Clinical Pharmacokinetics

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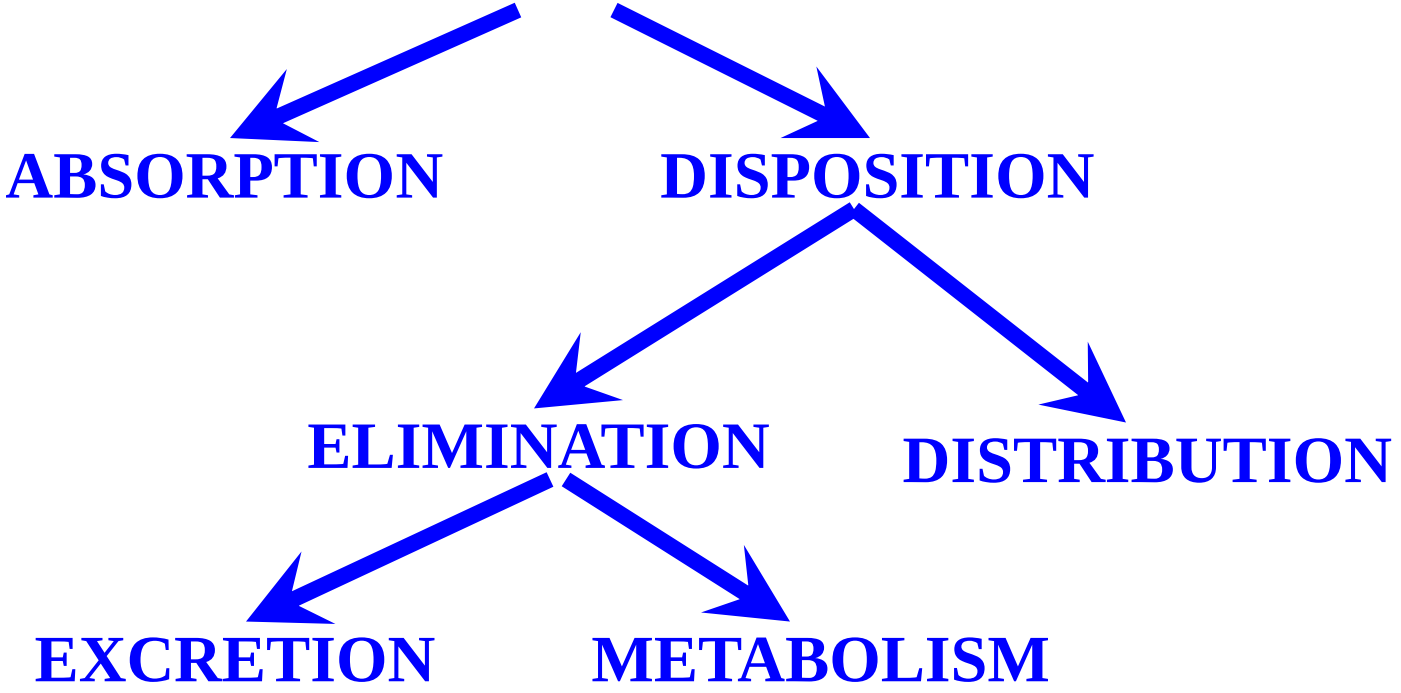
Pharmacokinetics

Pharmacokinetics is the science of the kinetics of drug absorption, distribution, and elimination (ie, metabolism and excretion).

Clinical pharmacokinetics is the application of pharmacokinetic methods to drug therapy in patient care. Clinical pharmacokinetics involves a multidisciplinary approach to individually optimized dosing strategies based on the patient's disease state and patient-specific considerations.

WHAT IS PHARMACOKINETICS?

PHARMACOKINETICS **is the study of the kinetics of drug absorption and disposition.**



Pharmacokinetic Parameters

Cp - Cp0 - D

K

Vd

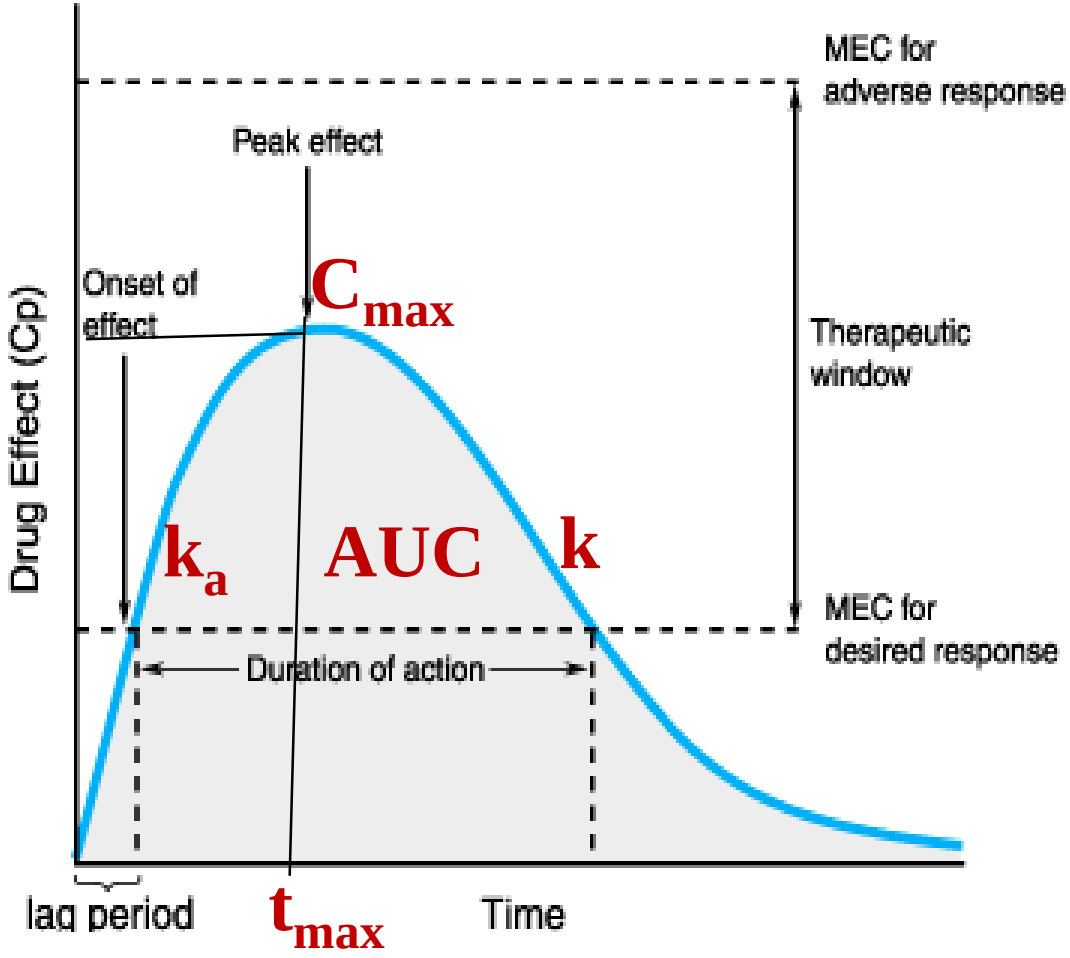
T1/2

Cl

AUC

Plasma Concentration-Volume of Distribution

Extravascular Pharmacokinetics

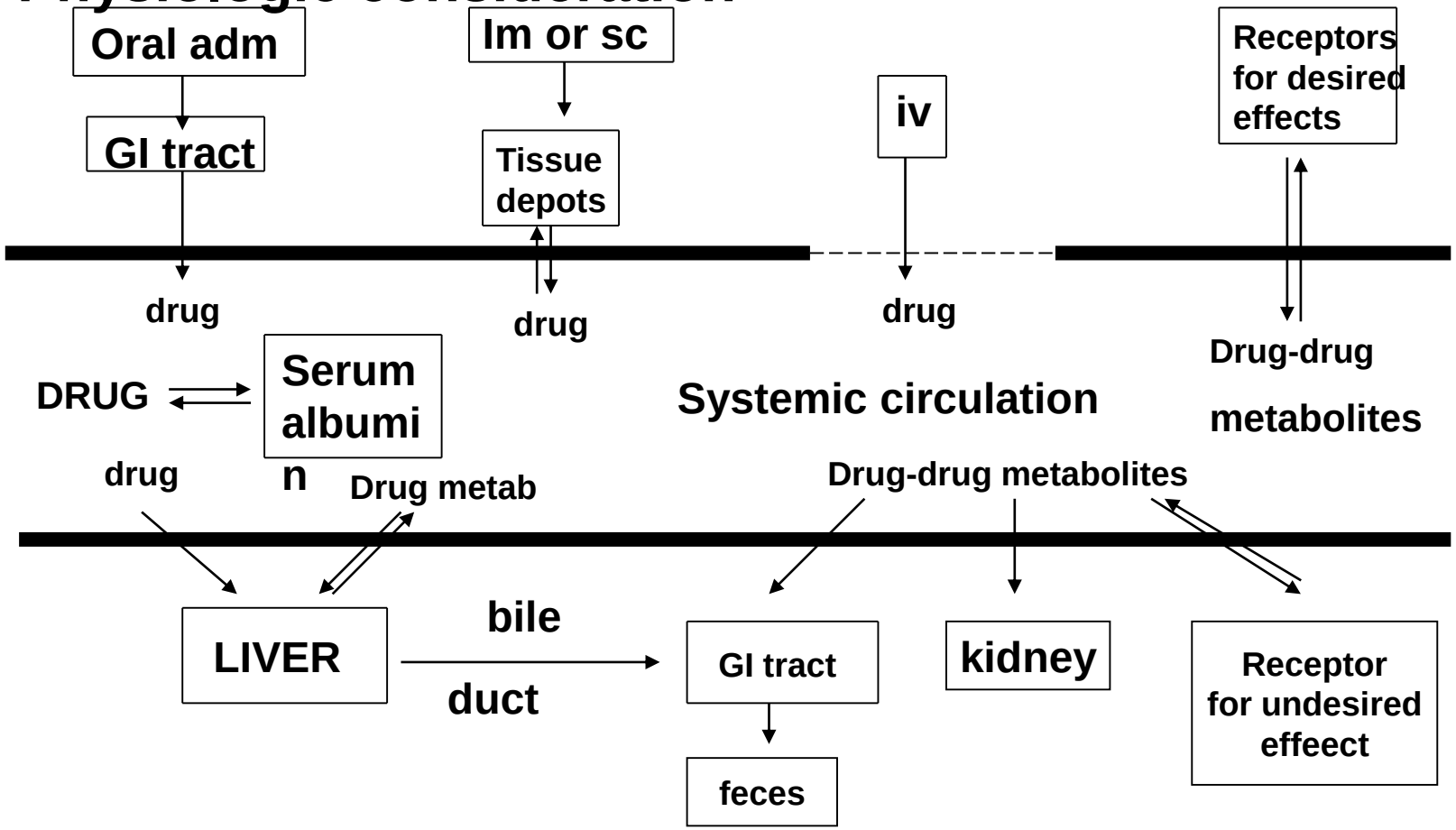


Volume of distribution

The apparent volume of distribution is not a true physiologic volume. Most drugs have an apparent volume of distribution smaller than, or equal to, the body mass. For some drugs, the volume of distribution may be several times the body mass.

Drug Distribution

- **Physiologic consideration**



Volumes of distribution

(In litres for average 70 Kg adult)

Warfarin	**7**
Gentamicin	**16**
Theophylline	**35**
Digoxin	**510**
Mianserin	**910**
Quinacrine	**50,000**

Small vol. Mainly stays in plasma little in tissues.

Medium vol. Similar concs in plasma and tissues

Large vol. Mainly in tissues, little in plasma.

Volume of distribution and body weight

A fixed dose injected into a small and a large individual will produce different concentrations. Vol Dis (calculate from D/ Cp^0) will therefore depend upon body size.

May be quoted as L/kg (Litres per kg body weight)

e.g. Theophylline Vol Dis = 0.48 L/kg
For 60 kg adult, Vol Dis = 0.48 L/kg x 60 kg
= 28.8 L

Using volume of distribution to calculate a dose

$Vd = D / Cp^0$

To calculate appropriate dose, re-arrange to:

$D = Vd \times Cp^0$

Calculation Practice

- **We want to achieve a blood concentration of theophylline of 15mg/L.**
- **A patient weighs 55kg.**
- **What dose is appropriate?**

Vol dis = 0.48L/kg X 55kg

= 26.4L

$Vd = D / Cp^0$

$D = Vd \times Cp^0$ = 26.4L X 15mg/L

= 396mg (Probably round to 400mg)

Distribution pattern

Onced absorbed, drugs reached systemic circulation and were distributed throughout the body, to receptor, other tissues (non receptor), eliminating organs, crossed the placenta, secreted in milk (ASI) and in fat tissues

Body fluids (totally 42 L for 70 kg subject BW)

1. **The vascular fluid (blood, ± 5L)**
2. **The extracellular fluid (± 15 L incl plasma 3L)**
3. **The intracellular fluid**

Physicochemical factors

Determined distr pattern of drugs, incl:

- **MW (low MW & water soluble drugs were uniformly distributed throughout the bodywater)**
- **Solubility**
- **pKa (only molecular form passed the physiological membrane)**
- **Partition coefficient (lipid soluble drugs tend to accumulate in fat tissues)**
- **Affinity to plasma protein (high affinity drugs, stay largely within the vascular system)**

Physiological factors

- **Membrane permeability (highly permeable: renal and hepatic capillaries, impermeable: brain capillaries; blood-brain barrier)**

- **Blood perfusion rate (kidneys>liver>heart> brain>fat>muscle> skin>bone)**

Exp: thiopental gets into the brain faster than muscle, whereas penicillin was viceversa

Thiopental is partly ionized and passes both organs easily. Perfusion limits the transport thus it can transfer to the brain more quickly.

Penicillin, being quite polar and thus slowly permeable. Permeability limits transfer thus it gets muscle easily (brain is impermeable)

Distribution process

- **Passive diffusion (Fick's law of diffusion)**
- **Hydrostatic pressure (a pressure gradient between the arterial end of the capillaries entering the tissue and the venous capillaries leaving the tissue).Responsible for penetration of water-soluble drugs.**

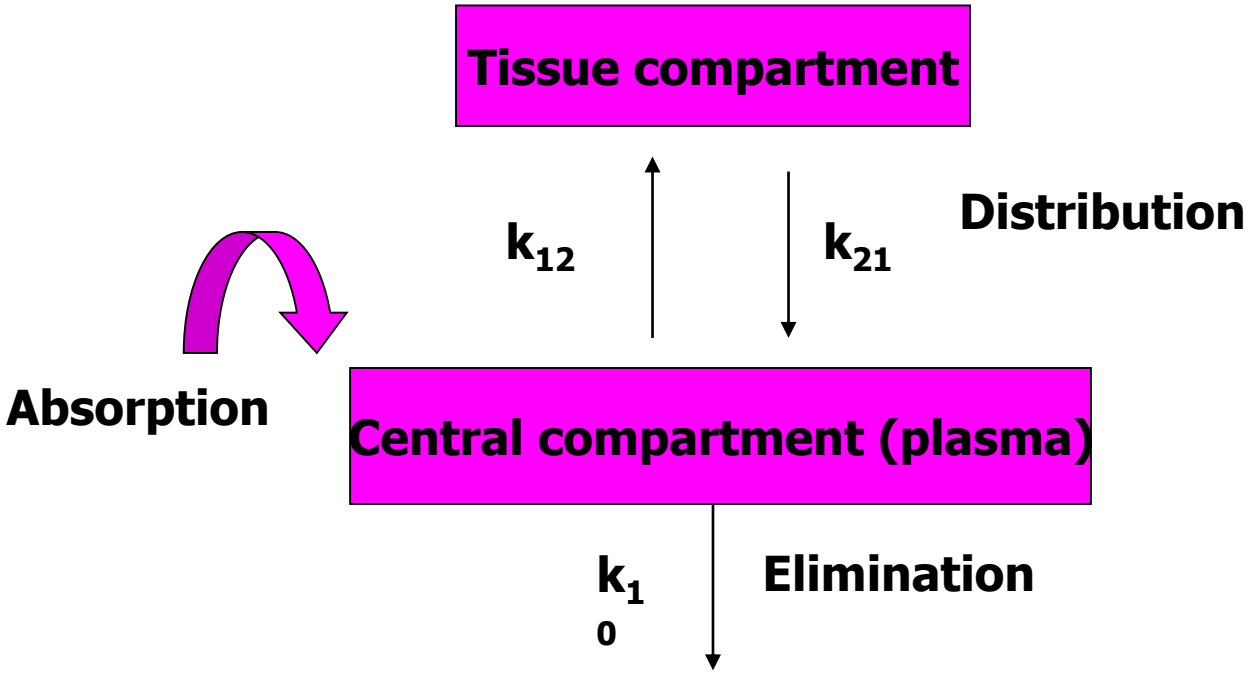
Perfusion or flow limited distribution.

- **If a drug difuses rapidly across the membrane so that blood flow is the rate limiting step (slower)**
  exp: thiopental, transport to the brain

Diffusion or permeability limited distribution.

- **If drug distribution is limited by the slow diffusion of drug across the membrane in the tissue**
  exp: penicillin, diffused very slowly due to its polarity

Two compartment open model



Apparent volume of distribution

- Lack of true volume characteristics (due to unknown tissue volume).

  Vd app of some drugs exceed total body water
  Defined as the hypothetical volume relating the drug plasma concentration to the weight of drug in the body

- A useful indicator of the type of distribution pattern, exp: V= 3-5 L (in an adult) the drug remain largely within the vascular system; V= 30 – 50 L the drug is distributed throughout the body water; V >>> total body water drugs are concentrated in one or more tissues (highly lipid soluble drugs distribute into fat tissue, digoxin is extensively bound by myocard protein)

Tabel 1. Apparent Vd of some drugs

Drug	Liters/kg	Liter/70 kg
Chloroquine	94 – 250	6600 – 17500
Nortriptyline	21	1500
Digoxin	7	500
Lidocaine	1.7	120
Theophylline	0.5	35
Tolbutamide	0.11	8

Basic equations

- $C_p = D_B/V_d$
- Distrib. Half life: $k_d = \frac{Q}{VR}$

  Q=blood flow to the organ,V=volume of the organ & R=ratio of drug conc in tissue to conc in blood
- $T_{1/2}$ elimination ⟺ Vd

  $CL = k\ V_d$

  $T_{1/2} = 0.693\ V_d/CL$

Calculation of Vd app.

- $V_{app} = D_B/C_p$
- $D_B = V_pC_p + V_tC_t$
- $V_{app} = V_p + V_t\,[f_u/f_{ut}]$, if f_u and f_{ut} are both unity, then

  $D_B/C_p = V_p + V_t$
- Estimation of V_{app}

$V_{app} = D_B/C_p$

Protein Binding

Major proteins to which dugs bind in plasma: albumin (acidic drugs), a1-acid glycoprotein (basic drugs), lipoproteins

Significance:

- **only free drug is able to cross membrane, the bound drug could serve as reservation**
- **Possibility of drug interaction by binding displacement**
- **Free drug conc was also determined by pathophysiological conditions relating with changes in the amount of protein in the body**

Drug-Protein Binding

- **Reversible**
  hydrogen or van der walls bound (weak)
- **Irreversible**
  cause toxicity such as hepatotoxicity due to binding of acetaminophen to liver protein

Effect of reversible protein binding on drug distribution & elimination

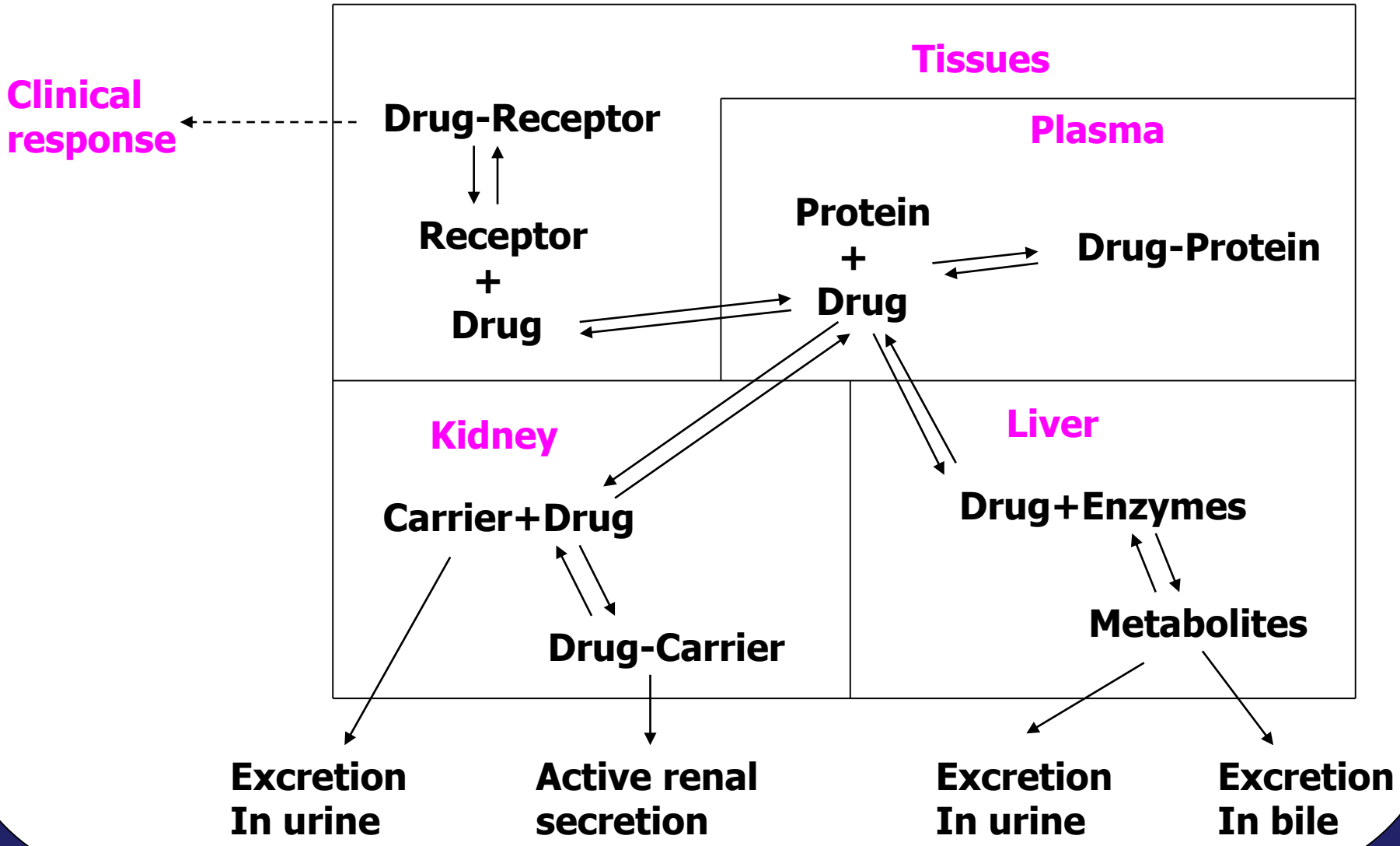


Table: Influence of protein binding on t1/2 & CL_R

Drug	% Bound	T1/2 (hr)	CL_R(mL/min/1.73m^2)
Ceftriaxone	96	8.0	10
Cefoperazone	90	1.8	19
Cefotetan	85	3.3	28
Ceforanide	81	3.0	44
Cefazolin	70	1.7	56
Moxalactam	52	2.3	64
Cefsulodin	26	1.5	90
Ceftazidime	22	1.9	85
Cephaloridine	21	1.5	125

Methods for studying drug-protein binding

- Equilibrium dialysis
- Dynamic dialysis
- Ultrafiltration
- Gel Chromatography
- Spectrophotometry
- Electrophoresis
- Circulatory dichroism

Clinical Significance

Factors that decrease plasma protein conc:

- **Liver disease: decrease protein synthesis**
- **Trauma, surgery: increased protein catabolism**
- **Burns: Distribution of albumin into extravascular space**
- **Renal disease: Excessive elimination of protein**

WHY BE CONCERNED ABOUT PHARMACOKINETICS AND DOSAGE REGIMENS?

Pharmacokinetics and Dosage Regimens Determine:

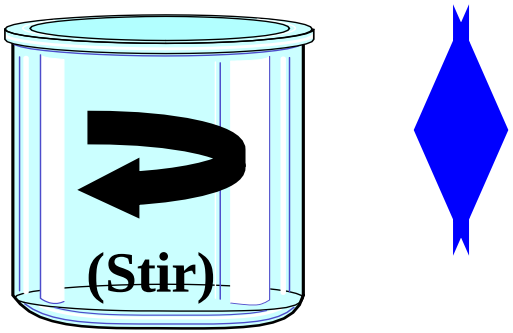
- How much drug is in the body at any given time
- How long it takes to reach a constant level of drug in the body during chronic drug administration
- How long it takes for the body to rid itself of drug once intake of drug has stopped

WARNING!!

THE STUDY OF PHARMACOKINETICS MAKES SOME PEOPLE ANXIOUS

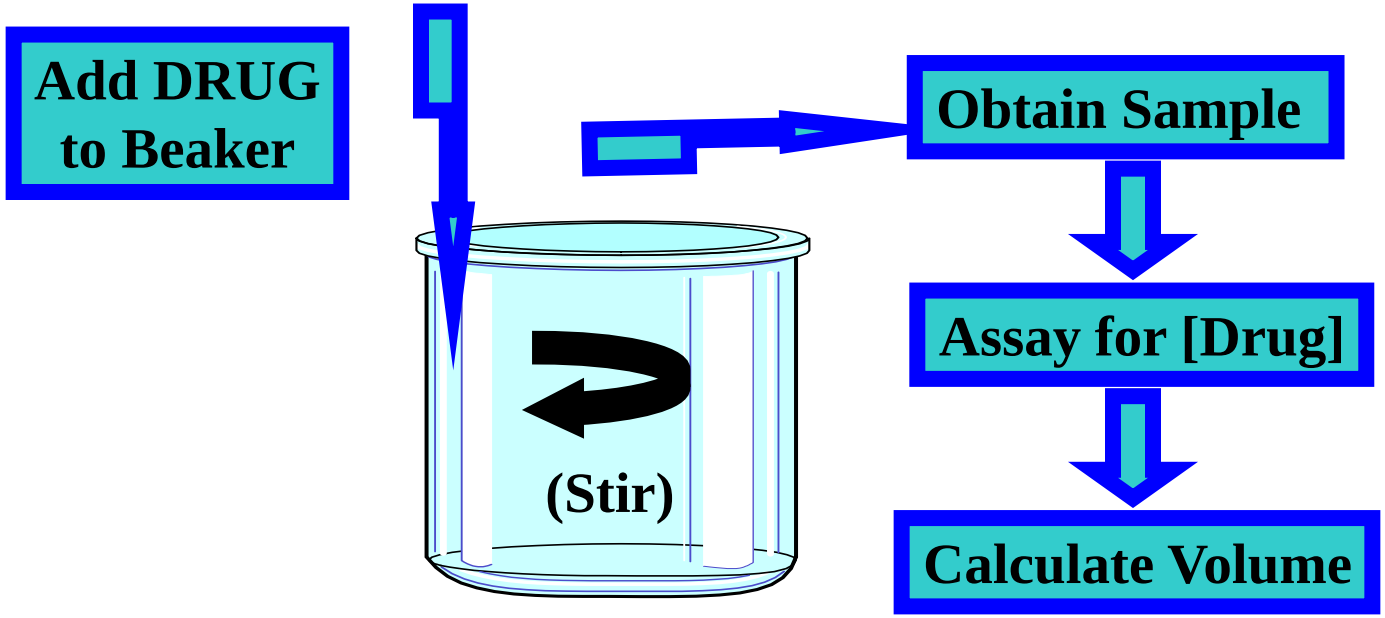
MAJOR CONCEPT #1

CONCEPT OF VOLUME OF DISTRIBUTION (V_D) OF DRUGS



As a first approximation, the body behaves like a well-stirred beaker, i.e., chemicals are dispersed throughout the container (body) rather quickly.

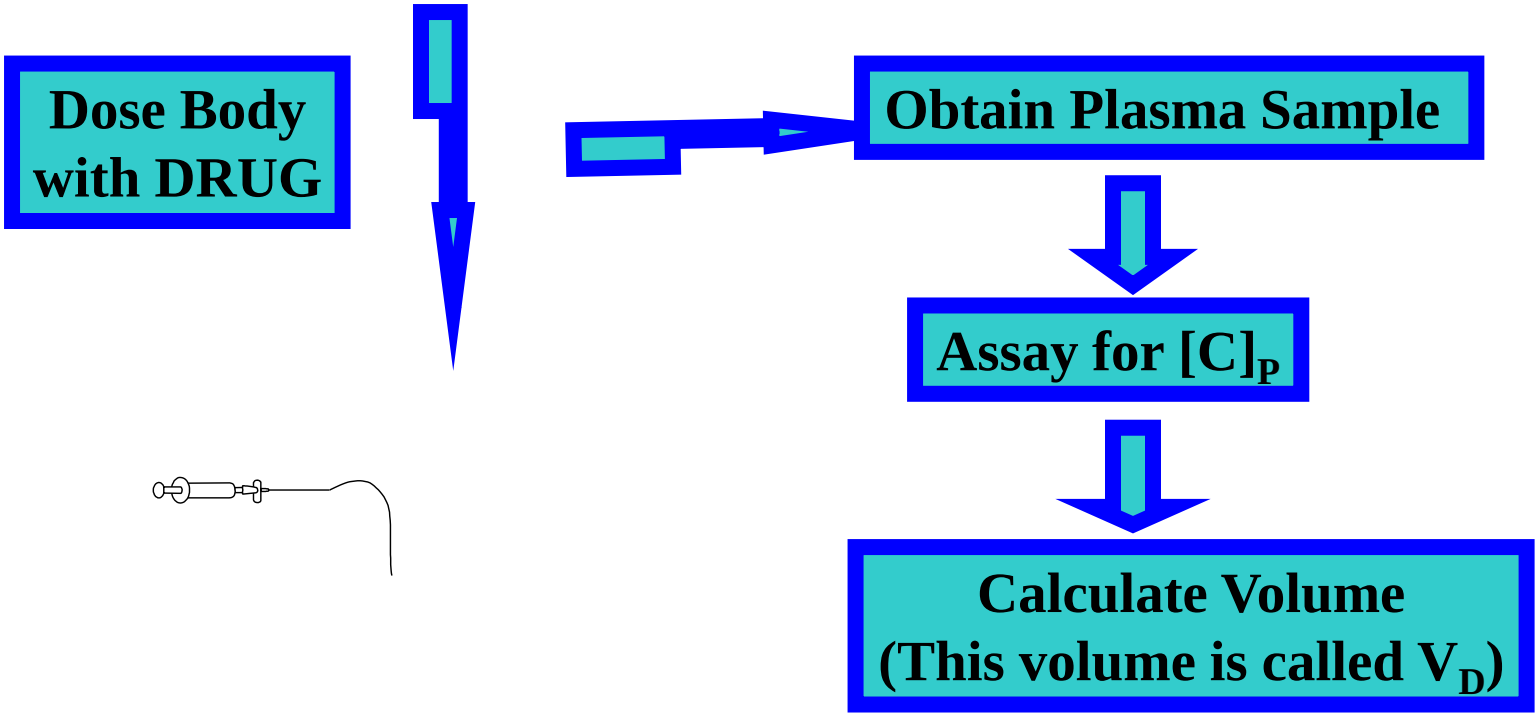
CONCEPT OF VOLUME OF DISTRIBUTION OF DRUGS: DEFINITION OF V_D



[Drug] = Amount Added ÷ Volume of Beaker

Volume of Beaker = Amount Added ÷ [Drug]

CONCEPT OF VOLUME OF DISTRIBUTION OF DRUGS: DEFINITION OF V_D



By DEFINITION: $V_D = D/[C]_P$

(where D is amount of drug in body and $[C]_P$ is concentration of drug in plasma)

CONCEPT OF VOLUME OF DISTRIBUTION OF DRUGS: DEFINITION OF V_D

WARNING: V_D is a calculated value that should not be taken literally as representing some real volume!!!!!

V_D is:

1. **a calculated value,**
2. **a reproducible value,**
3. **a clinically useful value.**

V_D is not a real volume with an independent existence. In this regard, the word "volume" is used in a metaphorical sense.

CONCEPT OF VOLUME OF DISTRIBUTION OF DRUGS: INTRODUCTION TO V_D

By DEFINITION: $V_D = D/[C]_P$

Rearranging: $D = V_D \times [C]_P$

Suppose you want a certain desirable $[C]_p$, call it $[C]_{P(target)}$

Substituting $[C]_{P(target)}$ for $[C]_P$: $D_{target} = V_D \times [C]_{P(target)}$

Where D_{target} is the amount of drug in body required to achieve a given $[C]_{P(target)}$

CONCEPT OF VOLUME OF DISTRIBUTION OF DRUGS: INTRODUCTION TO V_D

If patient has no drug in body to begin with, then can administer an amount (called "Loading Dose") to achieve a given D_{target} and $[C]_{P(target)}$

Since loading dose (LD) must provide D_{target} amount of drug in body, and since not all of an administered dose may be absorbed:

$$LD \times F = D_{target} \text{ or } LD = D_{target}/F \text{ or } (V_D \times [C]_{P(target)})/F$$

Where F is "Bioavailability" ,i.e., fraction (ranging from 0 to 1) of administered dose absorbed into body

CONCEPT OF VOLUME OF DISTRIBUTION OF DRUGS: INTRODUCTION TO V_D

(KEY EQUATION #1)

$$LD = \frac{V_D \times [C]_{P(target)}}{F}$$

CONCEPT OF VOLUME OF DISTRIBUTION OF DRUGS: INTRODUCTION TO V_D

$$LD = (V_D \times [C]_{P(target)})/F$$

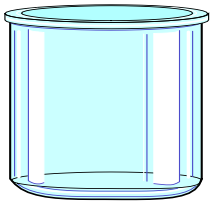
V_D and $[C]_{P(target)}$ and Fare THE determinants of loading dose (LD)!!

In other words, the amount of drug that must be given to achieve rapidly a target concentration of drug in the plasma is solely determined by V_D, F and $[C]_{P(target)}$.

CONCEPT OF VOLUME OF DISTRIBUTION OF DRUGS: DETERMINANTS OF V_D

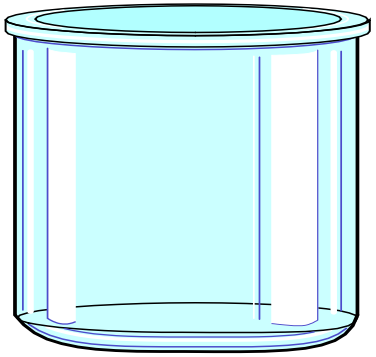
Distribution into Body Compartments

Small V_D



Restriction of Drug to Limited Areas of Body

vs

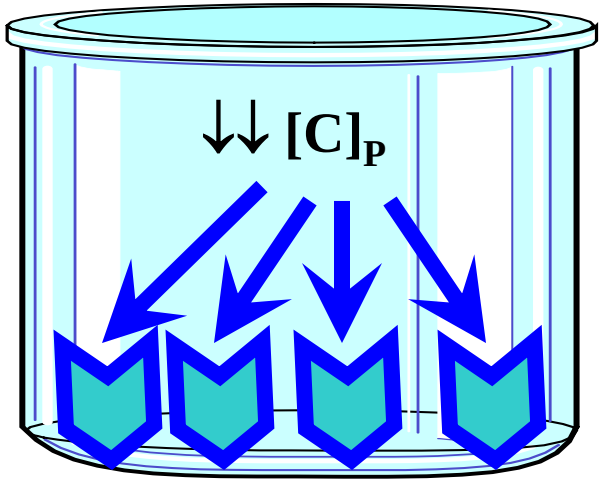


Large V_D

Free Assess of Drug to Many Areas of Body

CONCEPT OF VOLUME OF DISTRIBUTION OF DRUGS: DETERMINANTS OF V_D

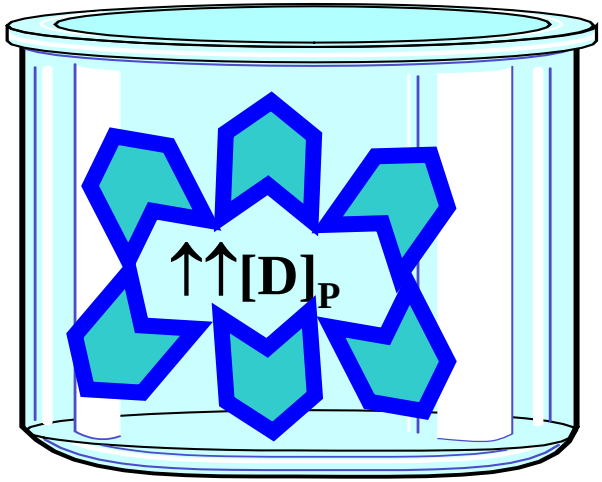
Tissue Binding



$$\uparrow\uparrow V_D = \frac{D}{\downarrow\downarrow [C]_P}$$

CONCEPT OF VOLUME OF DISTRIBUTION OF DRUGS: DETERMINANTS OF V_D

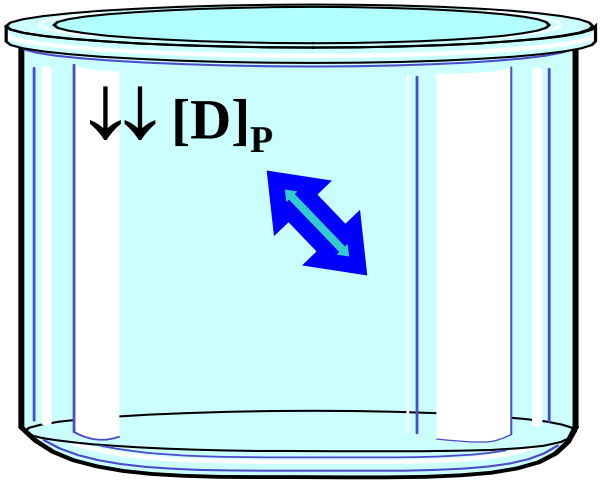
Plasma Protein Binding



$$\downarrow\downarrow V_D = \frac{D}{\uparrow\uparrow [C]_P}$$

CONCEPT OF VOLUME OF DISTRIBUTION OF DRUGS: DETERMINANTS OF V_D

Distribution into Fat

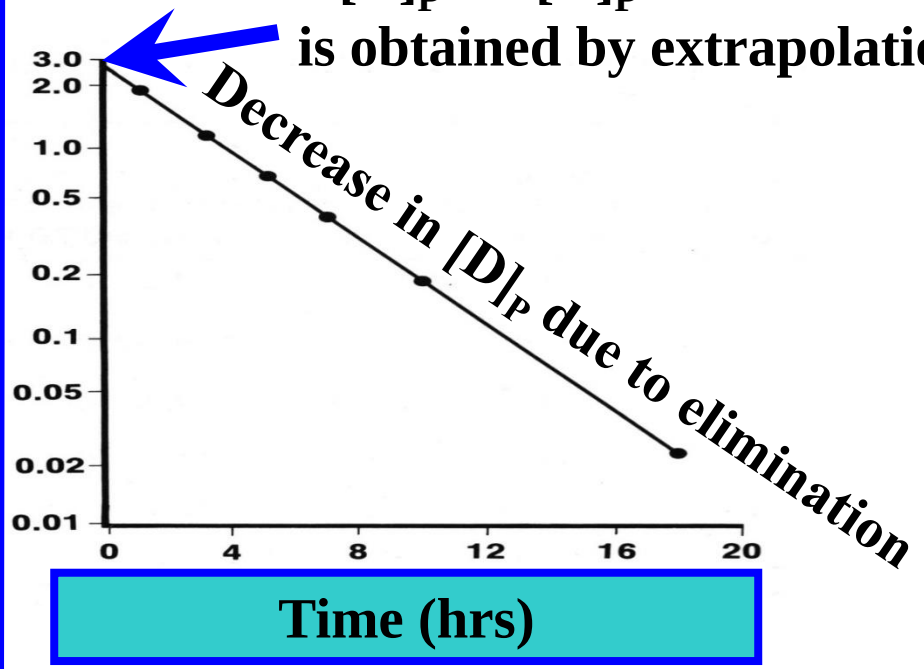


$$\uparrow\uparrow V_D = \frac{A}{\downarrow\downarrow [D]_P}$$

CONCEPT OF VOLUME OF DISTRIBUTION OF DRUGS: OBTAINING V_D

V_D is usually easy to obtain!

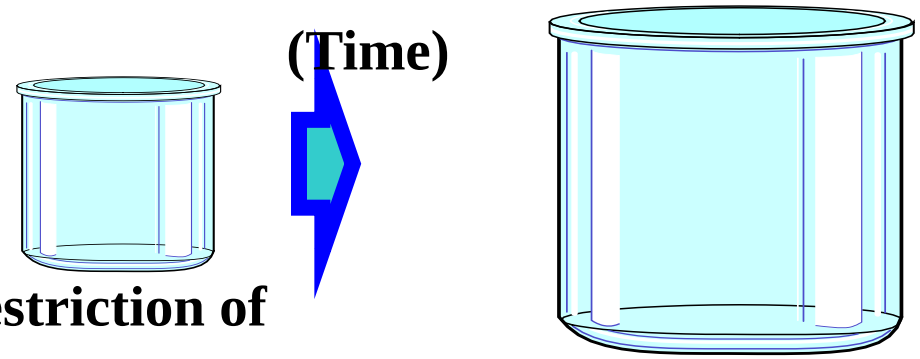
1. Give bolus of drug.
2. Measure plasma levels over time.
3. Extrapolate to find plasma level at time 0.



V_D = Amount in body at time 0/$[D]_p^0$ = $Dose_{IV}$ /$[D]_P^0$

CONCEPT OF VOLUME OF DISTRIBUTION OF DRUGS: OBTAINING V_D

One- versus Two-Compartment Behavior

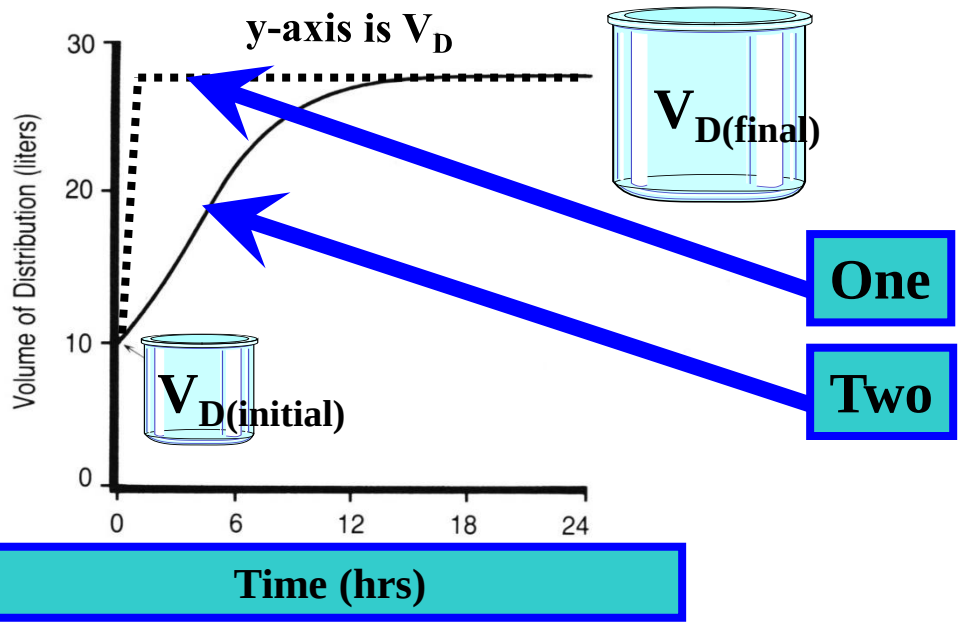


Initial Restriction of Drug to Limited Areas of Body

Slow Equilibration of Drug to Other Areas of Body

CONCEPT OF VOLUME OF DISTRIBUTION OF DRUGS: OBTAINING V_D

One- versus Two-Compartment Behavior

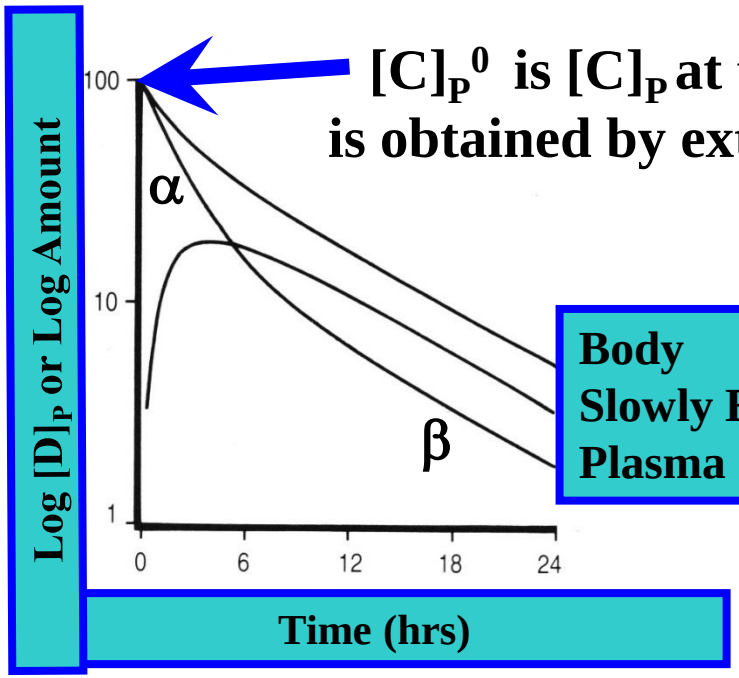


1-Compartment: $V_{D(final)}$ reached within minutes

2-Compartment: $V_{D(final)}$ reached only after noticeable delay

CONCEPT OF VOLUME OF DISTRIBUTION OF DRUGS: OBTAINING V_D

Two-Compartment Behavior



$[C]_P^0$ is $[C]_P$ at time 0 and is obtained by extrapolation

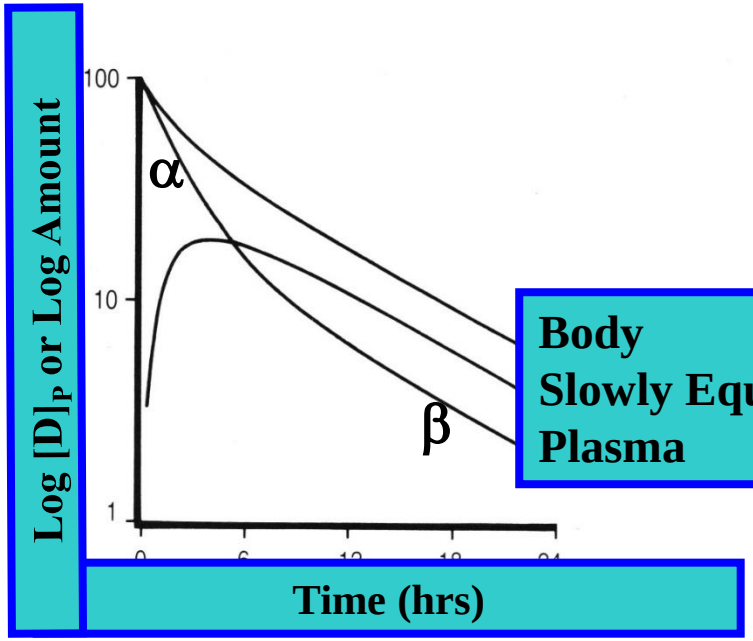
Body
Slowly Equilibrating Tissues
Plasma

$V_{D(initial)}$ is easy to obtain for 2-compartment behavior!

$$V_{D(initial)} = V_{D(\alpha)} = \text{Amount in body at time 0}/[C]_p^0 = \text{Dose}_{IV}/[C]_P^0$$

CONCEPT OF VOLUME OF DISTRIBUTION OF DRUGS: OBTAINING V_D

Two-Compartment Behavior



Body
Slowly Equilibrating Tissues
Plasma

$V_{D(final)}$ is difficult to obtain for 2-compartment behavior!

$V_{D(final)} = V_{D(\beta)}$ = Amount in body at time t after distribution / $[C]_P^{\text{time t after distribution}}$

Because of elimination, amount in body at time t after distribution $\neq$ $Dose_{IV}$

CONCEPT OF VOLUME OF DISTRIBUTION OF DRUGS: OBTAINING V_D

Two-Compartment Behavior

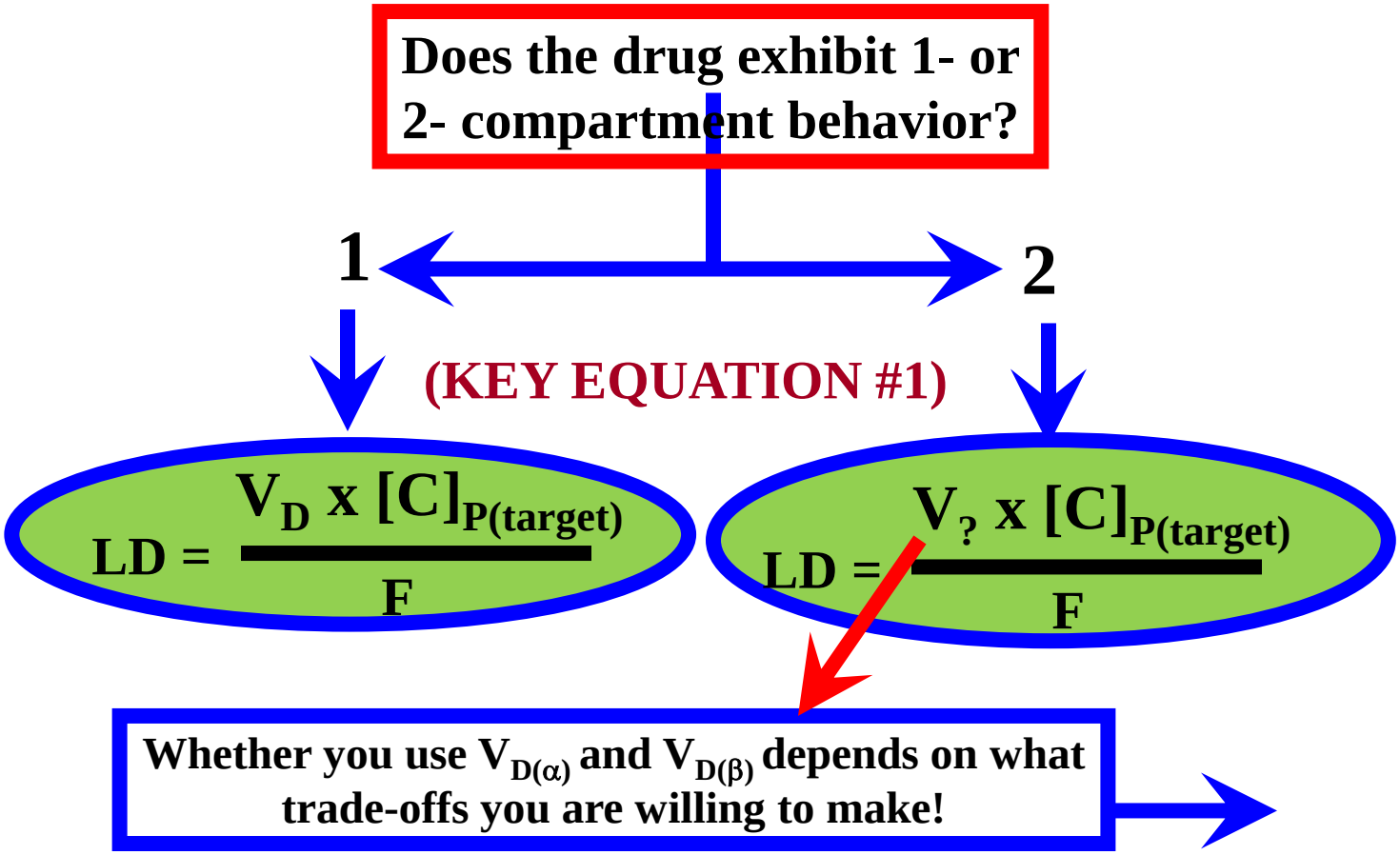
NOTE THAT:

- **Obtaining $V_{D(\beta)}$ requires advanced training in pharmacokinetics**
- **$V_{D(\alpha)}$ and $V_{D(\beta)}$ have different uses**
- **May run across another term called $V_{D(ss)}$**
- **$V_{D(ss)}$ is somewhat less than $V_{D(\beta)}$**
- **For practical purposes $V_{D(ss)}$ and $V_{D(\beta)}$ can be interchanged**

CONCEPT OF VOLUME OF DISTRIBUTION OF DRUGS: IMPORTANCE OF V_D

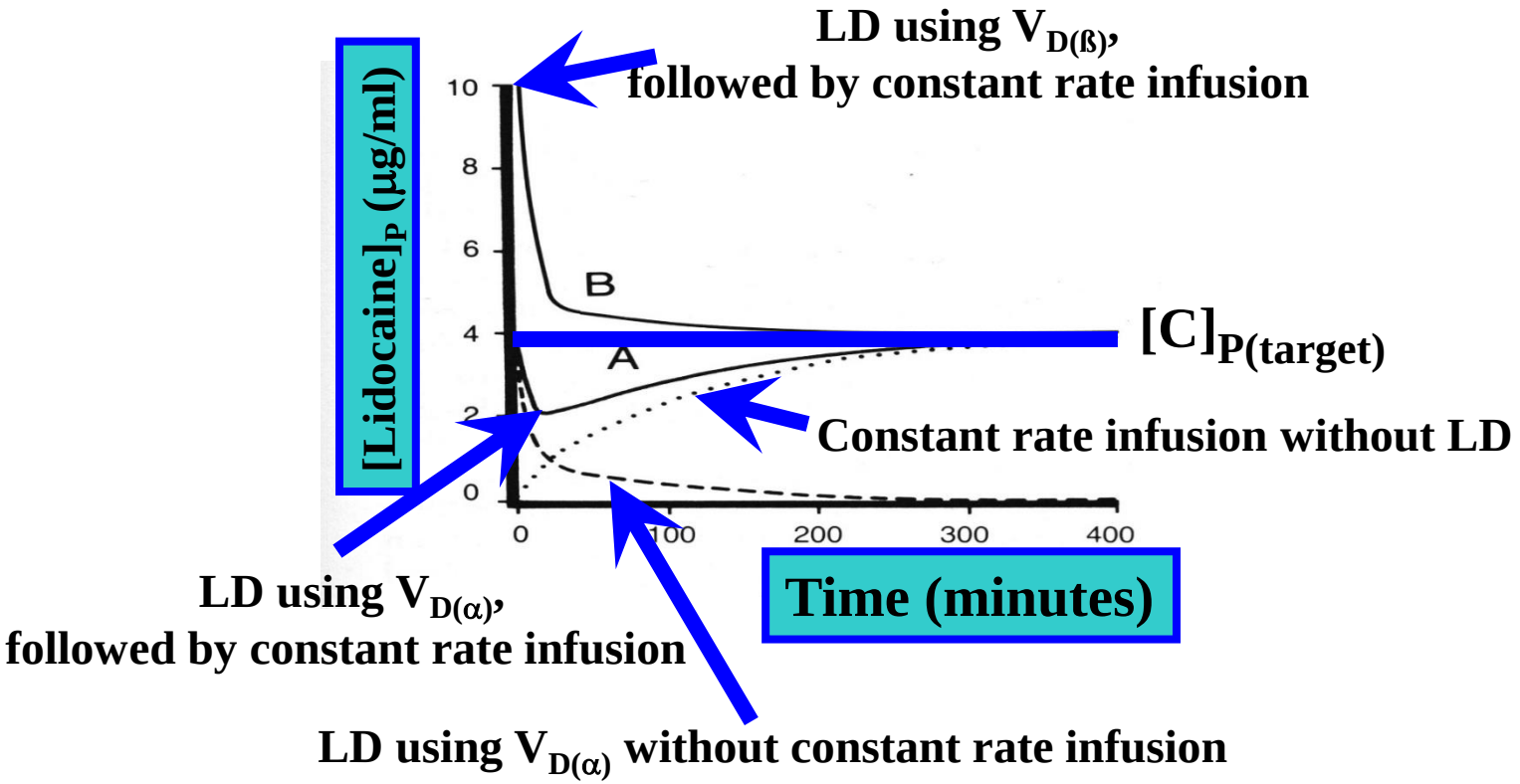
USEFUL FOR CALCULATING LOADING DOSE

CONCEPT OF VOLUME OF DISTRIBUTION OF DRUGS: IMPORTANCE OF V_D



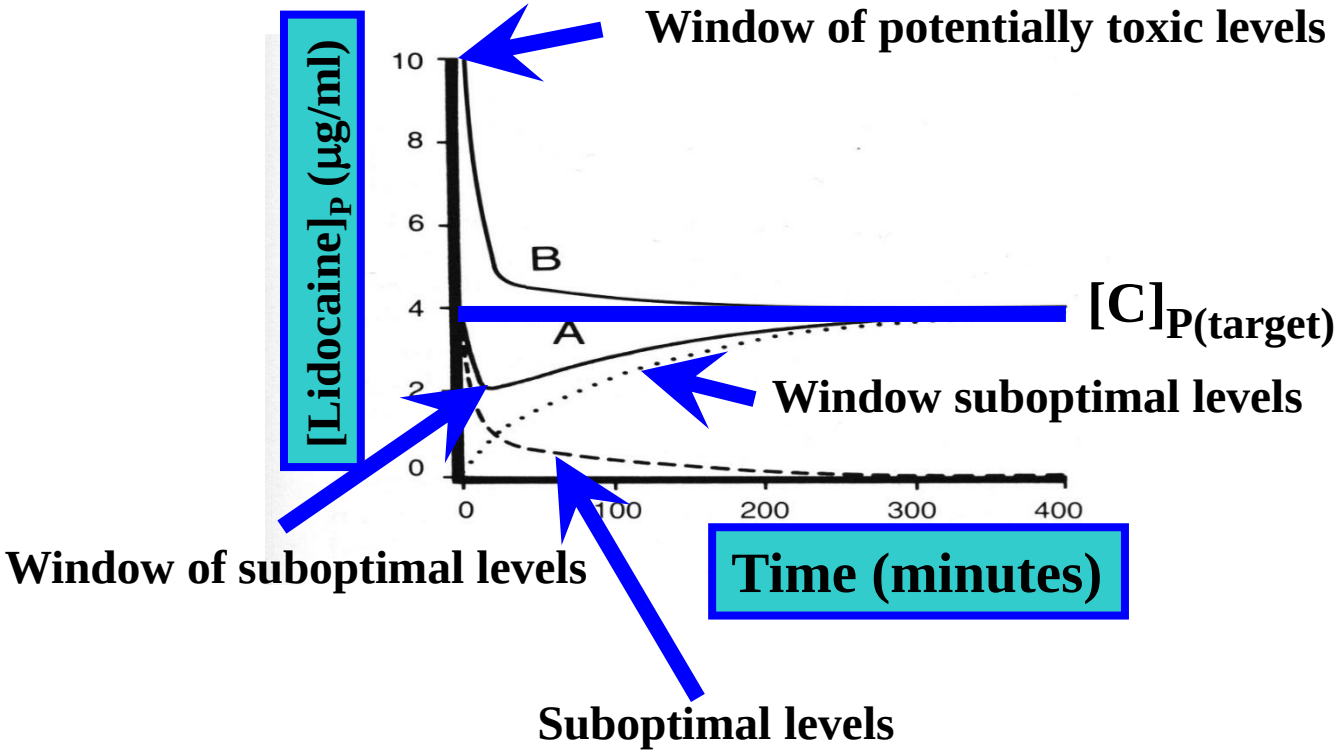
CONCEPT OF VOLUME OF DISTRIBUTION OF DRUGS: IMPORTANCE OF V_D

(example of 2-compartment drug; lidocaine)



CONCEPT OF VOLUME OF DISTRIBUTION OF DRUGS: IMPORTANCE OF V_D

(example of 2-compartment drug; lidocaine)



CONCEPT OF VOLUME OF DISTRIBUTION OF DRUGS: EXAMPLE OF USING V_D TO CALCULATE LD

Pharmacokinetic Parameters forDigoxin:

$[C]_{P(target)} = 1.5\ \mu g/L$

$V_D = 580\ L$

Oral Bioavailability = 0.7

Calculation of Oral LD For Digoxin:

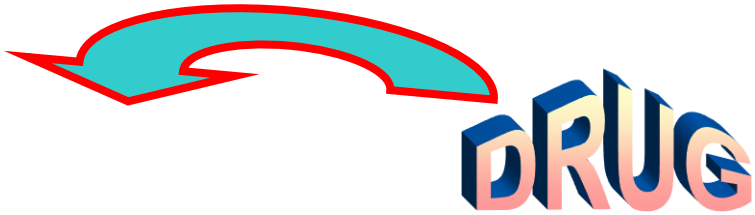
$LD = (V_D \times [C]_{P(target)})/F$

Oral LD = (580 L x 1.5 µg/L) /0.7

Oral LD = 1243 µg ~ 1.2mg

MAJOR CONCEPT #2

CONCEPT OF DRUG CLEARANCE (Cl)



Think of drug clearance as removal of drug from body by body's garbage disposal systems!

CONCEPT OF DRUG CLEARANCE (Cl): DEFINITION OF Cl

By Definition:

$$Cl = \frac{\text{Rate of Drug Elimination}}{[C]_P}$$

Units of Cl:

$$\frac{\text{Amount/Time}}{\text{Amount/Volume}} = \frac{\text{Volume}}{\text{Time}}$$

CONCEPT OF DRUG CLEARANCE: DEFINITION OF Cl

Example:

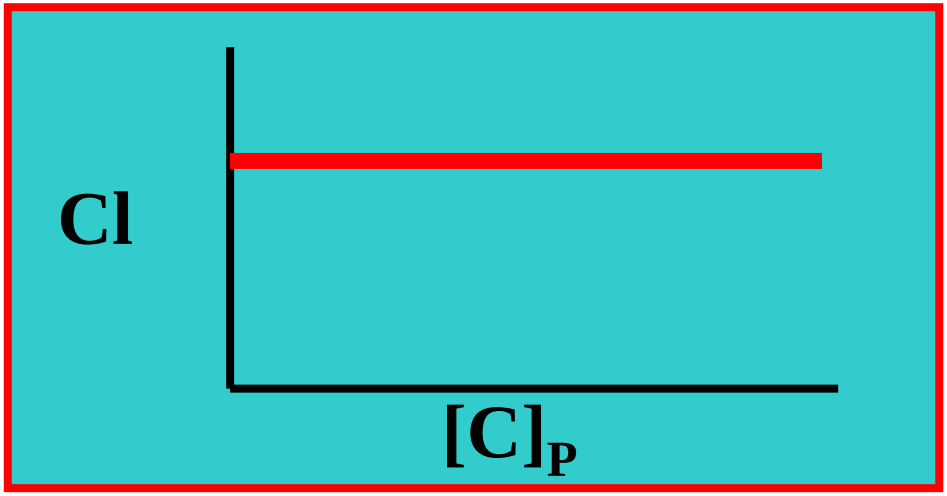
Rate of Drug Elimination = 10 mg/hr

$[C]_P$ = 4 mg/L

$$Cl = \frac{10\ mg/hr}{4\ mg/L} = 2.5\ L/hr$$

CONCEPT OF DRUG CLEARANCE: INTRODUCTION TO Cl

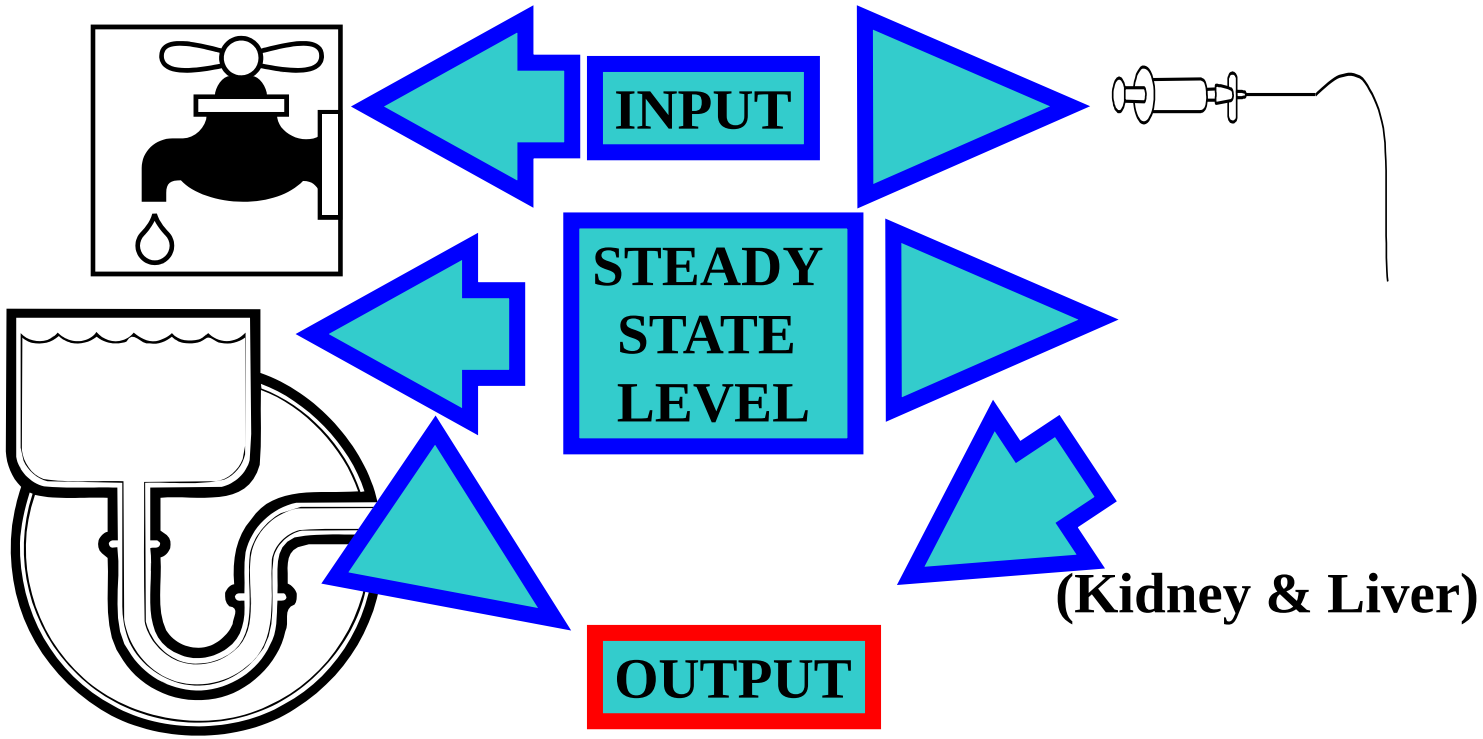
Cl is usually constant over a wide range of $[C]_P$



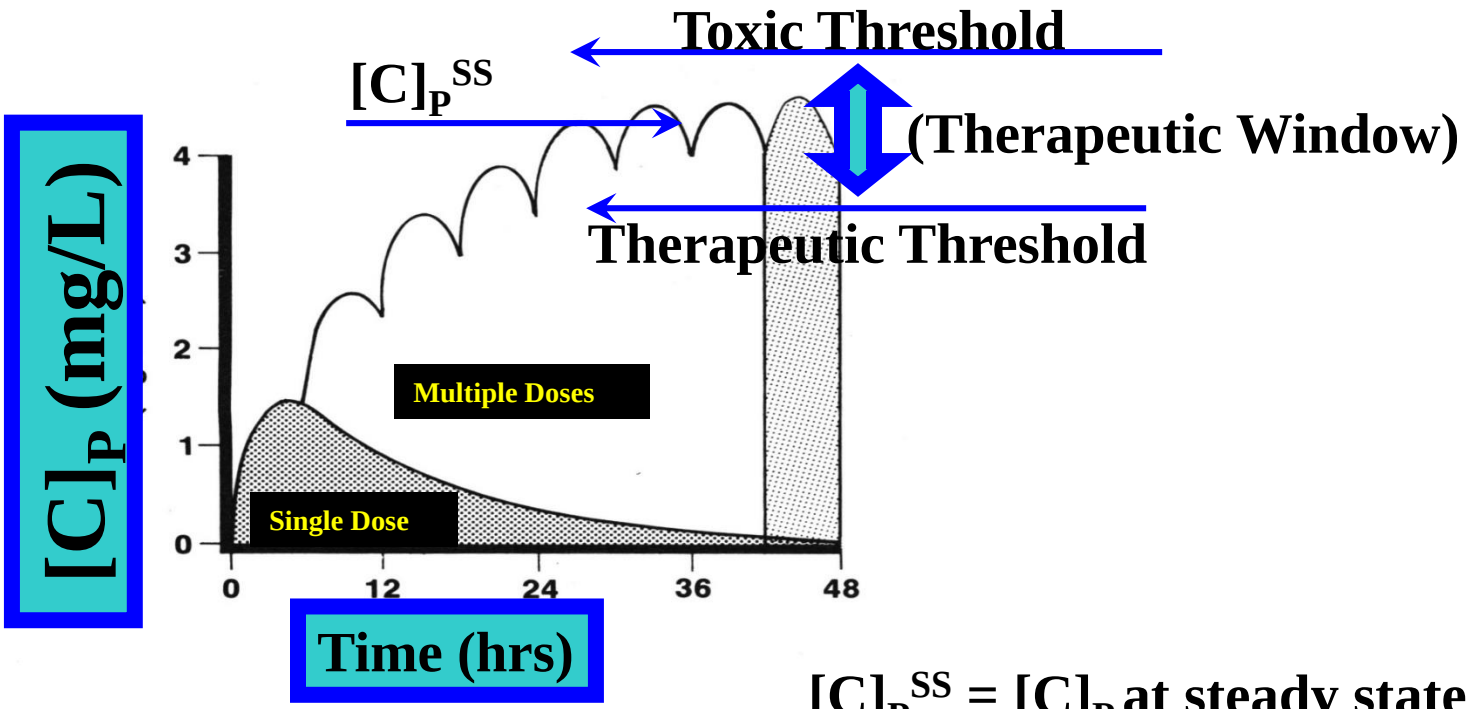
This is a consequence of the fact that most drugs are eliminated from body by 1st order kinetics ($dA/dt = -k \cdot A$).

CONCEPT OF DRUG CLEARANCE: INTRODUCTION TO Cl

Cl is a major determinant of $[C]_P$ at STEADY STATE ($[C]_P^{SS}$)



CONCEPT OF DRUG CLEARANCE: INTRODUCTION TO Cl



$[C]_P^{SS} = [C]_P$ at steady state

CONCEPT OF DRUG CLEARANCE: INTRODUCTION TO Cl

How does Cl influence $[C]_p^{SS}$?

By Definition:

Steady state is said to exist when:

Rate of Drug Administration (R_0) = Rate of Drug Elimination

(Input = Output)

CONCEPT OF DRUG CLEARANCE: INTRODUCTION TO Cl

By definition of Cl:

(Eq A) $$Cl = \frac{\text{Rate of Drug Elimination}}{[C]_P}$$

Rearranging Eq A:

(Eq B) $$[C]_P = \frac{\text{Rate of Drug Elimination}}{Cl}$$

CONCEPT OF DRUG CLEARANCE: INTRODUCTION TO Cl

Applying Eq B to Steady State: **(Eq C)**

$$[C]_P^{SS} = \frac{\text{Rate of Drug Elimination at Steady State}}{Cl}$$

By definition of steady state: **(Eq D)**

R_0 = Rate of Drug Elimination at Steady State

CONCEPT OF DRUG CLEARANCE: INTRODUCTION TO Cl

Substituting Eq D into Eq C:

(Eq E)

$$[C]_P^{SS} = \frac{R_0}{Cl}$$

CONCEPT OF DRUG CLEARANCE: INTRODUCTION TO Cl

Additional definitions:

Maintenance Dose (MD) = Amount of Drug Taken at Regular Intervals

Dosing Interval (DI) = Time Between MDs

Bioavailability (F) = Fraction of Administered Dose that is Absorbed into Systemic Circulation

CONCEPT OF DRUG CLEARANCE: INTRODUCTION TO Cl

Recognizing that:

$$\text{Rate of Drug Administration } (R_0) = \frac{\text{Amount of Drug Delivered to the Systemic Circulation}}{\text{Time}}$$

Substituting Definitions of F, MD, and DI:

(Eq F)

$$R_0 = \frac{F \times MD}{DI}$$

CONCEPT OF DRUG CLEARANCE: INTRODUCTION TO Cl

Substituting Eq F into Eq E:

$$[C]_P^{SS} = \frac{F \times MD}{DI \times Cl}$$

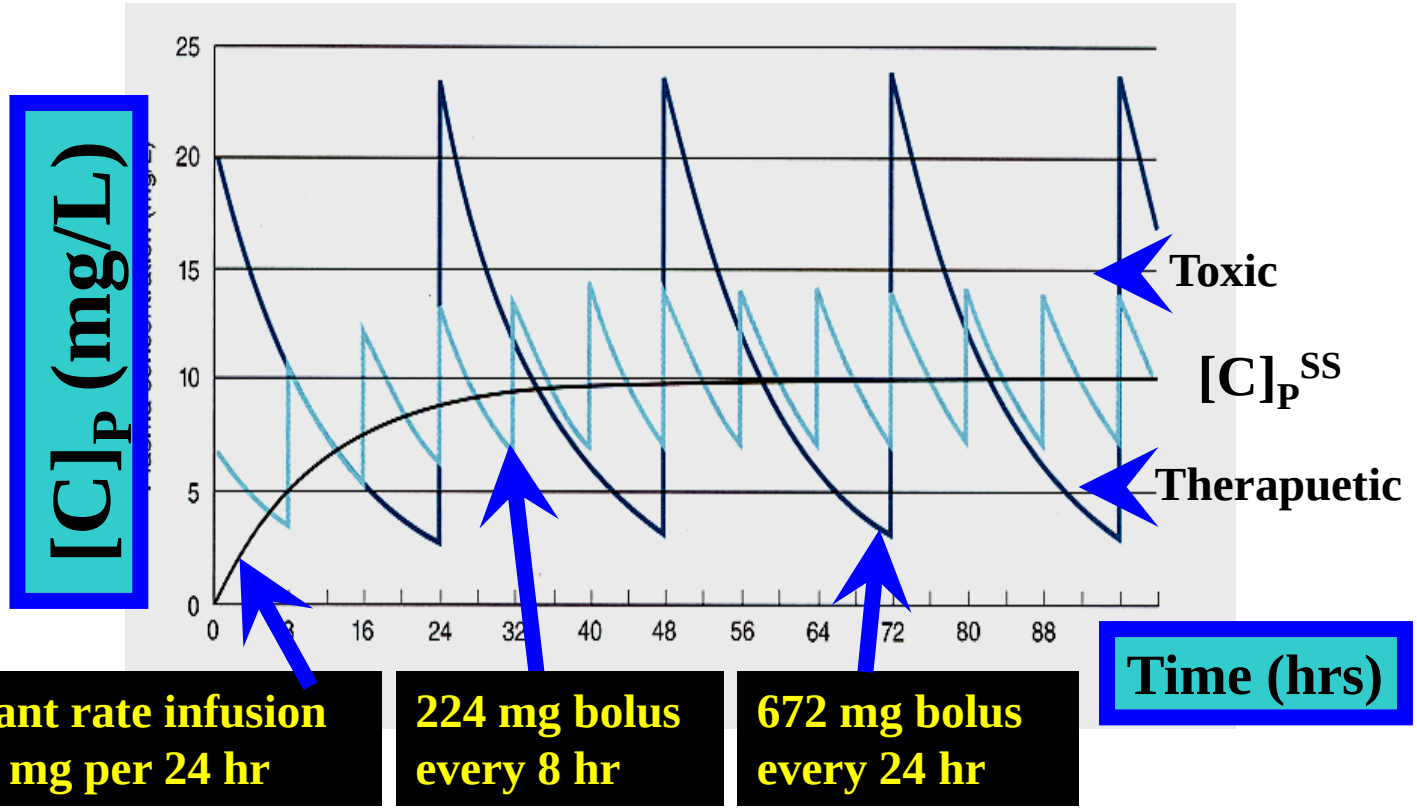
(KEY EQUATION #2)

CONCEPT OF DRUG CLEARANCE: INTRODUCTION TO Cl

Key Equation #2 reveals that $[C]_P^{SS}$ depends not on the absolute values of MD and DI, but on their ratio!

$$[C]_P^{SS} = \frac{F \times MD}{DI \times Cl}$$

CONCEPT OF DRUG CLEARANCE: INTRODUCTION TO Cl



$[C]_P^{SS}$ is same for all three regimens

CONCEPT OF DRUG CLEARANCE: INTRODUCTION TO Cl

Since $[C]_p^{SS}$ is a major determinant of

a) Therapeutic Response
b) Toxicity

Cl is important!!

CONCEPT OF DRUG CLEARANCE: INTRODUCTION TO Cl

Rearranging Key Equation #2:

$$MD/DI = \frac{[C]_P^{SS} \times Cl}{F} \qquad \text{(Eq G)}$$

Since our goal is to provide $[C]_{P(target)}$, we let:

$$[C]_P^{SS} = [C]_{P(target)} \qquad \text{(Eq H)}$$

CONCEPT OF DRUG CLEARANCE: INTRODUCTION TO Cl

Substituting Eq H into Eq G:

(Key Equation #3)

$$MD/DI = \frac{[C]_{P(target)} \times Cl}{F}$$

CONCEPT OF DRUG CLEARANCE: DETERMINANTS of Cl

Most drugs are cleared by the kidneys and/or liver, therefore:

Rate of Elimination =

Rate of Renal Elimination

+

Rate of Hepatic Elimination

(Law of conservation of mass!)

CONCEPT OF DRUG CLEARANCE: DETERMINANTS of Cl

Rate of Elimination/$[C]_P$ =

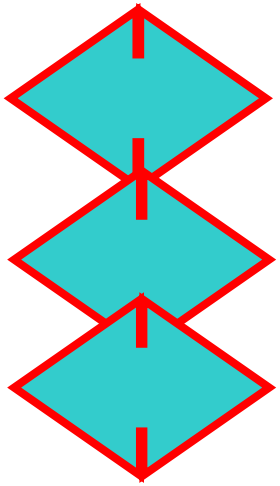
Rate of Renal Elimination/$[C]_P$

+

Rate of Hepatic Elimination/$[C]_P$

(Divide each term by $[C]_P$)

CONCEPT OF DRUG CLEARANCE: DETERMINANTS of Cl



Cl — **Rate of Elimination/$[C]_P$ =**

Cl_R — **Rate of Renal Elimination/$[C]_P$**

+

Cl_H — **Rate of Hepatic Elimination/$[C]_P$**

(By definition of Cl, Cl_R & Cl_H)

CONCEPT OF DRUG CLEARANCE: DETERMINANTS of Cl

$$Cl = Cl_R + Cl_H$$

DUE TO:

- **Glomerular filtration of drugs not bound to plasma proteins**

- **Secretion into renal tubules of acidic and basic drugs by transport systems in proximal tubule**

CONCEPT OF DRUG CLEARANCE: DETERMINANTS of Cl

$$Cl = Cl_R + Cl_H$$

REDUCED BY:

- **Reabsorption of lipophilic drugs from the renal tubule**
- **Renal diseases that decrease glomerular filtration and tubular secretion of drug**
- **Competition between drugs for secretion by transport systems in the proximal tubule**

CONCEPT OF DRUG CLEARANCE: DETERMINANTS of Cl

$$Cl = Cl_R + Cl_H$$

DUE TO:

- **Metabolism of drugs by liver enzymes**
- **Secretion of drugs into bile by transport systems in the hepatocytes**

CONCEPT OF DRUG CLEARANCE: DETERMINANTS of Cl

$$Cl = Cl_R + Cl_H$$

REDUCED BY:

- **Ionization of drugs which limits penetration of drug into hepatocytes**
- **Competition between drugs for metabolism and/or transport into bile**
- **Liver disease**
- **Genetic variation in drug metabolizing enzymes**

CONCEPT OF DRUG CLEARANCE: DETERMINANTS of Cl

$$Cl = Cl_R + Cl_H$$

INCREASED BY:

- **Induction of liver enzymes by same drug, other drugs and/or environmental chemicals**

- **Genetic variation in drug metabolizing enzymes**

CONCEPT OF DRUG CLEARANCE: OBTAINING Cl

There are many ways to obtain Cl:

- **Give IV infusion of drug to steady state, measure plasma levels and divide $[C]_p^{SS}$ by rate of infusion.**

$$Cl = \text{Rate of Infusion}/[C]_p^{SS}$$

- **Give IV bolus of drug, measure plasma levels over time, measure area under curve (AUC) and divide bolus dose by AUC.**

$$Cl = \text{Dose}/AUC$$

(Don’t worry about derivation!)

CONCEPT OF DRUG CLEARANCE: OBTAINING Cl

There are many ways to obtain Cl:

• Give IV bolus of drug, measure plasma levels over time, fit data to appropriate equation, obtain parameters from fit and calculate Cl:

1-compartment behavior | **2-compartment behavior**

$[C]_P^t = [C]_P^0 \bullet e^{-kt}$ **(Empirical)** $[C]_P^t = A \bullet e^{-\alpha t} + B \bullet e^{-\beta t}$

(Don't worry about derivation!)

$Cl = Dose/([C]_P^0/k)$ | $Cl = Dose/(A/\alpha + B/\beta)$

CONCEPT OF :
IMPORTANCE OF Cl

USEFUL FOR CALCULATING RATE OF DRUG ADMINISTRATION

CONCEPT OF DRUG CLEARANCE: IMPORTANCE of Cl

Note that Key Equation #3 tells us the rate of drug administration (MD/DI).

$$MD/DI = \frac{[C]_{P(target)} \times Cl}{F}$$

We must consult other equations to determine most appropriate DI and therefore MD.

CONCEPT OF DRUG CLEARANCE: IMPORTANCE of Cl

DEFINITION

Therapeutic Window (TW) =

$$\frac{\text{highest } [C]_P \text{ that is safe}}{\text{lowest } [C]_P \text{ that is therapeutically effective}}$$

CONCEPT OF DRUG CLEARANCE: IMPORTANCE of Cl

DEFINITION

Maximum Dosing Interval (DI_{max}):

The longest dosing interval that still provides non-toxic peak plasma levels of drug while providing therapeutically effective trough plasma levels of drug.

CONCEPT OF DRUG CLEARANCE: IMPORTANCE of Cl

DEFINITION

Elimination $t_{1/2}$:

Time required for drug elimination processes to decrease the amount of drug in the body by 50%.

(Much more on $t_{1/2}$ later!)

CONCEPT OF DRUG CLEARANCE: IMPORTANCE of Cl

DI_{max} is determined by interplay between therapeutic window (TW) and $t_{1/2}$.

(Don't worry about derivation!)

$$DI_{max} = 1.44 \times t_{1/2} \times \ln (TW)$$

(Key Equation #4)

- **If calculated DI_{max} is ~24 hrs, give all of daily dose once daily**
- **If calculated DI_{max} is too short, give daily dose by constant rate infusion over 24 hrs**
- **If DI_{max} is some fraction of the day, give daily dose in divide doses**

CONCEPT OF DRUG CLEARANCE: EXAMPLE OF CALCULATING DOSAGE REGIMEN

Pharmacokinetic Parameters forDigoxin:

$[C]_{P(target)}$ = 1.5 µg/L

Cl = 6.6 L/hr

Oral Bioavailability = 0.7

Calculation of Oral MD/DI For Digoxin:

$$\text{Oral MD/DI} = ([C]_{P(target)} \times Cl)/F$$

$$\text{Oral MD/DI} = (1.5\ \mu g/L \times 6.6\ L/hr)/0.7$$

$$\text{Oral MD/DI} = 14.1\ \mu g/hr$$

CONCEPT OF DRUG CLEARANCE: EXAMPLE OF CALCULATING DOSAGE REGIMEN

Pharmacokinetic Parameters for Digoxin:

$[C]_{P(effect)} > 0.8\ \mu g/L$

$[C]_{P(toxic)} > 2.5\ \mu g/L$

$t_{1/2} = 39$ hrs

Calculation of DI_{max} For Digoxin:

$$DI_{max} = 1.44 \times t_{1/2} \times \ln (TW)$$

$$DI_{max} = 1.44 \times 39 \text{ hrs} \times \ln (2.5/0.8)$$

$$DI_{max} = 64 \text{ hrs}$$

CONCEPT OF DRUG CLEARANCE: EXAMPLE OF CALCULATING DOSAGE REGIMEN

For convenience use DI of 24 hrs (< 64 hrs)

Oral MD/DI = 14.1 µg/hr

Oral MD/24 hrs = 14.1 µg/hr

Oral MD = 14.1 µg/hr x 24 hrs = 338.4 µg = 0.34 mg

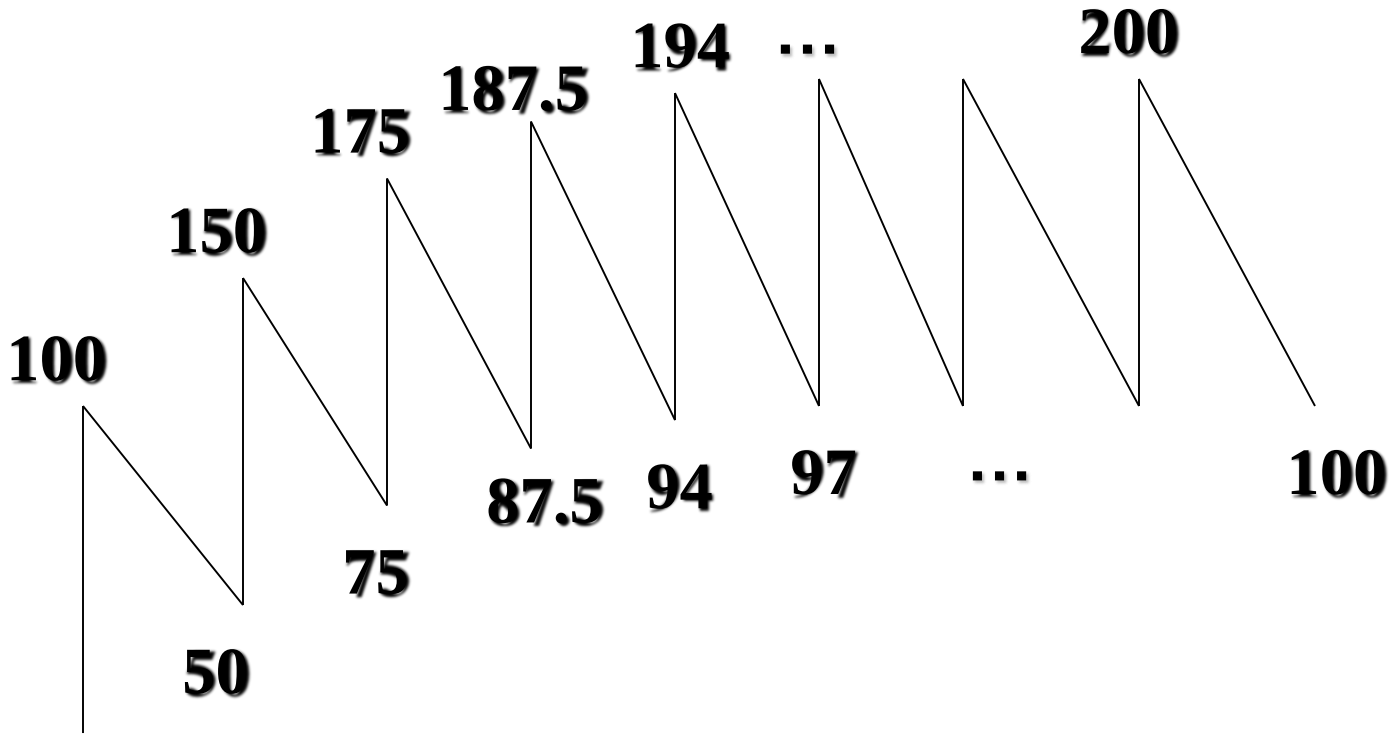
For convenience, round-off to nearest available dosage size, in this case 0.375 mg

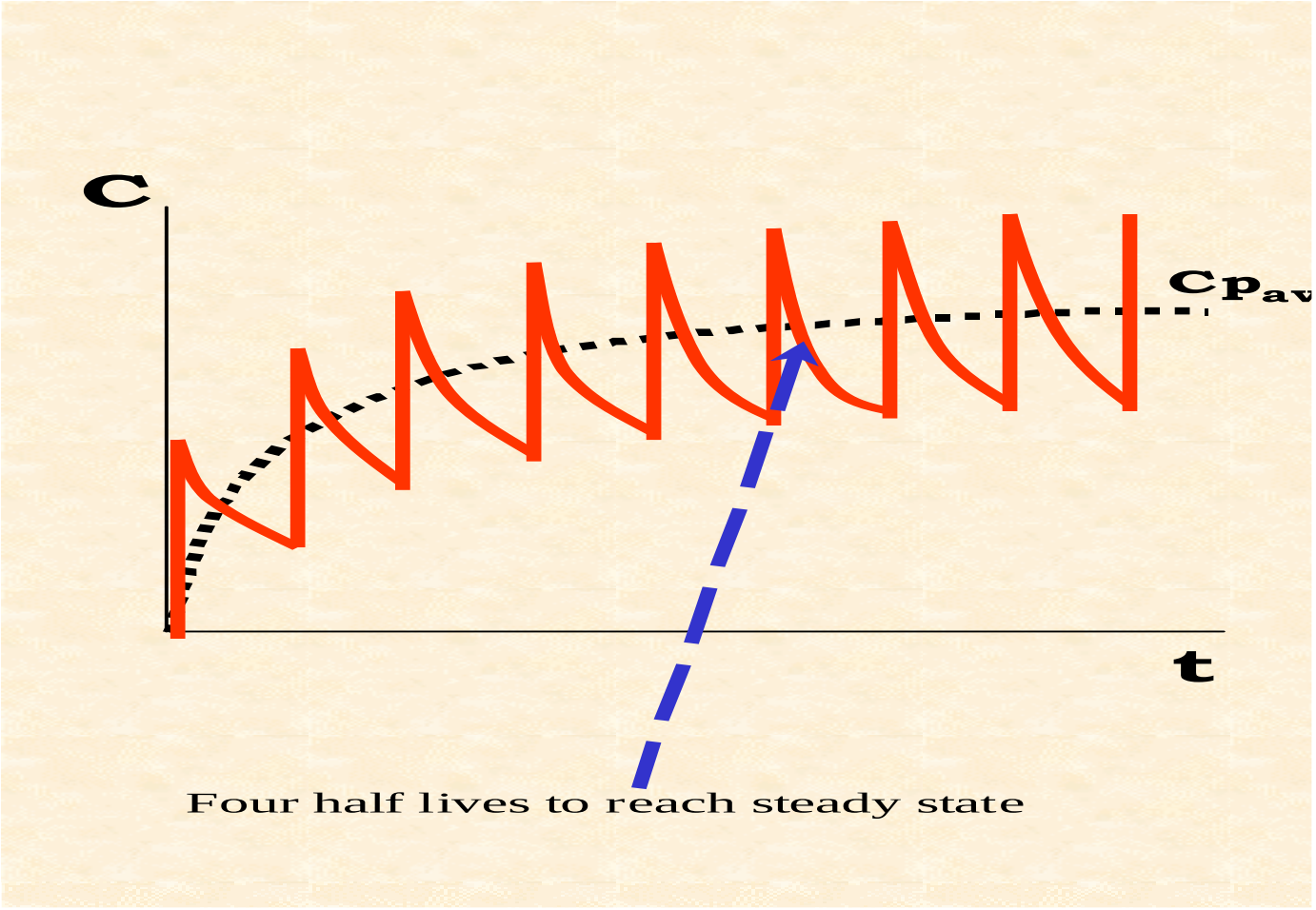
Administer one 0.375 mg tablet every day

MAJOR CONCEPT #3

CONCEPT OF ELIMINATION HALF-LIFE ($t_{1/2}$)

Accumulation to Steady State
100 mg given every half-life




C
$C_{P_{av}}$
t
Four half lives to reach steady state

CONCEPT OF ELIMINATION HALF-LIFE ($t_{1/2}$): DEFINITION of $t_{1/2}$

Time required for drug elimination processes to decrease the amount of drug in the body by 50%.

CONCEPT OF ELIMINATION HALF-LIFE: INTRODUCTION TO $t_{1/2}$

By definition:

(Eq I) $$Cl = \frac{\text{Rate of Drug Elimination}}{[C]_P}$$

Rearranging Eq I:

(Eq J)

Rate of Drug Elimination (i.e., $-dA/dt$) = $Cl \times [C]_P$

Substituting in Eq J the term D/V_D for $[C]_P$:

(Eq K) $$-dA/dt = Cl \times D/V_D$$

CONCEPT OF ELIMINATION HALF-LIFE: INTRODUCTION TO $t_{1/2}$

(Eq K) $-dA/dt = Cl \times D/V_D$

Rearranging Eq K:

(Eq L) $-dA/A = (Cl/V_D) \times dt$

Taking definite integral of Eq L over appropriate limits:

(Eq M)

$$\int_{A_{initial}}^{1/2A_{initial}} -dA/A = \int_{0}^{t_{1/2}} (Cl/V_D) \times dt$$

CONCEPT OF ELIMINATION HALF-LIFE: INTRODUCTION TO $t_{1/2}$

(Eq M)

$$\int_{A_{initial}}^{1/2A_{initial}} -dA/A = \int_{0}^{t_{1/2}} (Cl/V_D) \times dt$$

(KEY EQUATION #5)

$$t_{1/2} = \frac{0.693 \times V_D}{Cl}$$

CONCEPT OF ELIMINATION HALF-LIFE: DETERMINANTS OF $t_{1/2}$

(KEY EQUATION # 5)

$$t_{1/2} = \frac{0.693 \times V_D}{Cl}$$

Note that if:

- **Cl increases, $t_{1/2}$ decreases**
- **Cl decreases, $t_{1/2}$ increases**
- **V_D increases, $t_{1/2}$ increases**
- **V_D decreases, $t_{1/2}$ decreases**

CONCEPT OF ELIMINATION HALF-LIFE : OBTAINING $t_{1/2}$

There are many ways to obtain $t_{1/2}$:

- **Calculate from V_D and Cl using key equation #5**

CONCEPT OF ELIMINATION HALF-LIFE: OBTAINING of $t_{1/2}$

But which V_D do I use if 2-compartment behavior??

$$t_{1/2} = \frac{0.693 \times V_D}{Cl}$$

Note that as drug distributes, V_D increases from $V_{D(\alpha)}$ to $V_{D(\beta)}$. Consequently, elimination $t_{1/2}$ is rapidly changing (increasing) until distribution is complete.

CONCEPT OF ELIMINATION HALF-LIFE: OBTAINING $t_{1/2}$

But which V_D do I use if 2-compartment behavior??

For 2-compartment behavior, use $V_{D(\beta)}$ to calculate elimination $t_{1/2}$ since after distribution, this value is stable and, therefore, meaningful!

CONCEPT OF ELIMINATION HALF-LIFE: OBTAINING $t_{1/2}$

There are many ways to obtain $t_{1/2}$:

• Give IV bolus of drug, measure plasma levels over time, fit data to appropriate equation, obtain parameters from fit and calculate $t_{1/2}$:

1-compartment behavior

$$[C]_P^t = [C]_P^0 \bullet e^{-kt}$$

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

(Empirical)

(Don't worry about derivation!)

2-compartment behavior

$$[C]_P^t = A \bullet e^{-\alpha t} + B \bullet e^{-\beta t}$$

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

CONCEPT OF ELIMINATION HALF-LIFE: IMPORTANCE of $t_{1/2}$

Elimination $t_{1/2}$ is a major determinant of variations in $[C]_P$ around $[C]_P^{SS}$, i.e., peak-to-trough ratios.

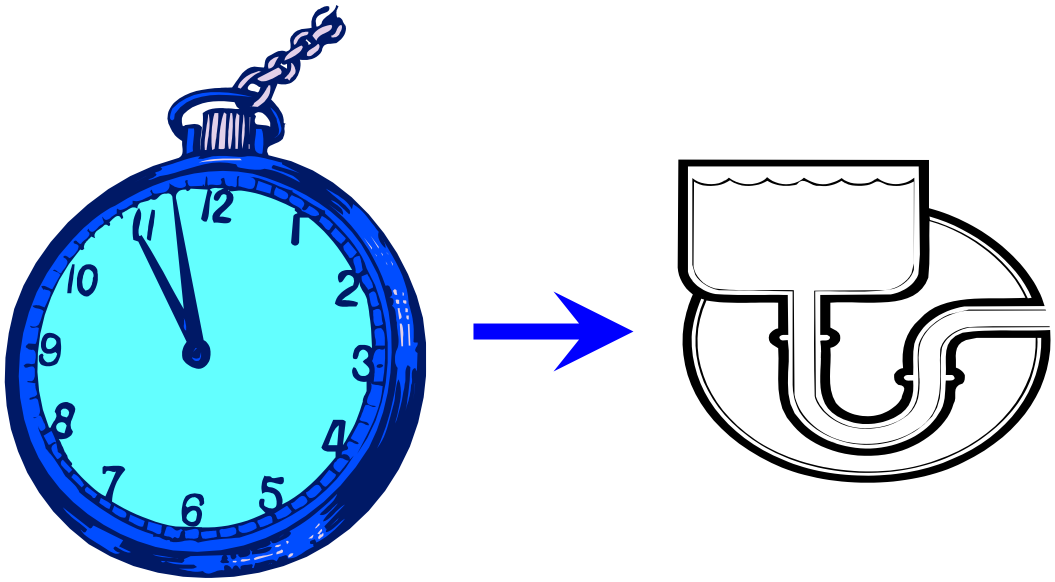
Elimination $t_{1/2}$ may place major constraints on the dosage regimen.

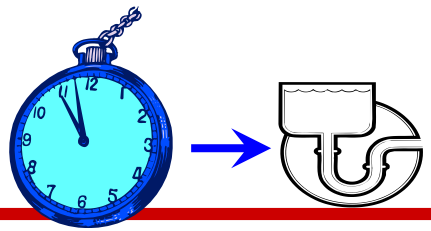
Elimination $t_{1/2}$ determines the time required for $[C]_P$ to achieve $[C]_P^{SS}$.

Elimination $t_{1/2}$ determines how much time is required for drug to be eliminated from body.

MAJOR CONCEPT #4

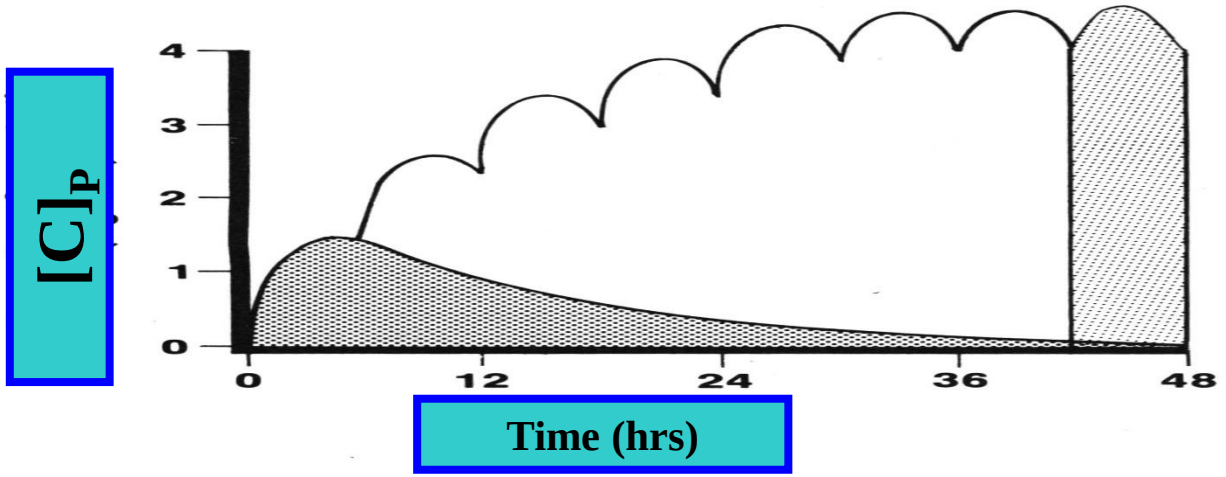
CONCEPT OF TIME TO STEADY STATE (t_{SS})





CONCEPT OF t_{SS} : DEFINITION of t_{SS}

t_{SS} is the time required to reach $[C]_P^{SS}$ if the dosing regimen only involves the repeated administration of drug using a specific MD/DI ratio.



CONCEPT OF t_{SS} : INTRODUCTION TO t_{SS}

Note that:

- **Theoretically, t_{ss} is infinity and $[C]_P^{SS}$ is never reached!!**
- **However, the time required to achieve any specified fraction of $[C]_P^{SS}$ can be calculated.**

CONCEPT OF t_{SS} : DETERMINANTS of t_{SS}

Note that:

- **For a drug with 1-compartment behavior, the time required to reach any specified fraction of $[C]_P^{SS}$ is a function only of elimination $t_{1/2}$.**

- **For a drug with 2-compartment behavior, the time required to reach any specified fraction of $[C]_P^{SS}$ is a function of elimination $t_{1/2}$; however, the half-life of the distribution process also contributes and complicates the situation.**

CONCEPT OF t_{SS} : DETERMINANTS of t_{SS}

If 1-compartment behavior, four elimination half-lives:

Provide 94% of $[C]_p^{SS}$ when treatment started

Reduce $[C]_p$ to 6% of $[C]_p^{SS}$ when treatment stopped

CONCEPT OF t_{SS} : DETERMINANTS of t_{SS}

If 2-compartment behavior, four elimination half-lives:

Provide > or = 94% of $[C]_P^{SS}$ when treatment started

Reduce $[C]_P$ to < or = 6% of $[C]_P^{SS}$ when treatment stopped

CONCEPT OF t_{SS} : DETERMINANTS of t_{SS}

BY GENERAL CONSENSUS

For both 1- and 2-Compartment Behavior:

$$t_{SS} = 4 \times t_{1/2}$$

CONCEPT OF t_{SS} : DETERMINANTS of t_{SS}

Where did all this come from?

The answer to this question requires requires advanced training in pharmacokinetics! (Just take it on faith!)

CONCEPT OF t_{SS} : IMPORTANCE OF t_{SS}

t_{SS} Is The Time Required To Reach:

- **an initial $[C]_P^{SS}$ when treatment is begun**
- **a new $[C]_P^{SS}$ when the dosage regimen is altered**
- **$[C]_P^{SS} = 0$ when treatment is stopped**

CONCEPT OF t_{SS} : EXAMPLE OF CALCULATIONS INVOLVING t_{SS}

Pharmacokinetic Parameters for Digoxin:

$t_{1/2}$ = 39 hrs

Calculation of t_{SS} for Digoxin:

$$t_{SS} = 4 \times t_{1/2}$$

$$t_{SS} = 4 \times 39 \text{ hrs} = 156 \text{ hrs} = 6.5 \text{ days!!}$$

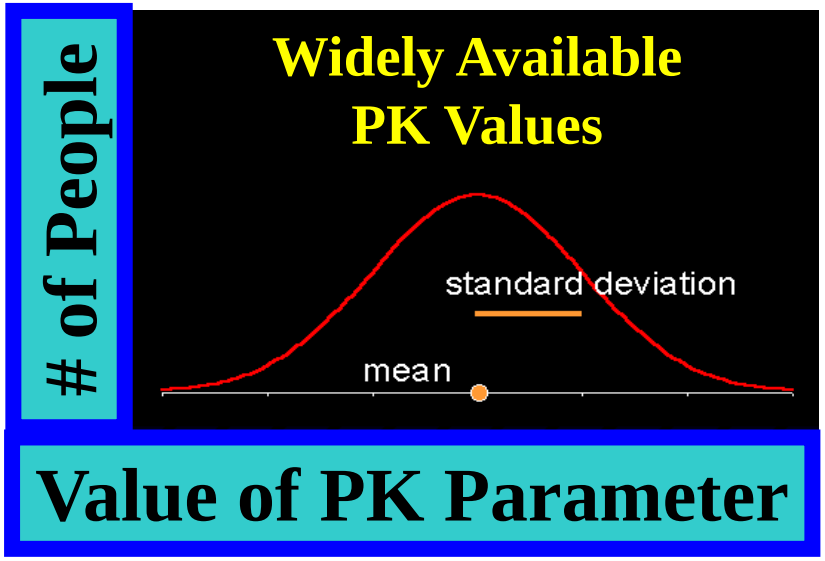
This is why a loading dose of digioxin is often prescribed.

Designing a Dosage Regimen

Designing a Dosage Regimen

Population versus Individual Values for PK Parameters

Rarely Available PK Values



Population values represent average values rather than the value for YOUR patient.

Individual values represent the values in YOUR patient, but they have to be determined in YOUR patient.

Designing a Dosage Regimen

Population versus Individual Values for PK Parameters

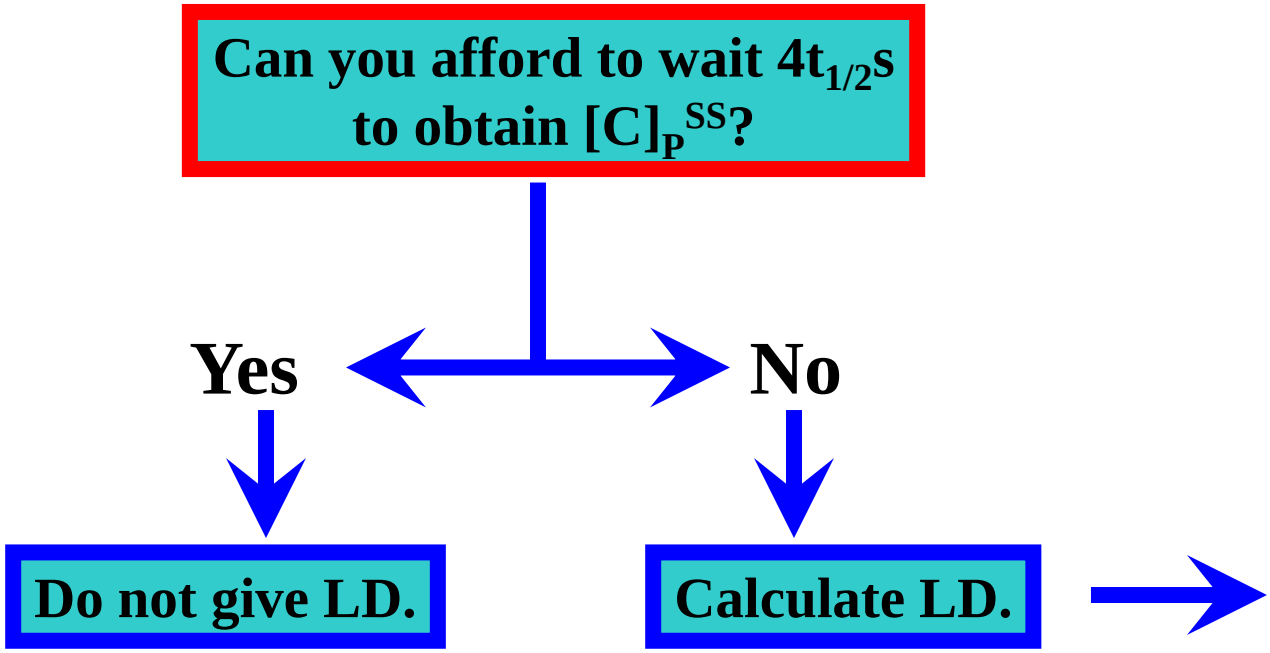
If available, of course use individual values for PK parameters.

You will nearly always have to settle for population values for PK parameters.

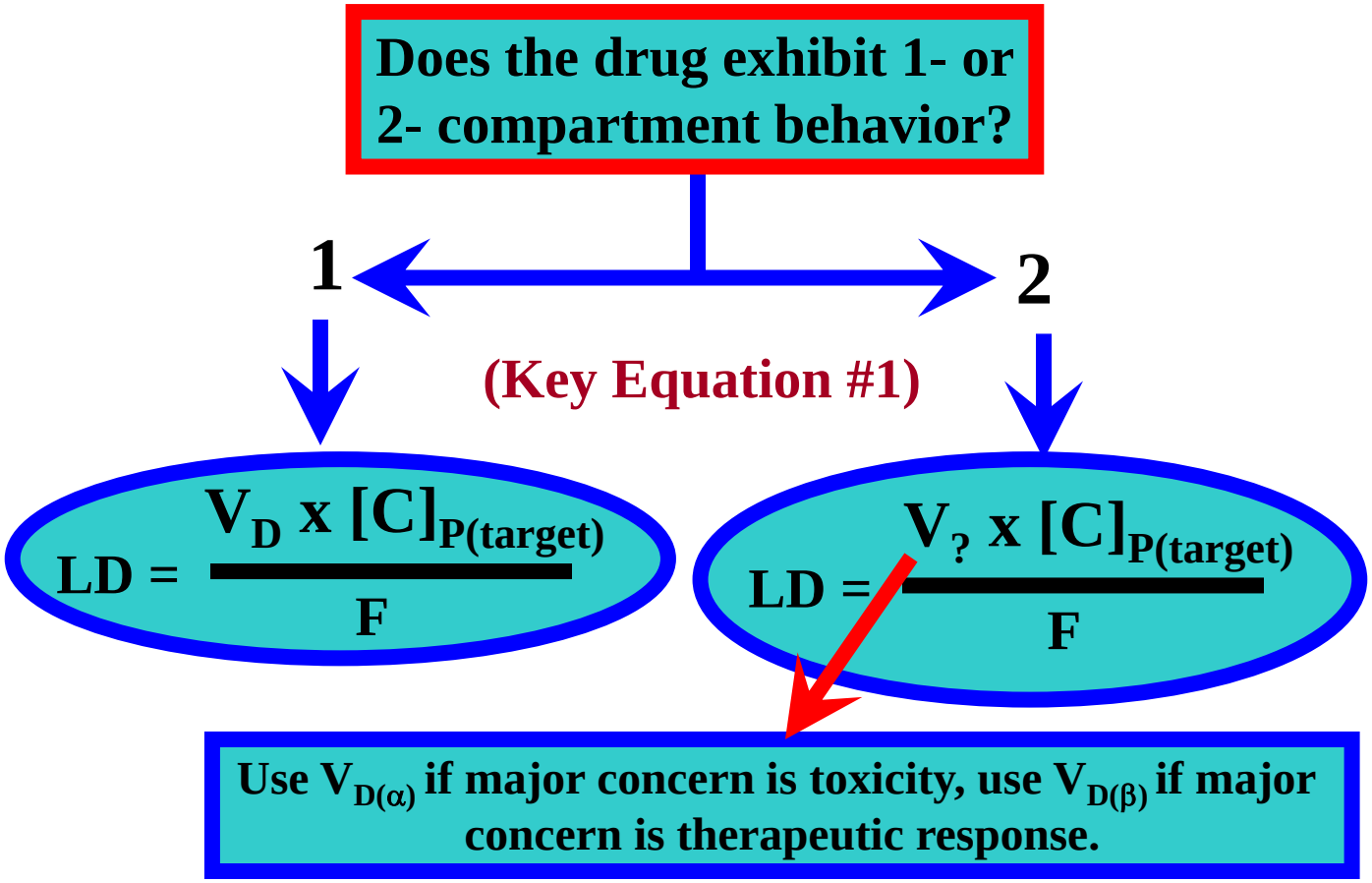
Designing a Dosage Regimen

Step #1:
Decide whether LD is required and, if so, calculate LD.

Designing a Dosage Regimen



Calculating Loading Dose



Designing a Dosage Regimen

Step #2:
Determine MD/DI Ratio.

Calculating MD/DI Ratio

(Key Equation #3)

$$MD/DI = \frac{[C]_{P(target)} \times Cl}{F}$$

Designing a Dosage Regimen

Step #3:
Determine DI.

Calculating a Dosing Interval

DI_{max} is determined by interplay between therapeutic window (TW) and $t_{1/2}$.

$$DI_{max} = 1.44 \times t_{1/2} \times \ln (TW)$$

(Key Equation #4)

- **If calculated DI_{max} is ~24 hrs, give all of daily dose once daily**
- **If calculated DI_{max} is too short, give daily dose by constant rate infusion over 24 hrs**
- **If DI_{max} is some fraction of the day, give daily dose in divide doses**

Designing a Dosage Regimen

Capacity-Limited Metabolism (Also called "Zero Order Kinetics")

- An infrequent, but important phenomenon

- Clearance is not constant with respect to $[C]_P$ because metabolizing enzymes are saturated at "therapeutic concentrations"

- Rate of drug elimination is fixed and cannot use clearance to calculate dosage regimen

- For such drugs, daily dose should not exceed fixed rate of elimination

Designing a Dosage Regimen

Ethanol is Eliminated by "Zero Order Kinetics"

- **For average adult, rate of metabolism is 10 g/hr**
- **45 ml of DRUG contains 14 g of ethanol**
- **If drink 45 ml of DRUG every hr, will accumulate 4 g ethanol/hr and develop coma in 48 hr**
- **However, can drink 30 ml DRUG (9 g ethanol) every hr with impunity**

Adjusting a Dosage Regimen

A dosage regimen may need to be adjusted if plasma clearance changes, for instance because of disease.

Adjusting a Dosage Regimen

Adjusting Dosage Regimens in Patients with Renal Disease

If drug is eliminated mostly by liver, no adjustment required.

If drug is eliminated mostly by kidney, either:

- **Re-evaluate need for drug and discontinue if possible**
- **Reduce dose**
- **Increase dosing interval**
- **Switch to drug eliminated mostly by liver**

Adjusting a Dosage Regimen

Adjusting Dosage Regimens in Patients with Liver Disease

If drug is eliminated mostly by kidney, no adjustment required.

If drug is eliminated mostly by liver, either:

- **Re-evaluate need for drug and discontinue if possible**
- **Reduce dose**
- **Increase dosing interval**
- **Switch to drug eliminated mostly by kidney**

Pharmacokinetics

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Professor of Pharmaceutics
and Industrial Pharmacy
Faculty of Pharmacy – Sana'a University

Pharmacokinetics

Pharmacokinetics is the science of the kinetics of drug absorption, distribution, and elimination (ie, metabolism and excretion).

Clinical pharmacokinetics is the application of pharmacokinetic methods to drug therapy in patient care. Clinical pharmacokinetics involves a multidisciplinary approach to individually optimized dosing strategies based on the patient's disease state and patient-specific considerations.

Pharmacokinetic Parameters

Cp - Cp0 - D

K

Vd

T1/2

Cl

AUC

Plasma Concentration-Volume of Distribution

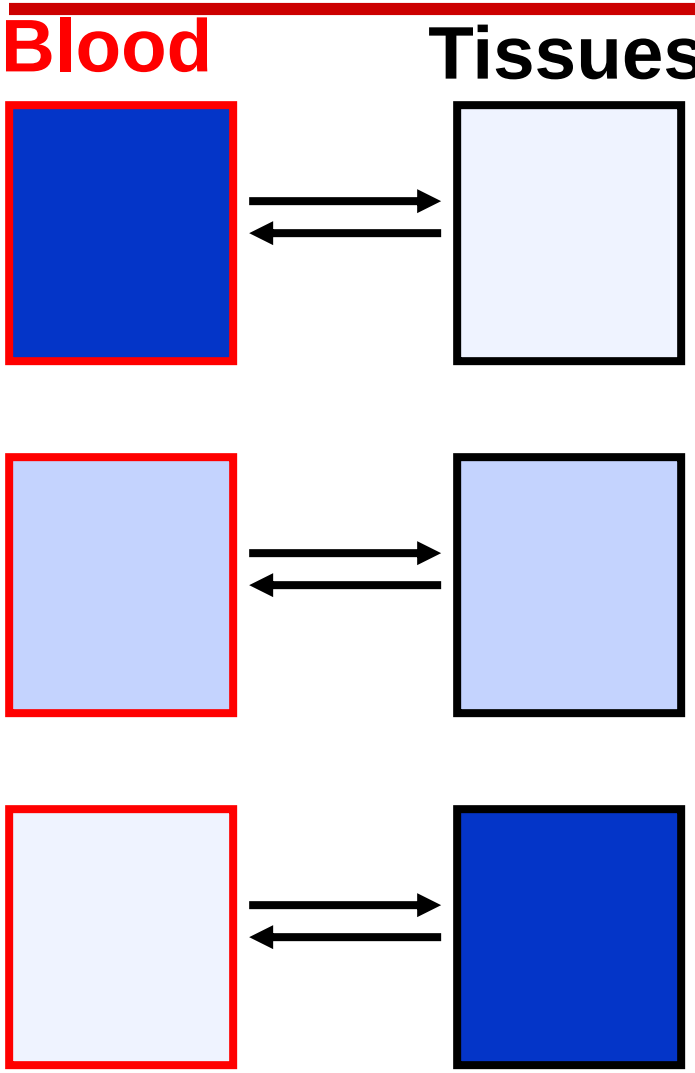
Volume of distribution

The apparent volume of distribution is not a true physiologic volume. Most drugs have an apparent volume of distribution smaller than, or equal to, the body mass. For some drugs, the volume of distribution may be several times the body mass.

Volume of distribution

For this dose, the small C p 0 will result in a large V D. Drugs with a large apparent V D are more concentrated in extravascular tissues and less concentrated intravascularly. If a drug is highly bound to plasma proteins or remains in the vascular region, then C p 0 will be higher, resulting in a smaller apparent V D. Consequently, binding of a drug to peripheral tissues or to plasma proteins will significantly affect V D. The apparent V D is a volume term that can be expressed as a simple volume or in terms of percent of body weight.

Patterns of distribution



Stays mainly in blood.

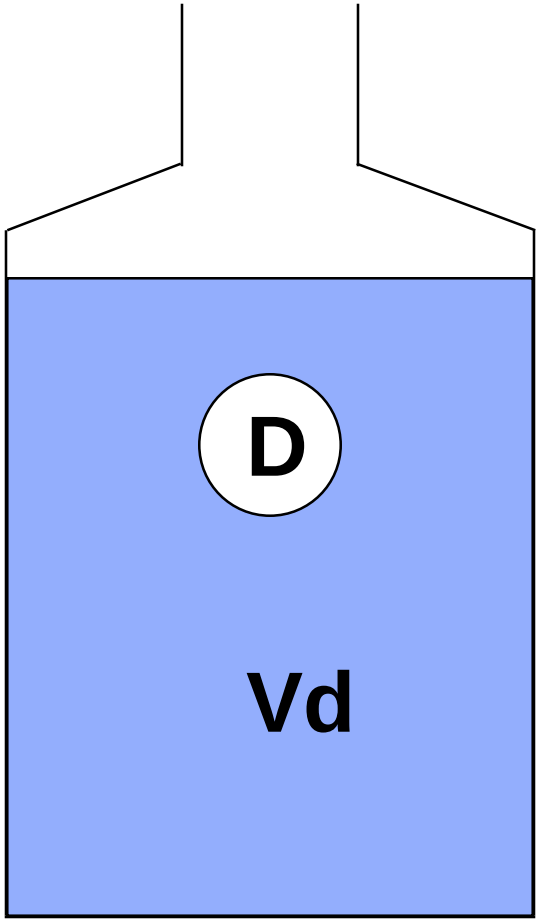
Distributes evenly.

Distributes strongly into tissue.

Volume of distribution

A measure of the tendency of a drug to move out of the blood into the tissues.
(Large Vol Dist indicates strong tendency to enter the tissues.)

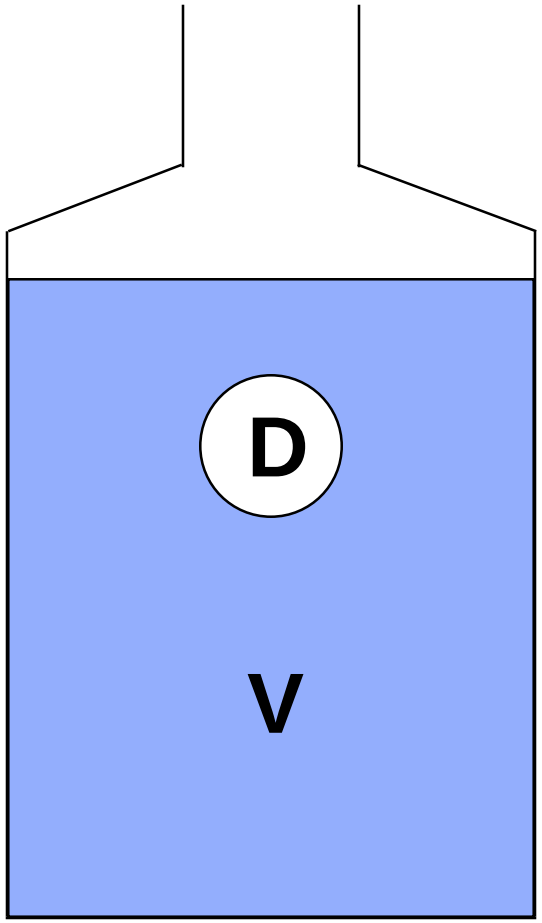
Volume of distribution



$Cp^0 = D/Vd$

$Vd = D/ Cp^0$

Volume of distribution



D = 50 mg

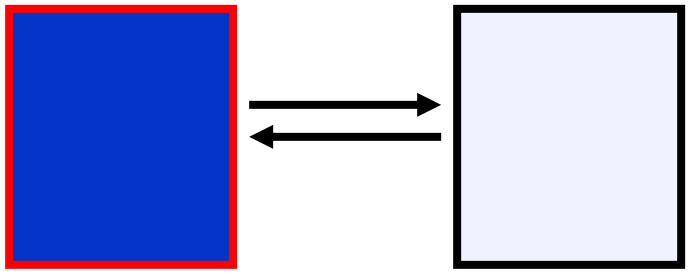
Cp^0 = 0.25 mg/L

Vd = D/ Cp^0 = 50mg / 0.25mg/L

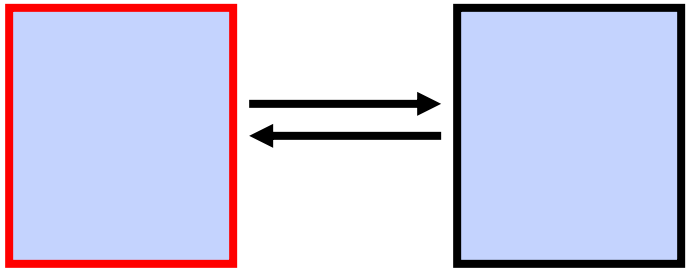
= 200 Litres

Relating pattern of distribution to volume of distribution

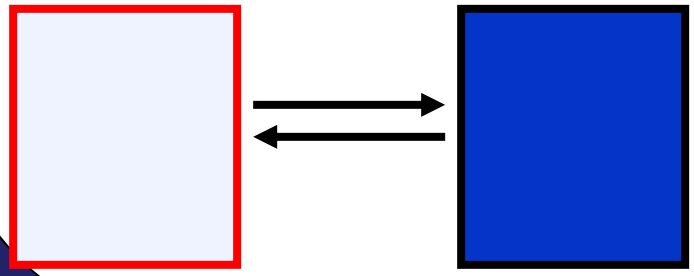
Blood **Tissues**



Stays mainly in blood.
Blood concentration high.
$V = D / Cp^0$ → small vol dist.



Distributes evenly.
Moderate blood concentration.
$V = D / Cp^0$ → medium vol dist



Distributes strongly into tissue.
Low blood concentration.
$V = D / Cp^0$ → large vol dist

Volumes of distribution

(In litres for average 70 Kg adult)

Warfarin	**7**
Gentamicin	**16**
Theophylline	**35**
Digoxin	**510**
Mianserin	**910**
Quinacrine	**50,000**

Small vol. Mainly stays in plasma little in tissues.

Medium vol. Similar concs in plasma and tissues

Large vol. Mainly in tissues, little in plasma.

Volume of distribution and body weight

A fixed dose injected into a small and a large individual will produce different concentrations. Vol Dis (calculate from D/ Cp^0) will therefore depend upon body size.

May be quoted as L/kg (Litres per kg body weight)

e.g. Theophylline Vol Dis = 0.48 L/kg
For 60 kg adult, Vol Dis = 0.48 L/kg x 60 kg
= 28.8 L

Using volume of distribution to calculate a dose

$Vd = D / Cp^0$

To calculate appropriate dose, re-arrange to:

$D = Vd \times Cp^0$

Calculation Practice

- **We want to achieve a blood concentration of theophylline of 15mg/L.**
- **A patient weighs 55kg.**
- **What dose is appropriate?**

Vol dis = 0.48L/kg X 55kg

= 26.4L

$Vd = D / Cp^0$

$D = Vd \times Cp^0$ = 26.4L X 15mg/L

= 396mg (Probably round to 400mg)

Elimination rate constant

It is assumed that for a given drug in a given patient, a fixed proportion of the dose is eliminated every hour (or day etc).

If this distinctive rate was (say) 10% per hour, then if the patient's body contained 50mg of the drug, elimination would occur at a rate of 5mg/h and if 100mg was present, the elimination rate would be 10mg/h and so on.

Units for elimination rate constant (K)

This distinctive proportion removed is called the elimination rate constant and is usually represented as K (or sometimes (K_{el}).

If the rate of removal was 10% per hour (as on the previous slide), K would be written as $0.1h^{-1}$. The reason for using 'h^{-1}' may not be immediately obvious, but it means 'per hour'. So as 0.1 is the same as 10%, '$0.1h^{-1}$' is simply shorthand for '10% per hour'.

Units for elimination rate constant (K)

For drugs that are eliminated very slowly, it may be more convenient to quote the proportion eliminated per day. In such a case units of 'day^{-1}' would be used. Thus, elimination at a rate of 5% per day would be written as 0.05 day^{-1}.

Other units such as Min^{-1} or Sec^{-1} are also acceptable, however therapeutically useful drugs are not generally eliminated so quickly as to require such units.

units of K

If it is necessary to convert K from one set of units to another, the obvious approach is in fact the correct one.

Example: Re-express K = 0.48day^{-1} in units of h^{-1}

A rate of 48% per day is equivalent to 2% per hour, so …

0.48day^{-1} = 0.02h^{-1}

K varies between drugs and between patients

Some drugs are eliminated much more quickly than others. Examples of average elimination rate constants are …

Phenobarbitone	**$0.007h^{-1}$**	**(Very slow)**
Theophylline	**$0.09h^{-1}$**	
Propranolol	**$0.18h^{-1}$**	**(Quick)**

K varies between drugs and between patients

Elimination rate also varies between patients. For example, with gentamicin, K might be $0.3h^{-1}$ in a patient with good renal function but only $0.015h^{-1}$ in a patient with severely compromised kidneys.

Half-life

The time required for a 50% reduction in plasma concentrations of drug.

Half-life is independent of how high or low the initial concentration may be.

Half-life and K

There will be an inverse relationship between K and half life.

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

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

Half-life and K

If $t_{\frac{1}{2}} = 5.4$ hours ...

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

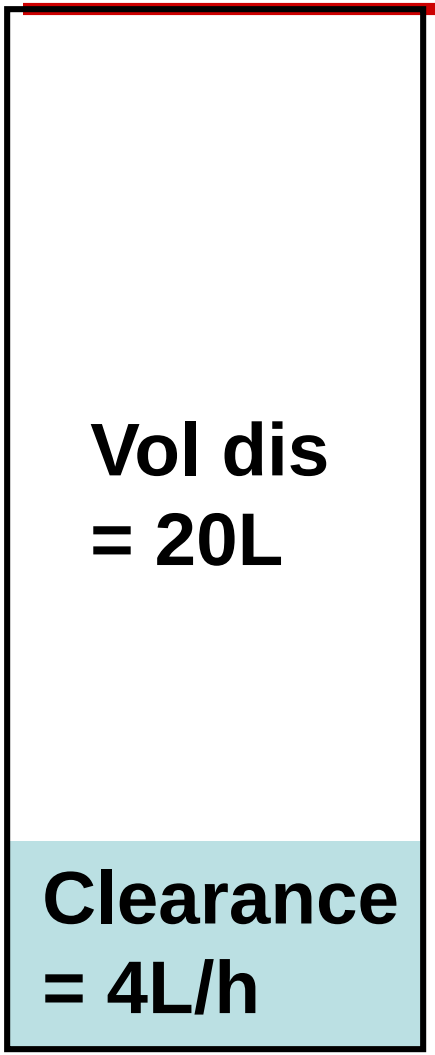
$$= \frac{0.693}{5.4\ h}$$

$$= 0.13\ h^{-1}$$

Clearance

Clearance **is a measure of drug elimination from the body without identifying the mechanism or process. Clearance (*drug clearance, systemic clearance, total body clearance, Cl_T*) considers the entire body as a drug-eliminating system from which many elimination processes may occur.**

Cl , Vd and K



We have already defined K as the proportional rate of removal of drug. If K = $0.2h^{-1}$, we know that drug is eliminated at a rate equivalent to 20% of the total body load per hour.

In this diagram, the total volume throughout which the drug is distributed is 20L and 4 out of the 20L is shown as being cleared of drug every hour. As 20% of the volume is cleared every hour, we are also removing 20% of the drug every hour and K must be $0.2h^{-1}$.

K therefore equals Clearance / Vol dist.

$$K = Cl/Vd \quad \text{or} \quad Cl = K \times Vd$$

Use of Cl = K.Vd

Q1) Calculate Cl if elim rate constant
= 0.015h^{-1} and vol dist = 80L.

Q2) Calculate K if Clearance = 200mL/h and vol dist = 20L.

Use of Cl = K.Vd

(1) Calculate Cl if elim rate constant = 0.015h^{-1} and vol dist = 80L.

Cl = K.Vd

= 0.015h-1 x 80L

= 1.2 L/h

Use of Cl = K.Vd

(2) Calculate K if Clearance = 200mL/h and vol dist = 20L.

$$Cl = K.Vd$$

$$K = Cl/Vd$$

$$= \frac{200mL/h}{20L}$$

$$= \frac{0.2L/h}{20L}$$

$$= 0.0125h^{-1}$$

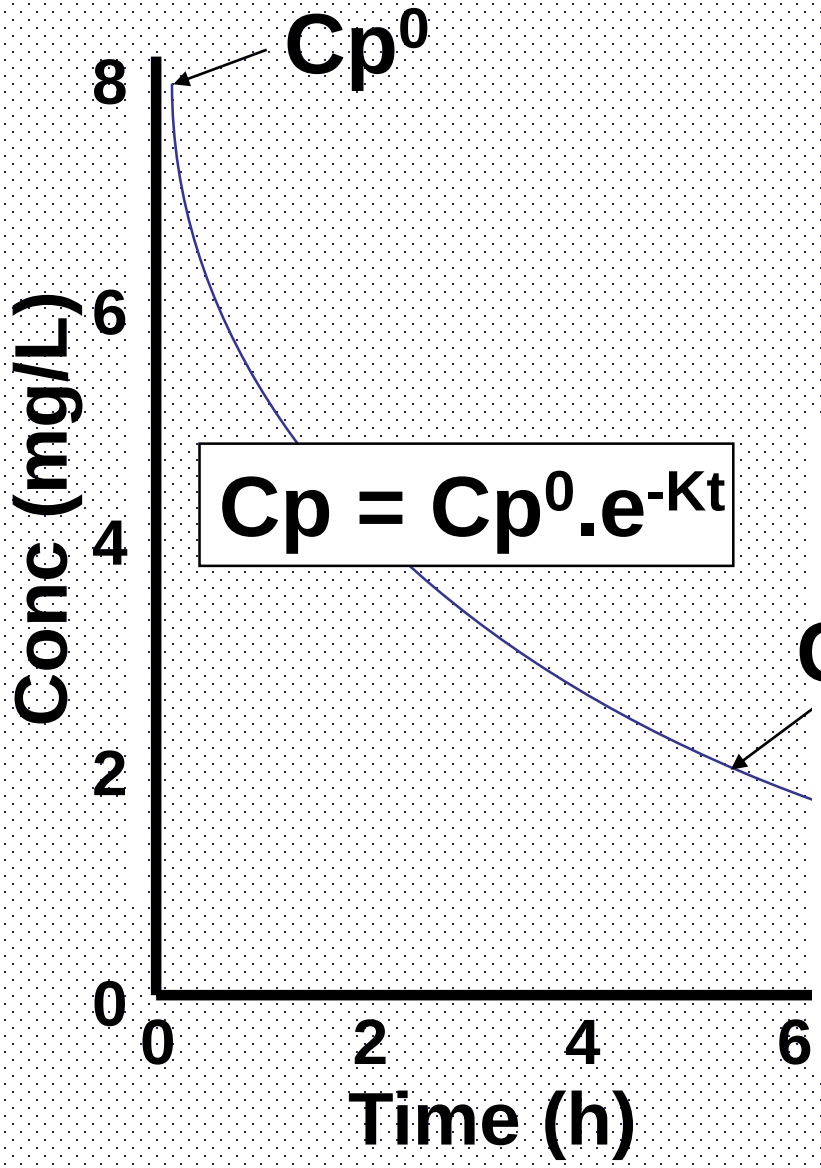
Always check that units match. mL & L don't!

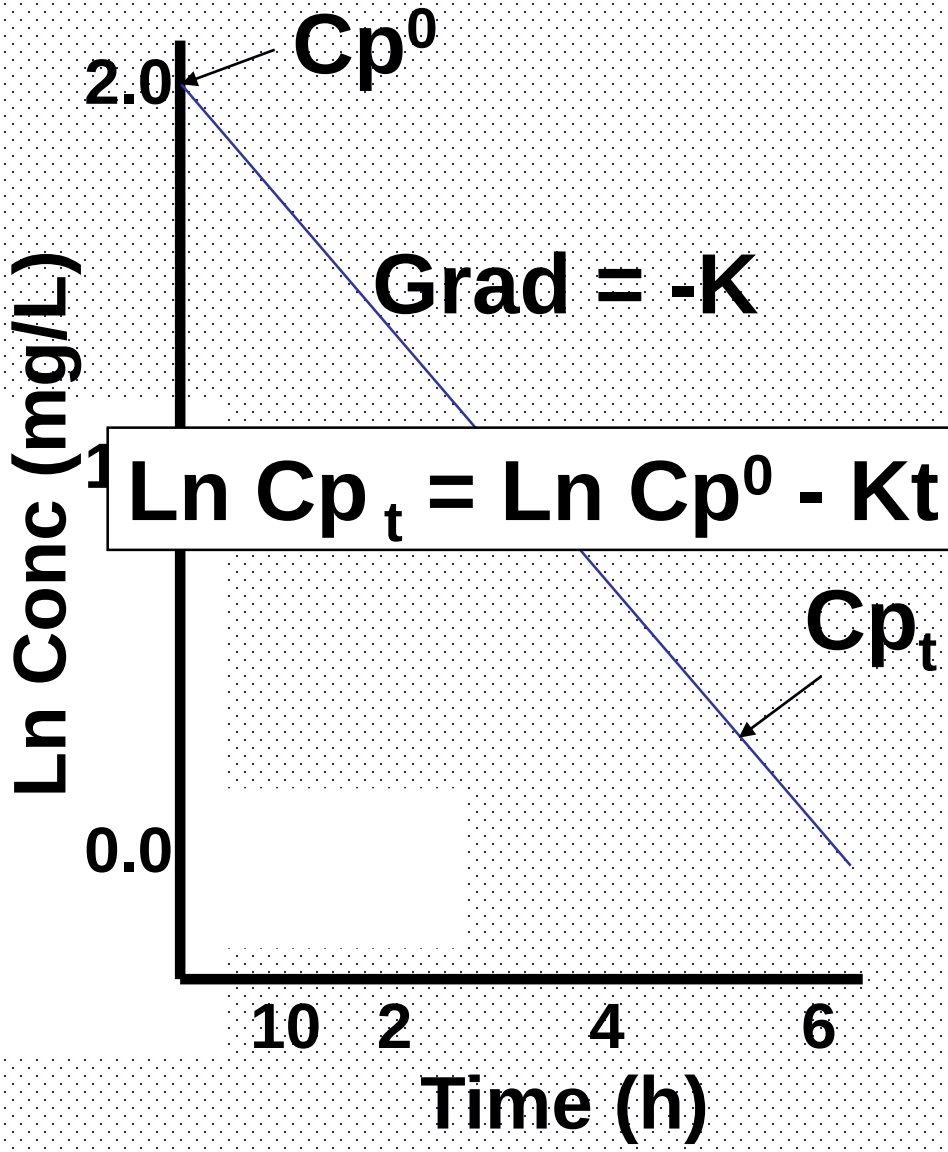
One-Compartment Open Model: Intravenous Bolus Administration:

One-Compartment Open Model: Intravenous Bolus Administration:

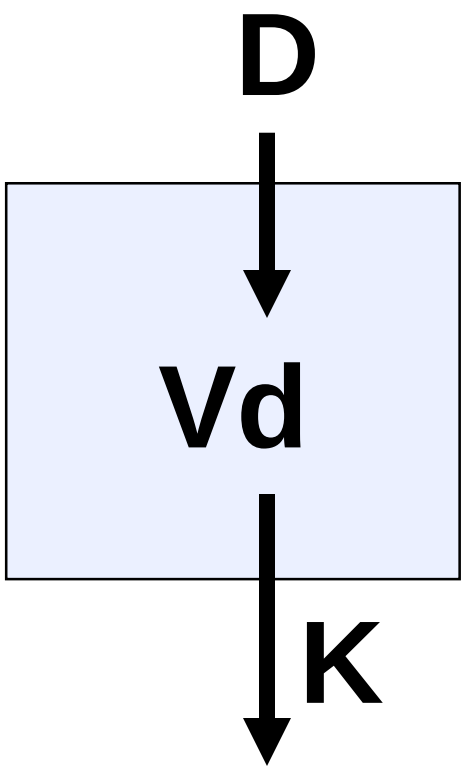
$$Cp = Cp^{0}.e^{-Kt}$$

Linearization





Single i.v. bolus dose into one compartment



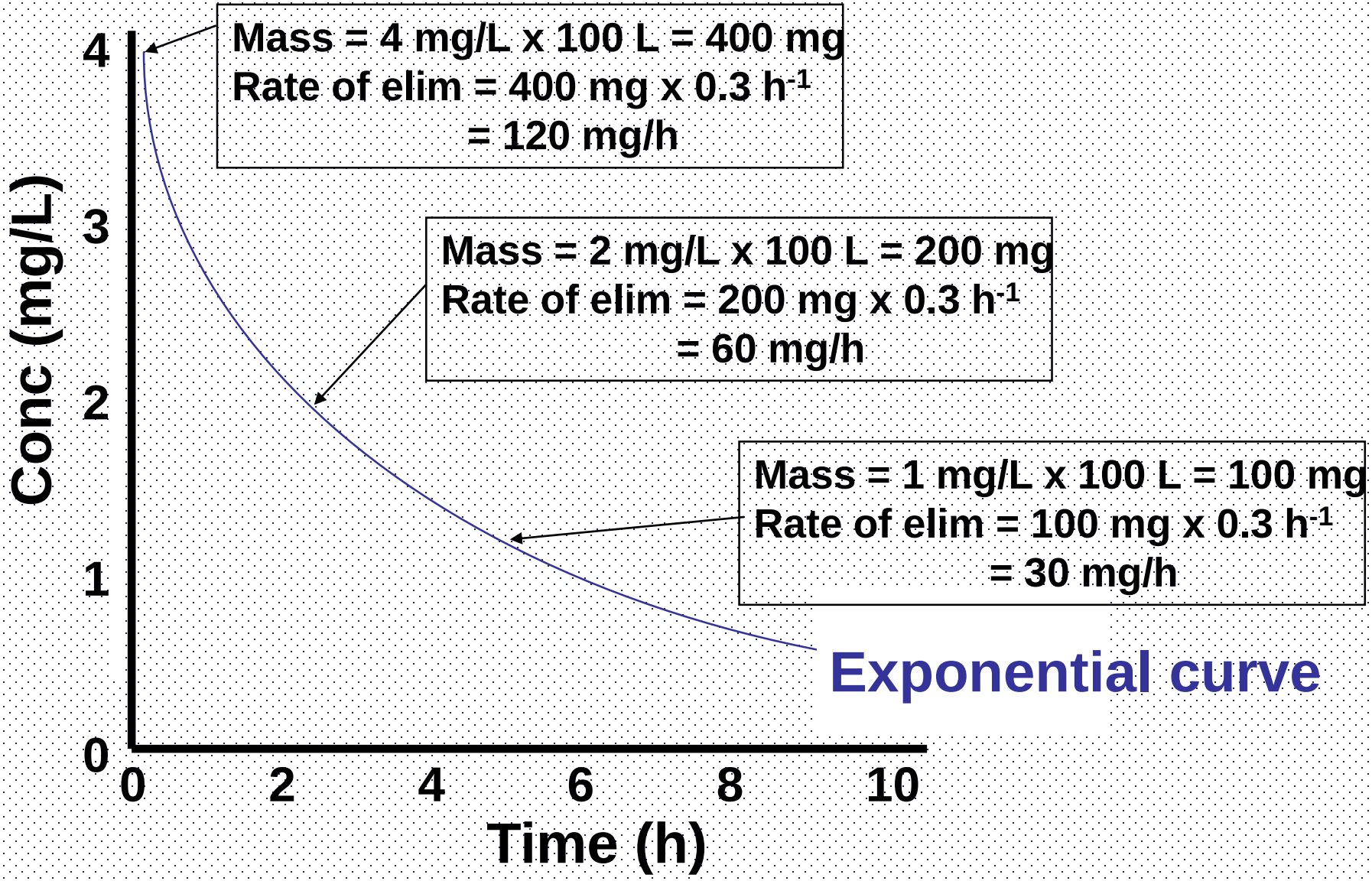
Dose = 400 mg

Vd = 100 Litres

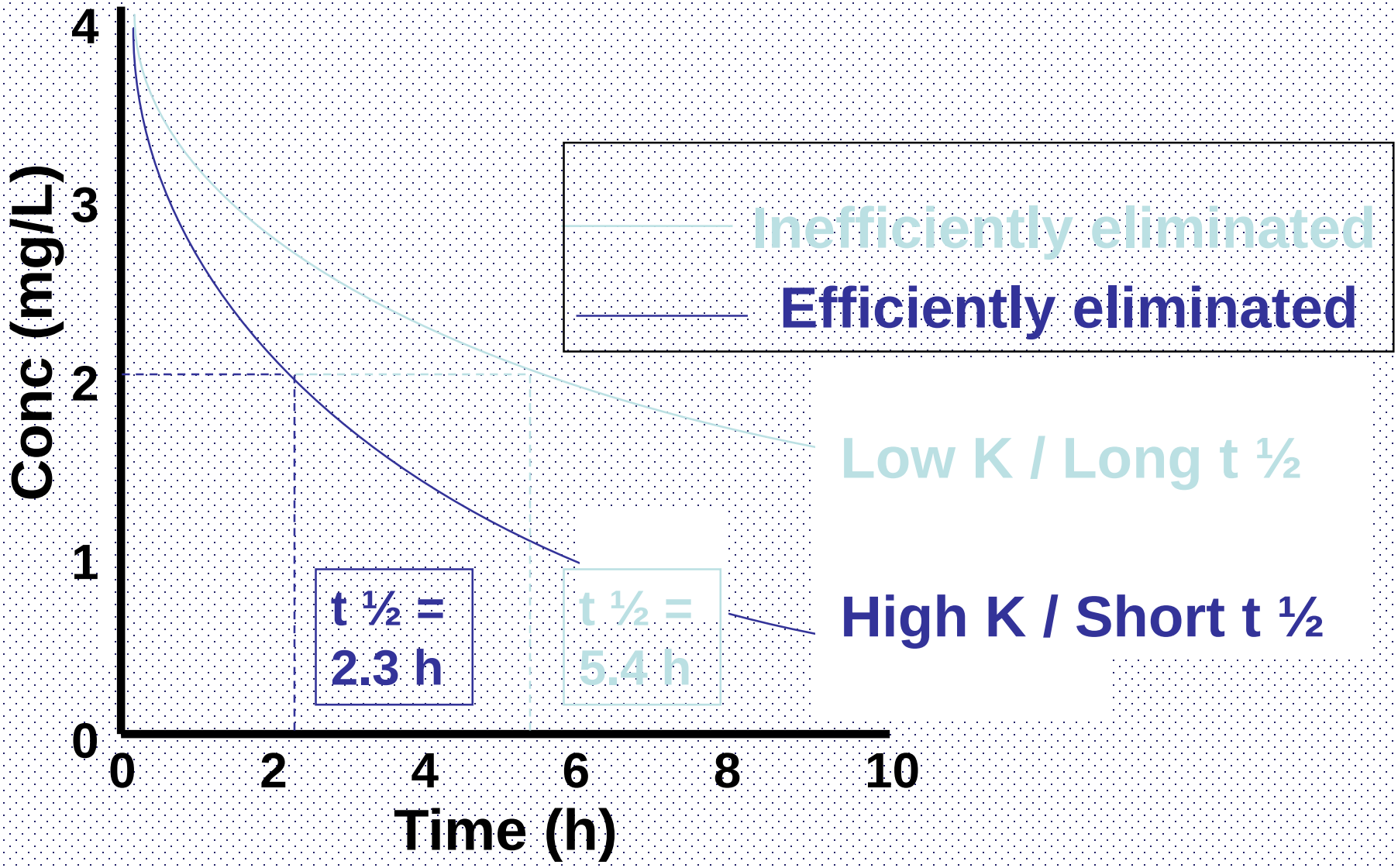
$K = 0.3\ h^{-1}$

Initial conc (Cp^0) = 4 mg/L

D=400 mg Vd = 100 L K = 0.3 h^{-1}

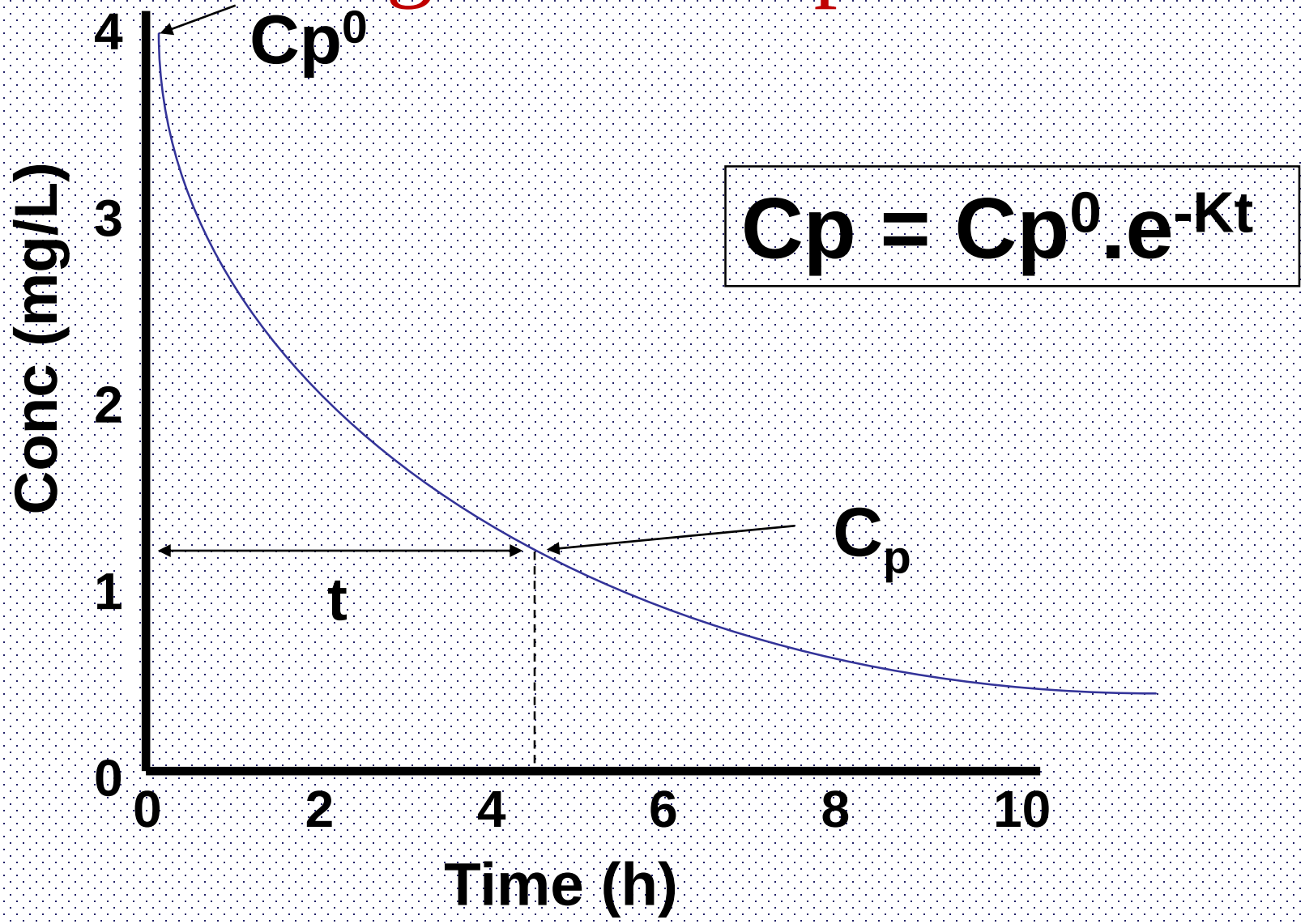


Half-life and K



Concentration at any time after iv injection

Predicting concentration at a given time point



Predicting concentration at a given time point

D = 10 mg Vd = 50 L K = 0.05 h-1

What conc. after 12 hours?

Cp^0 = D/Vd = 10mg/50L = 0.2mg/L =200µg/L

$Cp_t = Cp^0 . e^{-Kt}$

= 200µg/L . $e^{-0.05h-1 \times 12h}$

= 200µg/L . $e^{-0.6}$

= 200µg/L . 0.55

= 110 µg/L

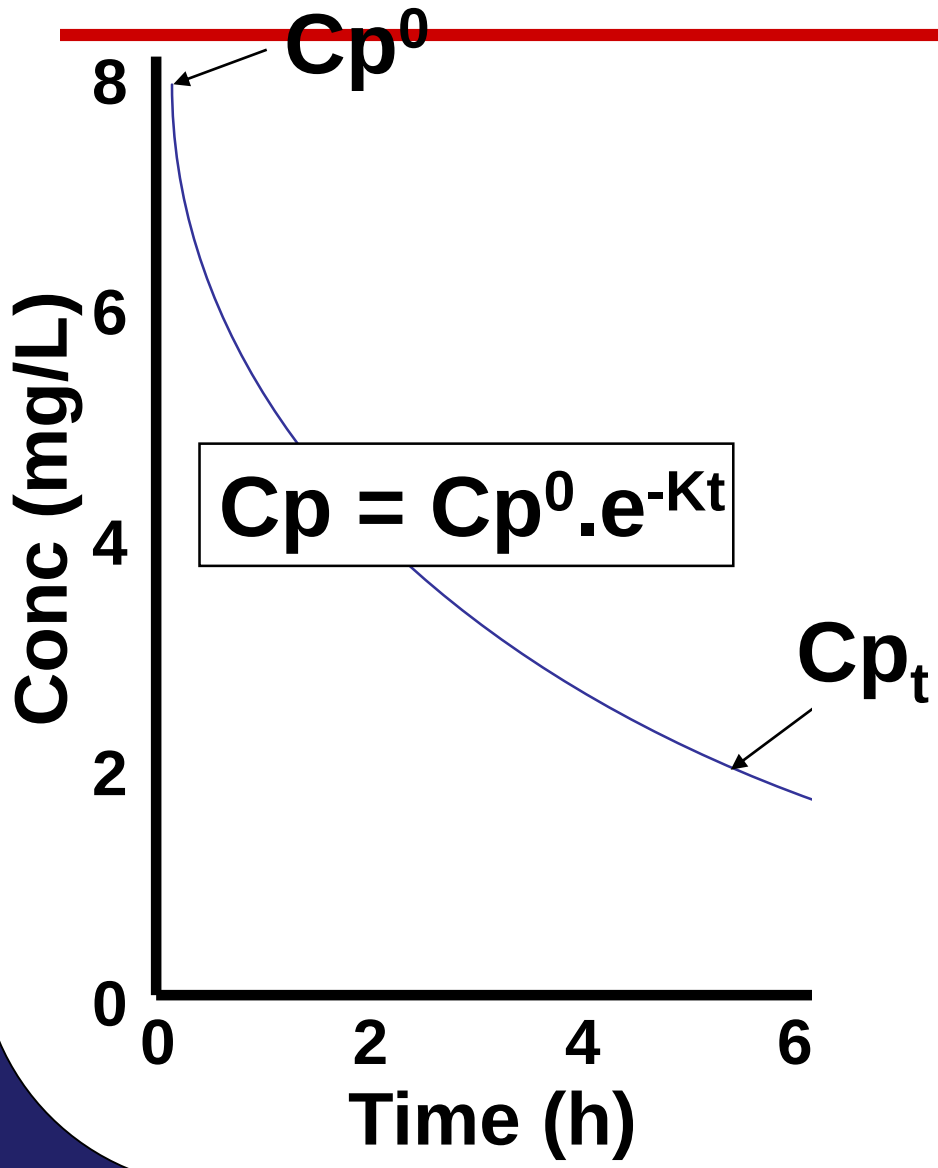
Graphical analysis of data following single iv bolus

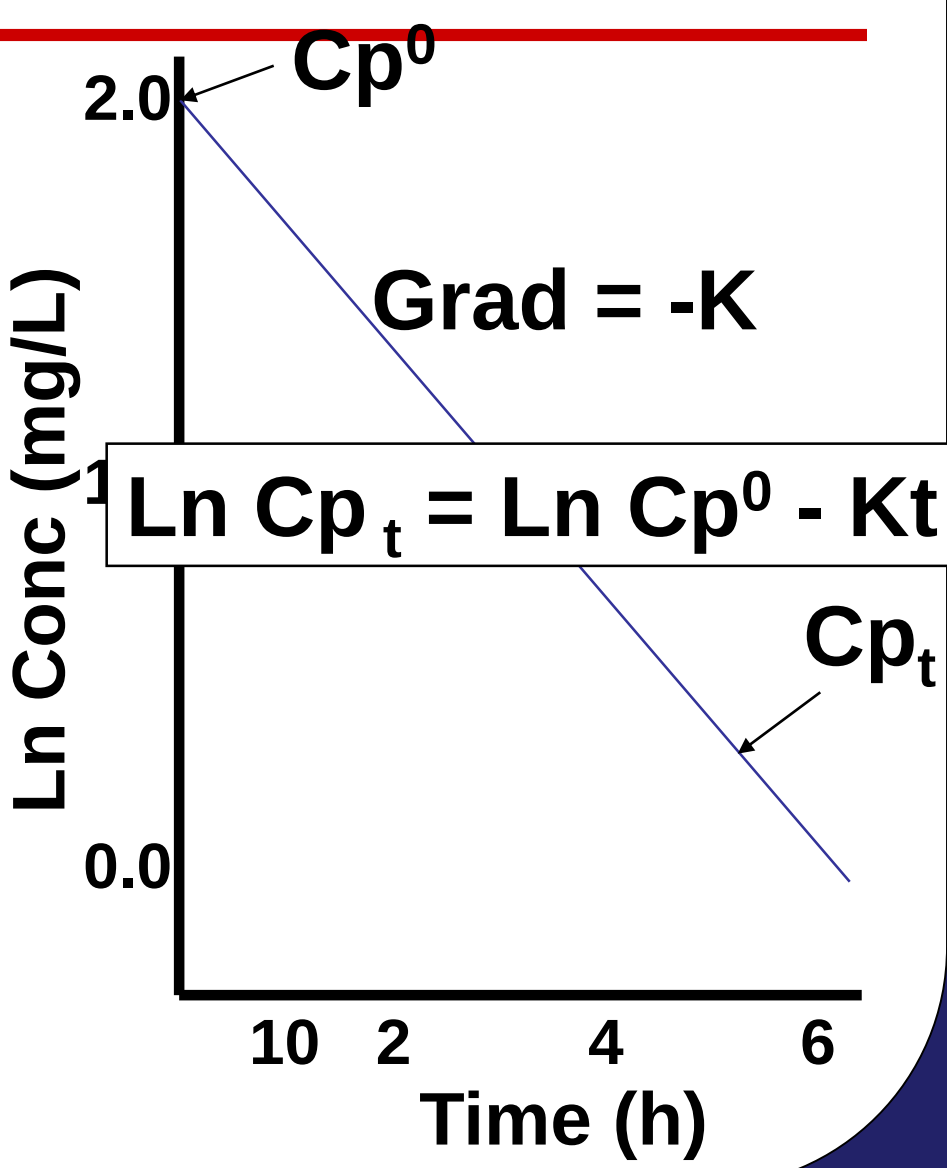
Area under the curve AUC

$$AUC = Cp^0 / K$$

$$AUC = D / Cl$$

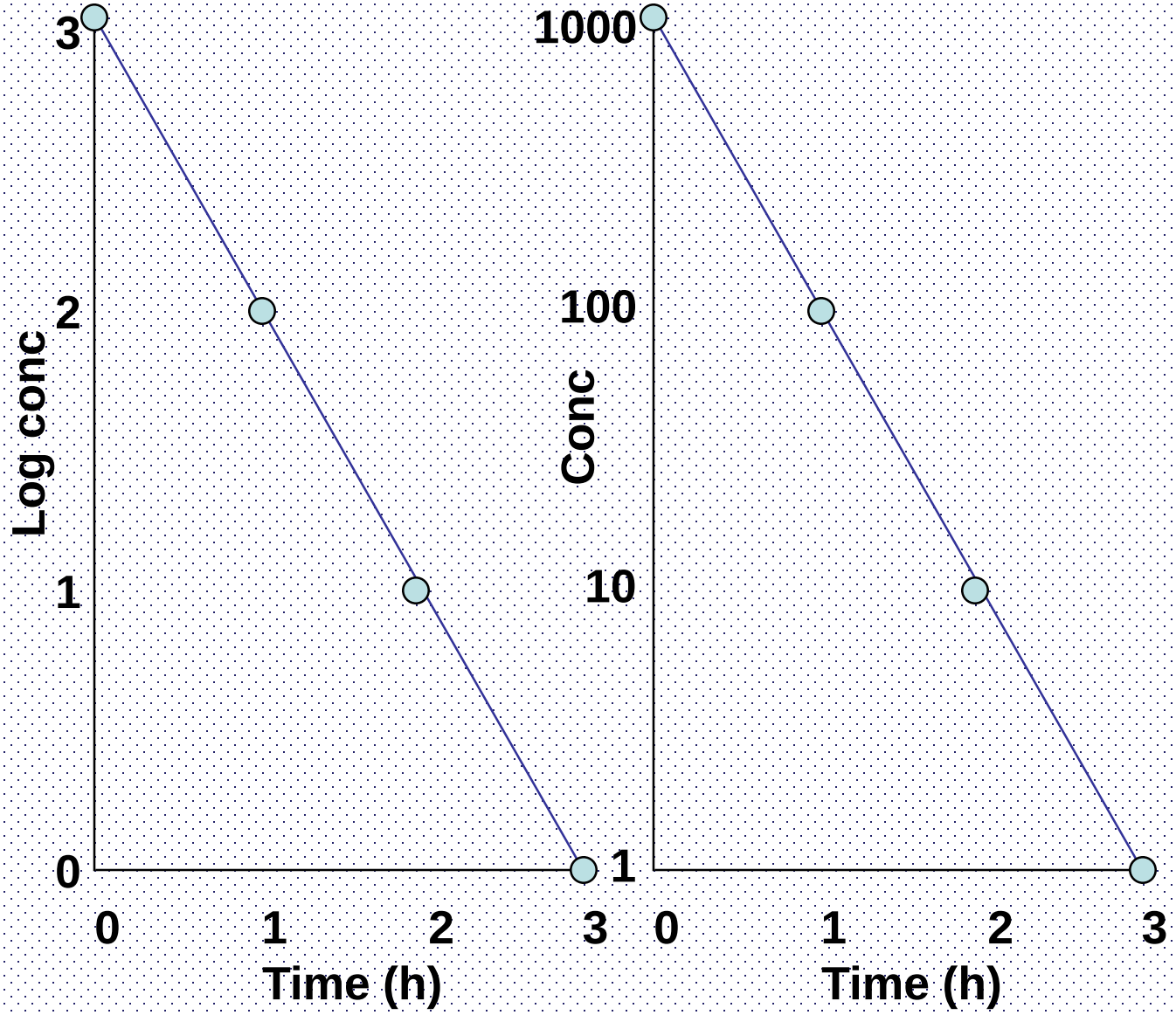
Linearization





Semi-log plots

T (h)	Conc (μM)	Log conc
0	1000	3
1	100	2
2	10	1
3	1	0

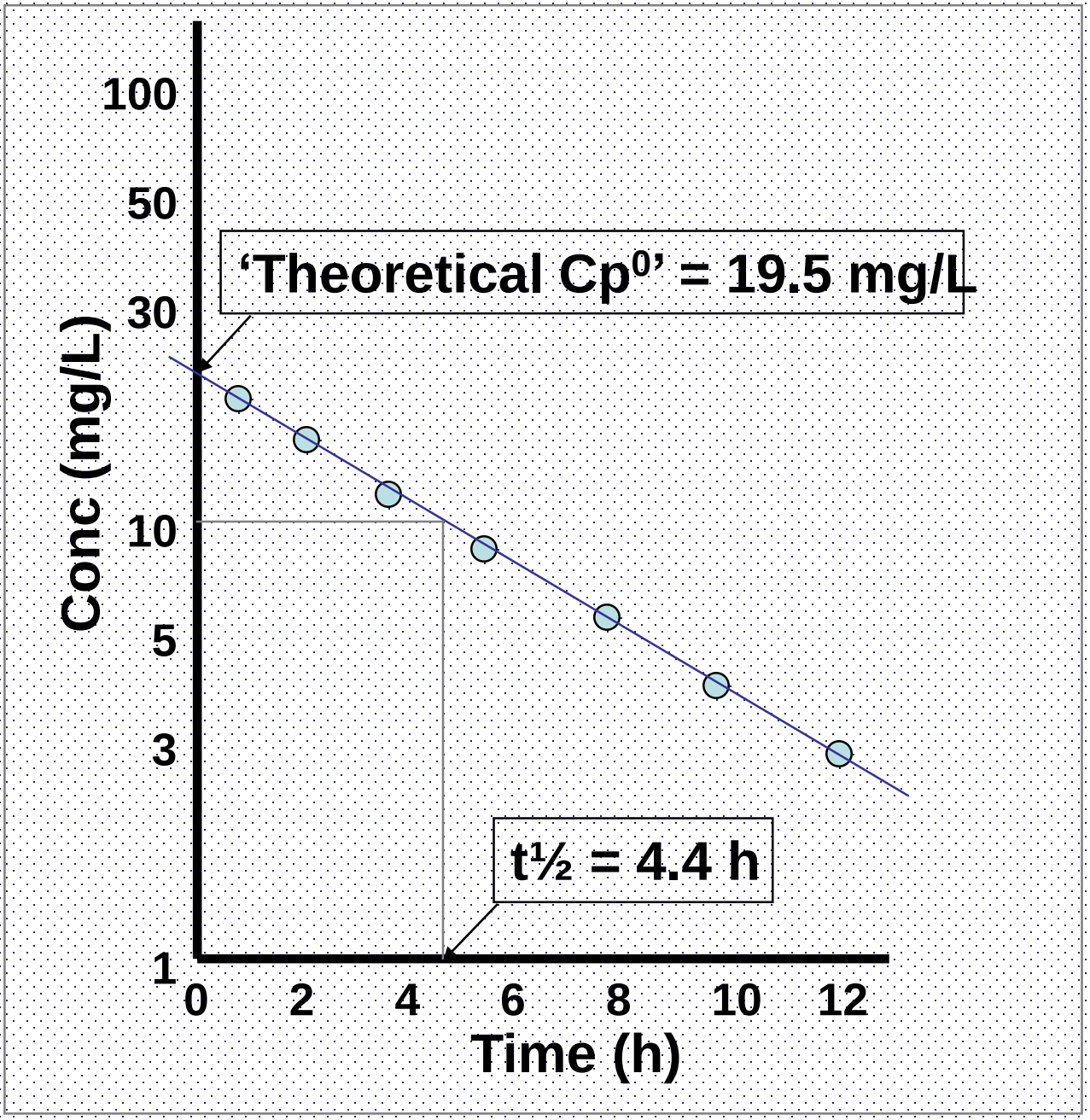


Example calculation

500 mg of drug given i.v. at time zero ...

Time (h)	Conc (mg/L)
1	17.0
2	14.0
4	10.0
6	7.4
8	5.3
10	3.8
12	2.8

Calculate:
Vd, K & Cl


100
50
30
10
5
3
1
Conc (mg/L)
‘Theoretical Cp⁰’ = 19.5 mg/L
t½ = 4.4 h
0
2
4
6
8
10
12
Time (h)

Analysis of data following i.v. bolus into a one compartment sytstem

$Vd = D / Cp^0$

= 500mg / 19.5mg/L

= 25.6 Litres

$K = 0.693 / t_{½}$

= 0.693 / 4.4h

= 0.158 h^{-1}

Cl = K.Vd

= 0.158 h^{-1} x 25.6 L

= 4.04 L/h

Predicting concentration at a given time point

D = 10 mg Vd = 50 L K = 0.05 h^{-1}

What conc. after 12 hours?

Cp^0 = D/Vd = 10mg/50L = 0.2mg/L = 200µg/L

$Cp_t = Cp^0 . e^{-Kt}$

= 200µg/L . $e^{-0.05h-1 \times 12h}$

= 200µg/L . $e^{-0.6}$

= 200µg/L . 0.55

= 110 µg/L

Predicting the time to reach a given concentration

$Cp^0 = 5$ mg/L $K = 0.02h^{-1}$

How long until Cp = 1 mg/L?

$Cp_t = Cp^0 . e^{-Kt}$

$Cp_t / Cp^0 = e^{-Kt}$

$1/5 = e^{-Kt}$

$0.2 = e^{-Kt}$ (Take natural logs of both sides)

$Ln(0.2) = -Kt$

$-1.609 = -Kt$ (Drop minus from both sides)

$1.609 = 0.02h^{-1} \times t$

$t = 1.609 / 0.02h^{-1}$

= 80.5 hours

Pharmacokinetics

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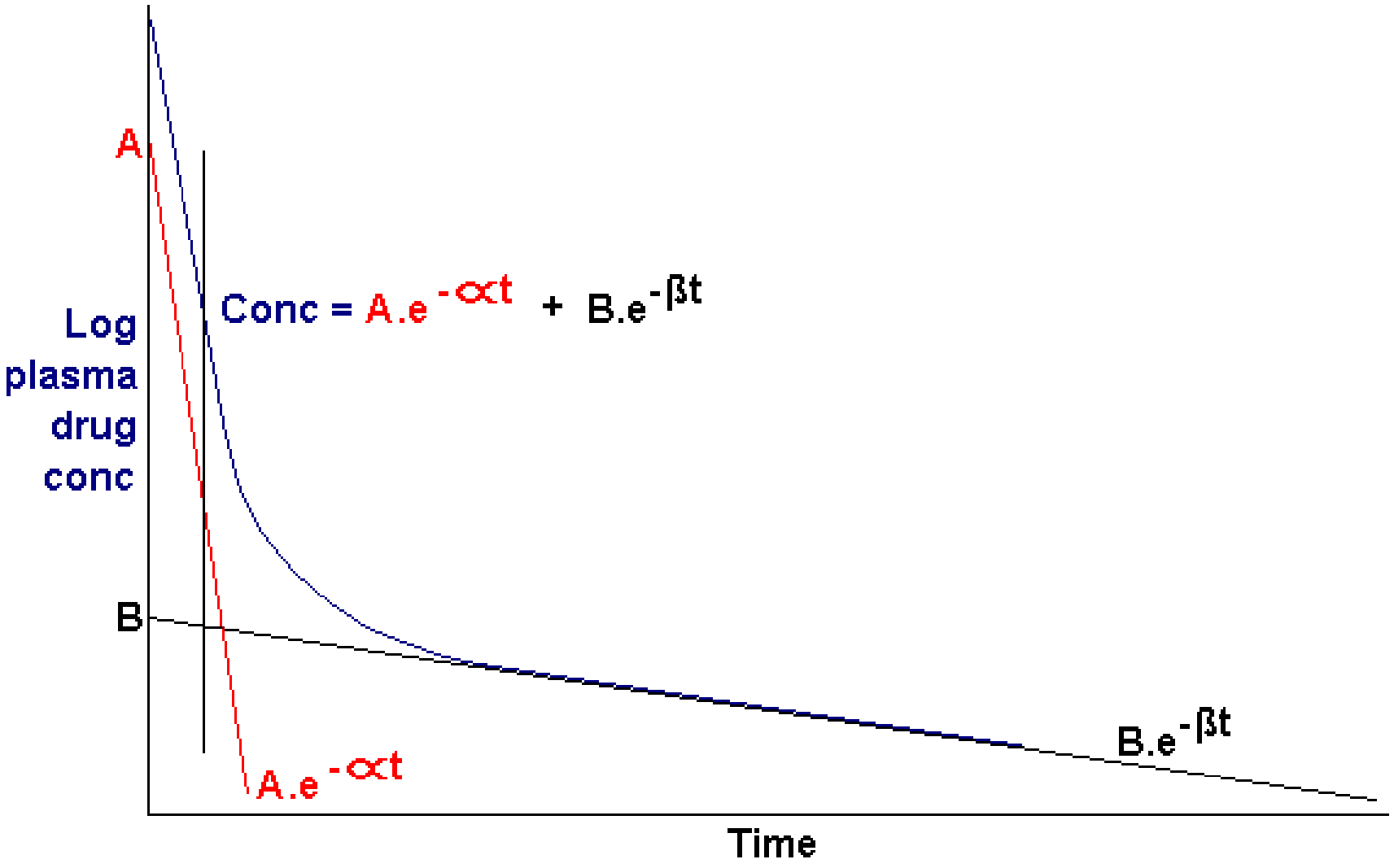
Faculty of Pharmacy – Sana'a University

Two-Compartments Open Model: Intravenous Bolus Administration:

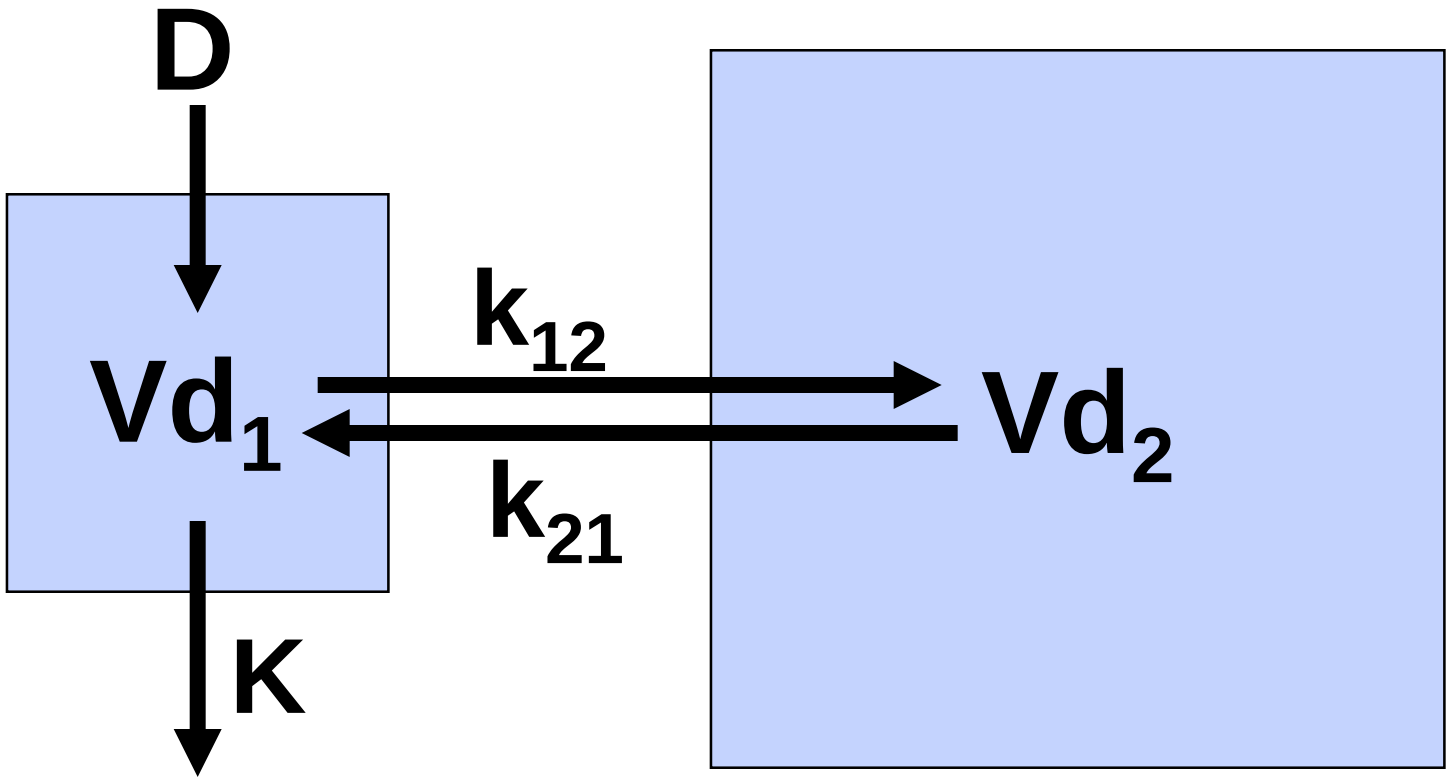
Two-Compartments Open Model: Intravenous Bolus Administration:

$$Cp = A.e^{-at} + B.e^{-bt}$$

Two compartments

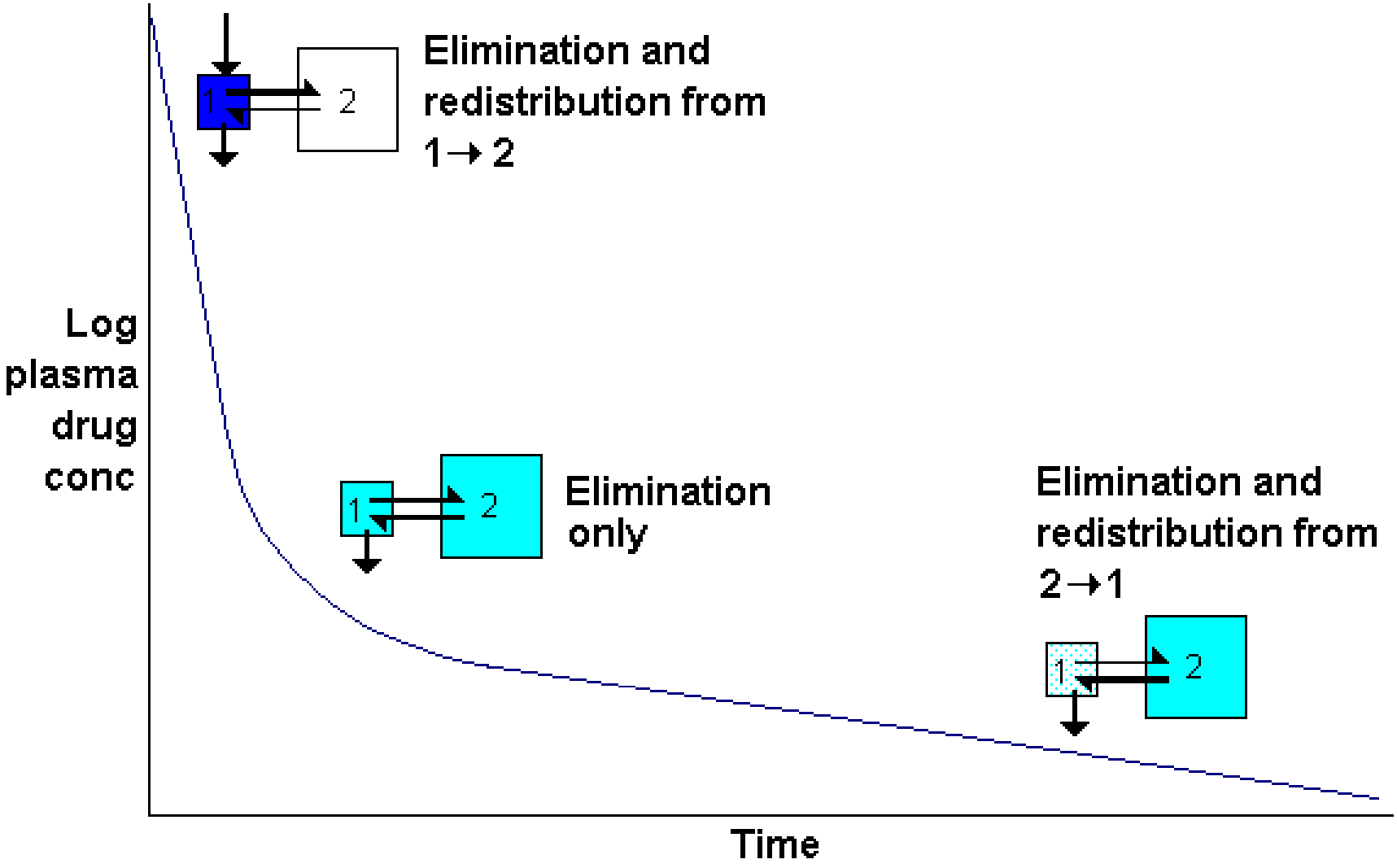


Two-Compartments

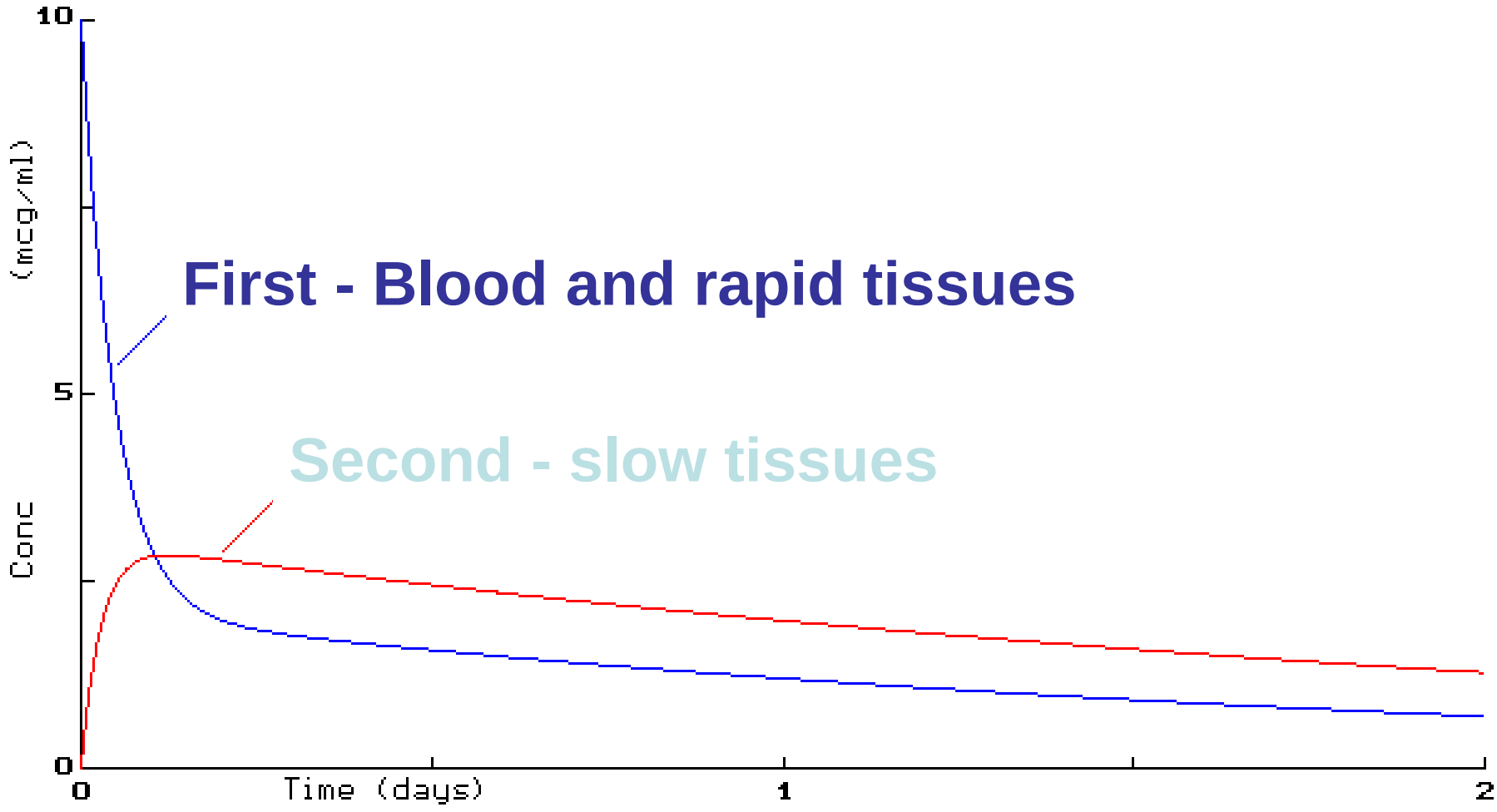


- Transfer constants (k_{12} & k_{21}) describe movement of drug between the two compartments.
- 'Volume at steady state' $Vd_{ss} = Vd_1 + Vd_2$

Two compartments



Both compartments



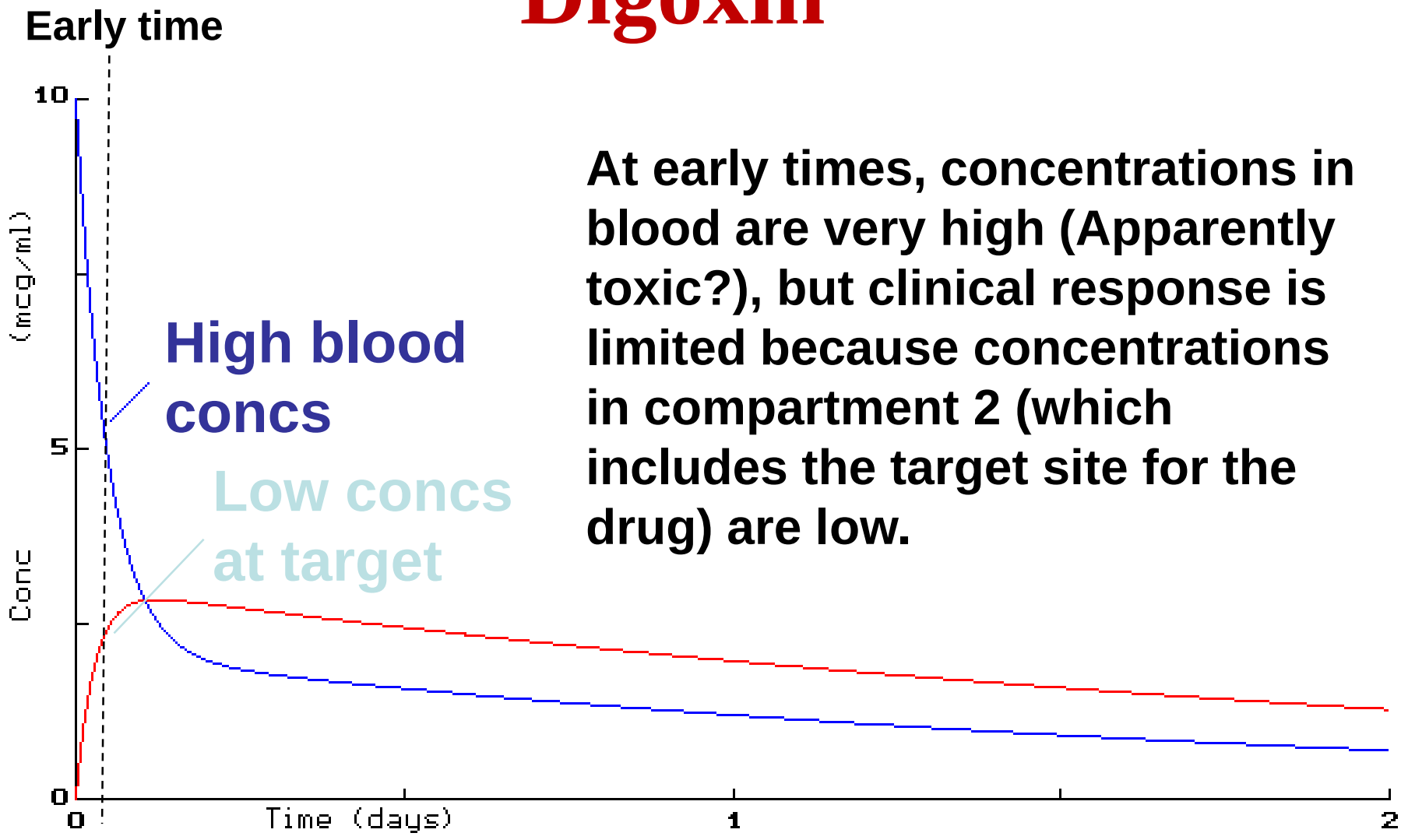
Interpreting blood drug levels

Case 1: Digoxin

Digoxin enters cardiac muscle slowly. So, for digoxin, cardiac muscle forms part of the second compartment.

Digoxin acts on cardiac muscle. Clinical effect is therefore related to concentrations in compartment 2, not those in the blood (part of compartment 1).

Interpreting blood drug levels - Digoxin



At early times, concentrations in blood are very high (Apparently toxic?), but clinical response is limited because concentrations in compartment 2 (which includes the target site for the drug) are low.

Interpreting blood drug levels - Digoxin

If blood samples are taken soon after dosing, the results are likely to be very misleading, as blood and cardiac muscle have not reached equilibrium. By later time points, discrepancies between blood and tissues levels are much less of a problem.

Usual rule is that, for digoxin, blood samples should not be taken less than 6 hours after dosing.

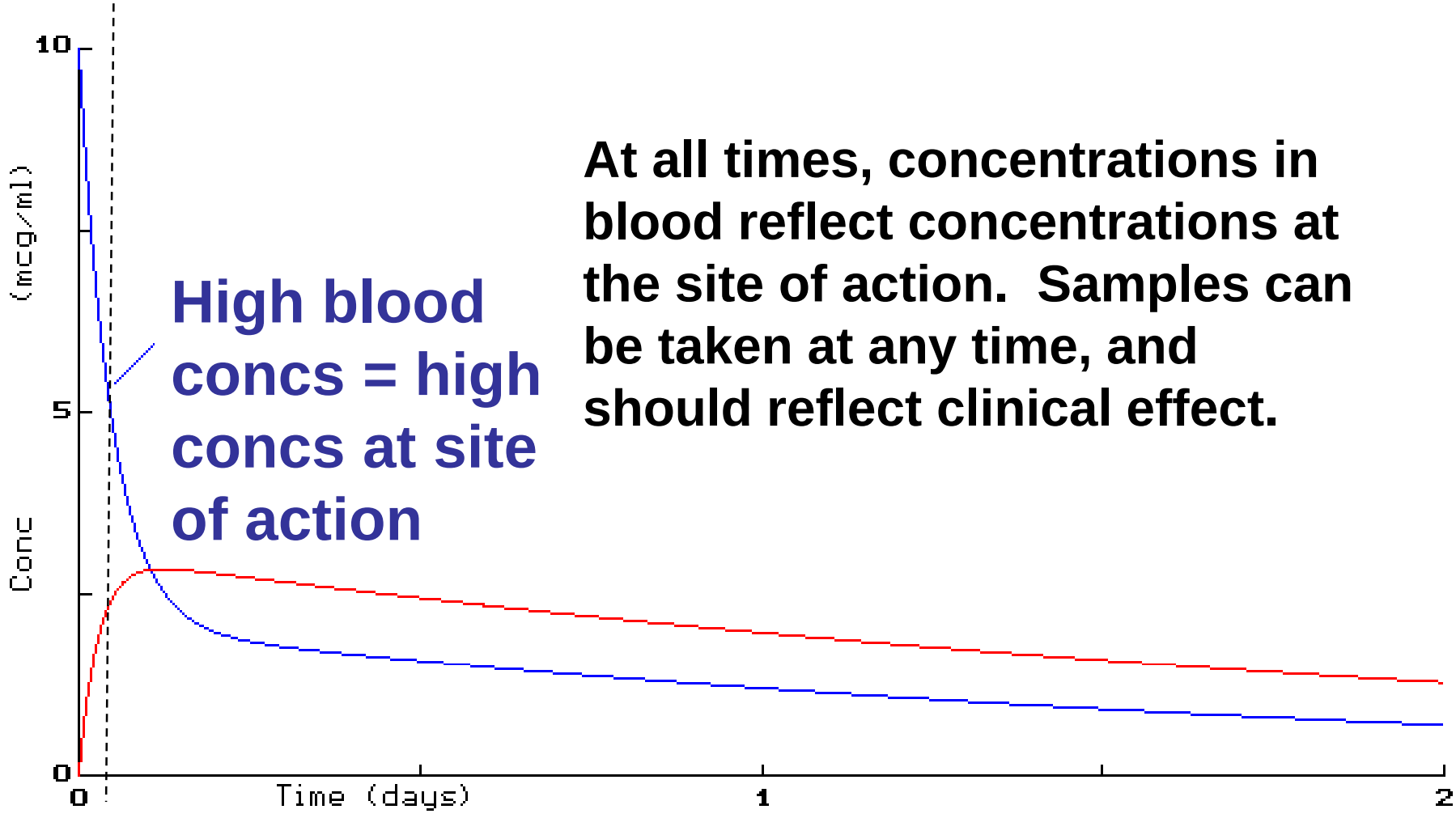
Interpreting blood drug levels

Case 2: Lidocaine

Lidocaine enters cardiac muscle rapidly. So, for lignocaine, cardiac muscle forms part of the first compartment.

Lidocaine also acts on cardiac muscle. But, clinical effect is related to concentrations in compartment 1 which does include the blood.

Interpreting blood drug levels - Lidocaine

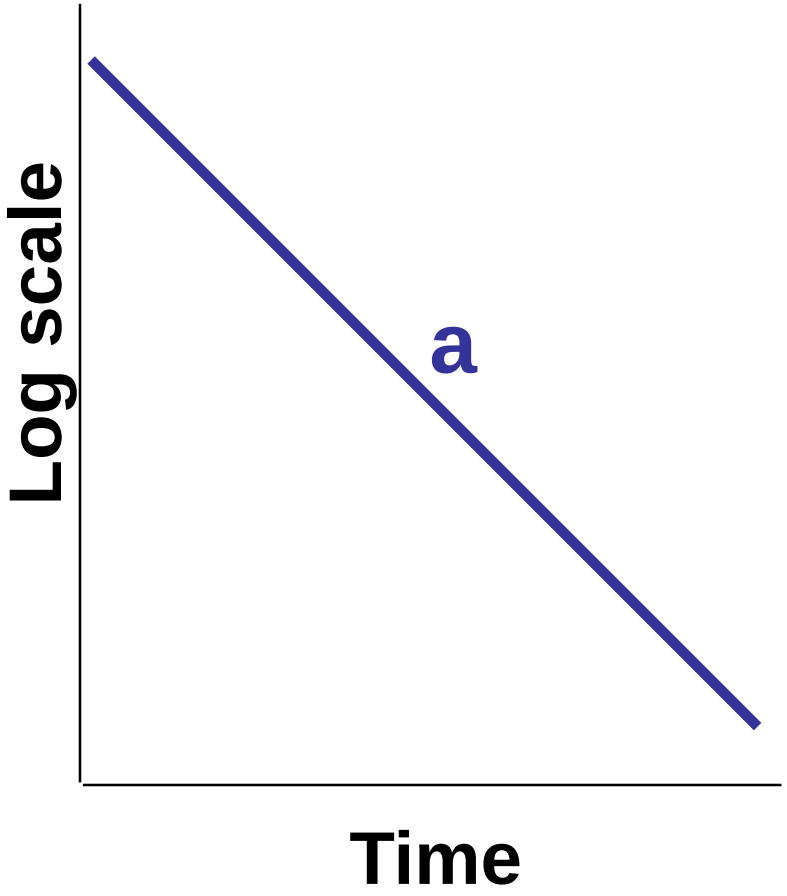


High blood concs = high concs at site of action

At all times, concentrations in blood reflect concentrations at the site of action. Samples can be taken at any time, and should reflect clinical effect.

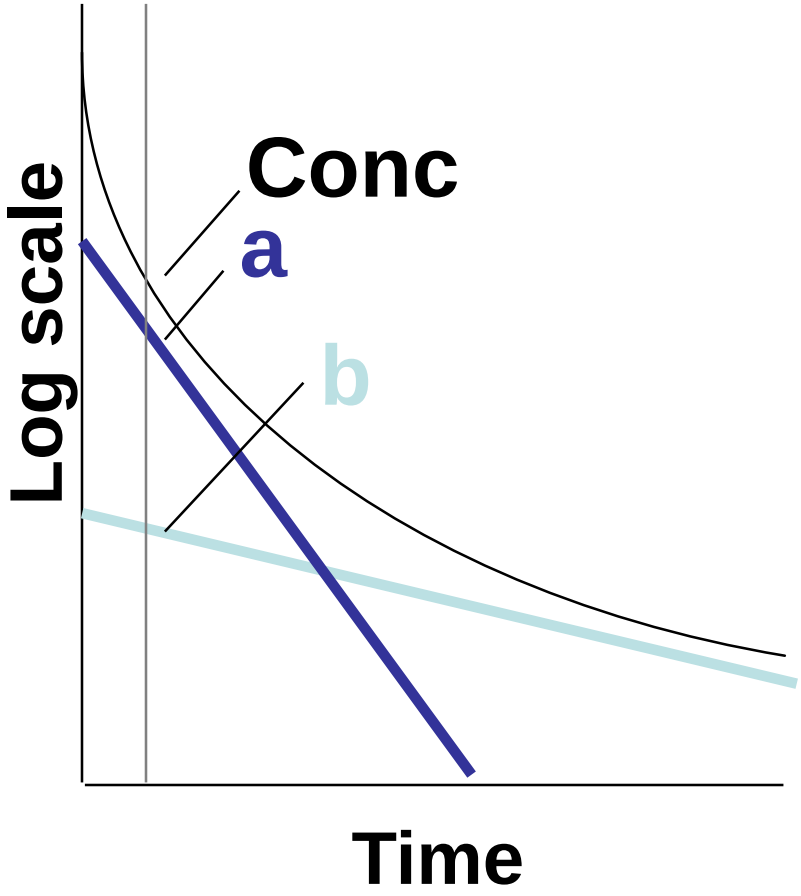
Analysis of data from two compartment systems

One compartment - one exponential



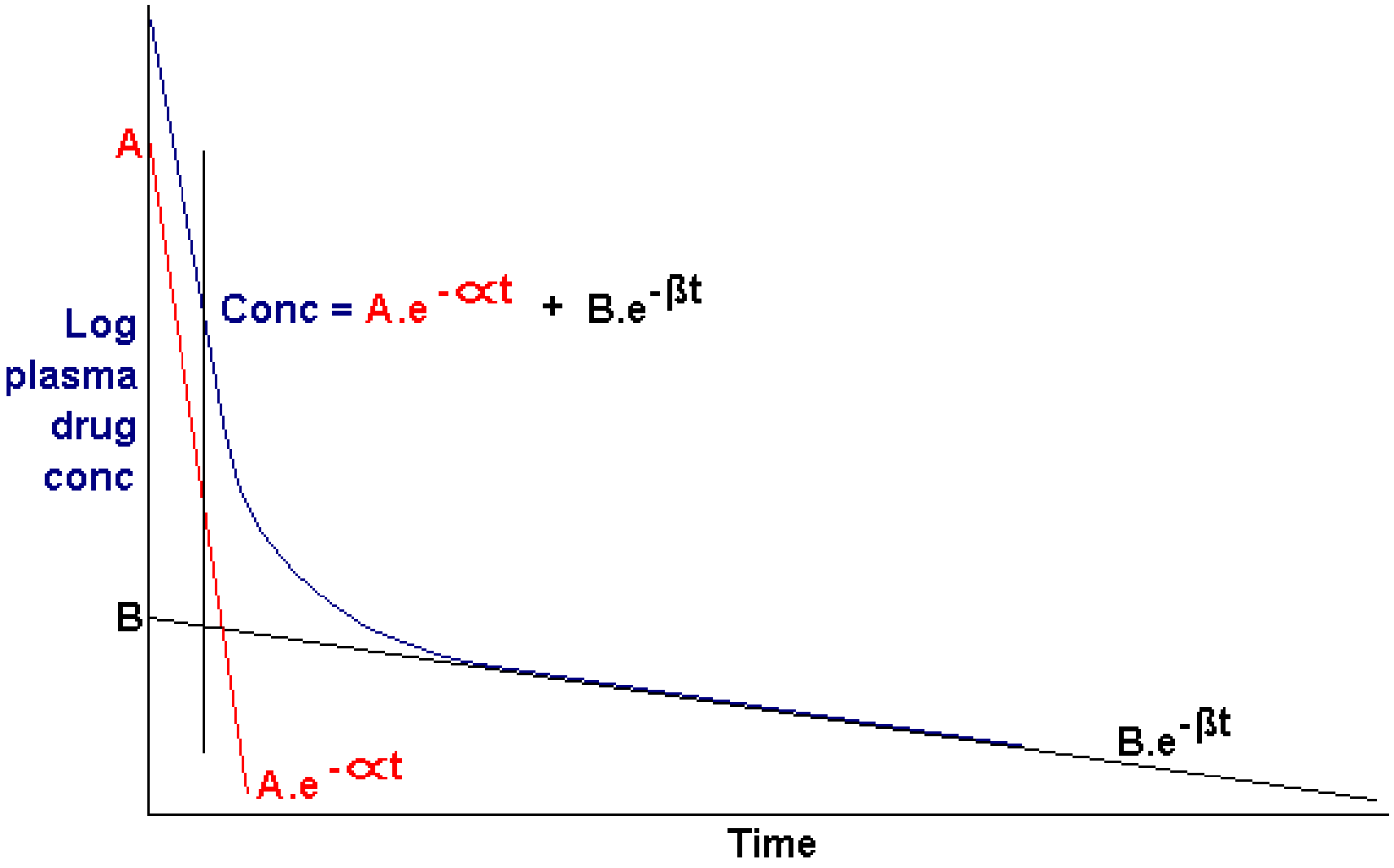
Conc = a

Two compartments - two exponentials



Conc = a + b

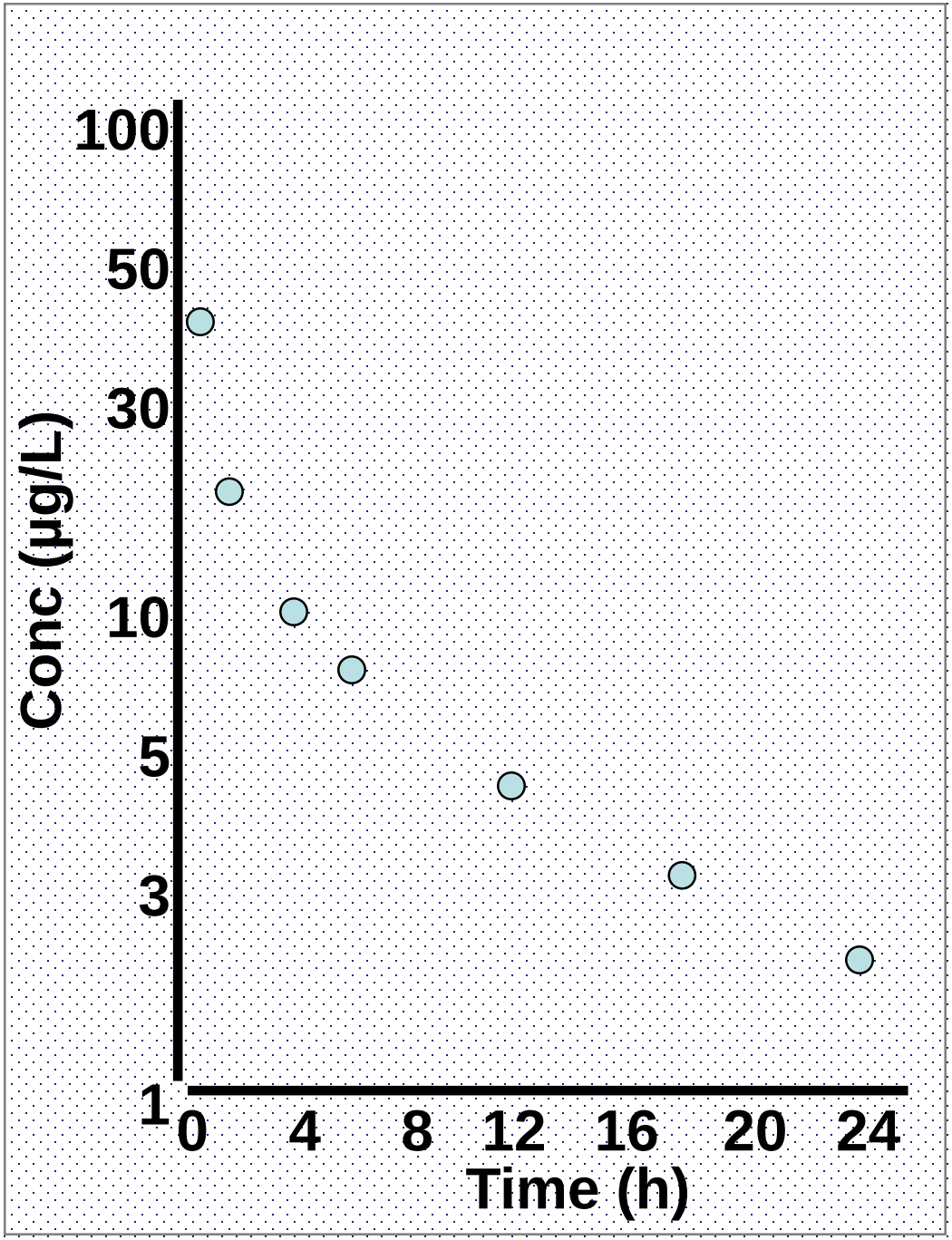
Two compartments



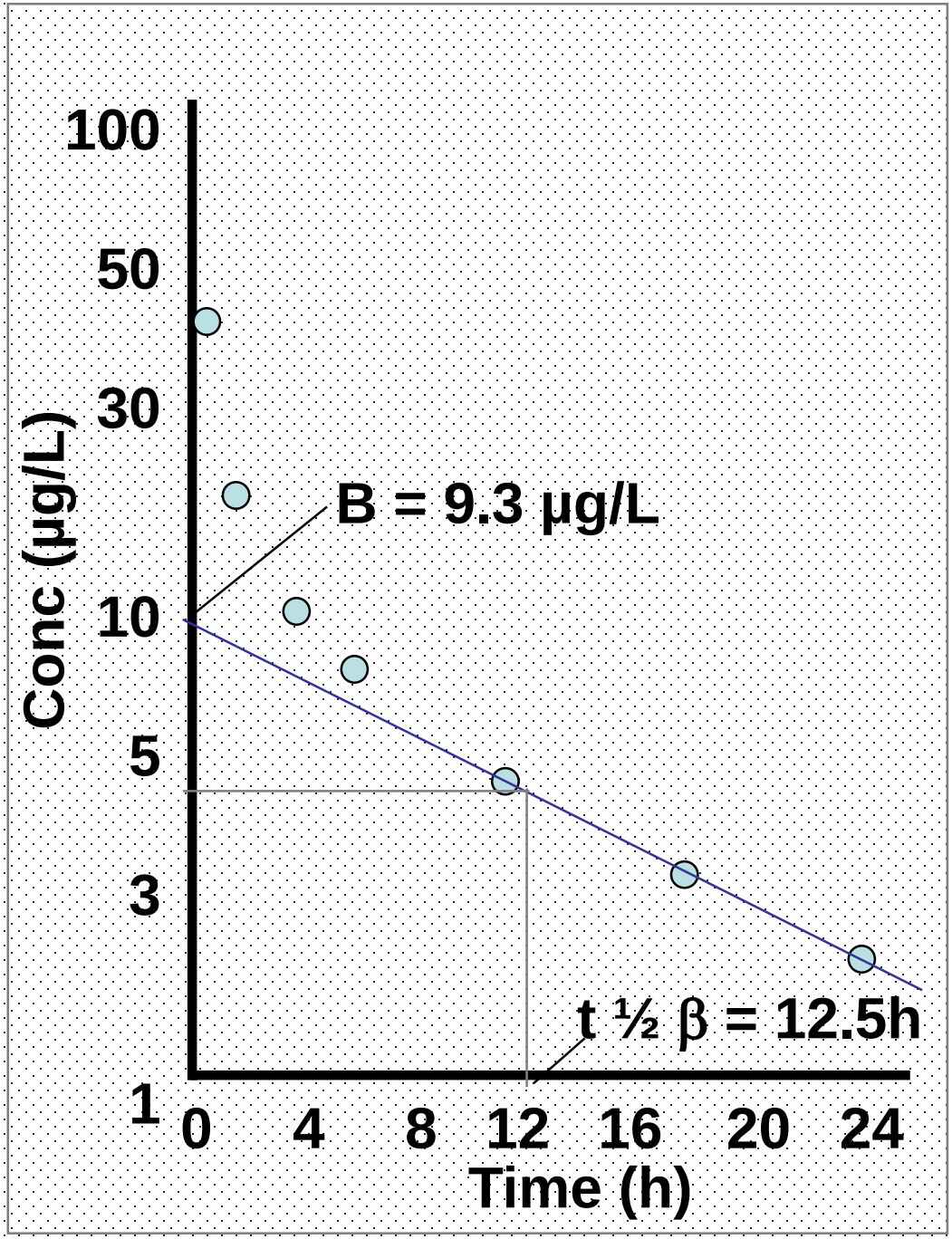
Two compartments

1mg drug injected i.v. at time zero

Time (h)	Conc (µg/L)	Value on β (µg/L) (from graph)	Value on α (µg/L) (Conc - β)
1	39.0		
2	22.0		
4	10.3		
6	7.29		
12	4.86		
18	3.50		
24	2.52		



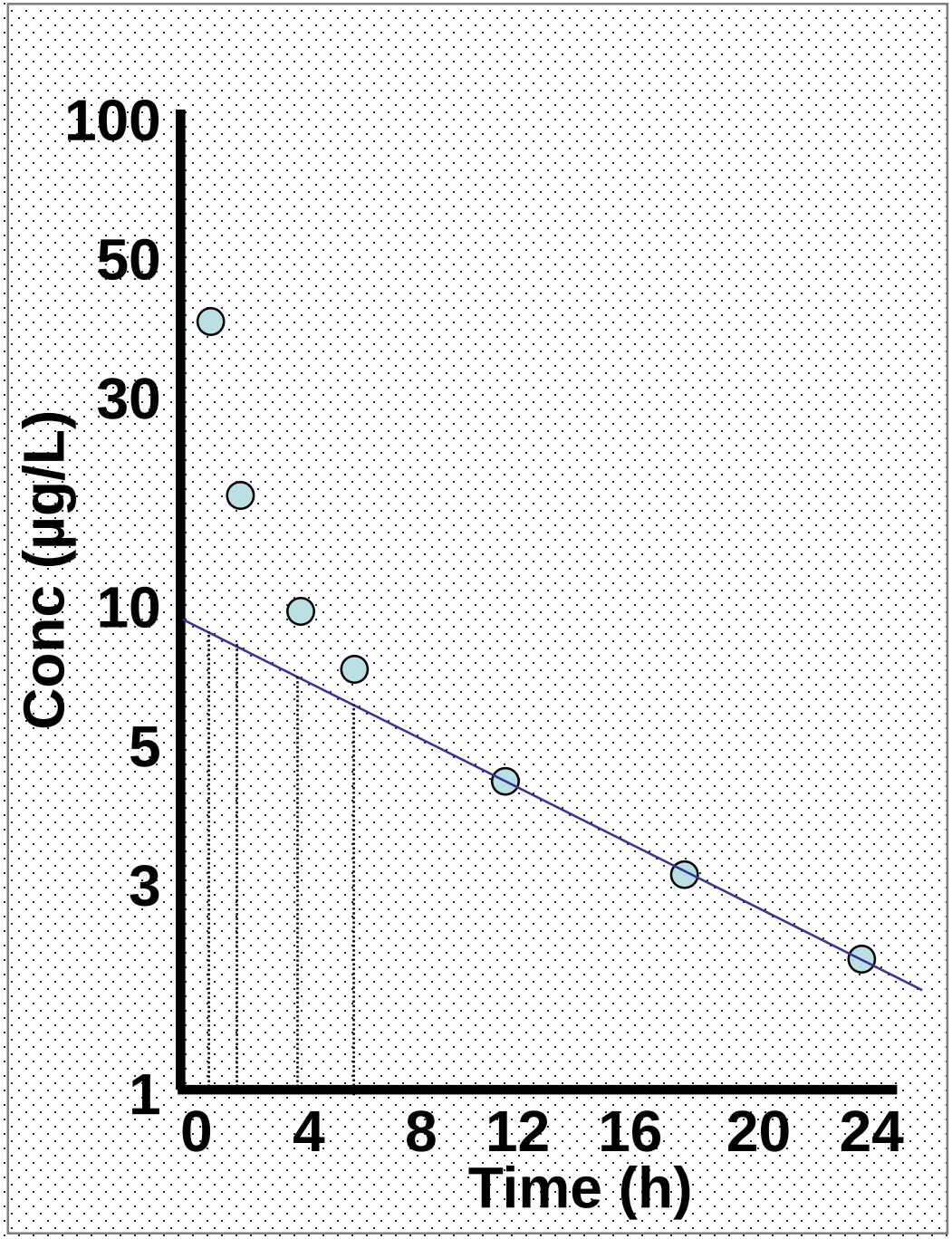
Obvious curvature demonstrates that this is a <u>two</u> compartment system.



Identify the 'terminal linear portion'. (A series of <u>at least</u> three points at the end of the graph that form a straight line.)

Fit line and extrapolate back to time zero.

Read off B and t ½ β



Read off values on β exponential at 1,2,4 hours etc.

Two compartments

1mg drug injected i.v. at time zero

Time (h)	Conc (µg/L)	Value on β (µg/L) (from graph)	Value on α (µg/L) (Conc - β)
1	39.0	9.00	
2	22.0	8.40	
4	10.3	7.50	
6	7.29	6.72	
12	4.86	4.86	
18	3.50	3.50	
24	2.52	2.52	

Remember that at any given time point, drug concentration is equal to the sum of the values on the two exponentials.

We now know the concentrations and the values on one of the exponentials, so we can calculate what the value must be on the other exponential.

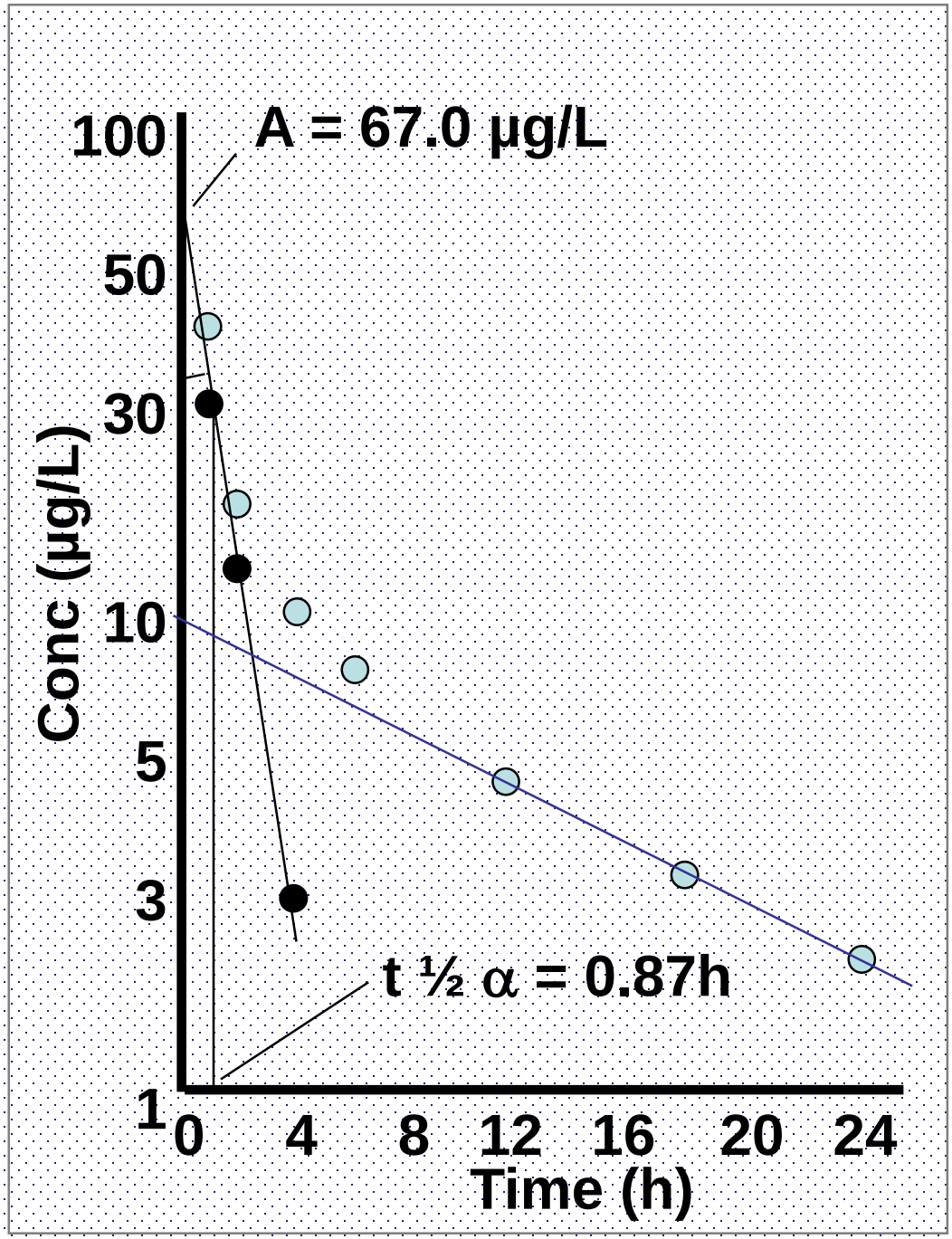
Conc = value on α + value on β

Value on α = Conc - value on β

Two compartments

1mg drug injected i.v. at time zero

Time (h)	Conc (µg/L)	Value on β (µg/L) (from graph)	Value on α (µg/L) (Conc - β)
1	39.0	9.00	30.0
2	22.0	8.40	13.6
4	10.3	7.50	2.8
6	7.29	6.72	0.57
12	4.86	4.86	0
18	3.50	3.50	0
24	2.52	2.52	0



Plot the α values back onto the graph ( ).

(Value at 6h is too low to plot and is likely to be very inaccurate.)

Fit line and extrapolate back to time zero.

Read off A and t ½ α .

Convert the half-life of each exponential into the associated rate-constant

$\alpha = 0.693 / t_{½\alpha}$

$= 0.693 / 0.87\ h$

$= 0.80\ h^{-1}$

$\beta = 0.693 / t_{½\beta}$

$= 0.693 / 12.5\ h$

$= 0.055\ h^{-1}$

Main pharmacokinetics values

A = 67.0 μg/L B = 9.3 μg/L
α = 0.797 h^{-1} β = 0.0554 h^{-1}

From these 4 values, we can calculate all the usual parameters like K, Cl etc.
The equations appear quite arbitrary and mind-numbingly boring, but are simple to apply, so long as you are careful!!!

Cp^0 and AUC

Cp0 = A + B

= 67.0 + 9.3 μg/L

= 76.3 μg/L

AUC = A/α + B/β

= 67.0 μg/L / 0.797 h^{-1} + 9.3 μg/L / 0.0554 h^{-1}

= 84.1 + 167.9 μg.h.L^{-1}

= 252.0 μg.h.L^{-1}

Elimination rate constant K

$$K = Cp^0 / AUC$$

$$= 76.3\ \mu g/L \ / \ 252.0\ \mu g.h.L^{-1}$$

$$= 0.303\ h^{-1}$$

Transfer constants
k_{12} & k_{21}

$$k_{21} = \frac{\alpha.\beta}{K}$$

$$= \frac{0.80 \times 0.055}{0.303} \ h^{-1}$$

$$= 0.145 \ h^{-1}$$

$$k_{12} = \alpha + \beta - k_{21} - K$$

$$= 0.80 + 0.055 - 0.145 - 0.303 \ h^{-1}$$

$$= 0.407 \ h^{-1}$$

Volumes of distribution Vd_1, Vd_2 & Vd_{ss}

$$Vd_1 = D / Cp^0$$

$$= 1000\ \mu g \ / \ 76.3\ \mu g/L$$

$$= 13.1\ L$$

$$Vd_{ss} = \frac{k_{12}}{k_{21}} + k_{21} \cdot Vd_1$$

$$= \frac{0.407 + 0.145\ h^{-1}}{0.145\ h^{-1}} \cdot 13.1\ L$$

$$= 49.9\ L$$

$$Vd_{ss} = Vd_1 + Vd_2$$

(Rearrange …)

$$Vd_2 = Vd_{ss} - Vd_1$$

$$= 49.9 - 13.1 \text{ L}$$

$$= 36.8 \text{ L}$$

Clearance (Cl)

Remember that the equation we have used previously:

$$Cl = K.Vd$$

is now inadequate.

We need to define which volume.

In fact, we use:

$$Cl = K.Vd_1$$

$$= 0.303\ h^{-1} \times 13.1\ L$$

$$= 3.97\ L.h^{-1}$$

Pharmacokinetics

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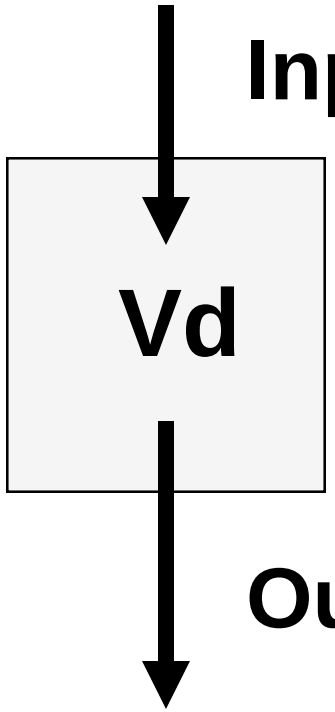
Constant Intravenous Infusion

Constant Intravenous Infusion

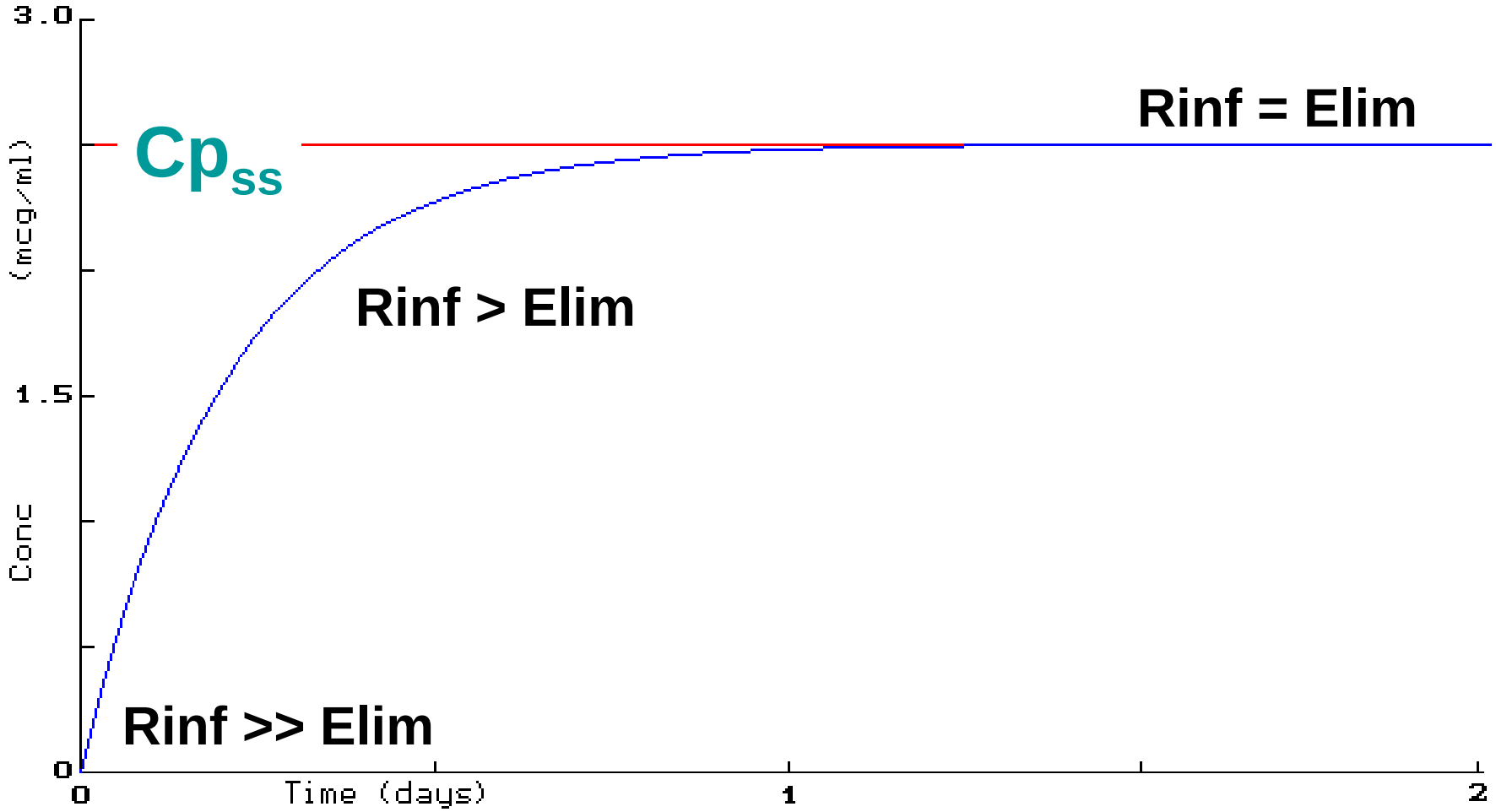
$$Cp_{ss} = R_{inf} / Cl$$

Constant iv. infusion



Rate of change in Ab
= Input - Output
= R_{inf} - Ab x K

I.V. Infusion


3.0
1.5
0
Conc
(mcg/ml)
Cp$_{ss}$
Rinf = Elim
Rinf > Elim
Rinf >> Elim
0
Time (days)
1
2

Predicting CP_{ss}

$$Cp_{ss} = \frac{R_{inf}}{Clearance}$$

This equation is general i.e. it is not restricted to one compartment models.

Calculating infusion rate

We want to achieve a Cp_{ss} of 15 mg/L.
Clearance = 3 Litre/h

$Cp_{ss} = R_{inf} / Cl$

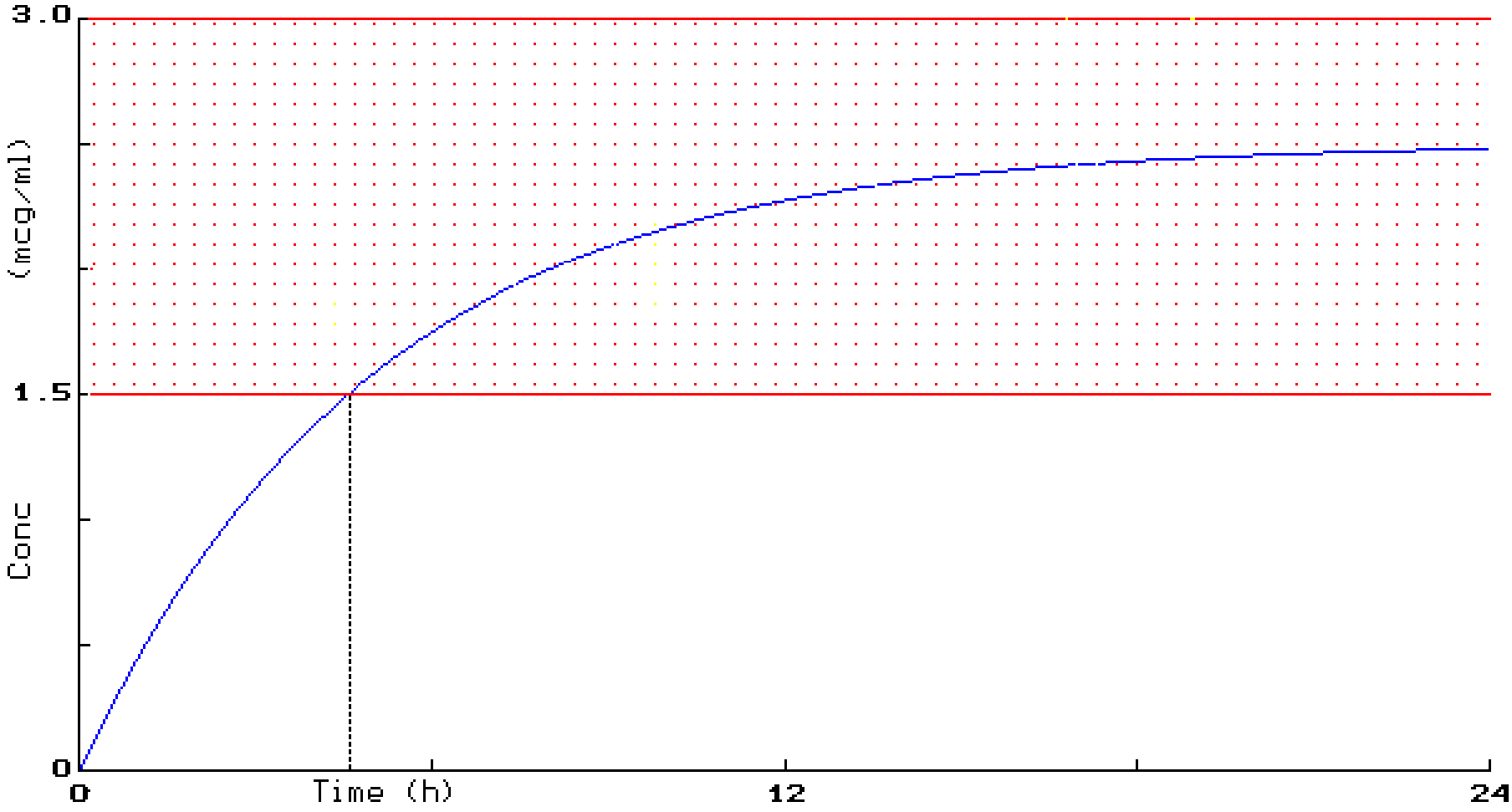
$R_{inf} = Cp_{ss} \times Cl$

$= 15$ mg/L x 3 Litre/h

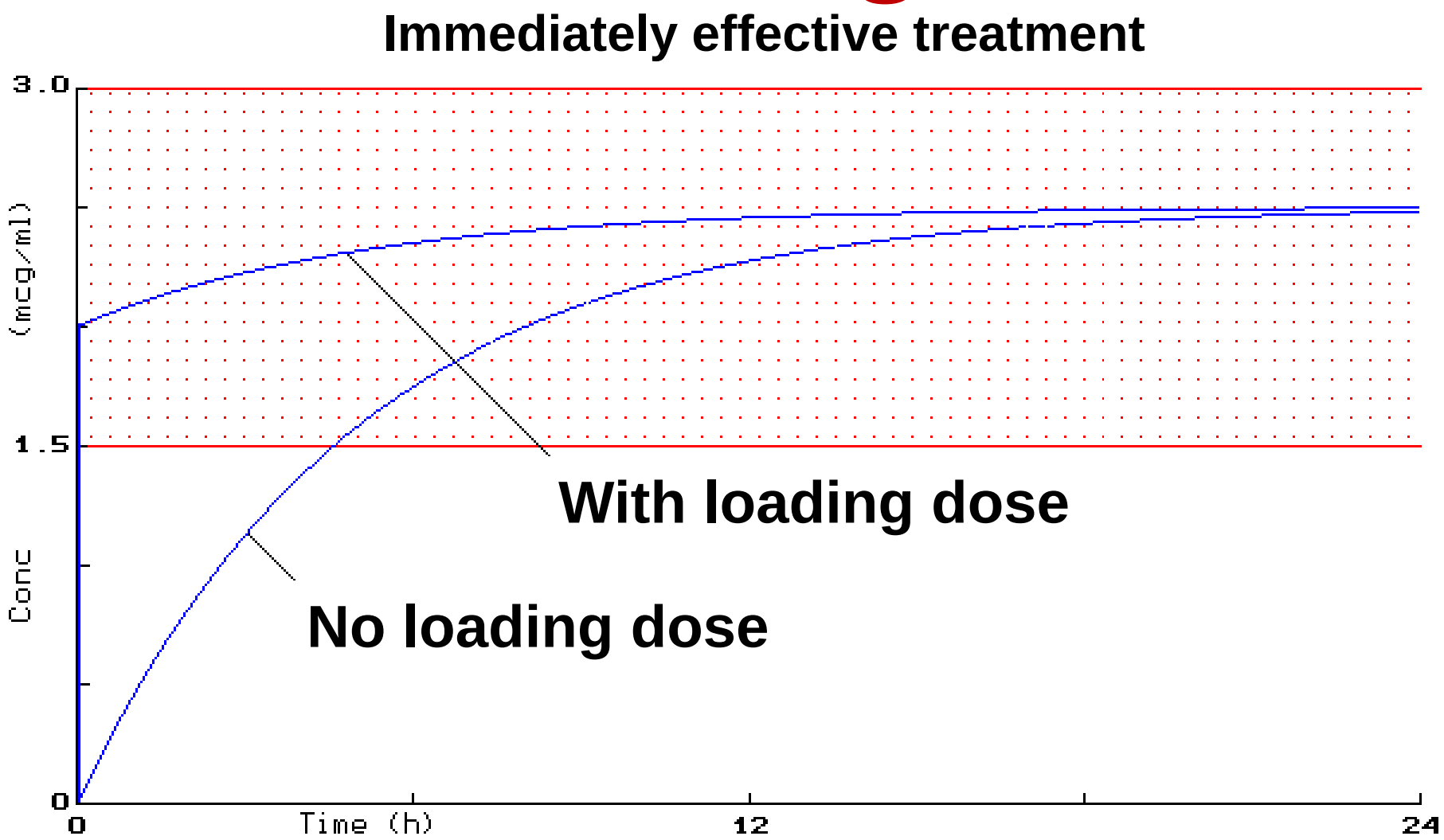
$= 45$ mg/h

Need for a loading dose

No effective treatment for (approx) first 4 hours



Use of a loading dose



Calculating loading dose

Concentration achieved = $\frac{\text{Loading dose}}{\text{Vol Dis}}$

$Cp = \frac{LD}{Vd}$

$LD = Cp \times Vd$

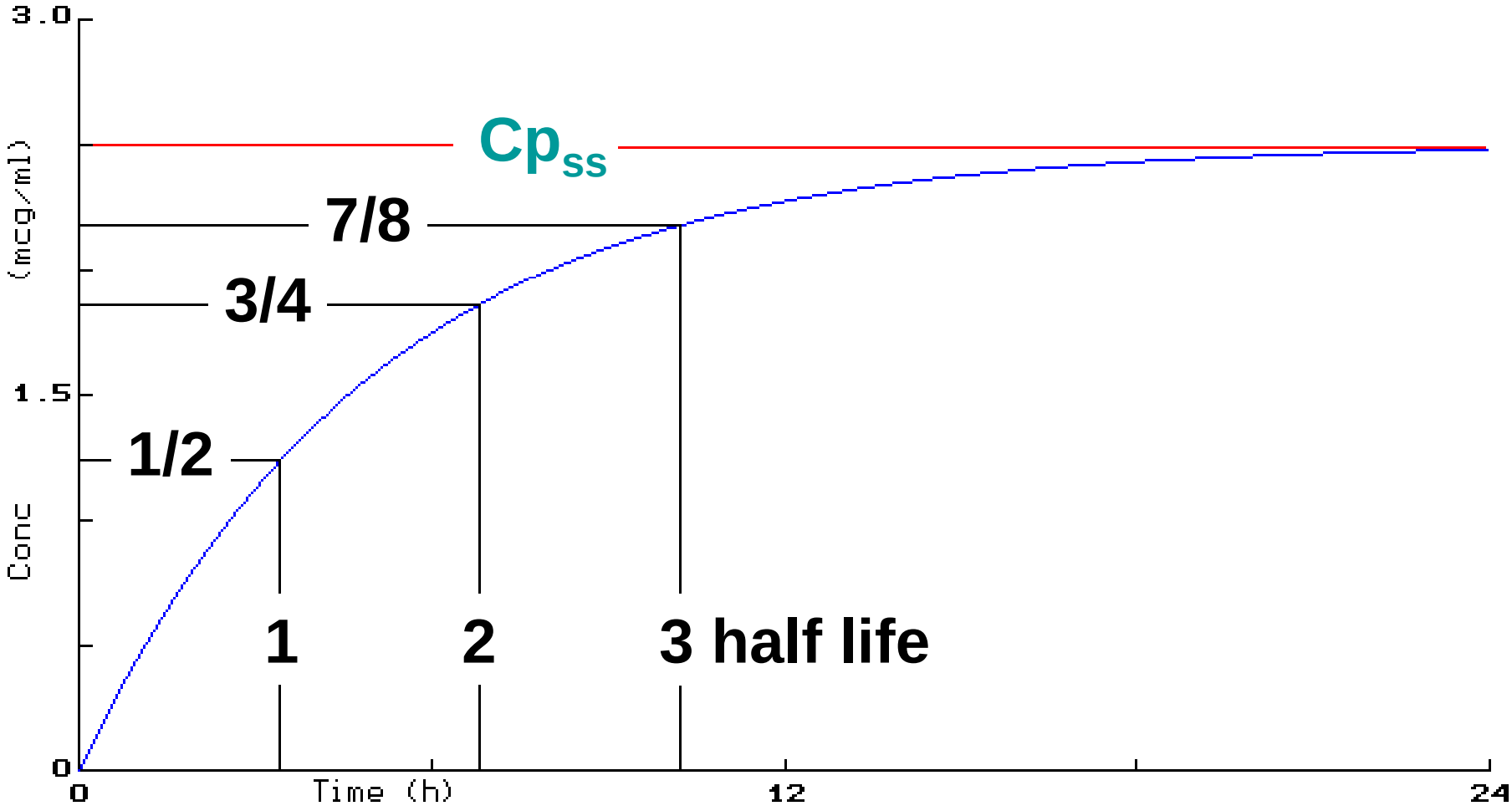
(LD is given i.v., so no need to consider F)

- **Target conc = 15 mg/L**
- **Vol dis = 50 Litres**

LD = 15 mg/L x 50 L

= 750 mg

Is a loading dose needed?



Is a loading dose needed?

- **Conc. must rise to at least 10 mg/L within 2 hours of commencing therapy**
- **Rinf = 40 $mg.h^{-1}$**
- **Vd = 33.6 L**
- **Cl = 2.8 $L.h^{-1}$**

Cpss = Rinf / Cl = 40$mg.h^{-1}$ / 2.8$L.h^{-1}$ = 14.3 mg/L

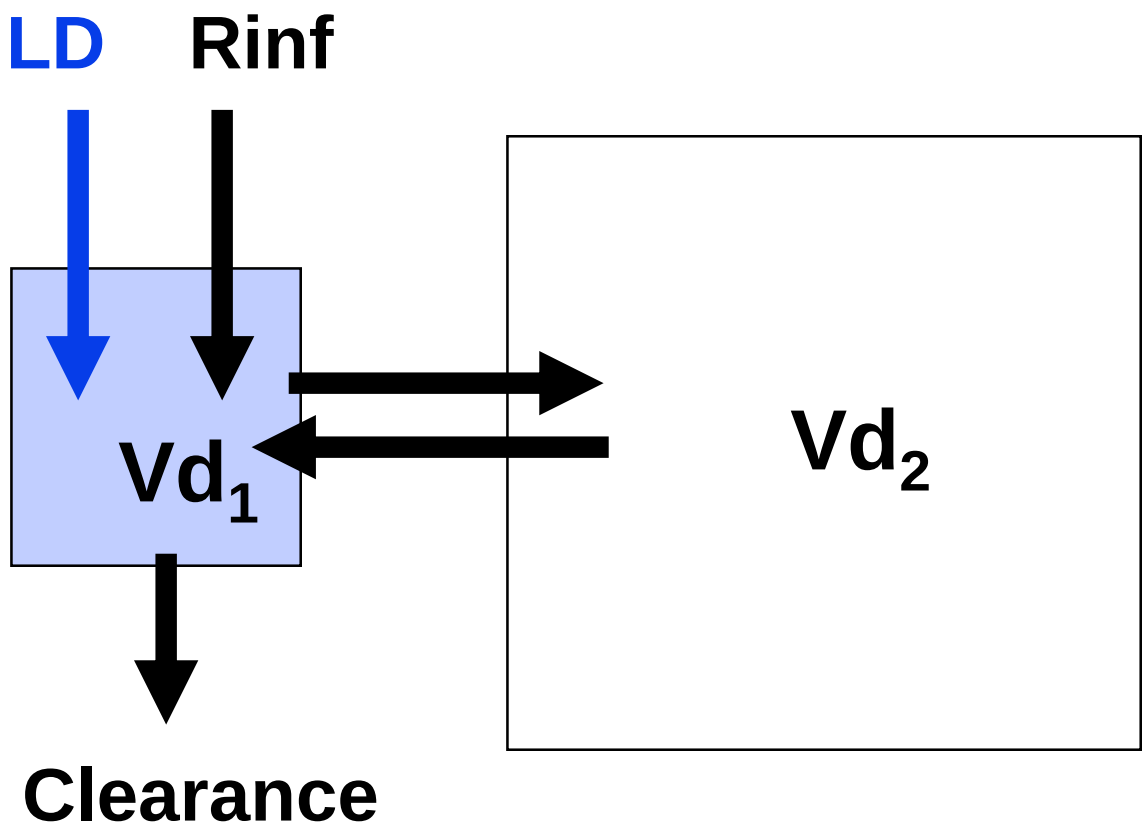
K = Cl / Vd = 2.8$L.h^{-1}$ / 33.6L = 0.083 h^{-1}

$t_{1/2}$ = 0.693 / K = 0.693 / 0.083h^{-1} = 8.35 h

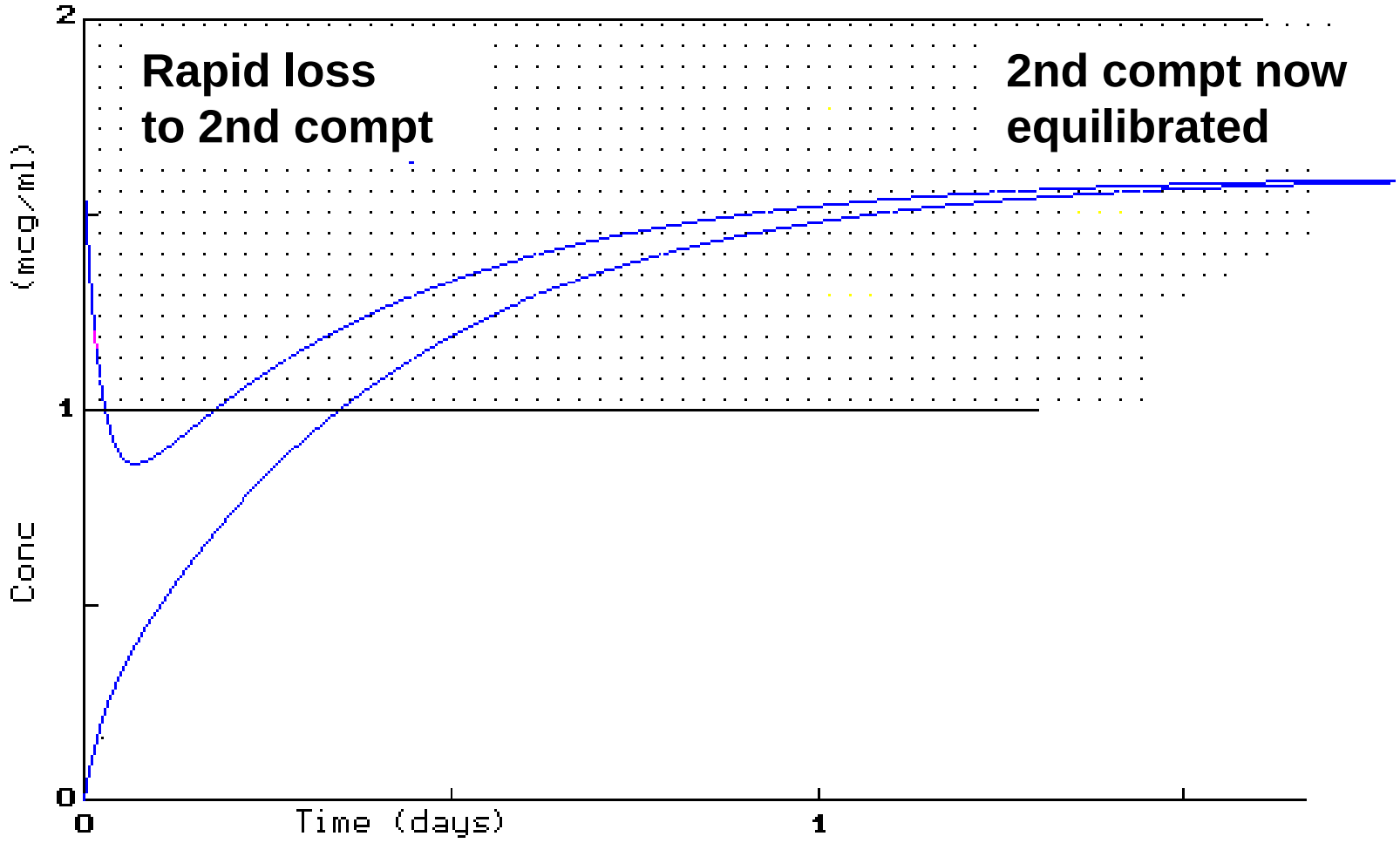
Concentration will rise to $\frac{14.3}{2}$ = 7.15 mg/L after 8.35 h

NO GOOD! We do need a Loading Dose

Infusion into two compartments



Infusion into two compartments



Possible solutions …

- **Use an additional loading some time into the infusion. May be timed according to clinical end-points. (i.e. wait until you see signs of under-dosing, then give second loading dose)**
- **Use an increased rate of infusion for an initial period and go to the 'normal' rate once the two compartments are more-or-less equilibrated.**

Example calculation

Drug infused at a rate of 5 mg/h
Plateau concentration = 4.5 µg/ml

a) What is the clearance of this drug?
(Units of L/day)

b) If the vol. dis. = 100L, what is the elimination rate constant?

Answer

Part a

Cpss = Rinf / Cl

Cl = Rinf / Cpss

= 5mg/h / 4.5 µg/ml

= 5,000µg/h / 4.5 µg/ml

= 1,111 ml/h

= 1.11 L/h

= 1.11 x 24 L/day

= 26.6 L/day

Part b

Cl = K.Vd

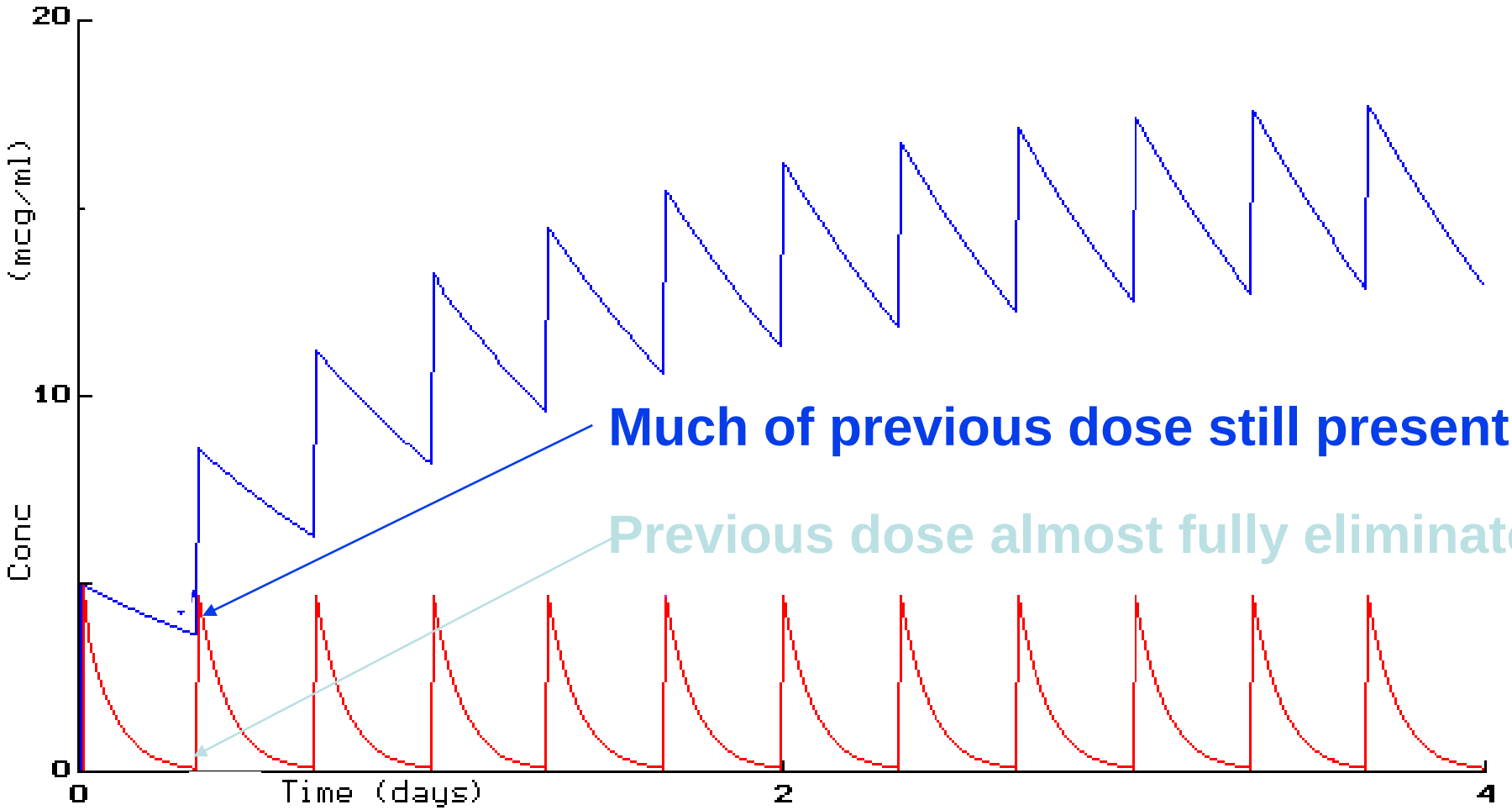
K = Cl/Vd

= 26.6L/day / 100L

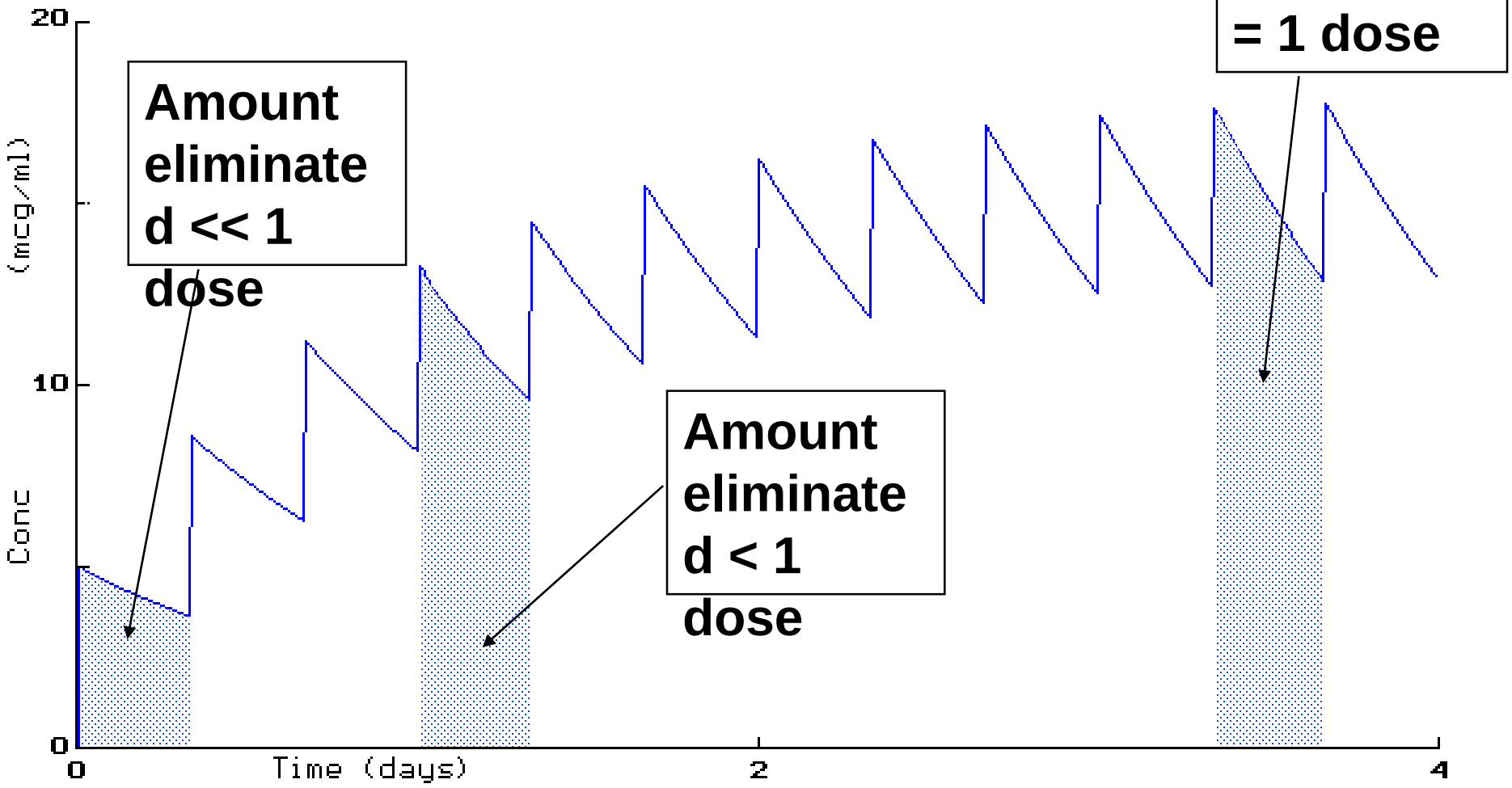
= 0.266 day^{-1}

- Constant i.v. infusion
- Multiple dosing

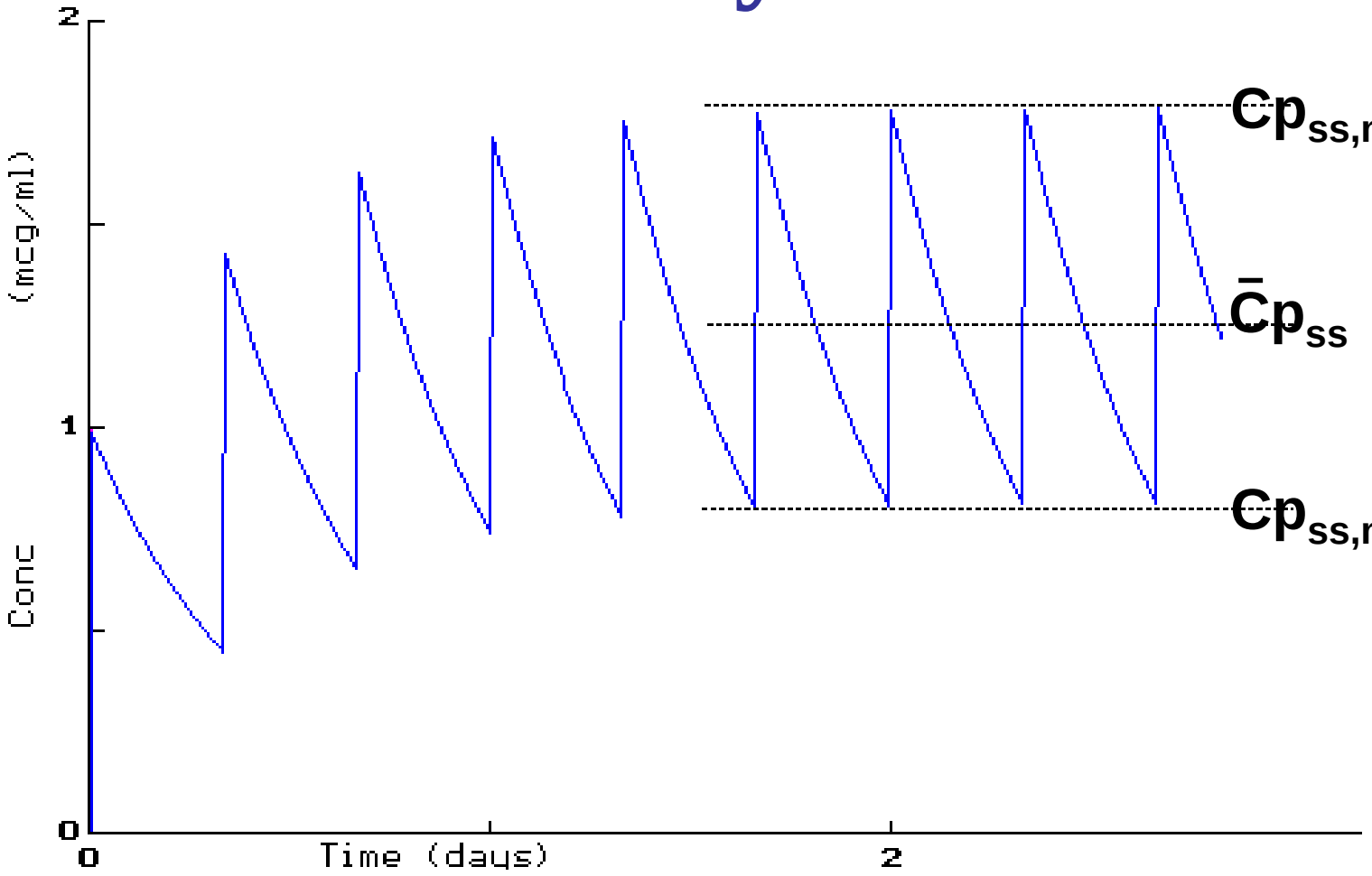
Accumulation



"Steady state"



Concentrations at Steady State



Predicting $\bar{C}p_{ss}$

Fractional bioavailability

Individual dose size

$$\bar{C}p_{ss} = \frac{F \cdot D}{Cl \cdot \tau}$$

Clearance

Dosage interval

e.g. If doses given twice daily, τ = 12 hours.

General equation

The equation for predicting $\bar{C}pss$:

$$\bar{C}pss = \frac{F.D}{Cl.\tau}$$

is very general:

- **Applicable to 1 or 2 compartment systems**
- **Applicable to any route of administration. If route is i.v., then F = 1.0 and we could just use:**

$$\bar{C}pss = \frac{D}{Cl.\tau}$$

Example calculation

What daily dose of Lithium to achieve $\bar{C}pss$ of 0.8 mMole/L, given that:

F = 100% Cl = 1.5 L/h

$$\bar{C}pss = \frac{F.D}{Cl.\tau}$$ **rearranges to:**

$$D = \frac{\bar{C}pss.Cl.\tau}{F}$$

$$D = \frac{0.8\ mMole/L \times 1.5\ L/h \times 24\ h}{1.0}$$

$$= 28.8\ mMole$$

$Cp_{ss,max}$ and $Cp_{ss,min}$

For many purposes it is adequate simply to adjust the average concentration to some target figure. But, occassionally it is necessary to keep Cpss,max and Cpss,min within certain limits.

The classic example is the aminoglycoside antibiotics (e.g. gentamicin) where effectiveness is associated with a Cpss,max greater than a certain figure and toxicity is avoided by keeping Cpss,min below a certain figure.

$Cp_{ss,max}$ and $Cp_{ss,min}$

$$Cp_{ss,max} = \frac{D}{Vd} \cdot \frac{1}{1 - e^{-K\tau}}$$

$$Cp_{ss,min} = Cp_{ss,max} - \frac{D}{Vd}$$

Unlike the equation for Cpss, these equations are not general. They are only applicable to:

- **Intravenous doses into**
- **One compartment systems**

Example calculation for Gentamicin

Vol dis = 17.5 Litres

K = 0.2 h^{-1}

Dosing = 80mg three times daily (i.v.)

Cpss,max should be between 4-8 mg/L

Cpss,min should be less than 2 mg/L

Will the regime be satisfactory?

$$C_{pss,max} = \frac{D}{Vd} \cdot \frac{1}{1 - e^{-K\tau}}$$

$$= \frac{80mg}{17.5L} \cdot \frac{1}{1 - e^{-0.2h^{-1} \times 8h}}$$

$$= 4.57mg/L \cdot \frac{1}{1 - e^{-1.6}}$$

$$= 4.57mg/L \cdot \frac{1}{1 - 0.202}$$

$$= 4.57mg/L \cdot \frac{1}{0.798}$$

$$= \underline{5.73mg/L}$$

$$C_{pss,min} = C_{pss,max} - \frac{D}{V_d}$$

$$= 5.73 \text{mg/L} - \frac{80 \text{ mg}}{17.5 \text{L}}$$

$$= 5.73 - 4.57 \text{ mg/L}$$

$$= \underline{1.16 \text{ mg/L}}$$

Will regime be satisfactory?

Requirement was ...

Cpss,max should be between 4-8 mg/L

Cpss,min should be less than 2 mg/L

Prediction is ...

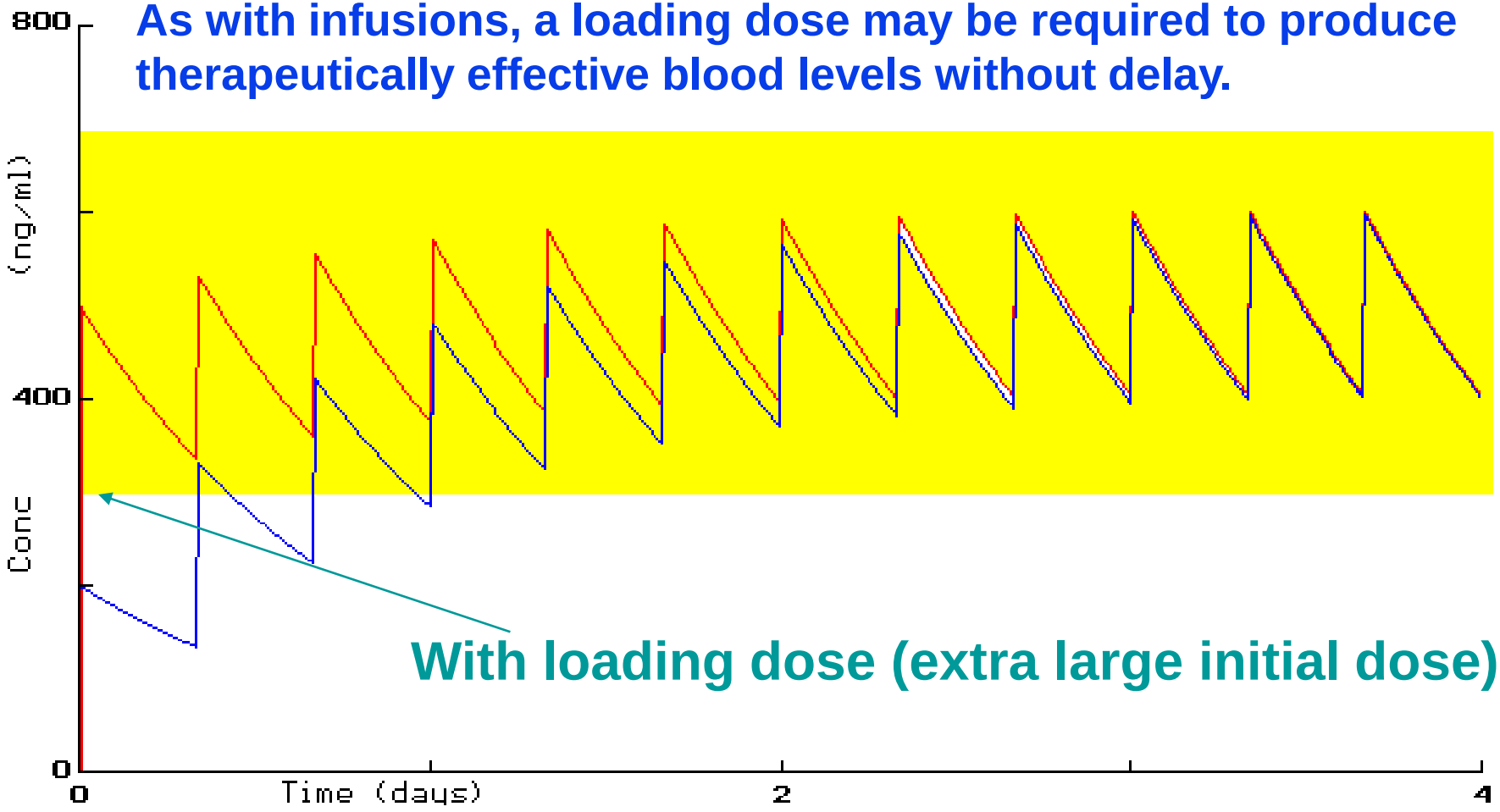
Cpss,max will be 5.73mg/L

Cpss,min will be 1.16 mg/L

Regime should be OK

Loading dose

As with infusions, a loading dose may be required to produce therapeutically effective blood levels without delay.



Loading dose

The formula is similar to that for i.v. infusion, except that we need to incorporate bioavailability (F) in case the route is extra-vascular.

$$LD = \frac{Target \times Vd}{F}$$

If route is i.v., can ignore F, as it will = 1.0

Loading dose - example

Wish to achieve immediate blood concentration of 50 µg/L
Vol dis = 200 Litres
Route is i.v.

$$LD = \frac{\text{Target} \times Vd}{F}$$

$$= \frac{50\ \mu g/L \times 200\ L}{1}$$

= 10,000 µg = 10 mg

Theophylline -Population data

Desirable concentration range = 10-20 mg/L
Vd = 0.48 L/Kg
Cl = 0.04 L/hr/Kg
S = 0.82 (For aminophylline)
F = 1.0

Theophylline

Examples of factors influencing clearance

Smoking	1.6
Congestive heart failure	0.4
Cirrhosis	0.5

New patient

We want to treat an 80Kg male asthmatic who is known to be a heavy smoker and has cirrhosis.

Aim is to use a constant i.v. infusion of aminophylline preceded by a loading dose (i.v.).

Estimate LD and Rinf.

Loading dose

Estimated Vol Dis = 0.48 L/Kg x 80Kg
= 38.4 L

Target conc = midway point within desirable range= 15 mg/L

$$LD = \frac{Cp.Vd}{S} = \frac{15\ mg/L \times 38.4\ L}{0.82} = 702\ mg$$

Recommend 700mg of aminophylline

Rate of infusion

Smoker Cirrhosis

Estimated clearance

= 0.04 L/hr/Kg x 80Kg x 1.6 x 0.5

= 2.56 L/h

Cpss = Rinf / Cl Rinf = Cpss x Cl

(Allow for salt factor)

Rinf = Cpss x Cl / S

= 15mg/L x 2.56L/h / 0.82

= 46.8 mg/h

Recommend 45 mg/h

Therapeutic drug monitoring

After infusion has been in use for a while, a blood sample is taken and found to contain 8 mg/L theophylline. The patient's breathing is still difficult.

Clearance is probably greater than we thought.

Dosage readjustment
Approach 1 (Not very efficient)

Re-calculate Clearance:

Rinf = Cpss x Cl / S

Cl = Rinf x S / Css

= 45mg/h x 0.82 / 8mg/L

= 4.61 L/h (Now an individualised estimate)

Recalculate rate of infusion:

Rinf = Cpss x Cl / S

= 15mg/L x 4.61L/h / 0.82

= 84.3 mg/h

Recommend 85 mg/h

Dosage readjustment
Approach 2 (More efficient)

On the basis of linear kinetics:

$$\frac{\text{New Rinf}}{\text{Old Rinf}} = \frac{\text{New Cpss}}{\text{Old Cpss}}$$

$$\text{New Rinf} = \text{Old Rinf} \times \frac{\text{New Cpss}}{\text{Old Cpss}}$$

$$\text{New Rinf} = 45\text{mg/h} \times \frac{15\text{mg/L}}{8\text{ mg/L}}$$

$$= 84.4\text{ mg/h}$$