Extravascular Equation

When a drug is administered extravascularly (e.g., orally, intramuscularly, subcutaneously, transdermally, etc.), absorption into the systemic vascular system must take place (Figure 2-7). 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:

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

Where:

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

Since the absorption rate constant is 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:

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

This approach works very well when the extravascular dose is rapidly absorbed and not a sustained- or extended-release dosage form.

$$V/F = D/C_0$$

The extrapolated serum concentration at time = zero (C0) is calculated using a variation of the intravenous bolus equation:

$$C_0 = C/e^{-k_e t}$$

For example, a patient is given an oral dose of valproic acid 750 mg as capsules. Six and twenty-four hours after the dose, the valproic acid serum concentrations are 51.9 mg/L and 21.3 mg/L, respectively. Calculate the The hybrid volume of distribution/bioavailability constant (V/F).

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. Fortunately, it is simple to convert single dose compartment model equations to their multiple dose and steady-state counterparts.

As an example of the conversion of a single dose equation to the steady-state variant, the one compartment model ***intravenous bolus*** equation is:

$$C = (D/V)e^{-k_e t}$$

the multiple dosing factor at steady state is multiplied into the expression at only one place, substituting the elimination rate constant (ke) for the rate constant in the multiple dosing factor:

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

τ is the dosage interval

For extravascular administered drugs:

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

- ***Intermittent Intravenous Infusion Equations***

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

Clinical pharmacokinetics

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 / d)] / (120 L/d) = 1.5 μg/L.

If an average steady-state concentration (Css) is known for a drug, the hybrid pharmacokinetic constant clearance/bioavailability (Cl/F) can be computed:

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

Designing individualized dosage regimens using one compartment model equations:

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.

Clinical pharmacokinetics

Design an individualized dosage regimens using one compartment model equations for the following:

Example 1: a patient that needs to be treated for complex partial seizures with intravenous phenobarbital. An initial dosage regimen is designed 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.

Example 2: 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.

Example 3: a patient with simple partial seizures that needs to receive valproic acid capsules (population pharmacokinetic parameters are V = 12 L, ke = 0.05 h−1, Tmax = 3 h, F = 1.0) and maintain steady-state maximum (Cssmax) and minimum (Cssmin) concentrations of 80 mg/L and 50 mg/L, respectively.

***Example* 4:** a patient with an atrial arrhythmia needing treatment with procainamide sustained-release tablets (clearance equals 24 L/h based on current procainamide continuous infusion; F = 0.85, τ = 12 h for sustained-release tablet) and an average steady-state procainamide concentration equal to 5 mg/L.