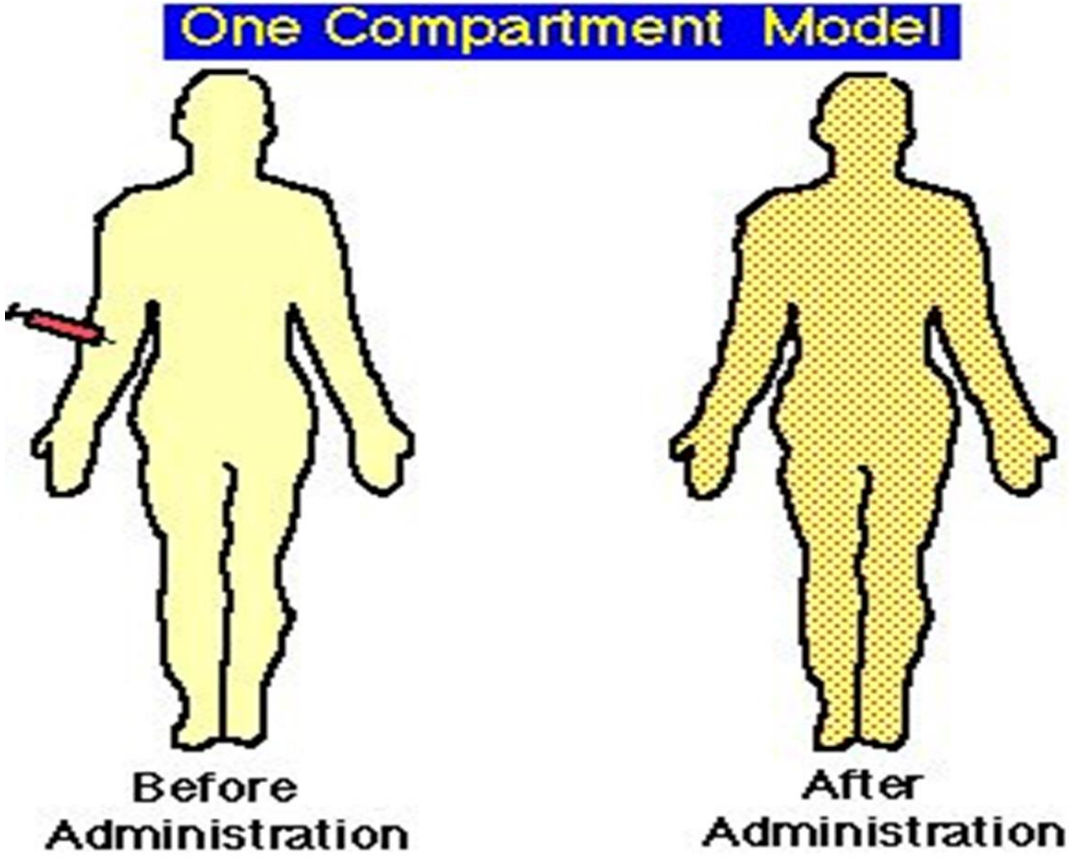
One-Compartment Open Model:
Intravenous Bolus Administration



Intravenous Bolus Administration

• One-Compartment Open Model

- The simplest route of drug administration from a modeling perspective is a rapid intravenous injection (IV bolus).

- 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 enter or leave the body (ie, the model is "open"), and the body acts like a single, uniform compartment.

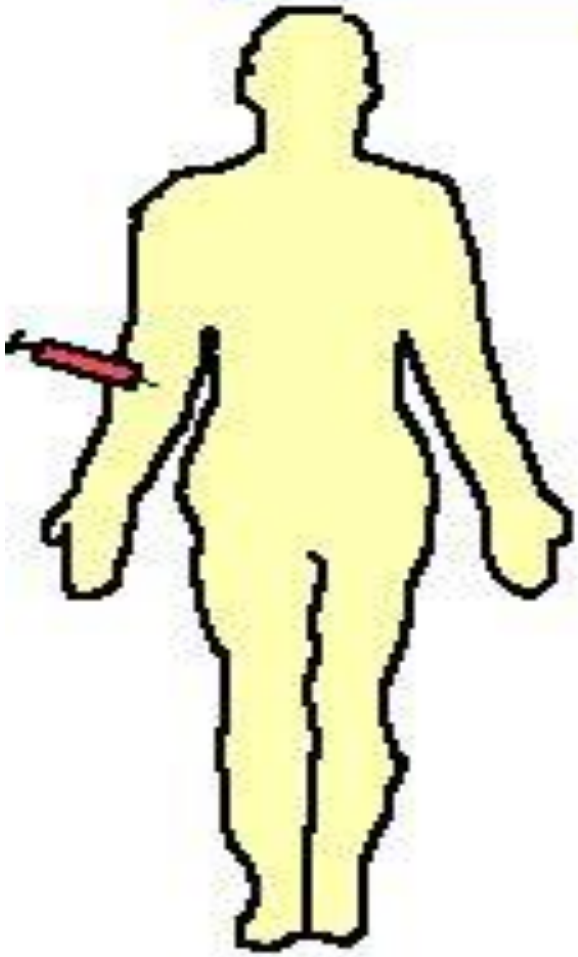
One-Compartment Open Model

- 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 throughout the compartment.

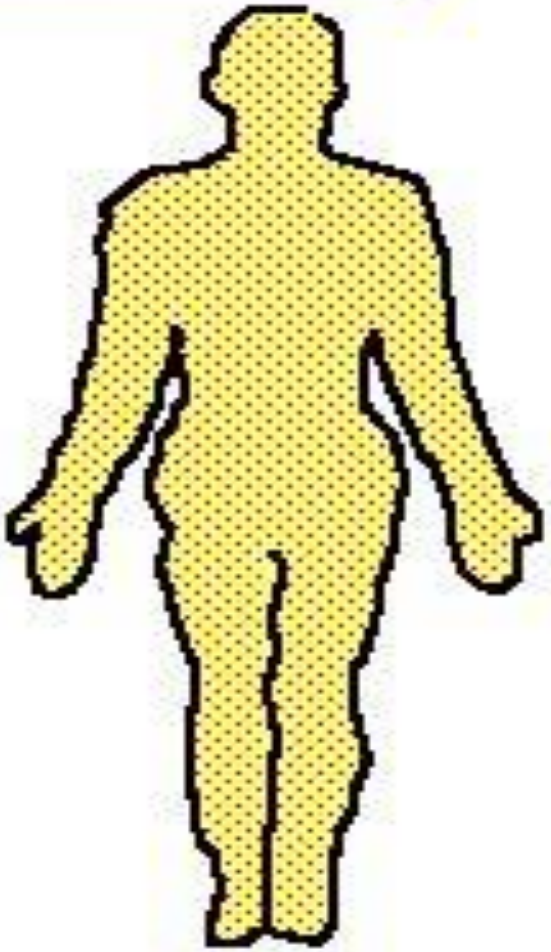
- Drug elimination also occurs from the compartment immediately after injection.

- In reality the body is infinitely more complex than a single compartment.

One Compartment Model



Before Administration



After Administration

One-Compartment Open Model

- In the body, when a drug is given in the form of an IV bolus, the entire dose of drug enters the bloodstream immediately, and the drug absorption process is considered to be instantaneous.

- In most cases, the drug distributes via the circulatory system to potentially all the tissues in the body.

- Uptake of drugs by various tissue organs will occur at varying rates, depending on:
  - The blood flow to the tissue.
  - The lipophilicity of the drug.
  - The molecular weight of the drug.
  - The binding affinity of the drug for the tissue mass.

- While drug distribution is complex,

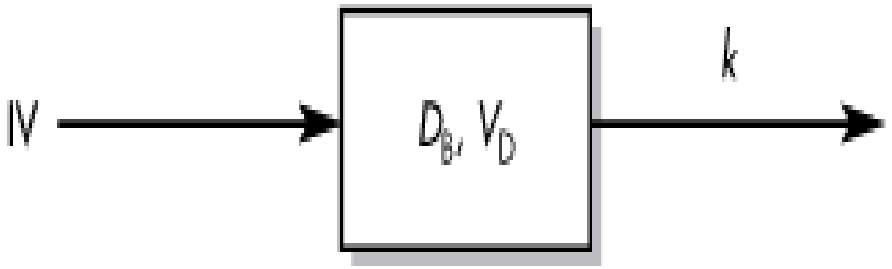
- if these processes are rapid enough, we can simplify our conceptualization as if the drug uniformly distributes into a single (one) compartment of fluid.

One-Compartment Open Model

- Most drugs are eliminated from the body either through the kidney and/or by being metabolized in the liver.
- The volume in which the drug is distributed is termed the ***apparent volume of distribution***, V_D.
- The apparent volume of distribution assumes that the drug is uniformly distributed in the body.
- The V_D is determined from the
  - the dose and
  - the plasma drug concentration resulting immediately after the dose is injected.

One-Compartment Open Model

- The one-compartment model that describes the distribution and elimination after an IV bolus dose is:



Pharmacokinetic model for a drug administered by rapid intravenous injection.

D_B = drug in body;

V_D = apparent volume of distribution;

k = elimination rate constant.

IV bolus Inj.: one-compartment model

- The one-compartment open model does not predict actual drug levels in the tissues.

- The model assumes that changes in the plasma levels of a drug will result in proportional changes in tissue drug levels, since their kinetic profile is consistent with inclusion within the vascular compartment and the various drug concentrations within the compartment are in equilibrium.

- The *drug in the body*, D_B, cannot be measured directly; however, accessible body fluids (such as blood) can be sampled to determine drug concentrations.

Elimination Rate Constant, k

- It is a pharmacokinetic parameter that governs the rate at which the drug concentration in the body declines over time.

- The rate of elimination for most drugs from a tissue or from the body is a first-order process.
  - The rate of elimination is dependent on the amount or concentration of drug present.
  - It has units of time^{-1} (eg, hr^{-1} or 1/hr).

Elimination Rate Constant, k

- The elimination rate constant represents the sum of metabolism (biotransformation) and excretion of the active drug.

$$k = k_m + k_e$$

- Where: k_m = first-order rate process of metabolism.

  k_e = first-order rate process of excretion.

The 1st Order Elimination Expression

- Each of these processes(metabolism or excretion) has its own first-order rate constant.

$$\frac{dD_B}{dt} = -kD_B$$

$$\int_{D_B^0}^{D_B} \frac{dD_B}{D_B} = \int_0^t -kdt$$

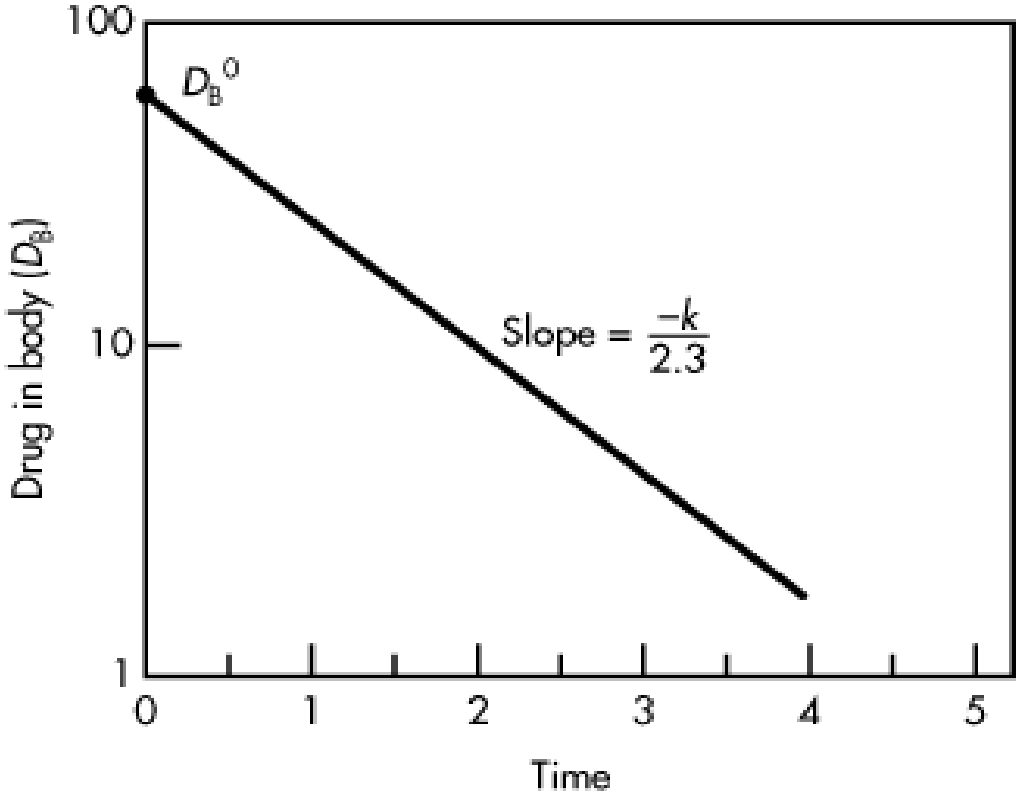
$$\log D_B = \frac{-kt}{2.303} + \log D_B^0$$

$$D_B = D_B^0 \bullet e^{-kt}$$

Where: D_B = drug in the body at time t and D_B^0 = drug in the body at $t = 0$

The 1st Order Elimination Expression

- When log D_B is plotted against t, a straight line is obtained:



Semilog graph of the rate of drug elimination in a one-compartment model.

The Apparent Volume of Distribution, V_D

- V_D is a pharmacokinetics parameter that describes the volume in which the drug is distributed.
- The apparent volume of distribution assumes that the drug is uniformly distributed in the body.
- The V_D is determined from the preinjected amount of the dose in the syringe and the plasma drug concentration resulting immediately after the dose is injected.

The Apparent Volume of Distribution, V_D

- The *volume of distribution* represents a volume that must be considered in estimating the amount of drug in the body from the concentration of drug found in the sampling compartment.

- Because the value of the volume of distribution does not have a true physiologic meaning in terms of an anatomic space, the term *apparent* volume of distribution is used.

- The V_D relates the concentration of drug in plasma (C_p) and the amount of drug in the body (D_B), as in the following equation:

The Apparent Volume of Distribution, V_D

$$D_B = C_P V_D$$

The Apparent Volume of Distribution, V_D

Example

- Exactly 1 g of a drug is dissolved in an unknown volume of water. Upon assay, the concentration of this solution is 1 mg/mL. What is the original volume of this solution?

- 1000 ml

- If, in the above example, the volume of the solution is known to be 1 L, and the concentration of the solution is 1 mg/mL, then, to calculate the total amount of drug present?

- 1000 mg

Calculation of Volume of Distribution, V_D

- In a one-compartment model (IV administration), the V_D is calculated with the following equation:

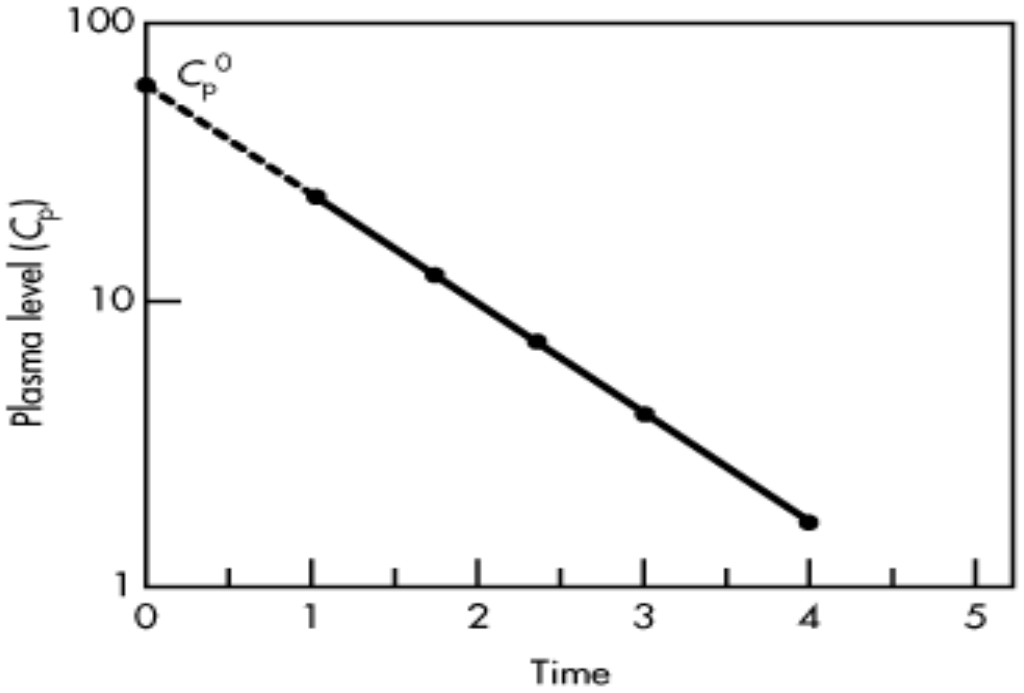
$$V_D = \frac{Dose}{C_P^0} = \frac{D_B^0}{C_P^0}$$

Where:

- ***C_p^o*** is determined by extrapolation, it represents the instantaneous drug concentration (concentration of drug at t = 0) after drug equilibration in the body.
- ***D_B^o*** the dose of drug given by IV bolus (rapid IV injection), at t = 0

Calculation of Volume of Distribution, V_D

- Because both D_B^0 and C_p^0 are known at t = 0, then the apparent volume of distribution, V_D, may be calculated:



Semilog graph giving the value of C_p^0 by extrapolation.

Calculation of Volume of Distribution, V_D

$$\frac{dD_B}{dt} = -kD_B$$

$$\frac{dD_B}{dt} = -kC_P V_D$$

$$dD_B = -kC_P V_D dt$$

$$\int_0^{D_o} dD_B = \int_0^{\infty} -kC_P V_D dt = -kV_D \int_0^{\infty} C_P dt$$

$$\int_0^{\infty} C_P dt = [AUC]_0^{\infty} \Rightarrow D_0 = kV_D [AUC]_0^{\infty}$$

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

Where:

- ***D_0*** the dose of drug given by IV bolus injection.
- ***AUC*** is the area under the curve of C vs t Curve.

The Apparent Volume of Distribution, V_D

- The apparent volume of distribution is not a true physiologic volume.
- 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.

The Apparent Volume of Distribution, V_D

- The apparent V_D is a volume term that can be expressed as terms of percent body weight, a 1-L volume is assumed to be equal to the weight of 1 kg.

- For example, if the V_D is 3500 mL for a subject weighing 70 kg, the V_D expressed as percent of body weight is:

$$\frac{3.5kg}{70kg} \times 100\% = 5\% \text{ of body weight}$$

The Apparent Volume of Distribution, V_D

- For each drug, the apparent V_D is a constant.

- In certain pathologic cases, the apparent V_D for the drug may be altered if the distribution of the drug is changed.
  - For example, in edematous conditions, the total body water and total extracellular water increase; this is reflected in a larger apparent V_D value for a drug that is highly water soluble.

- Changes in total body weight and lean body mass (which normally occur with age) may also affect the apparent V_D.

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

- The extent of distribution of drugs are controlled by two main physicochemical properties

1. Protein Binding

- a highly plasma protein bound drug (e.g., ibuprofen and similar drugs) will have a small Vd while a drug with high tissue protein binding (digoxin) will have a large Vd.

2. Partition Coefficient

- Unbound drugs distribute into the body depending upon their affinity towards tissues.
- For example a drug with high Po/w accumulates in fat tissues with a greater extent than does a very water soluble drug with poor Po/w.
- As Vd can be influenced by the body size and fat content.

- Most drugs have an apparent volume of distribution smaller than or equal to the body mass.
- For some drugs the V_D may be several times the body mass.
- Lipid soluble drugs that are bound negligible to plasma proteins have a large V_D, and are more concentrated extravascularly.
- Highly polar, poorly penetrant drugs that are highly bound to plasma proteins will have a smaller V_D.
- Drugs which bond to tissues will have a large V_D, because of low C_0 values.

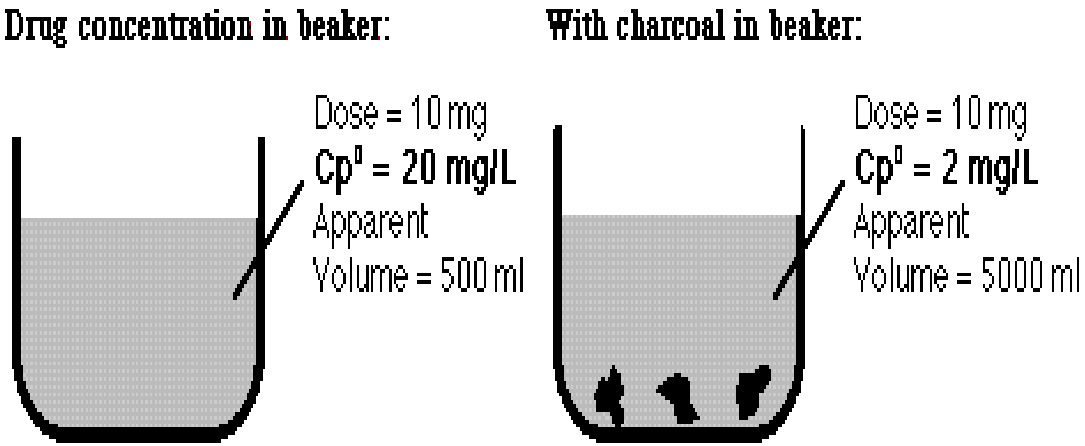
Example values for apparent volume of distribution

Drug	V (l/kg)	V (l, 70 kg)
Sulfisoxazole	0.16	11.2
Phenytoin	0.63	44.1
Phenobarbital	0.55	38.5
Diazepam	2.4	168
Digoxin	7	490

- The last figure, for digoxin, is much larger than body volume.

- Drug must be extensively distributed into tissue, leaving low concentrations in the plasma, thus the body as a whole **appears** to have a large volume, of distribution.

- Remember, this is not a physiological volume.



Apparent Volume of Distribution

Example:

- A drug has an elimination half-life of 4 hours. After the administration of a **250 mg dose**, plasma concentration at zero time point was found to be **5.65 mcg/mL**. What is the volume of distribution of the drug?

  - $V_d = D_0/C_0$
  - $D0$ = 250 mg = 250,000 mcg
  - V_d = 250,000 mcg/5.65 mcg/mL
  - = 44,248 mL or 44.3 L

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.

Drug Clearance in the One-Compartment Model

- The body is considered as a system of organs perfused by plasma and body fluids.
- Drug elimination from the body is an ongoing process due to both metabolism (biotransformation) and drug excretion through the kidney and other routes.
- Drug clearance refers to the volume of plasma fluid that is cleared of drug per unit time.
- Clearance may also be considered as the fraction of drug removed per unit time multiplied by the V_D.

Drug Elimination Expressed as Amount Per Time Unit

- The rate of drug elimination may be expressed in several ways, each of which essentially describes the same process, but with different levels of insight and application in pharmacokinetics.

- The expression of drug elimination from the body in terms of:
  - ❑Mass per unit time (eg, mg/min, or mg/hr).
  - ❑Volume per unit time (eg, L/hr or mL/min).
  - ❑Fraction eliminated per time unit.

Drug Elimination Expressed as Amount Per Time Unit

- For a **zero-order elimination process**, expressing the rate of drug elimination as mass per unit time is convenient because the rate is constant.

- In contrast, the rate of drug elimination for a first-order elimination process is not constant and changes with respect to the drug concentration in the body.

- For **a first-order elimination**, drug clearance expressed as volume per unit time is convenient because it is a constant.

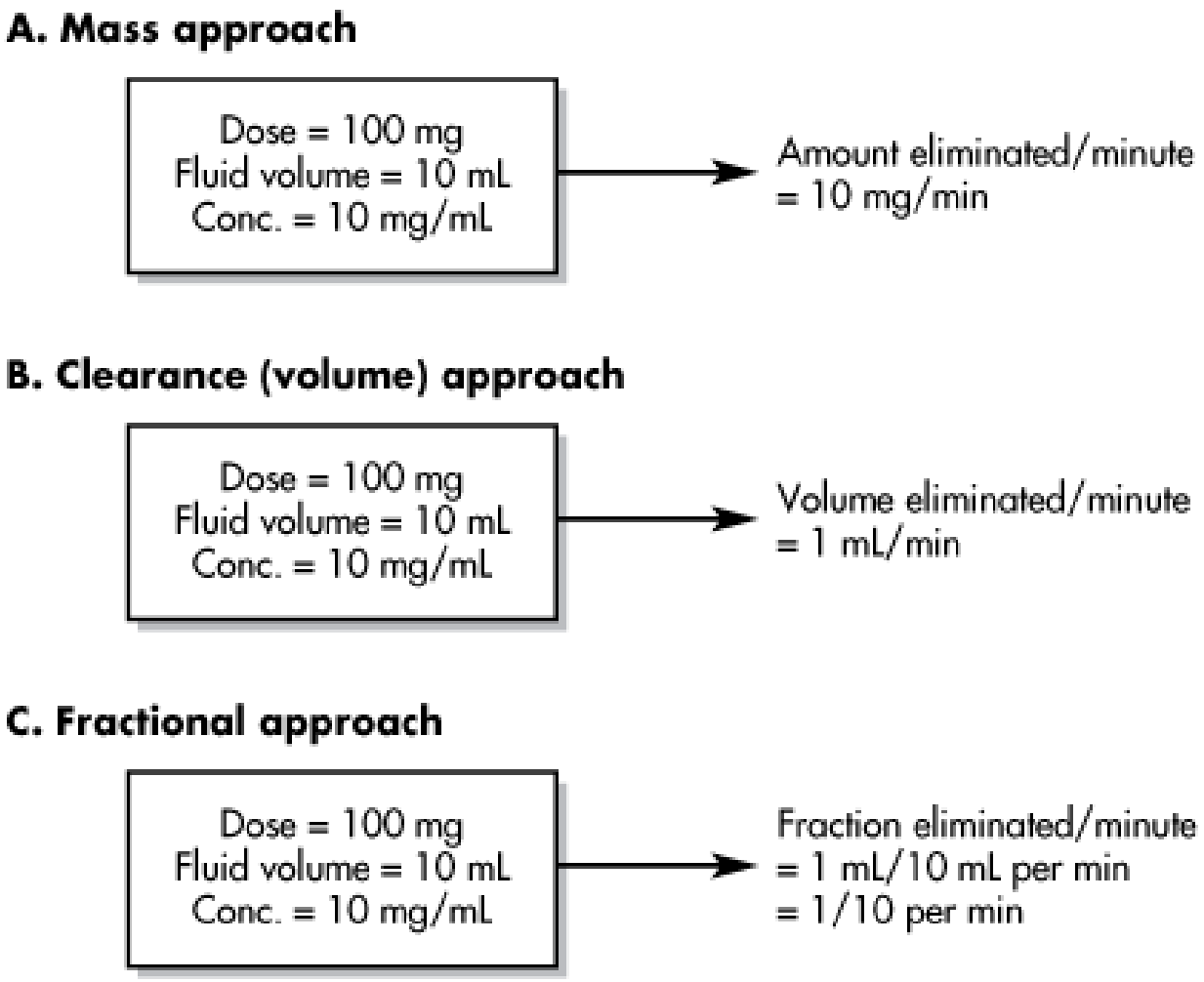


Diagram illustrating three different ways of describing drug elimination after a dose of 100 mg injected IV into a volume of 10 mL (a mouse, for example).

Drug Elimination Expressed as Volum Per Time Unit

- Clearance is a concept that expresses "the rate of drug removal" in terms of volume of drug solution removed per unit time .

- The drug concentration in the body will gradually decline by a first-order process such that the mass of drug removed over time is not constant.

- The plasma volume in the healthy state is relatively constant because water lost through the kidney is rapidly replaced with fluid absorbed from the gastrointestinal tract.

Drug Elimination Expressed as Volum Per Time Unit

- Since a constant volume of plasma (about 120 mL/min in humans) is filtered through the glomeruli of the kidneys, the rate of drug removal is dependent on the plasma drug concentration at all times.

- For many drugs, the rate of drug elimination is dependent on the plasma drug concentration, multiplied by a constant factor ($dC/dt = kC$). When the plasma drug concentration is high, the rate of drug removal is high, and vice versa.

Drug Elimination Expressed as Volum Per Time Unit

- The rate of drug elimination is:

$$\frac{dD_B}{dt} = -kC_P V_D$$

$$\frac{dD_B / dt}{C_P} = \frac{-kC_P V_D}{C_P}$$

$$\frac{dD_B / dt}{C_P} = -kV_D = -Cl$$

Where: dD_B/dt is the rate of drug elimination from the body (mg/hr).
C_p is the plasma drug concentration (mg/L).
k is a first-order rate constant (hr^{-1} or 1/hr).
V_D is the apparent volume of distribution (L).
Cl is clearance and has the units L/hr or mL/min.
The negative sign refers to the drug exiting from the body.

Drug Elimination Expressed as Fraction Eliminated Per Time Unit

- Consider a compartment volume, containing V_D liters. If *Cl* is expressed in liters per minute (L/min), then the fraction of drug cleared per minute in the body is equal to Cl/V_D.

- The fraction Cl/V_D is dependent on both the volume of distribution and the rate of drug clearance from the body.

- The rate of drug elimination is:

$$k = \frac{Cl}{V_D}$$

Cl and V_D

$$C_P = C_P^0 \bullet e^{-kt}$$

$$C_P = \frac{D_0}{V_D} \bullet e^{-(Cl/V_D)t}$$

- In practice, the mean values for *Cl* and V_D of a drug are obtained from the population values (derived from a large population of subjects or patients) in the literature.

- Those parameters will predict the plasma level of the drug after a new dose is given to the patient.

Example:

- When a preparation of phenytoin was administered to a patient, the volume of distribution was found to be **70 liters**, and the half-life of elimination was **1.5 hours**. What is the total clearance of phenytoin?

- $Cl_T = V_d$ liters × 0.693/1.5 hours

$= 70 \times 0.693/1.5 = 32.34$ L/hr

Clearance from Drug-Eliminating Tissues

- Clearance may be applied to any organ that is involved in drug elimination from the body.

- Clearance represents the sum of the clearances for each drug-eliminating organ:

$$Cl_T = Cl_R + Cl_{NR}$$

- Where:
  - Cl_R is renal clearance or drug clearance through the kidney.
  - Cl_{NR} is nonrenal clearance through other organs.

Clearance from Drug-Eliminating Tissues

- Generally, clearance is considered as the sum of renal, Cl_R, and nonrenal drug clearance, Cl_{NR}.

- Cl_{NR} is assumed to be due primarily to hepatic clearance (Cl_H) in the absence of other significant drug clearances, such as elimination through the lung or the bile, as shown in Equation:

$$Cl_T = Cl_R + Cl_H$$

The units for clearance are volume/time (eg, mL/min, L/hr).

Clearance from Drug-Eliminating Tissues

- *Cl* $_T$ may be defined as the rate of drug elimination divided by the plasma drug concentration.

$$Cl_T = \frac{\text{Elimination rate}}{\text{Plasma Concentration } (C_P)}$$

$$Cl_T = \frac{(dD_E / dt)}{C_P} = (\mu g / \min) / (\mu g / ml) = ml / \min$$

where :

D_E	is the amount of drug eliminated.
dD_E/dt	is the rate of drug elimination.

Clearance from Drug-Eliminating Tissues

$$\text{Drug elimination rate} = \frac{dD_E}{dt} = C_P \bullet Cl_T$$

For drugs that follow first-order elimination, the rate of drug elimination is dependent on the amount of drug remaining in the body.

$$\frac{dD_E}{dt} = kD_B = kC_P V_D$$

Substituting the elimination rate in equation for kC_pV_D in above Equation and solving for Cl_T gives Equation:

$$Cl_T = \frac{kC_P V_D}{C_P} = kV_D$$

Clearance from Drug-Eliminating Tissues

- For some drugs, the elimination rate process is more complex and a **noncompartment method** may be used to calculate certain pharmacokinetic parameters such as clearance.

- In this case, clearance can be determined directly from the plasma drug concentration-versus-time curve by:

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

Where: D_0 is the dose and $[AUC]^\infty_0 = \int^\infty_0 C_p dt$

Calculation of K from Urinary Excretion Data

- The elimination rate constant *k* may be calculated from urinary excretion data.

- In this calculation the excretion rate of the drug is assumed to be first order.

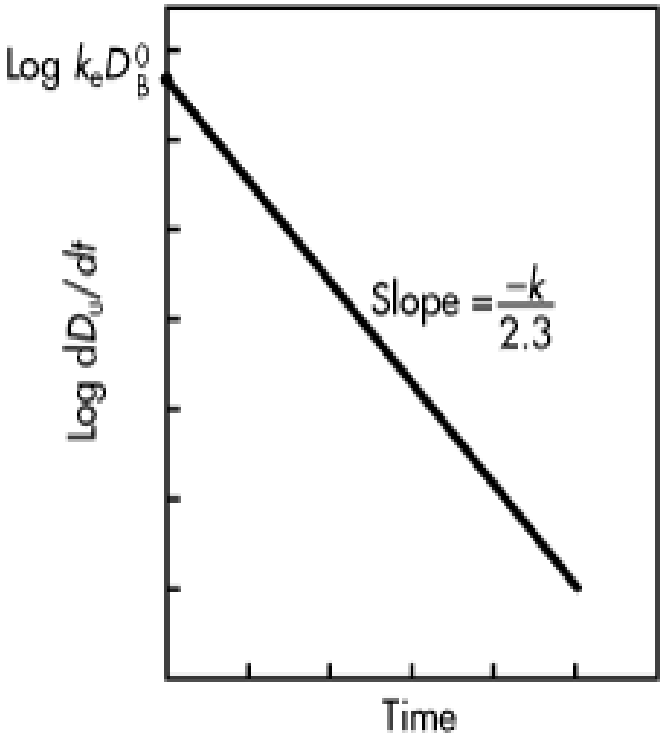
$$\frac{dD_u}{dt} = k_e D_B$$

$$\frac{dD_u}{dt} = k_e D_B^0 e^{-kt}$$

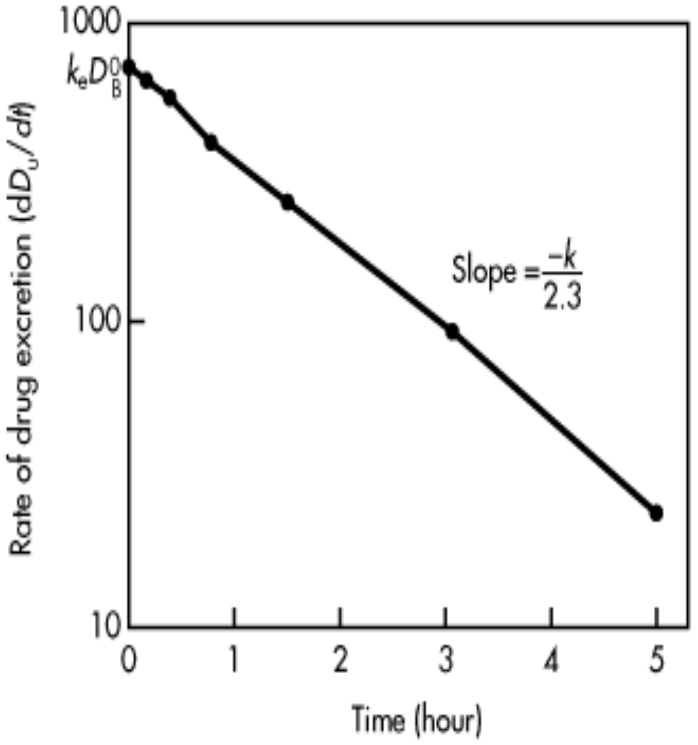
$$\log \frac{dD_u}{dt} = \frac{-kt}{2.3} + \log k_e D_B^0$$

Where:
k_e is the renal excretion rate constant.
D_u is the amount of drug excreted in the urine.

Calculation of K from Urinary Excretion Data



log rate of drug excretion versus *t* on regular paper.



Semilog graph of rate of drug excretion versus time

Calculation of K from Urinary Excretion Data

- The nonrenal rate constant (k_{nr}) for any route of elimination other than renal excretion can be found as follows:

$$k_{nr} = k - k_e$$

Where:
k_e is the renal excretion rate constant.
K_{nr} is the nonrenal rate constant.

Example

- 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:

Time (hours)	C_p (μg/mL)	D_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

Caculate k and $t_{1/2}$?

Solution

Solution

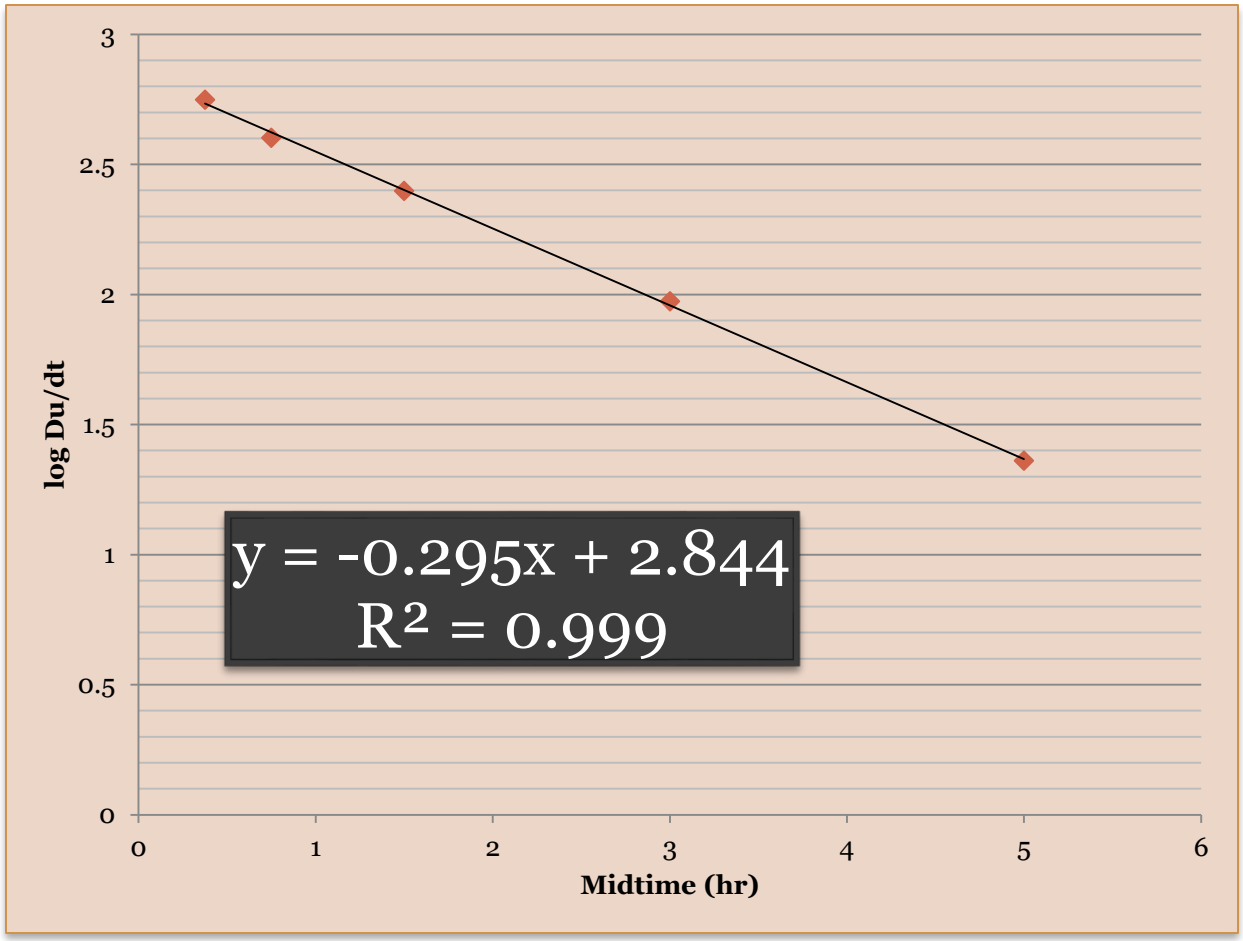
Set up the following table:

Time (hours)	D_u (mg)	D_u/t	mg/h	t^* (hours)
0.25	160	160/0.25	640	0.125
0.50	140	140/0.25	560	0.375
1.0	200	200/0.5	400	0.750
2.0	250	250/1	250	1.50
4.0	188	188/2	94	3.0
6.0	46	46/2	23	5.0

Here t^* = midpoint of collection period and t = time interval for collection of urine sample.

Solution

- Slope = -k/2.303
- K = o,68 hr^{-1}
- $t_{1/2}$ = 0.693/k
  = 1.01 hr



The Sigma-minus Method

- An alternative method for the calculation of the elimination rate constant *k* from urinary excretion data is the *sigma-minus method*, or *the amount of drug remaining to be excreted method*.

- The sigma-minus method is sometimes preferred over the previous method because fluctuations in the rate of elimination are minimized.

The Sigma-minus Method

$$\log(D_u^{\infty} - D_u) = \frac{-kt}{2.3} + \log D_u^{\infty}$$

where:

D_u is the cumulative amount of unchanged drug excreted in the urine.

D^{∞}_u is the amount of unchanged drug that is ultimately excreted in the urine.

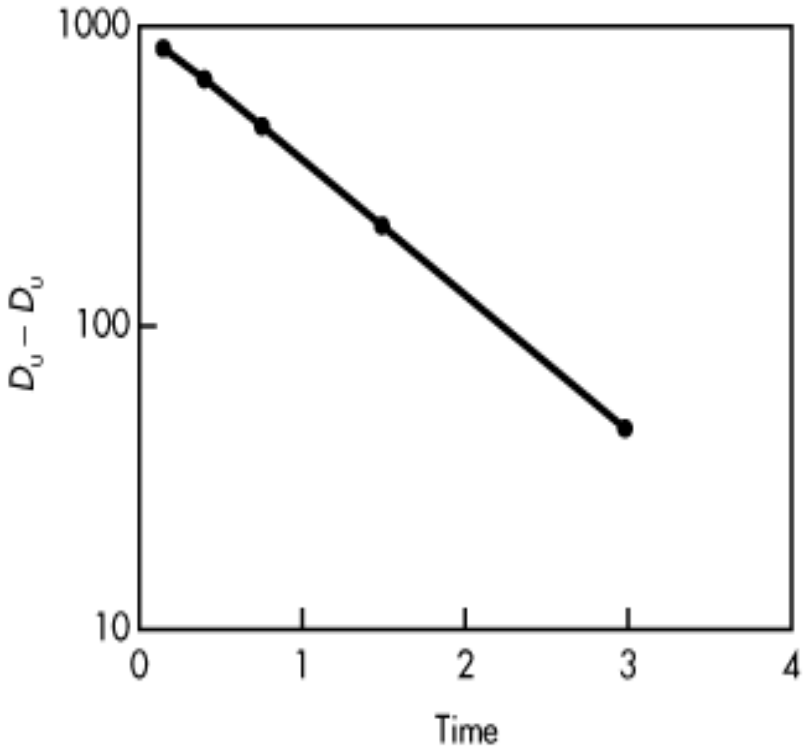
The above Equation describes the relationship for the amount of drug remaining to be excreted ($D^{\infty}_u - D_u$) versus time.

The Sigma-minus Method

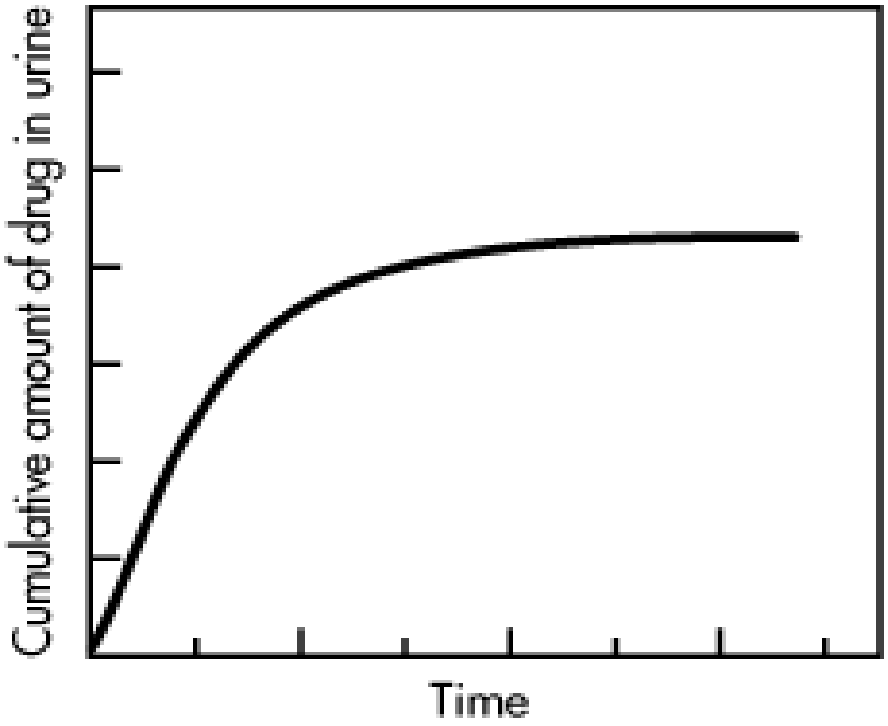
- A linear curve is obtained by graphing the logarithm scale of the amount of unchanged drug yet to be eliminated, log ($D^{\infty}_u - D_u$) versus time.

- On semilog paper, the slope of this curve is $-k/2.3$ and the y intercept is D^{∞}_u.

The Sigma-minus Method



Sigma-minus method, or the amount of drug remaining to be excreted method, for the calculation of the elimination rate constant.



Graph showing the cumulative urinary excretion of drug as a function of time.

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.

Problems in Obtaining Valid Urinary Excretion Data

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).