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

Extravascular Equation

$$C = \{(Fk_aD)/[V(k_a - k_e)]\}(e^{-k_et} - e^{-k_at})$$

t: time after the extravascular dose was given

(t = 0 at the time the dose was administered)

C: concentration at time = t

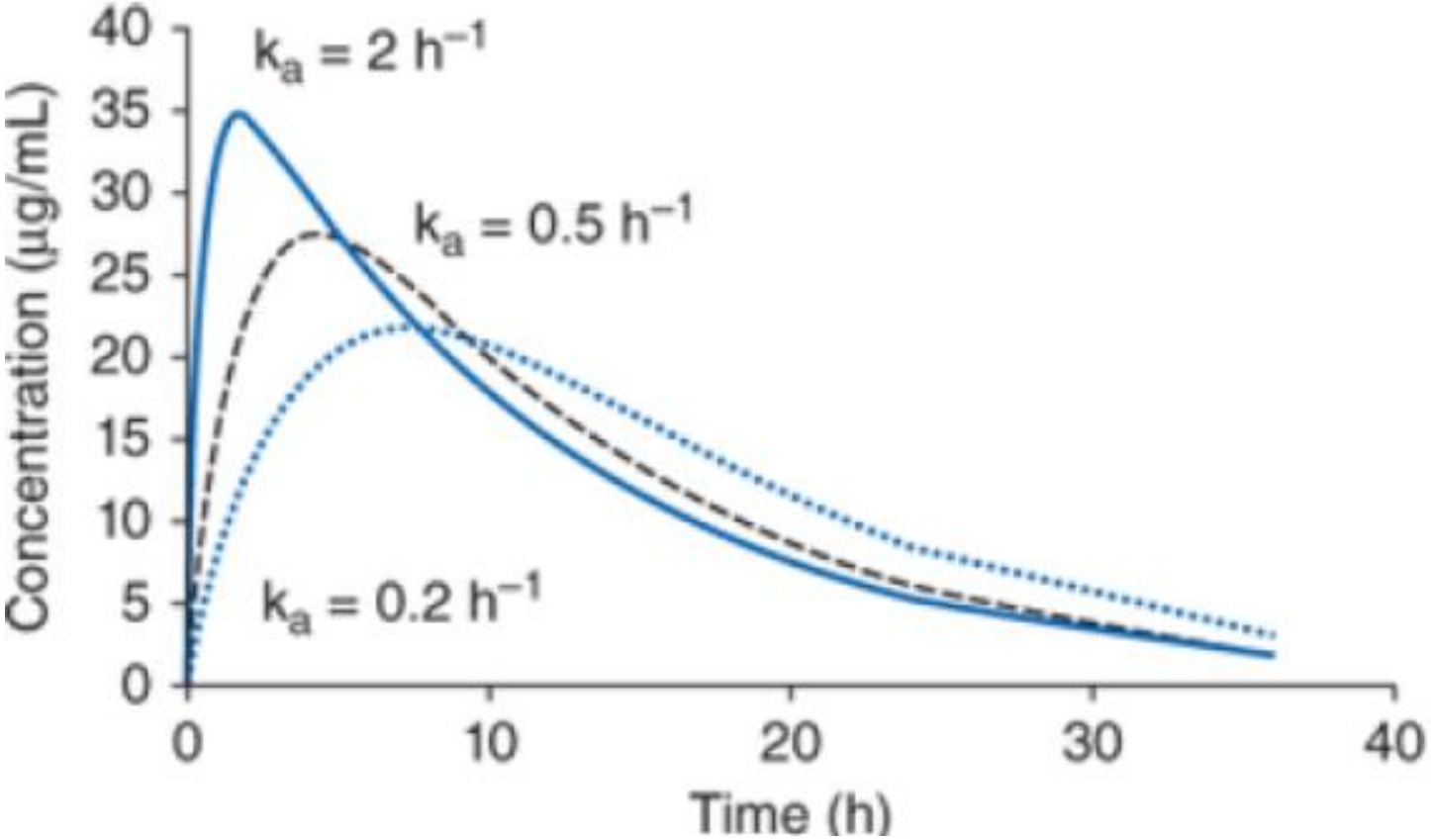
F: bioavailability fraction

k_a: absorption rate constant

D: dose

V: volume of distribution

k_e: elimination rate constant.



Serum concentration/time curves for extravascular drug administration for agents following a **one-compartment pharmacokinetics**. The absorption rate constant **(k_a)** 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.

Extravascular Equation

- 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

$t_{1/2}$= 4 hours

k_e = 0.173 h^{-1} V = 175 L

Ka = 2 h^{-1},

F = 0.85

Extravascular Equation

- The procainamide serum concentration 4 hours after a single dose would be equal to:

$$C = \frac{FK_aD}{V(k_a - k_e)}(e^{-k_et} - e^{-k_at})$$

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

$$= 1.3\ mg/L$$

Extravascular Equation

- 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.*

Extravascular Equation

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

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

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

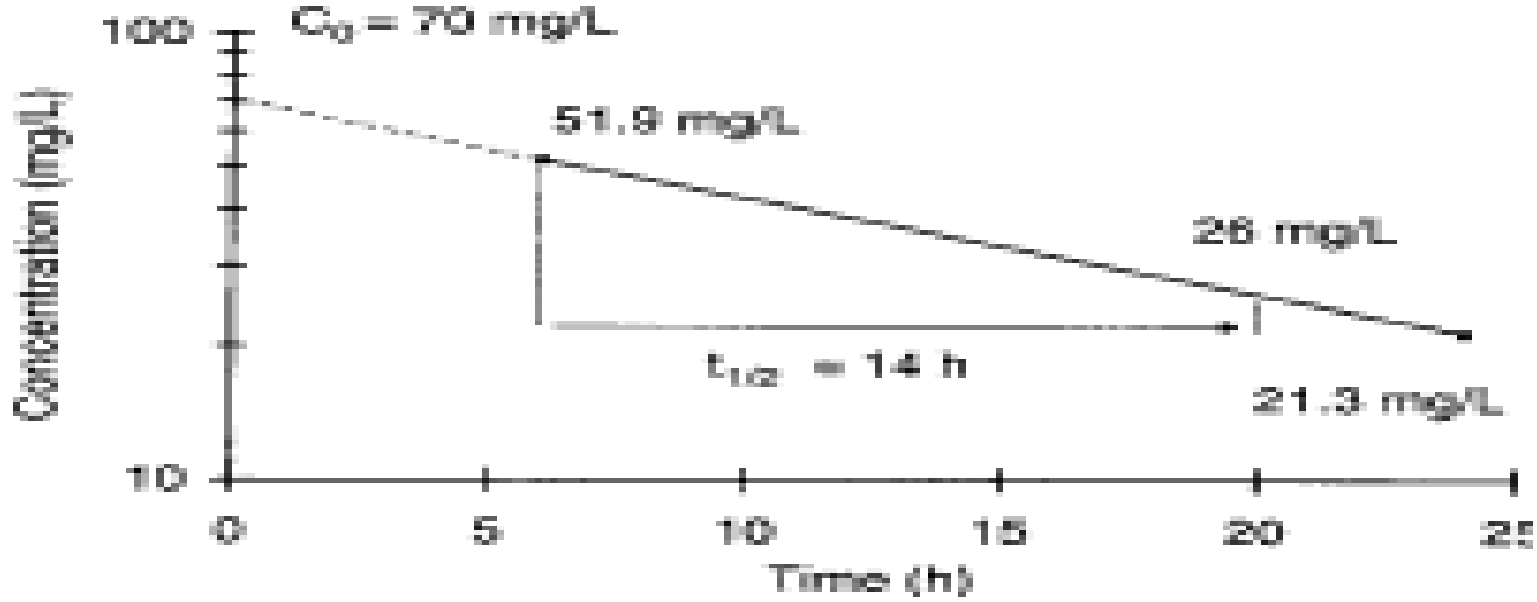
Extravascular Equation

- Pharmacokinetic constants can also be calculated and used in these equations.

- If two or more postabsorption, postdistribution serum concentrations are obtained after an extravascular dose, the Vd, Ke, and $t_{1/2}$ can be computed.

Extravascular Equation

- 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.



Half-life ($t_{1/2}$) is determined by measuring the time needed for serum concentrations to decline by 1/2 (from 51.9mg/L to 26mg/L), and is converted to the elimination rate constant (ke = $0.693/t_{1/2}$ = 0.693/14 h = 0.0495 h^{-1}). The concentration/ time line can be extrapolated to the concentration axis to derive the concentration at time zero (C_0 = 70 mg/L) and used to compute the hybrid constant volume of distribution/bioavailability fraction V/F=D/C_0 = 750mg/(70mg/L) = 10.7L.

Extravascular Equation

Alternatively,

$$ke = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$$

$$ke = -[\ln (51.9\ mg/L) - \ln (21.3\ mg/L)] /(6\ h - 24\ h) = 0.0495\ h^{-1}$$

$$t_{1/2} = 0.693/ke = 0.693/0.0495\ h^{-1} = 14\ h$$

$$C_0 = C/e^{-ke\ t}$$

$$= (21.3\ mg/L) /e^{-(0.0495\ h^{-1})(24h)} = 70\ mg/L$$

$$V/F = D/C_0 = 750mg/(70\ mg/L)$$

$$= 10.7L$$

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.

Multiple-dose and steady-state equations

- In order to change a single dose equation to the multiple dose version, it is necessary to multiply ***each exponential term*** in the equation by the multiple dosing factor:

$$(1 - e^{-nk_i \tau})/(1 - e^{-k_i \tau})$$

n: number of doses administered

K_i: the rate constant found in the exponential of the single dose equation

τ: dosage interval

Multiple-dose and steady-state equations

- At steady state, the number of doses (n) is large, the exponential term in the numerator of the multiple dosing factor ($-nk_i$ t) becomes a large negative number, and the exponent approaches zero.

- Therefore, the steady-state version of the multiple dosing factor becomes the following:

$$1/(1 - e^{-ki\,\tau})$$

K_i: the rate constant found in the exponential of the single dose equation

τ: dosage interval. Equations.docx

Examples

Multiple-dose and steady-state equations

- ***IV bolus.*** a patient with tonic-clonic seizures is given phenobarbital 100 mg intravenously daily until steady-state occurs. ke = 0.116 d^{-1}, V = 75 L.

- The steady-state concentration 23 hours [(23 h) / (24 h / d) = 0.96 d] after the last dose equals:

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

$$= (100\text{ mg}/75\text{ L})[e^{-(0.116\text{ d-1})(0.96\text{ d})} / (1 - e^{-(0.116\text{ d}^{-1})(1\text{ d})})]$$

$$= 10.9\text{ mg/L}$$

Multiple-dose and steady-state equations

- ***Intermittent intravenous infusion.*** A patient with gram-negative pneumonia is administered tobramycin 140 mg every 8 hours until steady state is achieved. V = 16 L, k e = 0.30 h^{-1}. The steady-state concentration immediately after a 1 hour infusion equal:

$$C = [k_0 /(k_e V)][(1 - e^{-ke\, t'}) \mathbf{/ (1 - e^{-ke\, T})}]$$

$$= [(140 \text{ mg/h}) / (0.30\ h^{-1} \cdot 16 \text{ L})][(1 - e^{(-0.30\ h^{-1} \cdot 1\ h)})/(1 - e^{(-0.30\ h^{-1} \cdot 8\ h)})]$$

$$= 8.3 \text{ mg/L}$$

Multiple-dose and steady-state equations

- The main difference between single-dose and multiple-dose calculations is in the **computation** of the **volume of distribution**.

- When a single dose of medication is given, the predose concentration is assumed to be ***zero***.

- However, when multiple doses are given, the predose concentration is ***not usually zero***.

Multiple-dose and steady-state equations

- A patient receiving theophylline 300 mg intravenously (bolus) every 6 hours has a predose concentration equal to 2.5 mg/L and postdose concentrations of 9.2 mg/L one hour and 4.5 mg/L five hours after the second dose is given.

$$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$$

$$= -[(\ln 9.2\ \text{mg/L}) - (\ln 4.5\ \text{mg/L})] / (1\ \text{h} - 5\ \text{h})$$

$$= 0.179\ \text{h}^{-1}$$

Multiple-dose and steady-state equations

$$V = D/[C_0 - C_{predose}]$$

$$C_0 = C/e^{-ke\ t}$$

$$= (9.2\ mg/L)\ /e^{(-0.179\ h-1)(1\ h)}$$

$$= 11.0\ mg/L$$

$$V = D/[C_0 - C_{predose}]$$

$$=(300\ mg)\ /\ (11.0\ mg/L - 2.5\ mg/L) = 35.3\ L$$

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:

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

F: bioavailability fraction
D: dose,
τ : dosage interval
Cl: drug clearance

Average steady-state concentration equation

- The steady-state concentration computed by this equation is the concentration that would have occurred if the dose, adjusted for bioavailability, was given as a continuous intravenous infusion.

- For example, 600 mg of theophylline tablets given orally every 12 hours (F = 1.0) would be equivalent to a 50 mg/h (600 mg/12 h = 50 mg/h) continuous intravenous infusion of theophylline.

Average steady-state concentration equation

- The average steady-state concentration equation is very useful when

1. *The half-life of the drug is long compared to the dosage interval.*

2. *If a sustained-release dosage form is used.*

Average steady-state concentration equation

Example

A patient is administered 250 µg of digoxin tablets daily for heart failure until steady state. F = 0.7, Cl = 120 L/d.

$C_{ss} = [F(D/\tau)]/Cl$

$= [0.7(250\ \mu g/d)] / (120\ L/d)$

$= 1.5\ \mu g/L.$

Average steady-state concentration equation

- Example, a patient receiving 600 mg of sustained-release theophylline every 12 hours has a steady-state concentration equal to 11.2 mg/L.

Cl/F = (D/ τ) / Css

= (600 mg/12 h) / 11.2 mg/L

= 4.5 L/h

Any Question ??