ONE-COMPARTMENT OPEN MODEL: INTRAVENOUS BOLUS ADMINISTRATION:

The one-compartment open model offers the simplest way to describe the process of drug distribution and elimination in the body.
This model assumes that the drug can leave the body (i.e., the model is "open"), and the body acts like a single, uniform compartment (kinetic).
The simplest route of drug administration from a modeling perspective is a rapid intravenous injection (IV bolus).

The simplest kinetic model that describes **drug disposition** in the body is to consider that the drug is injected all at once into a box, or compartment, and that the drug distributes instantaneously and homogenously (kinetically) throughout the compartment. Drug elimination also occurs from the compartment immediately after injection.

One-Comp. Open Linear Model

Assumptions

- Rapid Mixing

– drug is mixed instantaneously in blood or plasma.

- One compartment

– drug in the blood (plasma) is in rapid equilibrium with drug in the extravascular tissues.

- Linear Model

– drug elimination follows first order kinetics.

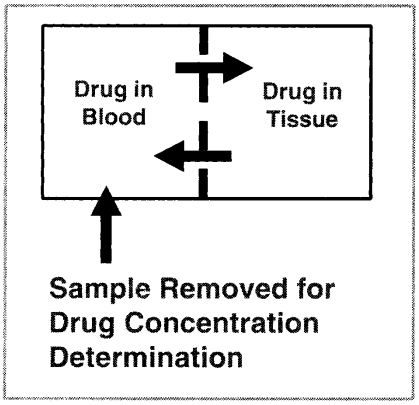


Figure 1.1. Blood is the fluid most often sampled for drug concentration determination.

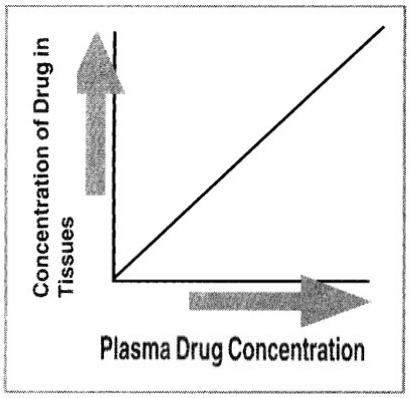


Figure 1.2. Relationship of plasma to tissue drug concentrations.

Changes in the plasma drug concentration reflect changes in drug concentrations in other tissues. However, the plasma drug concentration does not equal the concentration at other sites but rather indicates how it changes with time. Generally, if the plasma concentration of a drug is decreasing, the concentration in tissues will also decrease. Figure 1.3 is a simplified plot of the drug concentration versus time profile following an intravenous drug dose and illustrates the property of kinetic homogeneity.

The property of kinetic homogeneity is important for the assumptions made in clinical pharmacokinetics. It is the foundation on which all therapeutic and toxic plasma drug concentrations are established. That is, when studying concentrations of a drug in plasma, we assume that these plasma concentrations directly relate to concentrations in tissues where the disease process is to be modified by the drug (e.g., the central nervous system in Parkinson's disease or bone in osteomyelitis). This assumption, however, may not be true for all drugs.

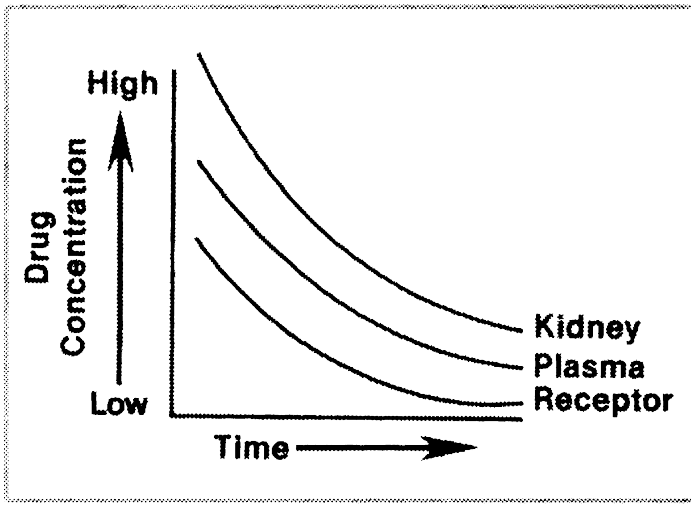


Figure 1.3. Drug concentration versus time.

Linear Kinetics (First order)

Elimination rate or change in concentration is proportional to the amount available for elimination.

Glumerular Filtration } Passive

-Tubular secretion

-Biliary secretion } Involve enzymatic processes (active)

-Biotransformation

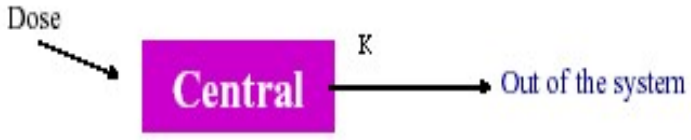
With a drug that follows first-order elimination, the amount of drug eliminated per unit time:

A. remains constant while the fraction of drug eliminated decreases.

B. decreases while the fraction of drug eliminated remains constant.

At therapeutic Levels most drugs do not reach the saturation levels of those enzymes.
Accordingly the whole elimination process can be approximated very well by first order kinetics.

1-Comp. Model: IV Bolus Dosing



Xt: the amount of drug remained in the compartment
K: first-order elimination rate constant (**OVERALL**)
(unit = time^{-1})

$$\text{Rate of elimnation} = \frac{dX}{dt} = -KX$$

$$X = X_o e^{-Kt}$$

$$C = C_o e^{-Kt}$$

$$Vd = Xt / Ct$$

$$\ln Cp = \ln Co - Kt$$

$$\log Cp = \log Co - \frac{Kt}{2.303}$$

Apparent Volume of Distribution (V_d)

This apparent volume of distribution is not a physiological volume. It won't be lower than blood or plasma volume but it can be much larger than body volume for some drugs.

It is a mathematical factor relating the amount of drug in the body and the concentration of drug in the measured compartment, usually plasma:

V_d = **AMOUNT of drug in the body** / **CONCENTRATION in plasma**

Factors affecting drug distribution:

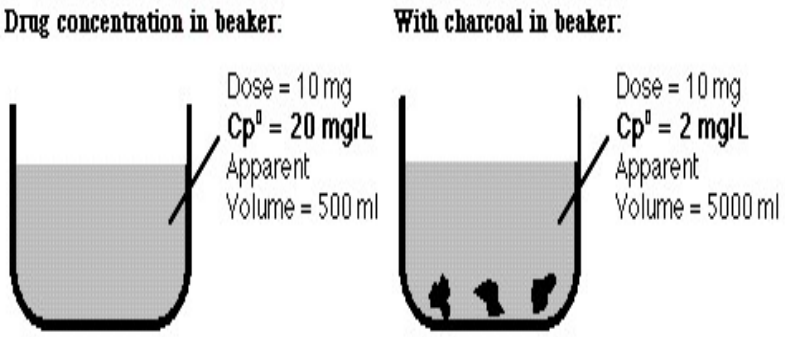
Rate of distribution

- Membrane permeability
  - Lipid Solubility
  - pH - pKa (pH-partition theory for ionizable molecules)
- Blood perfusion of organs and tissues

Extent of Distribution

- Plasma protein binding
- Intracellular binding

Definition: $V = \frac{\text{amount of drug in the body}}{\text{concentration measured in plasma}}$



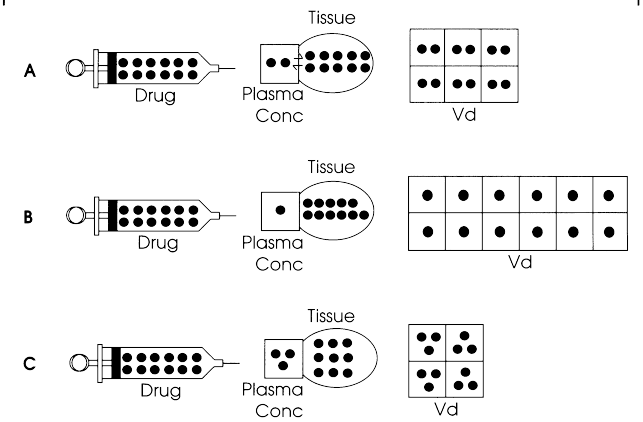


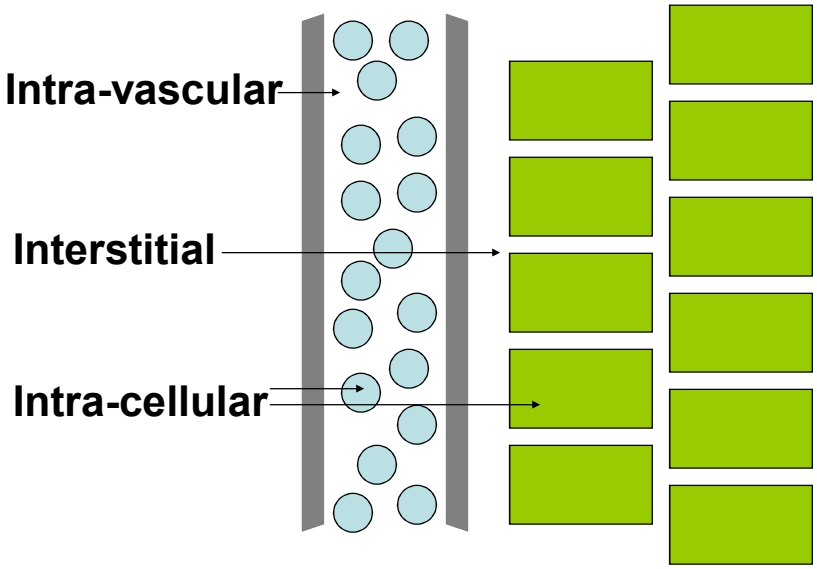
Figure 6. Volume of Distribution (A) The administration of a drug into the body produces a specific plasma concentration. The apparent volume of distribution (Vd) is the volume that accounts for the total dose administered based upon the observed plasma concentration. (B) Any factor that decreases the drug plasma concentration (e.g., decreased plasma protein binding) will increase the apparent volume of distribution. (C) Conversely, any factor that increases the plasma concentration (e.g., decreased tissue binding) will decrease the apparent volume of distribution.

Volume of Distribution

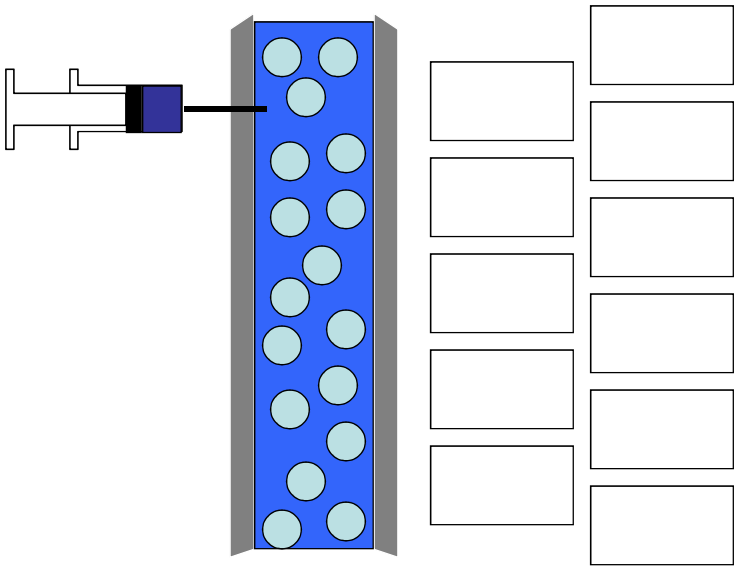
Erythropoietin	5 L	0.07 L/kg*
Warfarin	8 L	0.12 L/kg*
Phenytoin	45 L	0.63 L /kg*
Digoxin	500 L	7 L /kg*
Amiodarone	5000 L	70 L /kg*
Chloroquine	15000 L	215 L/kg*
Quinacrine	35000 L	500 L/kg*

*** Distribution Coefficient**

Body water

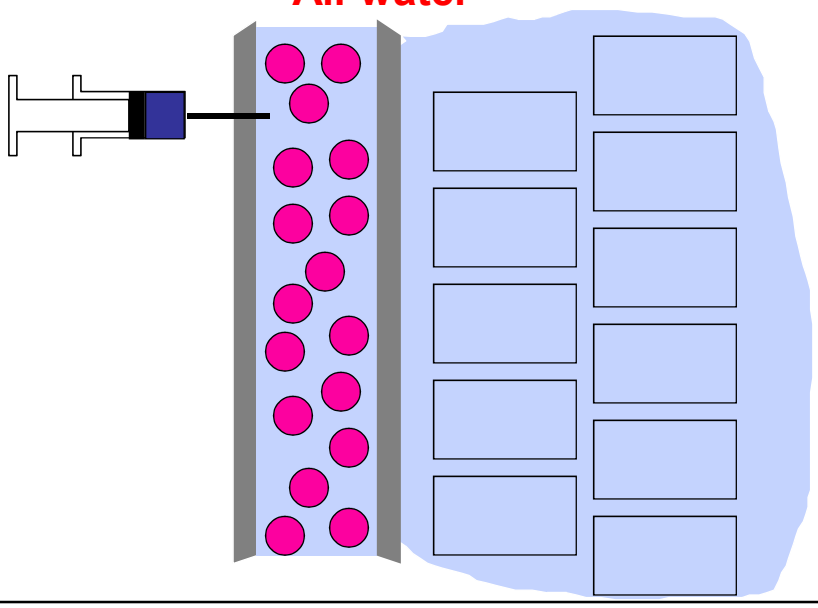


Distribution - Evan's Blue
Intra-vascular space only



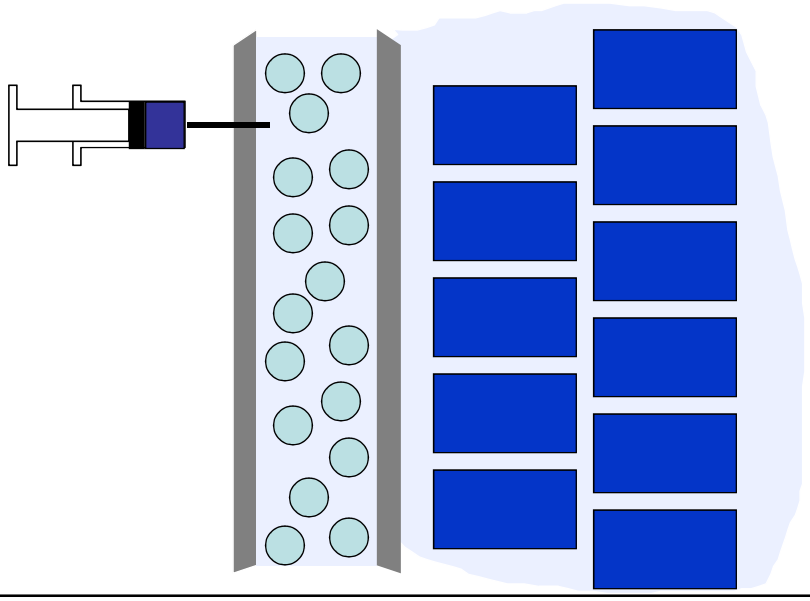
Distribution - Ethanol

All water



Distribution - Quinacrine

Concentration into cells



Volume of distribution

A measure of the tendency of a drug to move out of the blood plasma to some other site.

Volume of Distribution

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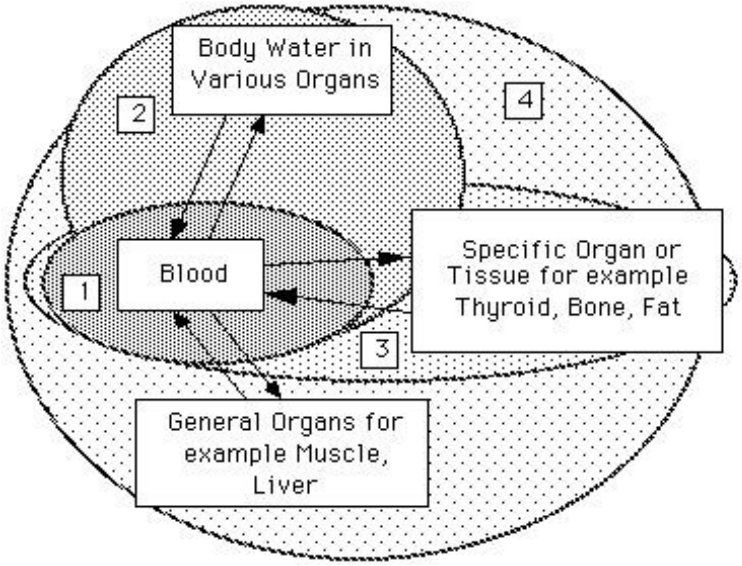
*** Distribution Coefficient**

Patterns of Vd



Relationship Between the Extent of Distribution and Vd in a 70 kg Normal Man

Vd, L	*% Body Weight*	*Extent of Distribution*
5	*7*	*Only in plasma*
5-20	*7-28*	*In extracellular fluids*
20-40	*28-56*	*In total body fluids.*
>40	*>56*	*In deep tissues; bound to peripheral tissues*

2-1. The volume of distribution equals _____ divided by initial drug concentration:

A. clearance

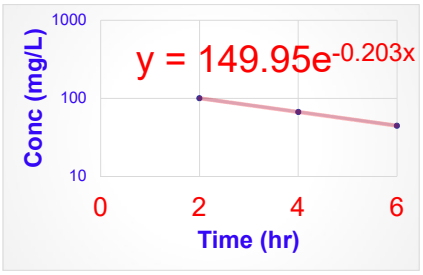
B. initial drug concentration

C. half-life

D. dose

2-2. A dose of 1000 mg of a drug is administered to a patient, and the following concentrations result at the indicated times below. Assume a one-compartment model.

Plasma Concentration (mg/L)	Time after Dose (hours)
100	2
67	4
45	6



An estimate of the volume of distribution would be:

A. 10 L.

B. 22.2 L.

C. 6.7 L.

D. 5 L.

2-3. If a drug is poorly distributed to tissues, its apparent volume of distribution is probably:

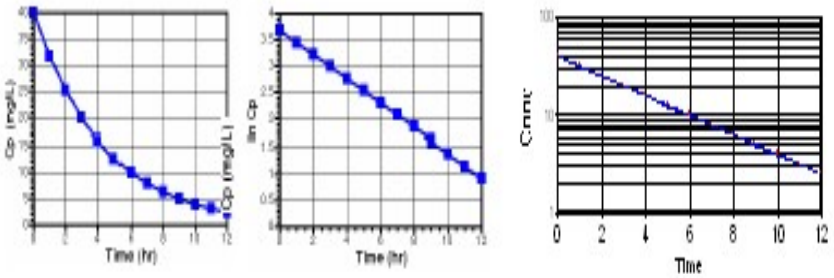
A. large.

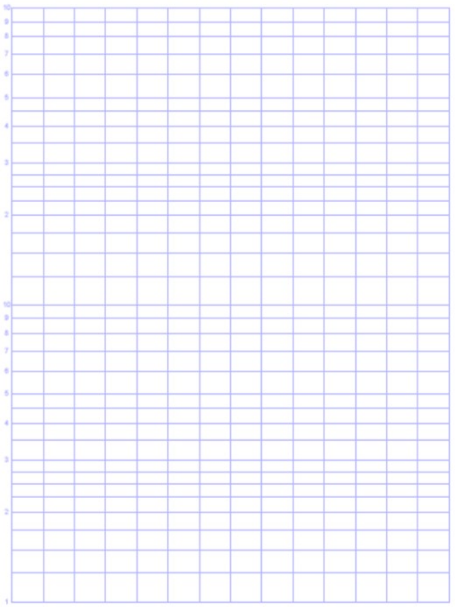
B. small.

Cp vs. Time Plots

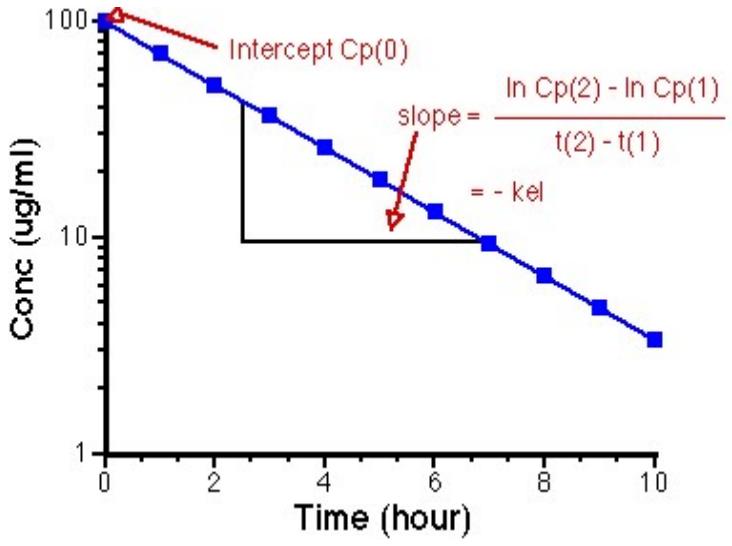
$C = C(0) \cdot e^{-kt}$ $\ln(C) = \ln C(0) - kt$ $\log_{10}(C) = \log_{10} C(0) - \frac{k}{2.303} t$

Cp vs. Time | Ln *Cp* vs. Time | Semi-log Plot *Cp* vs. Time

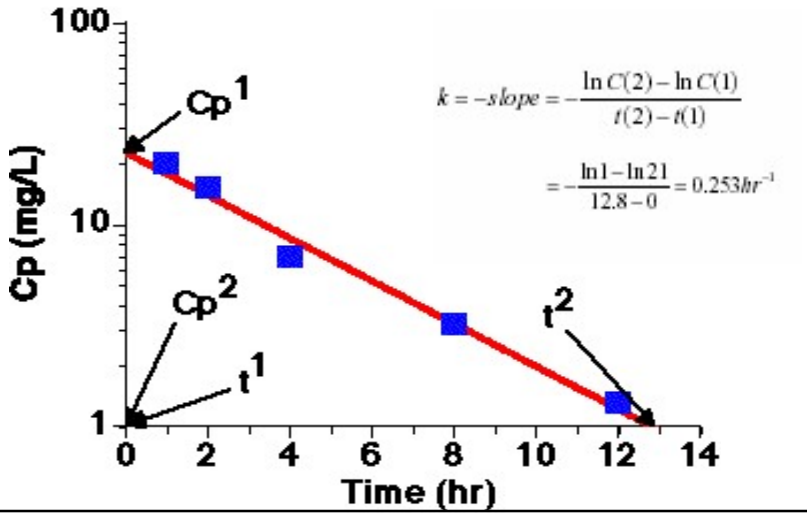




Determination of K



Cp versus Time Data					
Time (hr)	1	2	4	8	12
Cp (mg/L)	20	15	6.8	3.2	1.3



Elimination half-life ($t_{1/2}$)

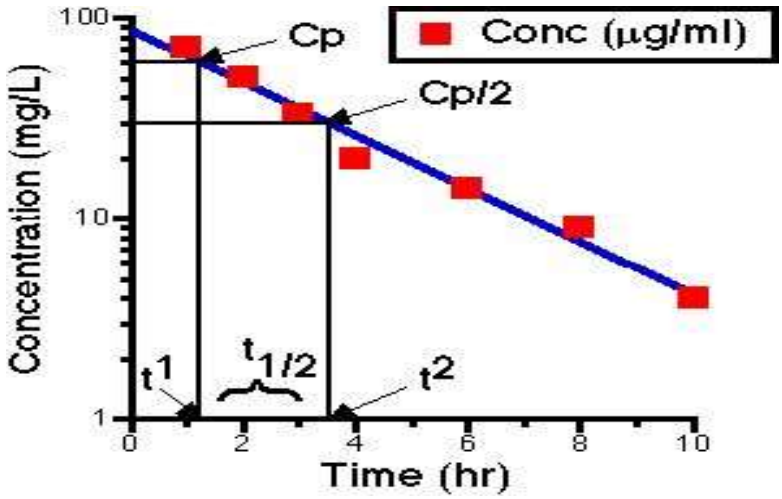
Definition: Elimination half-life is the time it takes the drug concentration in the blood to decline to one half of its initial value.

It is a secondary parameter :

The elimination half-life is dependent on the ratio of CL and V_D.

Unit : time (min, h, day)

Half-life



Fraction of Dose Remaining

n : the number of $t_{1/2}$ elapsed after a bolus IV dose

$n = t/t_{1/2}$ Fraction of dose remaining = $(1/2)^n$

Number of $t_{1/2}$ elapsed (n)	% Dose remaining	% Dose eliminated
1	50	50
2	25	75
3	12.5	87.5
4	6.25	93.75
5	3.125	96.875
6	1.563	98.437
7	.781	99.22
8	.039	99.61

Area Under the Conc. Time Curve
AUC

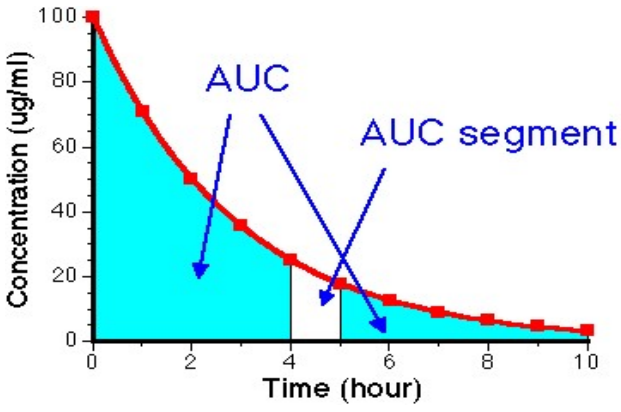
- **Model dependent Approach**

According to the equation (model)

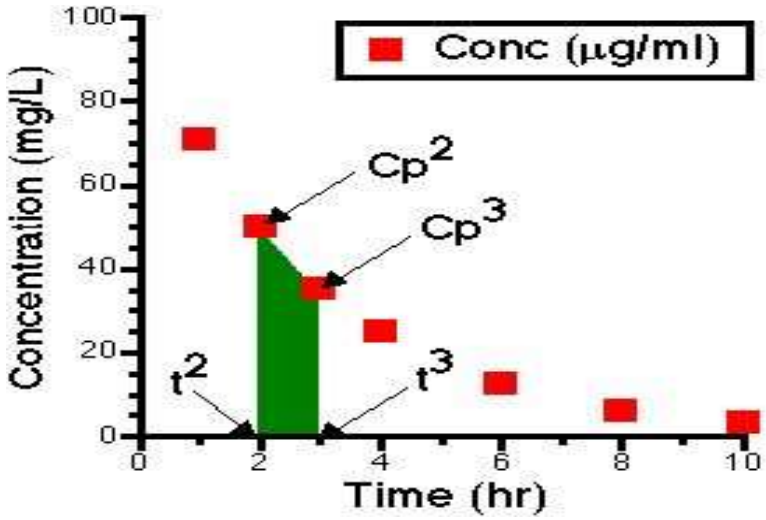
$$AUC = \frac{Xo}{K.Vd} = \frac{Xo}{Cl} = \frac{Co}{K}$$

2) **Model-independent Approach**

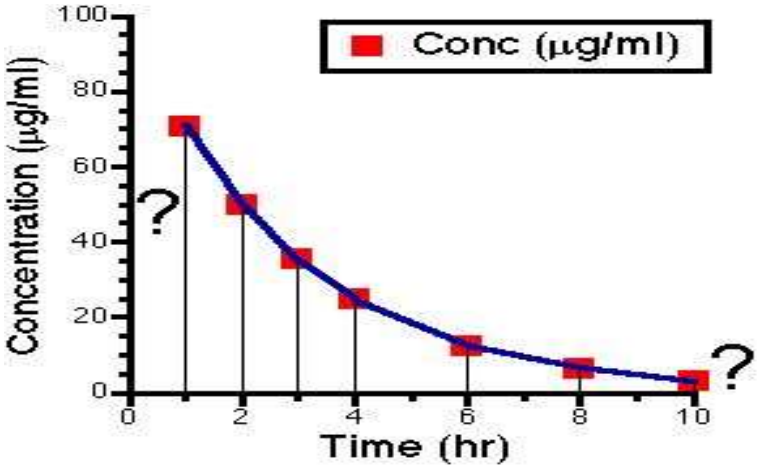
Trapezoidal Rule



Area between t2 and t3



Total Area



Clearance (CL)

Definition : Clearance of a drug is the ratio of the rate of elimination by all routs to the concentration of drug in plasma.

CL = Rate of elimination [mg / h]

C in plasma [mg /L]

Unit: Volume/Time [L/h] or adjusted for body weight [l/h/kg]

$$Cl = KVd$$

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

MD = Css

The definition of clearance is the volume of serum or blood completely cleared of the drug per unit time. Thus, the dimension of clearance is volume per unit time, such as L/h or mL/min.

The liver is most often the organ responsible for drug metabolism while in most cases the kidney is responsible for drug excretion.

The gastrointestinal wall, lung, and kidney can also metabolize some drugs, and some medications are eliminated unchanged in the bile

Clearance (CL)

Clearance has an additive character: it is the sum of clearances in all eliminating organs

$$CL = CL_{RENAL} + CL_{HEPATIC} + CL_{pulmonary} \ldots . \text{ other}$$

renal + nonrenal

2-6. The units for clearance are:

A. concentration/half-life.

B. dose/volume.

C. half-life/dose.

D. volume/time.

2-7. Total body clearance is the sum of clearance by the kidneys, liver, and other routes of elimination.

A. True

B. False

2-8. To determine drug clearance, we must first determine whether a drug best fits a one- or two-compartment model.

A. True

B. False

D-1. Drug Y is given by an intravenous injection and plasma concentrations are then determined as follows:

Time after Injection (hours)	Concentration (mg/L)
0	12
1	9.8
2	7.9
3	6.4
4	5.2
5	4.2
6	3.4
7	2.8
8	2.2

Is this drug eliminated by a first- or zero-order process? Defend your answer.

D-2. Which of the following patient scenarios is associated with a smaller volume of distribution?

A. Dose = 500 mg and initial serum concentration is 40 mg/L 500/40=12.5 L

B. Dose = 20 mg and initial serum concentration is 1.5 mg/L 20/1.5=13.3 L

D-3. Explain how a person who weighs 70 kg can have a volume of distribution for a drug of 700 L.

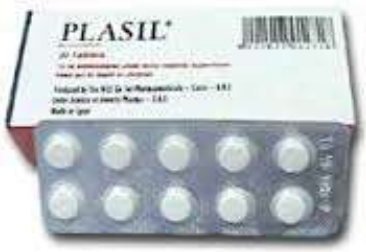
D-4. For drug X, individual organ clearances have been determined as follows:

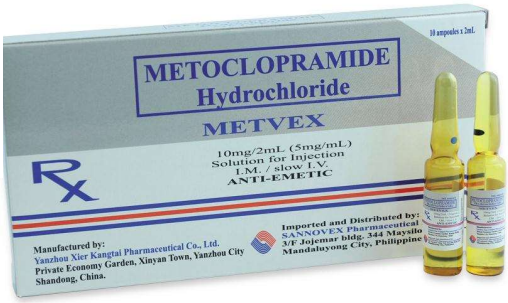
Renal clearance	180 mL/minute
Hepatic clearance	22 mL/minute
Pulmonary clearance	5.2 mL/minute

How would you describe the clearance of drug X?

Case 1

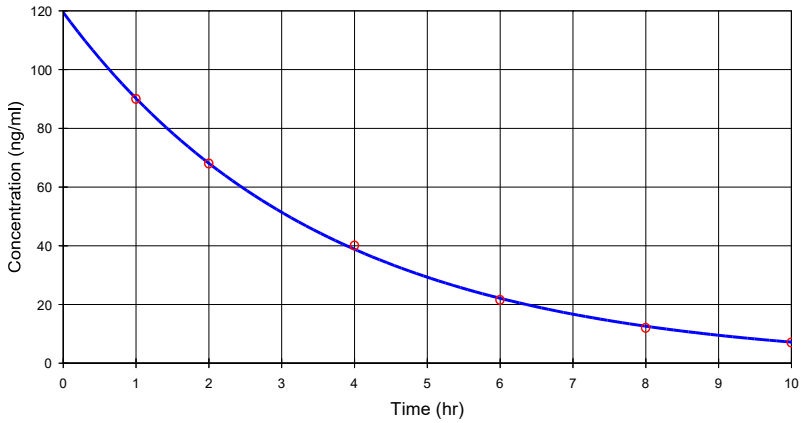
Ten mg metoclopramide were administered intravenously to a 72 kg patient. The minimum plasma concentration required to cause significant enhancement of gastric emptying is 50 ng/mL. The following plasma concentrations were observed after analysis of the specimen.

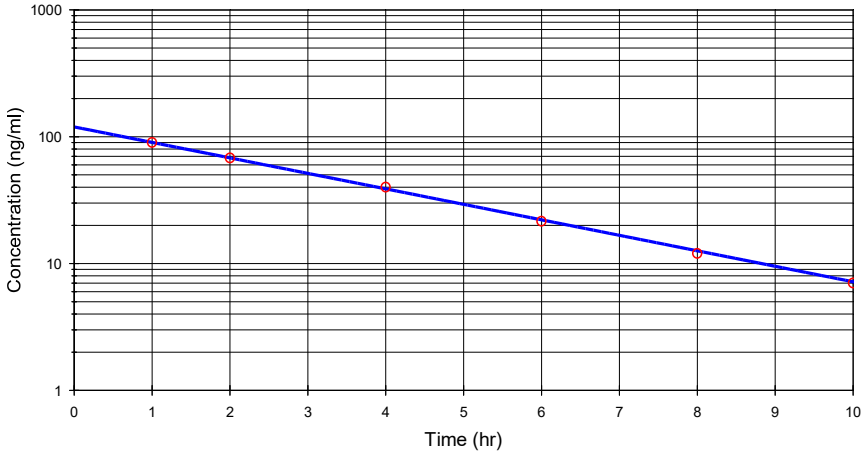




Time (h)	CP (ng/ml)
1	90
2	68
4	40
6	21.5
8	12
10	7

1) Plot the metoclopramide concentration-time data and draw a compartmental scheme showing the number of compartment involved.
2) Write the equation describing the disposition kinetics of the drug.
3) Calculate the biological half-life of the drug elimination ($t_{½}$), the overall elimination rate-constant (K), the volume (V_d), the coefficient of distribution and the duration of action (t_d).
4) Comment on the extent of metoclopramide distribution in the body.


Concentration (ng/ml)
120
100
80
60
40
20
0
0
1
2
3
4
5
6
7
8
9
10
Time (hr)


Concentration (ng/ml)
1000
100
10
1
0
1
2
3
4
5
6
7
8
9
10
Time (hr)

Metoclopramide 10 mg IV dose

AUC	**424.95**	**ng.hr/ml**
Vd	**83.33 L**	
Half-life	**2.465**	**hr**
K	**0.28 hr^{-1}**	
Cmax (Co)	**119.5**	**ng/ml**
Cl	**23.532**	**L/hr**

Case 2

An adult male patient was given the first dose of an antibiotic at 6:00 AM. At 12:00 noon the plasma level of the drug was measured and reported as 5 μg/ml. The drug is known to follow the one compartment model with a half-life of 6 hours. The recommended dosage regimen of this drug is 250 mg q.i.d. the minimum inhibitory concentration is 3 μg/ml.

Calculate the following:

1)Apparent volume of distribution

1) Vd=Xo/Co=250/10=25L

2)Expected plasma concentration at 10 AM.

2) $C_{t=4}$ = 6.3 mg/L

3. Duration of action of the first dose

$$3 = 10e^{-0.1155*t} \Rightarrow t = 10.4hr$$

4. Total body clearance

Cl=K*Vd=2.89 L/hr

5. Fraction of the dose in the body 5 hours after the injection

$$\frac{X}{Xo} = e^{-0.1155*5} = 0.56$$

6) **Total amount in the body 5 hours after the injection**

$$X = 250e^{-0.1155*5} = 140mg$$

7) **Exponential and logarithmic equation (pharmacokinetic model)**

$$C = 10e^{-0.1155*t}$$

$$LnC = 2.303 - 0.1155*t$$

$$LogC = 1 - 0.0502*t$$

8) **Total amount in the body immediately after injection of a second dose at 12:00 noon**

$$X = 250 + 125 = 375mg$$

9) **Duration of action of first dose only if dose administered at 6:00 AM was 500 mg.**

$$3 = 20e^{-0.1155*t} \Rightarrow t = 16.4hr$$

Case 3

A general anesthetic has a volume of distribution of 15 L and a minimum effective concentration of 2 µg/mL (the drug is effective as long as the drug concentration is above 2 µg/mL).

After administration of 120 mg of the drug as an IV bolus dose to a patient the drug produced anesthetic effect for 6 h.

a. Calculate the half-life of this drug.

3 hrs

a. Calculate the minimum effective concentration for the drug if the dose was 400mg.

2 mg/L

a. Calculate the expected duration of effect if an IV bolus dose of 240mg was administered.
9 hrs

a. Calculate the lowest dose that will produce an effect for 3 h.
60 mg

a. Calculate the expected duration of effect if 20mg was given as an IV bolus dose. Zero
20/15=1.33 mg/L. less than the MEC.

Case 4

The therapeutic range of a drug is 20-200 mg/L. After an intravenous bolus injection of 1.0 gm followed by regression analysis of the concentration of the drug in plasma (in units of mg/L) versus time (in hours), the following linear equation was obtained

$$\log Cp = 2 - 0.1t$$

Co=100 mg/L
Vd=10L
K=2.303*0.1
K=0.2303 hr^{-1}

Calculate the following
1) Duration of action (7 hr)
2) Total body clearance (2.303 L/hr)
3) Rate of elimination at 2 hours (dX/dt=K*X)

3) Rate of elimination at 2 hours

$$\frac{dX}{dt} = KX = 0.2303 * X_{t=2}$$

$$X_{t=2} = 1000 * e^{-0.2303*2} = 630.9mg$$

$$\frac{dX}{dt} = 145.3mg / hr$$

Case 5

Drug X has a therapeutic range of 15-80 mg/L. After an intravenous bolus injection of 500 mg of drug X, the concentration of the drug in plasma (in units of µg/ml) versus time (in hours), were described by the following equation

$$Ct = 50e^{-0.12t}$$

Co=50 mg/L
Vd=10L
K=0.12 hr^{-1}

Calculate the following

1) Duration of action after the 500-mg dose.(10 hr)
2) Amount **eliminated** at 2 hours (106.7 mg)
3) Rate of elimination at 2 hours.
(0.12x393.3=47.2 mg/hr)

Case 6

1) The plasma concentration–time profile after a single IV dose of 300mg of a drug was back extrapolated and the y-intercept was 7.5mg/L.

a. Calculate the Vd of this drug. (40 L)

b. b. Calculate the dose that should achieve an initial drug concentration of 12mg/L. (480mg)

Case 7

After IV bolus administration of 450mg of a drug, the initial drug concentration was found to be 15mg/L.

a. Calculate the Vd of this drug in this patient.(30L)

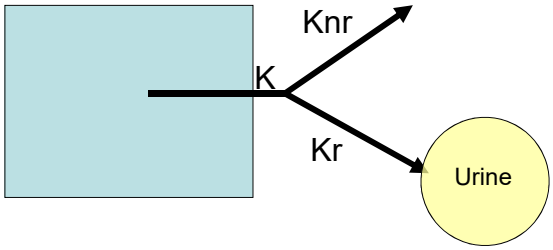
b. What is the IV bolus dose required to achieve an initial drug concentration of 20mg/L? (600mg)

c. If the patient receives a single IV bolus dose of 2g of the drug, calculate the expected initial drug concentration after this large dose. (66.7 mg/L)

Evaluation of Drug Kinetics By the Utilization of Urinary Excretion Data

One comp IV-Bolus

Clearance may be applied to any organ that is involved in drug elimination from the body. As long as first-order elimination processes are involved, clearance represents the sum of the clearances for each drug-eliminating organ



$$dXu/dt = KrX$$

Rate Method

- *log(dXu/dt) = log(KrX$_o$)-Kt/2.303*

$$\log \frac{\Delta Xu}{\Delta t} = \log KrXo - \frac{Kt}{2.303}$$

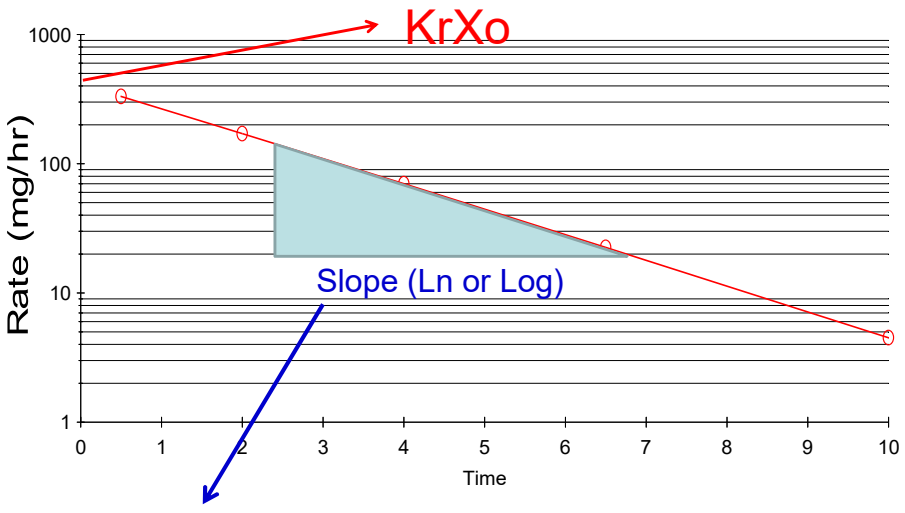
Example

After administration of 1000 mg of cefazolin, urine samples were collected and the following data were obtained

Time interval	Volume (ml)	Conc (mg/ml)
0-1	65	5.1
1-3	114	3.0
3-5	140	1.0
5-8	225	0.3
8-12	180	0.1

Rate Method

Time interval	Volume (ml)	Conc. (mg/ml)	Amount	Δt hr	ΔXu/ Δt	T-mid
0-1	65	5.1	331.5	1	331.5	0.5
1-3	114	3.0	342	2	171	2
3-5	140	1.0	140	2	70	4
5-8	225	0.3	67.5	3	22.5	6.5
8-12	180	0.1	18	4	4.5	10



$K=0.45hr^{-1}$, $t_{0.5}=1.54$ hr,
$Kr=0.41hr^{-1}$, $Knr=0.04hr^{-1}$

Sigma-Minus Method

$$Xu = \frac{KrXo}{K}(1 - e^{-Kt})$$

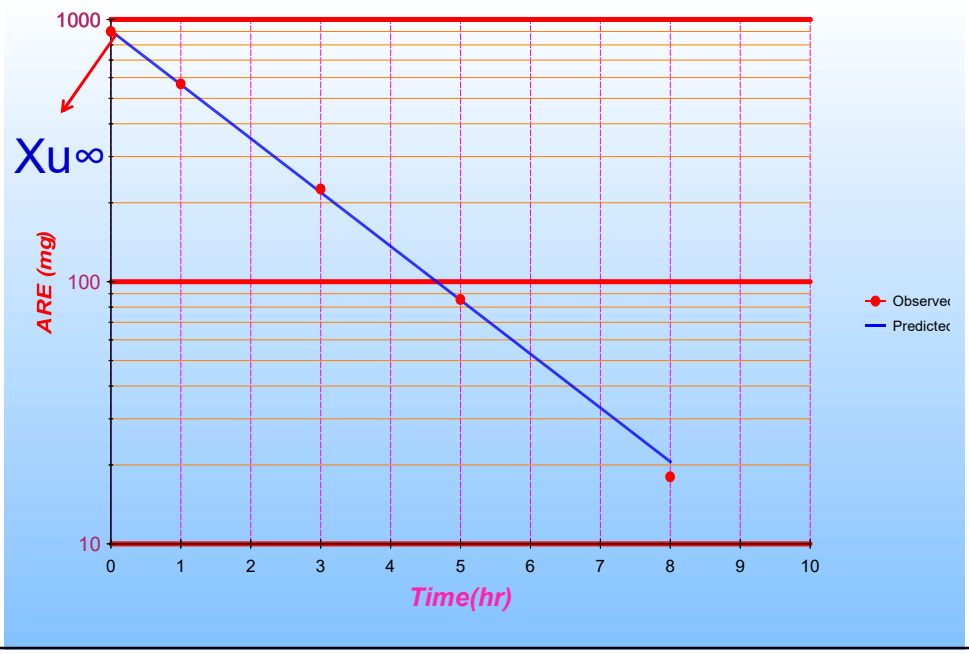
$$Xu = Xu^{\infty}(1 - e^{-Kt})$$

$$\log(Xu^{\infty} - Xu) = \log Xu^{\infty} - \frac{Kt}{2.303}$$

Sigma-Minus Method

Time interval	Volu (ml)	Conc (mg/ml)	Amount	Xu	ARE	T-end
0-1	65	5.1	331.5	331.5	567.5	1
1-3	114	3.0	342	673.5	225.5	3
3-5	140	1.0	140	813.5	85.5	5
5-8	225	0.3	67.5	881	18	8
8-12	180	0.1	18	899	0	

Sigma-Minus Method



Practice Problem

A single IV dose of an antibiotic was given to a 50-kg woman at a dose level of 20 mg/kg. Urine and blood samples were removed periodically and assayed for parent drug. The following data were obtained. Determine the different PK parameters:

Time (hr)	C_p (μg/mL)	Δx_u (mg)
0.25	4.2	160
0.50	3.5	140
1.0	2.5	200
2.0	1.25	250
4.0	0.31	188
6.0	0.08	46

Problems in Obtaining Valid Urinary Excretion Data.

Certain factors can make it difficult to obtain valid urinary excretion data. Some of these factors are as follows:

1. A significant fraction of the unchanged drug must be excreted in the urine.
2. The assay technique must be specific for the unchanged drug and must not include interference due to drug metabolites that have similar chemical structures.
3. Frequent sampling is necessary for a good curve description.

4. Urine samples should be collected periodically until almost all of the drug is excreted. A graph of the cumulative drug excreted versus time will yield a curve that approaches an asymptote at "infinite" time (∞). In practice, approximately seven elimination half-lives are needed for 99% of the drug to be eliminated.
5. Variations in urinary pH and volume may cause significant variation in urinary excretion rates.
6. Subjects should be carefully instructed as to the necessity of giving a complete urine specimen (ie, completely emptying the bladder).

Comparison of the Rate and the Sigma-Minus Methods

The rate method does not require knowledge of Xu_∞, and the loss of one urine specimen does not invalidate the entire urinary drug excretion study. The sigma-minus method requires an accurate determination of Xu_∞, which requires the collection of urine until urinary drug excretion is complete. A small error in the assessment of Xu_∞ introduces an error in terms of curvature of the plot, because each point is based on log (Xu_∞ – Xu) versus time.

Fluctuations in the rate of drug elimination and experimental errors including incomplete bladder emptying for a collection period cause appreciable departure from linearity using the rate method, whereas the accuracy of the sigma-minus method is less affected.

Lastly, the renal drug excretion rate (Kr) constant may be obtained from the rate method but not from the sigma-minus method !!!!.

Determination of k

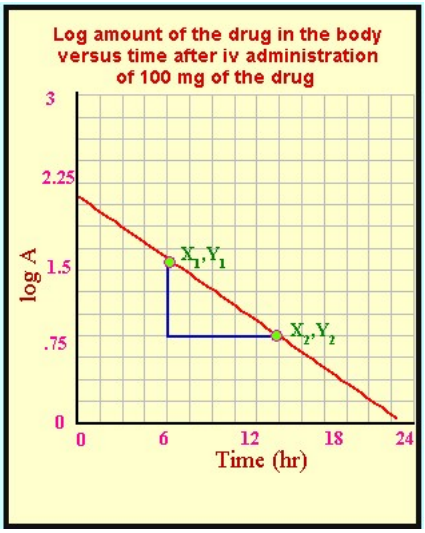
The first-order elimination rate constant (k) can be determined after iv administration of drugs by:

a- Plotting ln A versus time:
The slope of the resulting line = -k

b- Plotting log A versus time:
The slope of the resulting line = -k/2.303

The slope of a straight line is determined by choosing two points on the line and the slope will be:

$$\text{Slope} = \frac{y_2 - y_1}{x_2 - x_1}$$

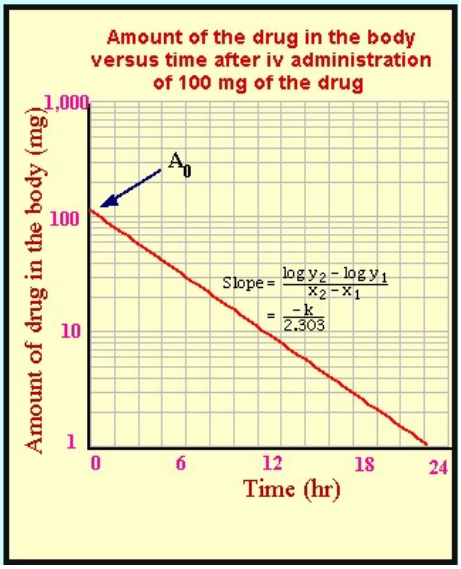


Plotting the amount of drug in the body versus time on a semilog graph paper will give a straight line.

The Y-intercept is equal to A_0
and the slope is - k/2.303

However, the slope of the line plotted on a semilog graph paper will be:

$$\text{Slope} = \frac{\log y_2 - \log y_1}{x_2 - x_1}$$



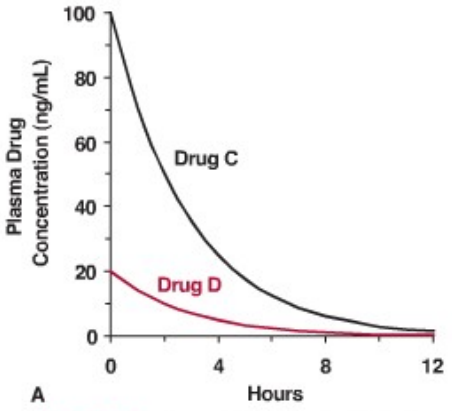


FIGURE 3-2. Drugs C (black line) and D (colored line) have the same half-life but have different initial concentrations and total exposure–time profiles. **A.** Regular (Cartesian) plot. **B.** Semilogarithmic plot. Doses of both drugs are the same.

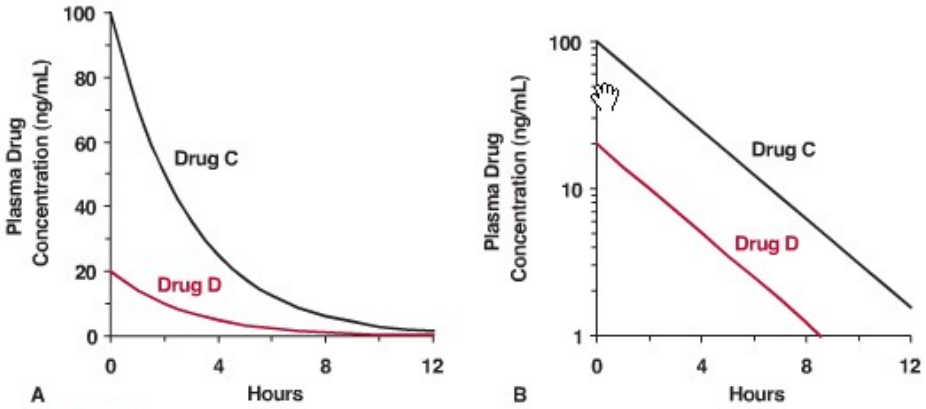


FIGURE 3-2. Drugs C (black line) and D (colored line) have the same half-life but have different initial concentrations and total exposure–time profiles. **A.** Regular (Cartesian) plot. **B.** Semilogarithmic plot. Doses of both drugs are the same.

Example: After administration of an iv dose of theophylline the amount of theophylline remaining in the body after 3 hours was 250 mg and after 8 hours was 100 mg. Calculate the elimination rate constant of theophylline in this patient.

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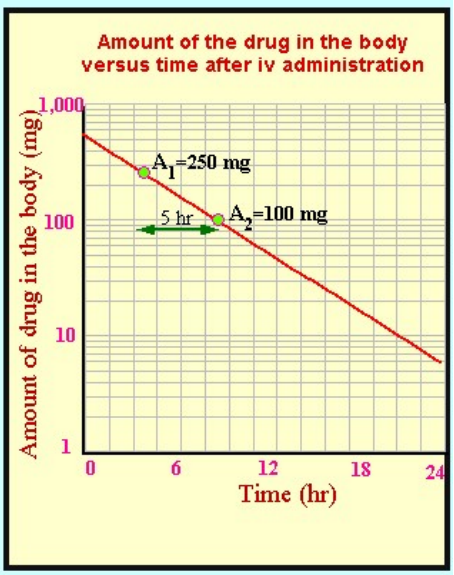


Example: After administration of an iv dose of theophylline the amount of theophylline remaining in the body after 3 hours was 250 mg and after 8 hours was 100 mg. Calculate the elimination rate constant of theophylline in this patient.

$$A_{8hr} = A_{3hr} e^{-k(8-3)hr}$$

$$100\ mg = 250\ mg\ e^{-k(5hr)}$$

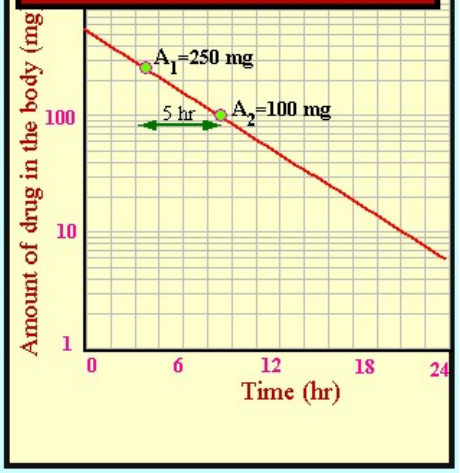
$$\frac{100\ mg}{250\ mg} = e^{-k(5hr)}$$

$$\ln \frac{100}{250} = -k(5hr)$$

$$-0.916 = -k(5hr)$$

$$k = 0.183\ hr^{-1}$$

You can substitute for the values of A_1, A_2 and t in any of the equations to calculate the elimination rate constant



Example: After administration of an iv dose of theophylline the amount of theophylline remaining in the body after 3 hours was 250 mg. What will be the amount remaining in the body after 8 hours if the elimination rate constant of theophylline in this patient is 0.183 hr^{-1} ?

$$A_2 = A_1\ e^{-k\,t}$$

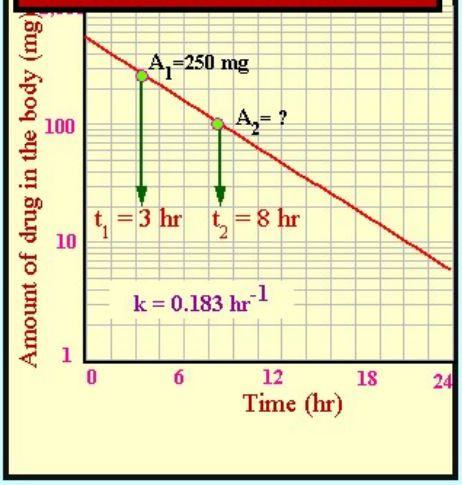
$$A_{8hr} = A_{3hr} e^{-k(8-3)hr}$$

$$A_{8hr} = 250\ mg\ e^{-0.183\ hr^{-1}(5hr)}$$

$$A_{8hr} = 250\ mg\ (0.4)$$

$$A_{8hr} = 100\ mg$$

You can substitute for the values of A_1, k and t in any of the equations to calculate the elimination rate constant



Example: After administration of an iv dose of theophylline the amount of theophylline remaining in the body after 3 hours was 250 mg. What is the time required for the amount of the drug in the body to decrease to 100 mg, if the elimination rate constant of theophylline in this patient is 0.183 hr^{-1} ?

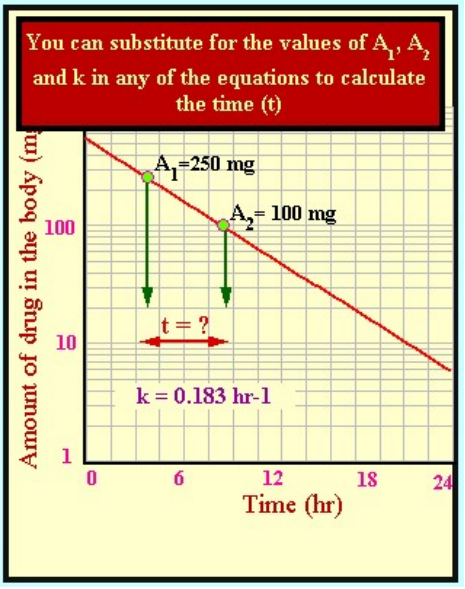
$$A_2 = A_1 e^{-k(t_2 - t_1)hr}$$

$$100mg = 250mg\ e^{-0.183\,hr^{-1}(t_2 - t_1)hr}$$

$$\ln\frac{100mg}{250mg} = -0.183\ hr^{-1}(t_2 - t_1)hr$$

$$-0.916 = -0.183\ hr^{-1}(t_2 - t_1)hr$$

$$(t_2 - t_1) = 5\ hr$$



Example: After administration of an iv dose of theophylline, the amount of theophylline remaining in the body after 8 hours was 100 mg. What was the amount of theophylline in the body after 3 hours of theophylline administration, if the elimination rate constant of theophylline in this patient is 0.183 hr^{-1} ?

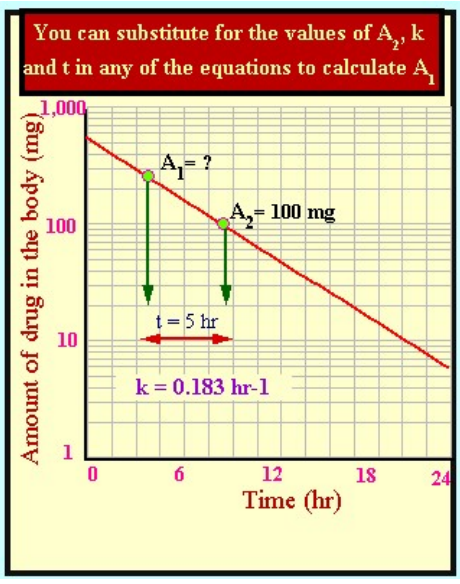
$$A_2 = A_1 e^{-k(t_2 - t_1)hr}$$

$$A_{8\,hr} = A_{3\,hr}\, e^{-k(8-3)hr}$$

$$100mg = A_{3\,hr}\, e^{-0.183\ hr^{-1}(8-5)hr}$$

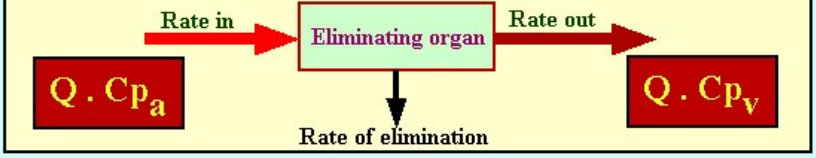
$$100mg = A_{3\,hr}\,(0.4)$$

$$A_{3\,hr} = 250\ mg$$



Physiological approach to TBC

Consider an eliminating organ:



The rate of drug entering the organ is the product of organ blood flow (Q) and the concentration of the drug in the arterial blood (Cp_a), and the rate of drug leaving the organ is the product of organ blood flow (Q) and the concentration of the drug in the venous blood (Cp_v).

The rate of drug elimination = rate in - rate out

$$= Q \cdot Cp_a - Q \cdot Cp_v$$

$$= Q\,(Cp_a - Cp_v)$$

Determination of TBC

after a single iv drug administration

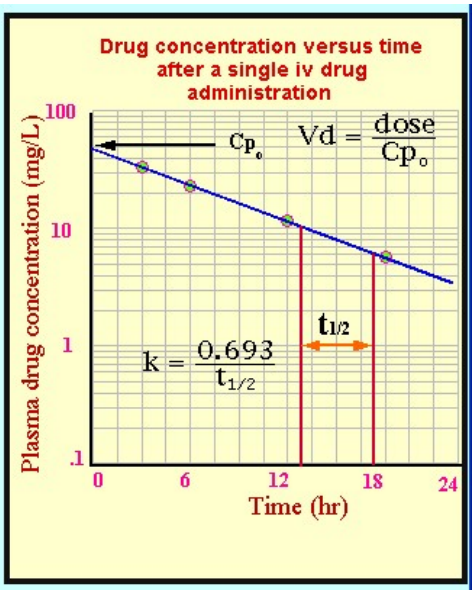
a- An iv dose of the drug is administered, then plasma samples are obtained.

b- Draw the best line that goes through the samples.

c- Starting at any point on the line, find out the half life of the drug.

d- The Y-intercept is the plasma concentration at time zero (Cp_o).

$$TBC = k\,Vd$$



Calculation of the clearance

From the drug excretion rate data

Determination of the overall drug excretion rate from the body is not easy. The renal drug excretion rate can be determined easily by measuring the amount of the drug excreted in urine over a certain period of time. This can be used to determine the renal clearance.

a- The amount of the drug excreted in urine is determined over a short time interval.

b- Calculate the renal excretion rate (amount/time interval).

c- Obtain the average plasma conc during the urine collection interval (conc at the middle of the urine collection interval).

$$\frac{\text{Drug excretion rate}}{\text{Cp at the same time}} = \text{Renal Clearance}$$

The renal clearance is equal to the TBC only when the drug is completely excreted unchanged in urine

Clearance and k

$$TBC = k\ Vd$$

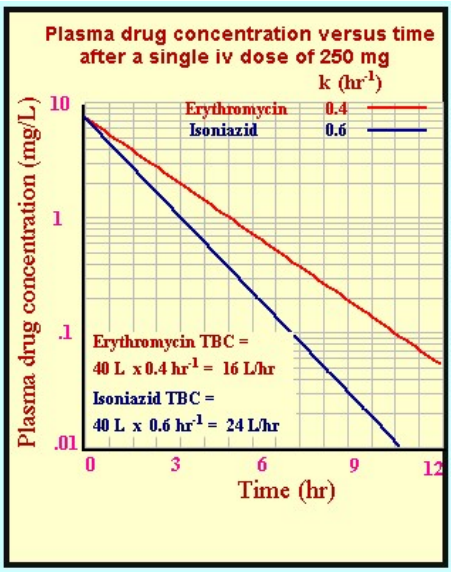
Drugs that have larger k have higher TBC, if Vd is similar.

For example:

Erythromycin	Isoniazid
$k = 0.4\ hr^{-1}$	$k = 0.6\ hr^{-1}$
Vd = 0.6 L/kg	Vd = 0.6 L/kg

Isoniazid has larger TBC

The two profiles have similar initial conc because Vd is similar. However the profiles have different slopes because k is different.



Clearance and Vd

TBC = k Vd

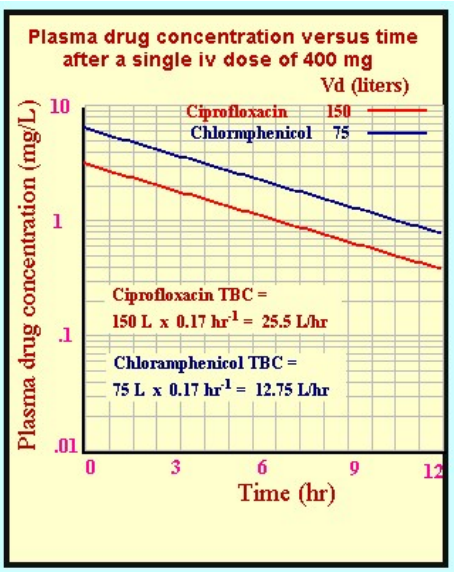
Drugs that have higher Vd have higher TBC, if k is similar (similar half life).

For example:

Ciprofloxacin	Chloramphenicol
$k = 0.17\ hr^{-1}$	$k = 0.17\ hr^{-1}$
Vd = 2 L/kg	Vd = 1 L/kg

Ciprofloxacin has larger TBC

Notice that the two profiles are parallel because k is similar. However the initial conc is different because Vd is different.



Example: After iv administration of 500 mg procainamide to a patient, the plasma concentration-time profile can be described by the following equation:

$$Cp = 5\ e^{-0.2\,t}$$

What is the TBC of procainamide in this patient ?

$k = 0.2\ hr^{-1}$

$$Vd = \frac{Dose}{Cp_o}$$

$$Vd = \frac{500\ mg}{5\ mg / L} = 100\ L$$

$TBC = 0.2\ hr^{-1} 100\ L = 20\ L/hr$

This equation is in the form of:

$$Cp = Cp_o\ e^{-k\,t}$$

$k = 0.2\ hr^{-1}$

$$Vd = \frac{Dose}{Cp_o}$$

$TBC = k\ Vd$