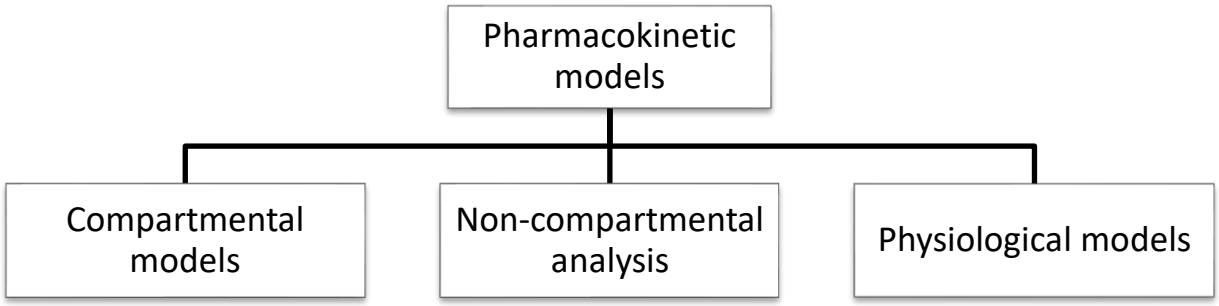
Pharmacokinetic Models

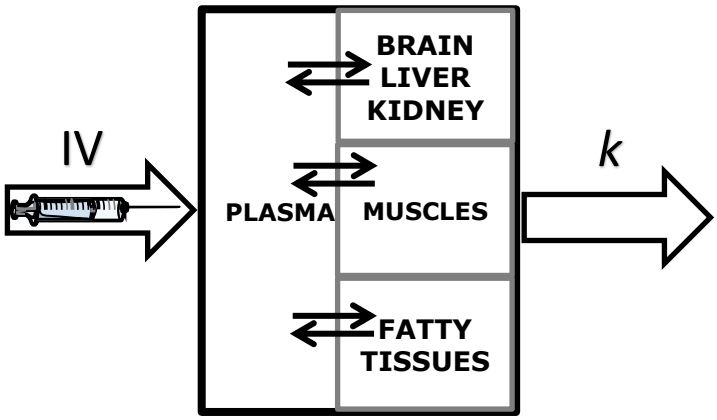


Compartmental models

The most commonly employed approach to the pharmacokinetic characterization of a drug is to represent the body as a system of compartments, even though these compartments usually have no physiologic or anatomic reality, and to assume that the rate of transfer between compartments and the rate of drug elimination from compartments follow first-order or linear kinetics.

➢ One-compartment open model

- The one-compartment open model assumes that the body can be described as a single, uniform compartment (ie, one compartment), and that drugs can enter and leave the body (ie, open model).
- This model is useful for the pharmacokinetic analysis of drugs that distribute rapidly throughout the body.
- Following IV bolus administration, it assumes that the drug is administered instantly into the body, and it is instantaneously and rapidly distributed throughout the body.
- Drug elimination occurs immediately upon entering the body.



Elimination rate constant

- Drug elimination from the body can occur by several pathways, including urinary and biliary excretion, excretion in expired air, and biotransformation in the liver or other fluids or tissues.
- The elimination of most drugs in humans and animals at therapeutic doses can be characterized as a first-order process (ie., the rate of elimination of drug from the body at any time is proportional to the amount of drug in the body at that time).
- The first-order elimination rate constant, ***K,*** characterizing the overall elimination of a drug from a one compartment model represents the sum of two or more rate constants characterizing individual elimination processes:
- $K = k_e + k_m + k_b + ...$

The rate of loss of drug from the body is given by

$$\frac{dDB}{dt} = - K.\ D_B$$

Where D_B is the amount of drug in the body at time *t* after injection. *K* is the first -order elimination rate constant for the drug. The negative sign indicates that drug is being lost from the body.

$$D_B = D_B^0 \,.\, e^{-kt}$$

Where ***e*** represents the base of the natural logarithm (ln). Taking the natural logarithm of both sides gives:

$\ln D_B = \ln D_B^0 - kt$

The equation can be converted to common logarithms

$$\log D_B = \log D_B^0 - \frac{kt}{2.3}$$

$\ln x = 2.303 \log x$

The slope and the elimination rate constant (*k*)

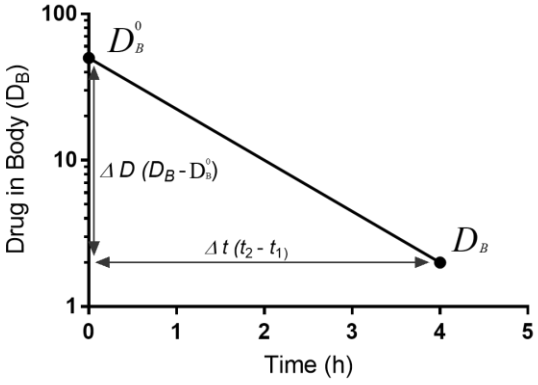
$\log D_B = \log D_B^0 - \frac{kt}{2.3}$

$\log DB - \log D_B^0 = \frac{-kt}{2.3}$

$\frac{(\log D_B - \log D_B^0)}{t} = \frac{-k}{2.3}$

$\frac{(y_2 - y_1)}{(x_2 - x_1)} = \frac{-k}{2.3}$

$$Slope = \frac{-k}{2.3}$$



The volume of distribution (V_D)

The rate and extent of distribution to the tissue organs depends on several processes and properties.

1. Tissues in the body are presented the drug at various rates, depending on the blood flow to that organ.
2. The drug may have different abilities to cross from the vasculature to the organ depending on the molecular weight of the drug.
3. Tissues also have different affinity for the drug, depending on lipophilicity and drug binding.
4. Large organs may have a large capacity for drugs to distribute to.

IN one-compartment model, we assume that the rate of change of drug concentration in plasma reflects quantitatively the change in drug concentrations throughout the body. In other words, if we see a 20% decrease in drug concentration in plasma over a certain period of time, we assume that the drug concentrations in kidney, liver, cerebrospinal fluid, and all other fluids and tissues also decrease by 20% during this time.

The ratio of drug concentrations in the various tissues and fluids is constant. Consequently, there will exist a constant relationship between drug concentration in the plasma C and the amount of drug in the body:

$$D_B = V_D C_P$$

The volume of distribution is the apparent volume (V_D) in which the drug is dissolved. The term ***apparent*** volume of distribution is used because the value of the volume of distribution does not have a true physiologic meaning in terms of an anatomic space.

$\log D_B = \log D_B^0 - \frac{kt}{2.3}$

If $D_B = V_D C_P$ then

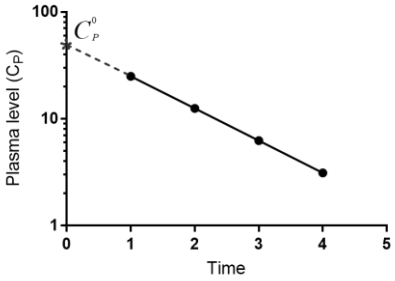
$\log C_P = \log C_P^0 - \frac{kt}{2.3} \quad \Longleftrightarrow \quad C_P = C_P^0 \cdot e^{-kt}$

Calculation of the volume of distribution in one-compartment model

- The one-compartment open model considers the body a constant-volume system or compartment. Therefore, the apparent volume of distribution for any given drug is a constant.
- If the volume of solution in which the drug is dissolved and the drug concentration of the solution are known, then the total amount of drug present in the solution may be calculated. This relationship between drug concentration, volume in which the drug is dissolved, and total amount of drug present is given in the following equation:

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

- The dose of drug given by IV bolus (rapid IV injection) represents the amount of drug in the body, D_B^0 , at t = 0.
- C_P^0 can be determined by extrapolating the linear line of plasma concentration (semilog presentation) to t 0 as shown in the figure:



Most drugs have an apparent volume of distribution smaller than, or equal to, the body mass. If a drug is highly bound to plasma proteins or the molecule is too large to leave the vascular compartment, then C_P^0 will be higher, resulting in a smaller apparent V_D.

For example, the apparent volume of distribution of warfarin is small, approximately 0.14 L/kg, much less than the total body mass. This is because warfarin is highly bound to plasma proteins, making it hard to leave the vascular compartment.

For some drugs, the volume of distribution may be several times the body mass. In this case, a very small C_P^0 may occur in the body due to concentration of the drug in peripheral tissues and organs, resulting in a large V_D. Drugs with a large apparent V_D are more concentrated in extravascular tissues and less concentrated intravascularly. For example, the apparent volume of distribution of digoxin is very high, 7.0 L/kg, much greater than the body mass. This is because digoxin binds extensively to tissues, especially muscle tissues.

The apparent V_D is a volume term that can be expressed as a simple volume or in terms of percent of 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

$$\frac{3.5\ kg}{70\ kg} \times 100 = 5\%$$

If V_D is a very large number—that is, >100% of body weight—then it may be assumed that the drug is concentrated in certain tissue compartments. In the digoxin example above, 7.0 L/kg is estimated to be 700% of body weight. Thus, the apparent V_D is a useful parameter in considering the relative amounts of drug in the vascular and in the extravascular tissues.

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 increases; this is reflected in a larger apparent V_D value for a drug that is highly water soluble. Similarly, changes in total body weight and lean body mass (which normally occur with age, less lean mass, and more fat) may also affect the apparent V_D.

Clearance (*Cl*)

Clearance is a measure of drug elimination from the body without identifying the mechanism or process.

Drug Clearance in the One-Compartment Model

Clearance considers the entire compartment as a drug-eliminating system from which many elimination processes may occur

Expression of Clearance

1. **Drug elimination expressed as amount per unit time**

Expression of drug elimination as mass per unit time (eg, mg/min, or mg/h). It is more convenient for zero-order elimination processes because it is constant.

2. **Drug elimination expressed as volume per unit time**

Clearance expressed as volume per unit time (eg, L/h or mL/min). It is convenient for first-order processes. Clearance (volume of fluid removed of drug) for a first-order process is constant regardless of the drug concentration because clearance is expressed in volume per unit time rather than drug amount per unit time.

3. **Drug elimination expressed as fraction eliminated per unit time**

Expressing drug elimination as the fraction of total drug eliminated. This expression is applicable if we are dealing with an amount or a volume.

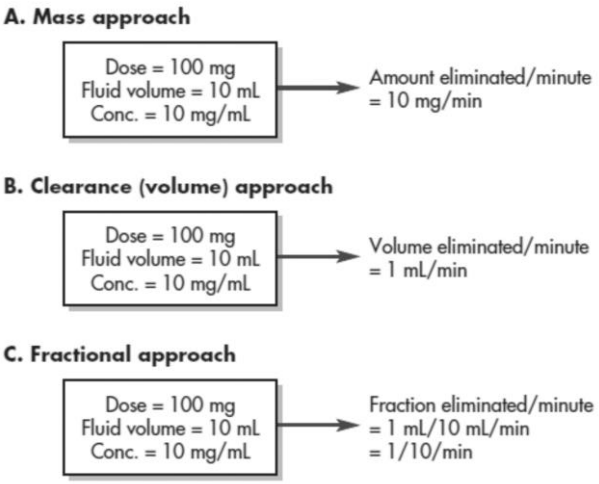


Diagram illustrating three different ways of describing drug elimination after a dose of 100 mg injected IV into a volume of 10 mL.

In case that clearance 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.

- Drug clearance and the volume of distribution as independent parameters (both values are independent of plasma concentration).

$$K = \frac{Cl}{VD}$$

Calculation of k from urinary excretion data

For first-order kinetics,
Excretion rate ∝ Amount of the drug in the body

Excretion rate = K_e . Amount of the drug in the body

$$\frac{dDu}{dt} = K_e \,.\, D_B$$

Where k_e is the renal excretion rate constant, D_u is the amount of drug excreted in the urine, and D_B is the amount of the drug in the body at time *t*.

- $D_B = D_B^0 \,.\, e^{-kt}$

Then,

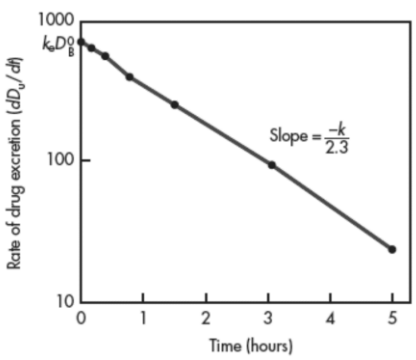
$$\frac{dDu}{dt} = K_e \,.\, D_B^0 \,.\, e^{-kt}$$

$$\ln \frac{dDu}{dt} = \ln K_e \,.\, D_B^0 - kt \text{ (natural log for both sides)}$$

$$\log \frac{dDu}{dt} = \log K_e \,.\, D_B^0 - \frac{kt}{2.3} \text{ (change to common log)}$$

$$\frac{(\log \frac{dDu}{dt} - \log K_e \,.\, D_B^0)}{t} = \frac{-k}{2.3}$$

- A straight line is obtained from this equation by plotting log *dD*u/*dt* versus time on a semilog paper dD_u/dt against time.
- The slope of this curve is equal to –*k*/2.3 and the *y* intercept is equal to $K_e \,.\, D_B^0$.
- For rapid intravenous administration, D_B^0 is equal to the dose D_0
- Both k_e and *k* can be determined by this method



Notes,

- Urine is produced at an approximate rate of 1 mL/min and collected in the bladder until voided for collection. Thus, the drug urinary excretion rate (dD_u/dt) cannot be determined experimentally for any given instant.
- Therefore, the average rate of urinary drug excretion, D_u/t, is plotted against the time corresponding to the midpoint of the collection interval, t^*.

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

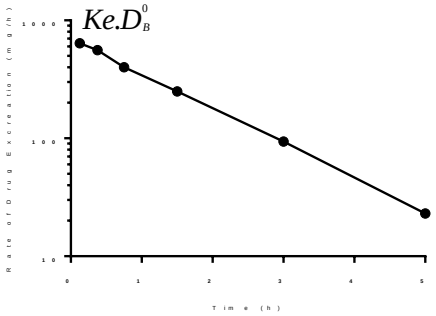
What is the elimination rate constant, k, for this antibiotic?

Solution

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.

Plot the data on a semilog paper



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

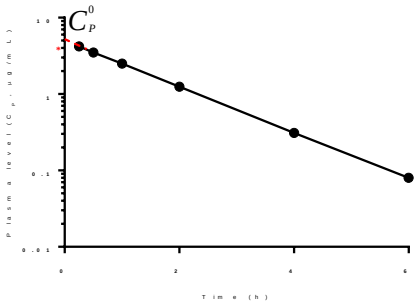
$$\textbf{Slope} = \frac{(y_2 - y_1)}{(x_2 - x_1)} = \frac{-k}{2.3}$$

$$\frac{(\log 250 - \log 400)}{(1.5 - 0.75)} = \frac{-k}{2.3}$$

$$\frac{(2.398 - 2.602)}{0.75} = \frac{-k}{2.3}$$

$$k = 0.626\ h^{-1}$$

- The the elimination rate constant, *K*, can also be calculated from the slope of the plasma-concentration time curve.



Time (hours)	C_p (μg/mL)
0.25	4.2
0.50	3.5
1.0	2.5
2.0	1.25
4.0	0.31
6.0	0.08

$$\frac{(\log 1.25 - \log 3.5)}{(2-0.5)} = \frac{-k}{2.3} \qquad k = 0.685\ h^{-1}$$