Clinical Pharmacokinetic Equations and Calculations

One-Compartment Model Equations for linear Pharmacokinetics

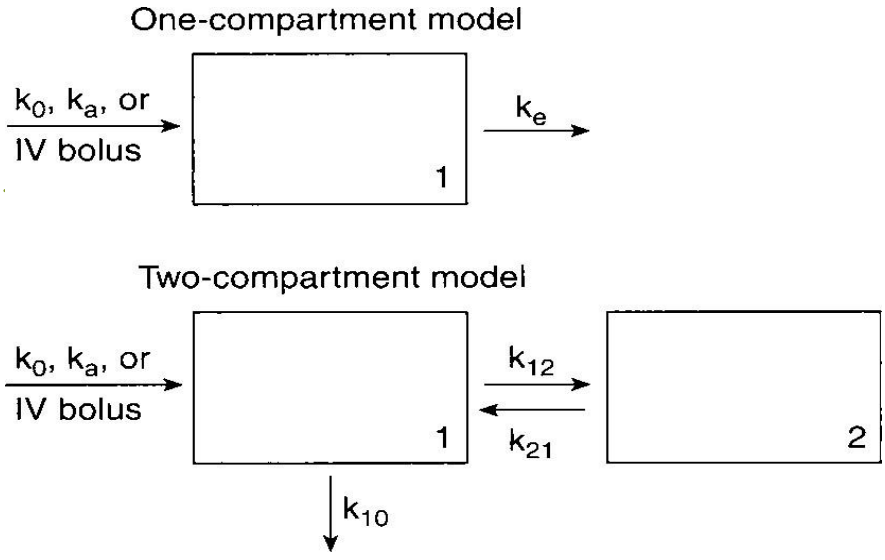
- The body can be represented as a series of discrete sections.

- The simplest model is the one-compartment model which depicts the body as one large container where drug distribution between blood and tissues occurs instantaneously.

- Drug is introduced into the compartment by infusion (ko), orally through absorption (ka), or IV bolus; distributes immediately into a volume of distribution (V); and is removed from the body via metabolism and elimination via the elimination rate constant (ke).

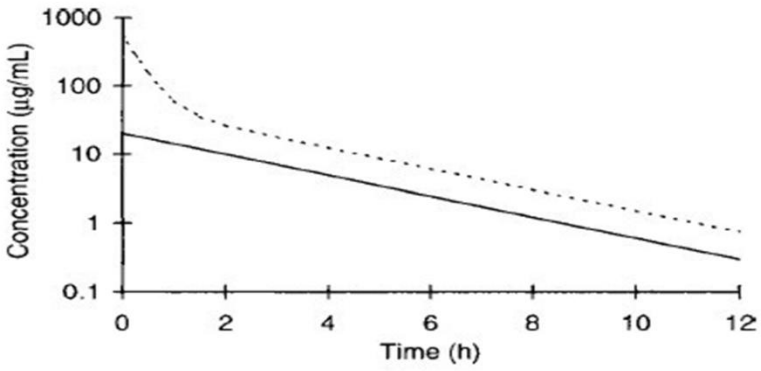
• The simplest multicompartment model is a two compartment model which represents the body as a central compartment into which drug is administered and a peripheral compartment into which drug distributes.

- The central compartment (1) is composed of blood and tissues which equilibrate rapidly with blood. The peripheral compartment (2) represents tissues that equilibrate slowly with blood. Rate constants (k12, k21) represent the transfer between compartments and elimination from the body (k10).



Intravenous Bolus

When a drug is given as an intravenous bolus and the drug distributes from the blood into the tissues quickly, the serum concentrations often decline in a straight line when plotted on semilogarithmic axes.



• Many drugs given intravenously cannot be given as an actual intravenous bolus because of side effects related to rapid injection.

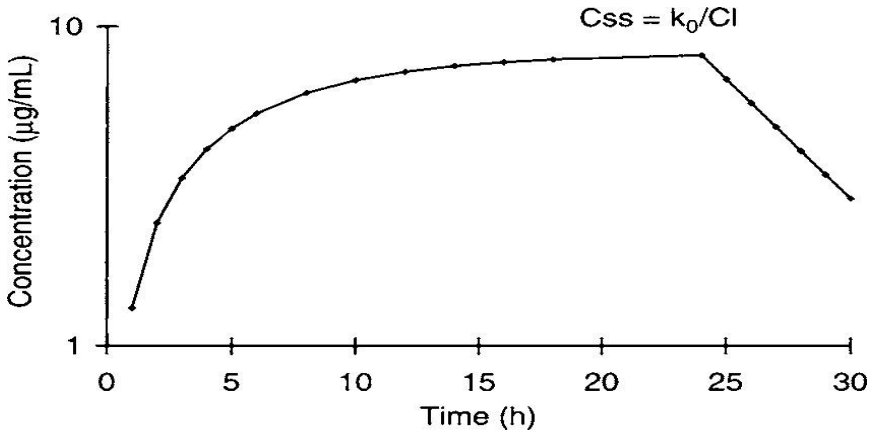
• A short infusion of 5– 30 minutes can avoid these types of adverse effects, and if the intravenous infusion time is very short compared to the half-life of the drug , so a large amount of drug is not eliminated during the infusion time, intravenous bolus equations can still be used.

$$\mathbf{C = C_0\, e^{-ket}} \qquad\qquad \mathbf{C = (D/V)\, e^{-ket}}$$

• For example, a patient is given a theophylline loading dose of 400 mg intravenously over 20 minutes. Because the patient received theophylline during previous hospitalizations, it is known that the volume of distribution is 30 L, the elimination rate constant equals 0.115 h^{-1}, and the half-life is ($t_{1/2}$ = 0.693/ke = 0.693/0.115 h^{-1} = 6 h). To compute the expected theophylline concentration 4 hours after the dose was given, a one compartment model intravenous bolus equation can be used:

$C = (D/V)\, e^{-ket} = (400\ mg/30L)\, e^{-(0.115\ h-1)\ (4\ h)} = 8.4\ mg/L.$

Continuous and Intermittent Intravenous Infusion



If a drug is given as a continuous intravenous infusion, serum concentrations increase until a steady-state concentration (Css) is achieved in 5 half-lives. When the infusion is discontinued, serum concentrations decline in a straight line.

• In this case, a one compartment model intravenous infusion equation can be used to compute concentrations while the infusion is running:

$C = (k_0/Cl)(1 - e^{-ke\,t})$ $C = [k_0/(ke\ V)](1 - e^{-ke\,t})$

k_0 :the drug infusion rate (amount per unit time, such as mg/h or µg/min)

Cl :the drug clearance

Ke: elimination rate constant

t: the time that the infusion has been running

• If the infusion is allowed to continue until steady state is achieved, the steady-state concentration (Css) can be calculated easily:

$Css = k_0/Cl$

Css = k0 /(ke V)

• If the infusion is stopped, postinfusion serum concentrations (C postinfusion) can be computed by the following equation:

$C\ postinfusion = Cend\ e^{-ke\ t\ postinfusion}$

ke: elimination rate constant t postinfusion: postinfusion time

t postinfusion = 0 at end of infusion and increases from that point

• For example, a patient is administered 60 mg/h of theophylline, V = 40 L and ke = 0.139 h^{-1}.The serum concentration of theophylline after receiving the drug for 8 hours and at steady state can be calculated:

$C = (k_0/Cl)(1 - e^{-ket})$

$= [k_0/(keV)](1 - e^{-ket})$

$= [(60\ mg/h)/(0.139\ h{-}1 \quad 40\ L)](1 - e^{-(0.139\ h-1)(8\ h)}) = 7.2\ mg/L$

$Css = k_0/(ke\ V)$

$= (60\ mg/h)/(0.139\ h{-}1 \quad 40\ L) = 10.8\ mg/L.$

• If the infusion only run for 8 hours, the serum concentration 6 hours after the infusion stopped would be:

$C_{postinfusion} = C_{end} e^{-ke\ t\ postinfusion}$

$= (7.2\ mg/L)e^{-(0.139\ h-1)(6\ h)} = 3.1\ mg/L.$

• If the infusion run until steady state was achieved, the serum concentration 6 hours after the infusion ended would be:

$C_{postinfusion} = C_{end} e^{-ke\ tpostinfusion}$

$= (10.8\ mg/L)e^{-(0.139\ h-1)(6\ h)} = 4.7\ mg/L.$

• Even if serum concentrations exhibit a distribution phase after the drug infusion has ended, it is still possible to use one compartment model intravenous infusion equations for the drug without a large amount of error.

• The strategy used in this instance is to infuse the medication and wait for the distribution phase to be over before measuring serum drug concentrations in the patient.

• For example, gentamicin, tobramycin, and amikacin are usually infused over one-half hour. When administered this way, these aminoglycoside antibiotics have distribution phases that last about one-half hour.

• Using this strategy, aminoglycoside serum concentrations are obtained no sooner than one-half hour after a 30-minute infusion in order to avoid the distribution phase.

• If aminoglycosides are infused over 1 hour, the distribution phase is very short and serum concentrations can be obtained immediately

• For example, a patient is given an intravenous infusion of gentamicin 100 mg over 60 minutes. it is known that the volume of distribution is 20 L, the elimination rate constant = 0.231 h^{-1}, and the half-life = 3 h ($t_{1/2}$ = 0.693/ke = 0.693/0.231 h^{-1} = 3 h). To compute the gentamicin concentration at the end of infusion, a one compartment model intravenous infusion equation can be employed:

$C = [k_0/(keV)](1 - e^{-kt})$

$= [(100\ mg/1\ h)/(0.231\ h-1 \quad 20\ L)](1 - e^{-(0.231\ h-1)(1\ h)}) = 4.5\ mg/L.$

• If a steady-state concentration is obtained after a continuous intravenous infusion has been running uninterrupted for 3–5 half-lives, the drug clearance (Cl) can be calculated by rearranging the steady-state infusion formula:

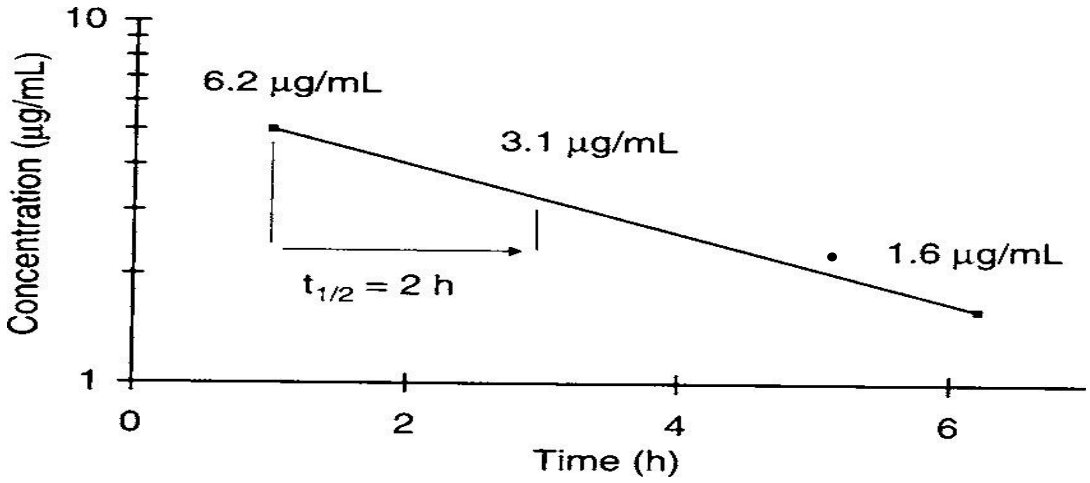
$Cl = k_0/Css$

• For example, a patient receiving procainamide via intravenous infusion (k_0 = 5 mg/min) has a steady-state procainamide concentration measured as 8 mg/L. Procainamide clearance can be computed using the following expression:

$Cl = k_0/Css$ = (5 mg/min) / (8 mg/L) = 0.625 L/min.

• Example, a patient was given a single 120-mg dose of tobramycin as a 60-minute infusion, and concentrations at the end of infusion (6.2 mg/L) and 4 hours after the infusion ended (1.6 mg/L) were obtained.

$$C_{postinfusion} = C_{end}\, e^{-ke\, t_{postinfusion}}$$



Tobramycin concentrations are plotted on semilogarithmic axes, and a straight line is drawn connecting the concentrations. Half-life is determined by measuring the time needed for serum concentrations to decline by one-half from 6.2 mg/L to 3.1 mg/L, (ke) can be calculated by:

$ke = 0.693/t_{1/2} = 0.693/2\ h = 0.347\ h^{-1}$

• Alternatively, the elimination rate constant can be calculated by using this equation :

$$ke = -(\ln C1 - \ln C2)/(t1 - t2)$$

t1 and C1 are first time/concentration pair and t2 and C2 are second time/concentration pair;

$ke = -[\ln (6.2\ mg/L) - \ln (1.6\ mg/L)] / (1\ h - 5\ h) = 0.339\ h^{-1}$

$t_{1/2} = 0.693/ke = 0.693/0.339\ h^{-1} = 2\ h.$

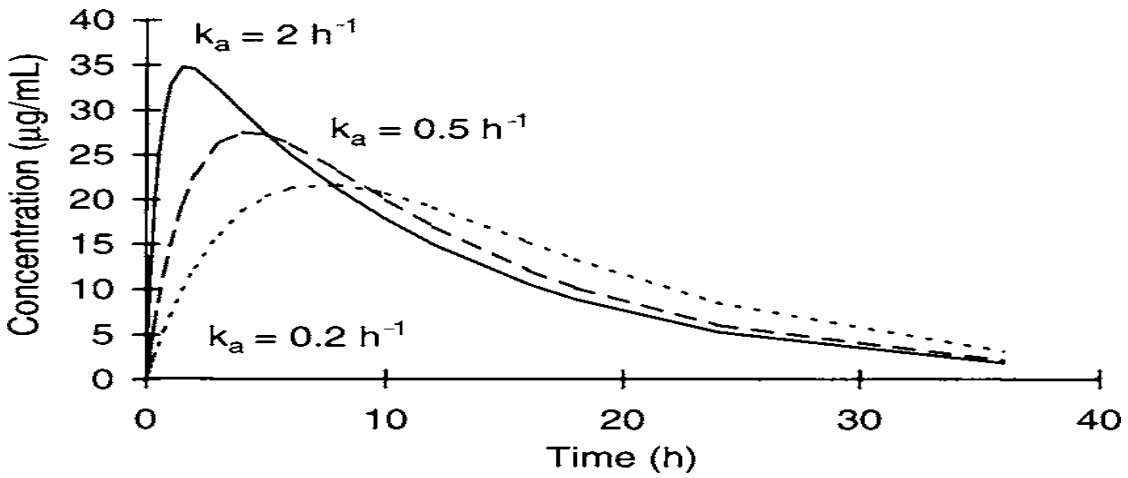
Extravascular Equation

• When a drug is administered extravascularly (e.g., orally, intramuscularly, subcutaneously, transdermally, etc.), absorption into the systemic vascular system must take place.

• If serum concentrations decrease in a straight line when plotted on semilogarithmic axes after drug absorption is complete, a one compartment model extravascular equation can be used to describe the serum concentration/time curve.

$$C = \frac{Fk_aD}{V(k_a - k_e)}(e^{-k_e t} - e^{-k_a t})$$

t: time after the extravascular dose was given (t = 0 at the time the dose was administered) C: concentration at time = t F: bioavailability fraction ka: absorption rate constant D: dose V: volume of distribution ke: elimination rate constant.



Serum concentration/time curves for extravascular drug administration for agents following a one-compartment pharmacokinetics. The absorption rate constant (ka) controls how quickly the drug enters the body. A large absorption rate constant allows drug to enter the body quickly while a small absorption rate constant permits drug to enter the body more slowly.

• An example of the use of this equation would be a patient that is administered 500 mg of oral procainamide as a capsule. It is known from prior clinic visits that the patient has t= 4 hours , ke = 0.173 h-1 , V = 175 L, Ka = 2 h-1 , and F = 0.85. The procainamide serum concentration 4 hours after a single dose would be equal to:

$$C = \frac{Fk_aD}{V(k_a - k_e)}(e^{-k_e t} - e^{-k_a t})$$

$$C = \frac{(0.85)(2\ h^{-1})(500\ mg)}{(175\ L)(2\ h^{-1} - 0.173\ h^{-1})}(e^{-(0.173\ h^{-1})(4\ h)} - e^{-(2\ h^{-1})(4\ h)})$$

$$C = 1.3\ mg/L$$

• If the serum concentration/time curve displays a distribution phase, it is still possible to use one compartment model equations after an extravascular dose is administered. In order to do this, serum concentrations are obtained only in the postdistribution phase.

• Since the absorption rate constant is also hard to measure in patients, it is also desirable to avoid drawing drug serum concentrations during the absorption phase in clinical situations.

• When only postabsorption, postdistribution serum concentrations are obtained for a drug that is administered extravascularly, the equation simplifies to:

$$C = [(FD)/V]e^{-k_e t}$$

Multiple-Dose and Steady-State Equations

In most cases, medications are administered to patients as multiple doses, and drug serum concentrations for therapeutic drug monitoring are not obtained until steady state is achieved. For these reasons, multiple dose equations that reflect steady state conditions are usually more useful in clinical settings than single dose equations.

Intravenous bolus $C = (D/V)[e^{-k_e t}/(1 - e^{-k_e \tau})]$

Extravascular administered drugs $C = (FD/V)[e^{-k_e t}/(1 - e^{-k_e \tau})]$

Intermittent Intravenous Infusion $C = (k_0/Cl)(1 - e^{-k_e t}) = [k_0/(k_e V)](1 - e^{-k_e t})$

Where τ is the dosage interval

Average Steady-State Concentration Equation

A very useful and easy equation can be used to compute the average steady-state concentration (Css) of a drug:

$$Css = [F(D/\tau)]/Cl$$

Example: A patient is administered 250 µg of digoxin tablets daily for heart failure until steady state. The pharmacokinetic constants for digoxin in the patient are: F = 0.7, Cl = 120 L/d. The average steady-state concentration would equal:

Css = [F(D/τ)]/Cl = [0.7(250 µg /1 d)] / (120 L/d) = 1.5 µg/L.

Michaelis-Menten or Saturable Pharmacokinetics

• Drugs that are metabolized by the cytochrome P-450 enzymes and other enzyme systems may undergo Michaelis-Menten or saturable pharmacokinetics. This is the type of nonlinear pharmacokinetics that occurs when the number of drug molecules overwhelms or saturates the enzyme's ability to metabolize the drug.

• In this case the rate of drug removal is described by the classic Michaelis- Menten relationship that is used for all enzyme systems:

rate of metabolism = (Vmax . C)/(Km + C)

Vmax = the maximum rate of metabolism or maximum elimination rate

Km = the enzyme capacity and equal to the substrate concentration when the rate of metabolism = Vmax/2.

C = the substrate or drug concentration

• The clinical implication of Michaelis-Menten pharmacokinetics is that the clearance of a drug is not a constant as it is with linear pharmacokinetics, but it is concentration or dose-dependent. As the dose or concentration increases, the clearance rate decreases as the enzyme approaches saturable conditions: Cl = Vmax / (Km + C).

Example: phenytoin follows saturable pharmacokinetics with average Michaelis-Menten constants of Vmax = 500 mg/d and Km = 4 mg/L. The therapeutic range of phenytoin is 10–20 mg/L.

Cl = Vmax/(Km + C)

Cl = (500 mg/d) / (4 mg/L +10 mg/L) = 36 L/d

Cl = (500 mg/d)/(4 mg/L + 20 mg/L) = 21 L/d

As the steady-state concentration of phenytoin increases from 10 mg/L to 20 mg/L, clearance decreases from 36 L/d to 21 L/d

• The volume of distribution (V) is unaffected by saturable metabolism and is still determined by the physiological volume of blood (VB) and tissues (VT) as well as the unbound concentration of drug in the blood (fB) and tissues (fT):

As doses or concentrations increase for a drug that follows Michaelis-Menten pharmacokinetics, half-life becomes longer for the drug:

↑t1/2 =(0.693 V)/↓Cl.

Under steady-state conditions, the rate of drug administration equals the rate of drug removal. Michaelis- Menten equation can be used to compute the maintenance dose (MD) required to achieve a target steady-state serum concentration (Css):

$$MD = Vmax.Css / Km + Css$$

When the therapeutic range for a drug is far below the Km value for the enzymes that metabolize the drug , this equation simplifies to:

MD = (Vmax/Km) Css or, since Vmax /Km is a constant, MD = Cl.Css

So when Km >> Css, drugs that are metabolized follow linear pharmacokinetics (known as First-order pharmacokinetics).

When the therapeutic range for a drug is far above the Km value, the rate of metabolism becomes a constant equal to Vmax. Under these conditions only a fixed amount of drug is metabolized because the enzyme system is completely saturated and cannot increase its metabolic capacity (known as Zero-order pharmacokinetics).

Most medications are metabolized following linear pharmacokinetics due to the therapeutic ranges of most drugs are far below the Km for the enzymes that metabolize the agent. However, even in these cases saturable drug metabolism can occur in drug overdose (drug concentration far exceeds the therapeutic range).

Designing individualized dosage regimens using one compartment model

The goal of therapeutic drug monitoring is to customize medication doses that provide the optimal drug efficacy without adverse reactions.

One compartment model equations can be used to compute initial drug doses employing population pharmacokinetic parameters that estimate the constants for a patient.

The patient's own, unique pharmacokinetic parameters can be computed once doses have been administered and drug serum concentrations measured. At that time, individualized dosage regimens at steady state can be designed for a patient.

ROUTE OF ADMINISTRATION	DOSAGE INTERVAL (τ), MAINTENANCE DOSE (D OR k_0), AND LOADING DOSE (LD) EQUATIONS
Intravenous bolus	$\tau = (\ln Css_{max} - \ln Css_{min})/k_e$ $D = Css_{max} V(1 - e^{-k_e\tau})$ $LD = Css_{max} V$
Continuous intravenous infusion	$k_0 = Css\ Cl = Css\ k_e V$ $LD = CssV$
Intermittent intravenous infusion	$\tau = [(\ln Css_{max} - \ln Css_{min})/k_e] + t'$ $k_0 = Css_{max} k_e V[(1 - e^{-k_e\tau})/(1 - e^{-k_e t'})]$ $LD = k_0/(1 - e^{-k_e\tau})$
Extravascular (postabsorption, postdistribution)	$\tau = [(\ln Css_{max} - \ln Css_{min})/k_e] + T_{max}$ $D = [(Css_{max} V)/F][(1 - e^{-k_e\tau})/e^{-k_e T_{max}}]$ $LD = (Css_{max} V)/F$
Average steady-state concentration (any route of administration)	$D = (Css\ Cl\ \tau)/F = (Css\ k_e V\tau)/F$ $LD = (CssV)/F$

Symbol key: Css_{max} and Css_{min} are the maximum and minimum steady-state concentrations, k_e is the elimination rate constant, V is the volume of distribution, Css is the steady-state concentration, k_0 is the continuous infusion rate, t' is the infusion time, T_{max} is the time that Css_{max} occurs, F is the bioavailability fraction.

Q/ Design an individualized dosage regimens using one compartment model equations for a patient that needs to be treated for complex partial seizures with intravenous phenobarbital by using population pharmacokinetic parameters (ke = 0.139 d^{-1}, V = 50 L) to achieve maximum (Cssmax) and minimum (Cssmin) steady-state concentrations equal to 30 mg/L and 25 mg/L, respectively.

Q/ Design an individualized dosage regimens using one compartment model equations for a patient receiving tobramycin for the treatment of intraabdominal sepsis. Using pharmacokinetic parameters (V = 20 L, ke = 0.087 h^{-1}) previously measured in the patient using serum concentrations, compute a tobramycin dose (infused over 1 hour) that would provide maximum (Cssmax) and minimum (Cssmin) steady-state concentrations of 6 mg/L and 1 mg/L, respectively.