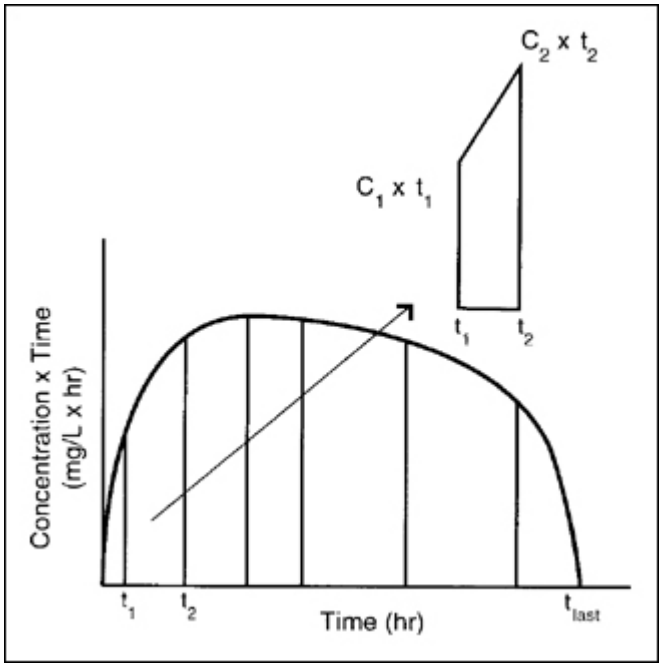
the plot of drug concentration × time versus time

--- linear trapezoidal method



$$AUMC_{0\text{-}\infty} = \int_0^{\infty} t \bullet C_p(t)\, dt$$





Noncompartmental analysis

Moment analysis: **AUMC**

--- "area under the drug concentration versus time" versus "time" curve

--- linear trapezoidal method

$$[AUMC]_t^{\infty} = \text{terminal area} = \frac{(C_{last} \times t_{last})}{\lambda} + \frac{C_{last}}{\lambda^2}$$

C_{last} = last observed plasma concentration

t_{last} = time of the last observed plasma concentration

λ = terminal elimination rate constant from the concentration versus time curve. λ is used here (instead of K) to indicate that this represents elimination in a model-independent or noncompartmental analysis.

Unit: (concentration $\times$ time) $\times$ time (e.g., $\mu g \cdot hr^2/ml$)

Noncompartmental analysis

Moment analysis: **AUC vs AUMC**

AUC:

--- Quantification of the extent of exposure of a drug and of its clearance from the body.

--- It is a more reliable parameter than individual C_p in terms of evaluating the extent of overall exposure of a drug.

AUMC:

--- Evaluation of the extent of drug distribution.

--- It is useful to estimate V_{ss} and the persistence of a drug in the body.

Noncompartmental analysis

Moment analysis: **calculating AUC and AUMC**

Example: estimates of AUC and AUMC from drug plasma concentration (C_p) obtained after oral administration.

Time (hr)	C_p (μg/ml)	$C_p \cdot t$ (μg·hr/ml)	AUC (μg·hr/ml)	AUMC (μg·hr^2/ml)
0	0	0	0	0
1	10	10	5	5
2	20	40	15	25
3	30	90	25	65
4	20	80	25	85
6	10	60	30	140
7	0	0	5	30
			$AUC_{0\text{-}7}$: 105	$AUMC_{0\text{-}7}$: 350

Noncompartmental analysis

Moment analysis: **Estimating PK parameters**

Mean Residence Time (MRT):

--- The average time for all the drug molecules to transit or reside in the body.

--- An alternative concept to describe how drug molecules move in and out of a system.

--- Unit: time (e.g., hr)

--- Calculation from NCA approach:

$$MRT_{0-\infty} = \frac{AUMC_{0-\infty}}{AUC_{0-\infty}}$$

MRT from previous example:

AUC_{0-7}: 105 μg·hr/ml; $AUMC_{0-7}$: 350 μg·hr^2/ml.

MRT = AUMC/AUC = 350 / 105 = 3.33 hr

Noncompartmental analysis

Moment analysis: **Estimating PK parameters**

Mean Residence Time (MRT):

--- MRT_{iv}: MRT of a drug following intravenous injection.

--- MRT_{po}: MRT of a drug following oral administration.

--- Mean Absorption Time (MAT):

average time required for the drug to reach the systemic circulation from the gastrointestinal tract after oral administration.

$MAT = MRT_{po} - MRT_{iv}$

$$MRT_{po} = \frac{AUMC_{po}}{AUC_{po}}$$

$K_a = 1/MAT$

K_a : first order absorption rate constant

Noncompartmental analysis

Moment analysis: **Estimating PK parameters**

Systemic clearance or total body clearance (CL_T):

--- It relates the dosing rate of a drug to its steady-state concentration.

--- It is used to calculate a maintenance-dosing regimen.

--- It is usually obtained after a single intravenous bolus dose.

--- Unit: volume/time (e.g., L/hr)

--- Calculation from NCA approach: $$CL_T = \frac{Dose_{iv}}{AUC_{iv}}$$

Noncompartmental analysis

Moment analysis: **Estimating PK parameters**

Apparent volume of distribution at steady state (V_{ss}):

--- It relates total amount of drug in the body to a particular C_p after a single dose.

--- It is not affected by changes in elimination or clearance of the drug.

--- Calculation from NCA approach:

$$V_{ss} = MRT_{iv} \cdot CL_T = \frac{AUMC_{iv}}{AUC_{iv}} \cdot \frac{Dose_{iv}}{AUC_{iv}}$$

Noncompartmental analysis

Moment analysis: **Estimating PK parameters**

Example 1:

A subject received a drug in a dose of 150 mg following iv bolus administration. Blood samples were obtained and the AUC and AUMC were calculated as 72 μg·hr/ml and 588 μg·hr^2/ml, respectively. Using noncompartmental methods, calculate the CL_T, V_{ss}, and MRT of the drug in this patient.

Noncompartmental analysis

Moment analysis: **Estimating PK parameters**

Example 2:

The same subject from example 1 received the same drug in a dose of 500 mg following oral administration. Blood samples were obtained and the AUC and AUMC were calculated as 156 μg·hr/ml and 1572 μg·hr^2/ml, respectively. Using noncompartmental methods, calculate the MAT, K_a (assume first order absorption), and bioavailability F of the drug in this patient.

Reference

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

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

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

The End

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