Therapeutic Drug Monitoring
TDM

Chapter 2: Clinical PK Equations and Calculations

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Stage 5 second semester

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Intravenous Bolus Equation

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

t is the time after the intravenous bolus was given (t = 0 at the time the dose was administered)

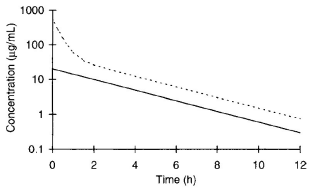
C is the concentration at time = **t**

D is the dose administered

V is the volume of distribution

$\mathbf{k_e}$ is the elimination rate constant.

Intravenous Bolus Equation



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

$C = C_{p_0}\ e^{-K_e t}$

1. Drug is given as IV bolus and quickly distributes from the blood into the tissues. One compartment

2. Short infusion of 5–30 minutes or is very short compared to $t_{1/2}$ so that a large amount of drug is not eliminated during the infusion time

3. If drug given by I.V infusion and distribution is slow?

   it is still possible to use IV bolus equation **if**
   - ✓ the duration of the distribution phase and infusion time << $t_{1/2}$
   - ✓ ↓↓ amount of drug is eliminated during the infusion and distribution phases

$C = (D/V)e^{-k_e t}$ $t = 0$

$= C_0$ $e^0 = 1$

At $t = 0$

$V = D/C_0$ ……..or

$V = D/[C_0 - C_{predose}]$, if not first dose

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

$K_e = -(\ln C_1 - \ln C_2) / (t_1 - t_2)$ $C = C_{p_0}\ e^{-K_e t}$

Example, a patient is given a theophylline loading dose of 400 mg intravenously over 20 minutes. The patient had received theophylline during previous hospitalizations where the volume of distribution was estimated to be 30 L. knowing that the elimination rate constant equals 0.116 h^{-1}. What is the expected theophylline concentration 4 hours after the dose was given?

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

$t_{1/2} = 0.693/k_e = 0.693/0.115\ h^{-1} = 6\ h$

a one-compartment model intravenous bolus equation can be used:

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

$= (400\ mg/30\ L)e^{-(0.115\ h-1)(4\ h)} = 8.4\ mg/L$

Example, a patient was given an intravenous loading dose of phenobarbital 600 mg over a period of about an hour. One day and four days after the dose was administered phenobarbital serum concentrations were measured and found to be 12.6 mg/L and 7.5 mg/L, respectively.

1. What is the half life of the drug?

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

Using C_1 12.6 mg/ml, C_2 7.5 mg/ml, t_1 1d, t_2 4d,

$K_e = 0.173\ d^{-1}$

$k_e = 0.693/t_{1/2}$

$t_{1/2} = 0.693/0.173\ d^{-1} = 4\ d$

2. Calculate the volume of distribution for phenobarbital in this patient.

Infusion time (1h) is) << $t_{1/2}$: use IV bolus eq

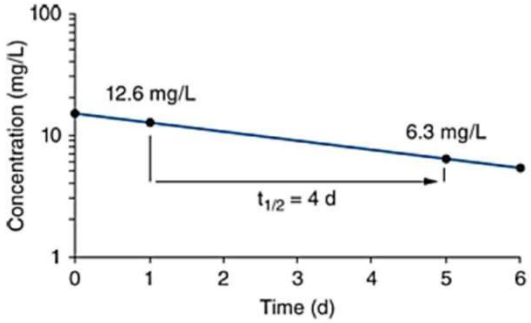
$$C = (D/V)e^{-k_e t}$$

C= 12.6 mg/L, D = 600 mg, Ke = 0.173 d^{-1}, t = 1d

→ V= 40L

Or: we can calculate C_0 using $C_0 = C/e^{-ke\ t}$ using any C and t combinations: C_0 = 15 mg/L,

and V = D/ C_0 = 600 mg/(15 mg/L) = 40 L

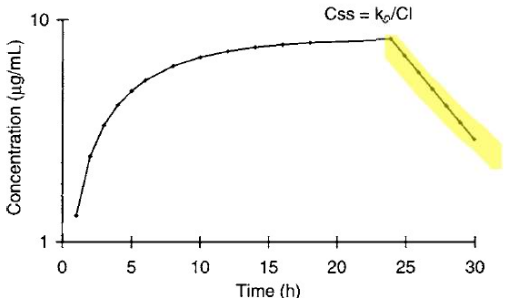


Source: Larry A. Bauer: Applied Clinical Pharmacokinetics, 3rd Edition
www.accesspharmacy.com

If two or more serum concentrations are obtained after an intravenous bolus dose → patient's PK parameters (K_e, V, $t_{1/2}$) can be calculated

Continuous and Intermittent Intravenous Infusion Equations

Some drugs are administered using a continuous intravenous infusion, and if the infusion is discontinued the serum concentration/time profile decreases in a straight line when graphed on a semi logarithmic axes

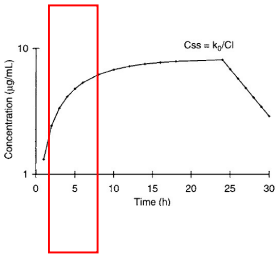


We can calculate the concentration at any time depending on

- the infusion is running or stopped
- we are in study state or not

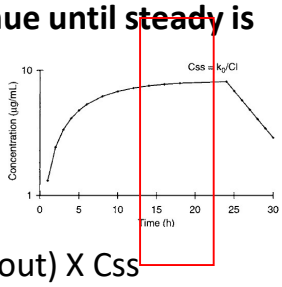
1. If the infusion is still running:

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



- where
  - k_0: drug infusion rate (mg/h or µg/min)
  - Cl: drug clearance, Cl = k_eV
  - K_e: elimination rate constant
  - t: the time that the infusion has been running.

2. If the infusion is allowed to continue until steady is achieved:



remember from last lecture,

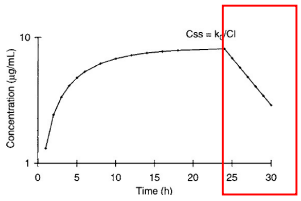
maintenance dose (rate in) = Cl (rate out) X Css

Cl= MD / Css → Css = MD/Cl

In case of continuous infusion, MD= K_0

$$Css = k_0 / Cl = k_0 / (k_e V)$$

3. If the infusion is stopped



- If the infusion is stopped, post infusion serum concentrations ($C_{postinfusion}$) can be computed by calculating the concentration when the infusion ended (C_{end}) using the appropriate equation in the preceding section, and the following equation

$$C_{postinfusion} = C_{end} e^{-k_e t_{postinfusion}}$$

  - k_e is the elimination rate constant
  - $t_{postinfusion}$ is the postinfusion time ($t_{postinfusion}$ = 0 at end of infusion and increases from that point)

- Example, a patient is administered 60 mg/h of theophylline. It is known from previous hospital admissions that the patient has the following pharmacokinetic parameters for theophylline: V = 40 L and ke = 0.139 h^{-1}.

1) Calculate the serum concentration of theophylline in this patient after receiving the drug for 8 hours and at steady state.

- Continuous infusion case:

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

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

- Infusion reached Css

  $Css = k_0/(k_e V)$ = (60 mg/h)/ (0.139 h^{-1} . 40 L) = 10.8 mg/L

2) What is theophylline serum concentration 6 hours after the infusion stopped if

a) the infusion was ran for 8 h only?

b) the infusion was run until steady state is reached?

a) $C_{postinfusion} = C_{end}\ e^{-ke\ tpostinfusion}$, where $C_{end} = C_{8h}$

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

b) $C_{postinfusion} = C_{end}\ e^{-ke\ tpostinfusion}$, where $C_{end} = C_{ss}$

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

Calculating PK parameters for patient receiving IV infusion

- **The elimination rate constant**

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

- **The volume of distribution (V) and Cl**
  - **If we reached steady state (3-5 t ½)**

$$Cl = k_0/C_{ss} \qquad V = Cl/K_e$$

- **If the IV infusion stopped before Css**

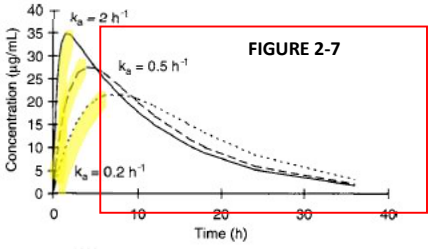
$$V = \frac{k_0(1 - e^{-k_e t'})}{k_e[C_{max} - (C_{predose} e^{-k_e t'})]}$$

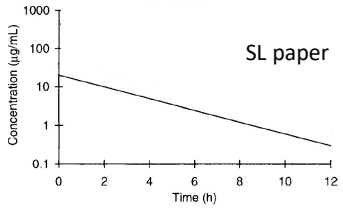
C predose = used only if we have multiple dose and we have predose concentration but when we are in first dose or Cpredose not given in the question Cpredose= zero

- **Extravascular Equation**

drug is administered extravascularly (e.g., orally intramuscularly, subcutaneously ,transdermally, etc.)

absorption into the systemic vascular system





If serum concentrations decrease in a straight line when plotted on semi logarithmic axes after drug absorption is complete

a one compartment model extravascular equation can be used to describe the serum concentration/time curve

- **Extravascular Equation**

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

The absorption rate constant describes how quickly drug is absorbed with a large number indicating fast absorption and a small number indicating slow absorption

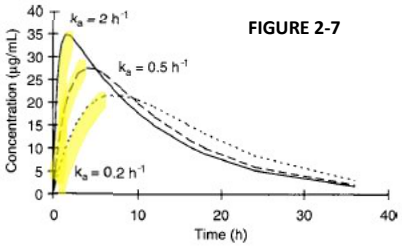
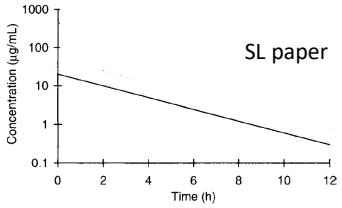


FIGURE 2-7



SL paper

After the end of absorption phase the C can be calculated by equation of I.V bolus

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

- Example: a patient is administered 500 mg of oral procainamide as a capsule. It is known from prior clinic visits that the patient has a half-life equal to 4 hours and a volume of distribution of 175 L. The capsule that is administered to the patient has an absorption rate constant equal to 2 h^{-1}, and an oral bioavailability fraction of 0.85. What is procainamide serum concentration 4 hours after a single dose?

$k_e = 0.693/t_{1/2} = 0.693/4\ h = 0.173\ h^{-1}$

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

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

$$C = 1.3\ mg/L$$

The hybrid volume of distribution/bioavailability (V/F) parameter

- volume of distribution relate the dose given with the obtained concentration
- In extravascular route not all the dose enter the blood stream so we use (V/F) to indicate the value of **volume of distribution**

$V/F = D/C_0$…….or

$V/F = D/ [C_0 - C_{predose}]$, if not first dose

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

$C_0 = C/e^{-ket}$

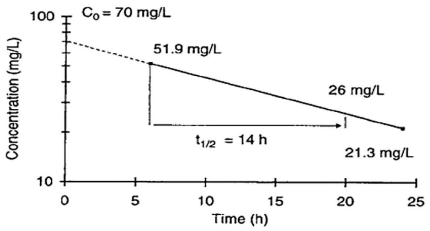
$K_e = -(\ln C_1 - \ln C_2) / (t_1 - t_2)$

- Even though the absolute volume of distribution and bioavailability cannot be computed without the administration of intravenous drug, the hybrid constant can be used in extravascular equations in place of V/F

- Example: a patient is given an oral dose of valproic acid 750 mg as capsules. 6 and 24 hours after the dose, the valproic acid serum concentrations are 51.9 mg/L and 21.3 mg/L, respectively.
- Determine $t_{1/2}$, K_e, V/F graphically and mathematically?

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

$V/F = D/C_0 = 750\ mg/70\ L = 10.7\ L$



Mathematically,

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

$= -[\ln (51.9\ mg/L) - \ln (21.3\ mg/L)]/ (6\ h - 24\ h)$

$= 0.0495\ h^{-1}$

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

$C_0 = C/e^{-ket}$ modified from IV bolus equation (hint: remember it is a straight line equation that you can rearrange)

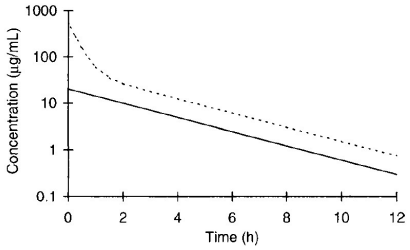
$= (21.3\ mg/L) / e^{-(0.0495\ h^{-1})} (24\ h)$

$= 70\ mg/L$

$V/F = D/C_0 = 750\ mg/ (70\ mg/L) = 10.7\ L$

If drug distribution is not rapid?!

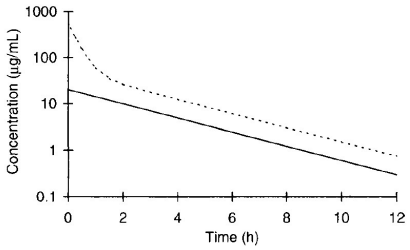
For IV bolus dose: still possible to use a one compartment model intravenous bolus equation if the duration of the distribution phase is small compared to the half-life of the drug and only a small amount of drug is eliminated during the infusion and distribution phases.



The strategy used in this situation is to infuse the medication and wait for the distribution phase to be over before obtaining serum concentrations in the patient.

If drug distribution is not rapid?!

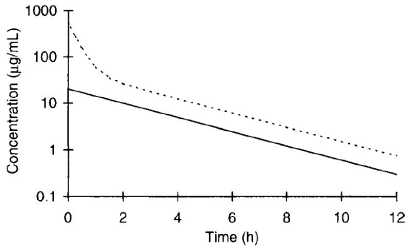
For IV infusion case: still possible to use one compartment model intravenous infusion equations for the drug without a large amount of error.



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.

If drug distribution is not rapid?!

For extravascular administration: still possible to use one compartment model equations after an extravascular dose is administered.

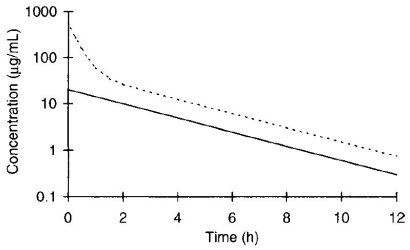


The strategy used in this instance is to obtain serum concentrations in the postdistribution phase only.

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.

If drug distribution is not rapid?!

For extravascular administration: still possible to use one compartment model equations after an extravascular dose is administered.



When only postabsorption, postdistribution serum concentrations are obtained for a drug that is administered extravascularly,

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

Applicable for rapidly absorbed dosage forms and not SR

Multiple-Dose and Steady-State Equations

TABLE 2-1 Single-Dose, Multiple-Dose, and Steady-State One-Compartment Model Equations

ROUTE OF ADMINISTRATION	SINGLE DOSE	MULTIPLE DOSE	STEADY STATE
Intravenous bolus	$C = (D/V)e^{-k_e t}$	$C = (D/V)e^{-k_e t}\,[(1 - e^{-nk_e\tau})/(1 - e^{-k_e\tau})]$	$C = (D/V)[e^{-k_e t}/(1 - e^{-k_e\tau})]$
Continuous intravenous infusion	$C = [k_0/(k_e V)](1 - e^{-k_e t})$	N/A	$Css = k_0/Cl = k_0/(k_e V)$
Intermittent intravenous infusion	$C = [k_0/(k_e V)](1 - e^{-k_e t'})$	$C = [k_0/(k_e V)][(1 - e^{-k_e t'})\,[(1 - e^{-nk_e\tau})/(1 - e^{-k_e\tau})]$	$C = [k_0/(k_e V)][(1 - e^{-k_e t'})/(1 - e^{-k_e\tau})]$
Extravascular (postabsorption, postdistribution)	$C = [(FD)/V]e^{-k_e t}$	$C = [(FD)/V]e^{-k_e t}\,[(1 - e^{-nk_e\tau})/(1 - e^{-k_e\tau})]$	$C = (FD/V)[e^{-k_e t}/(1 - e^{-k_e\tau})]$
Average steady-state concentration (any route of administration)	N/A	N/A	$Css = [F(D/\tau)]/Cl$

Symbol key: C is drug serum concentration at time = t, D is dose, V is volume of distribution, k_e is the elimination rate constant, n is the number of administered doses, τ is the dosage interval, k_0 is the infusion rate, Cl is clearance, t' is infusion time, N/A is not applicable.

- 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.

Multiple-Dose and Steady-State Equations

TABLE 2-1 Single-Dose, Multiple-Dose, and Steady-State One-Compartment Model Equations

ROUTE OF ADMINISTRATION	SINGLE DOSE	MULTIPLE DOSE	STEADY STATE
Intravenous bolus	$C = (D/V)e^{-k_e t}$	$C = (D/V)e^{-k_e t}[(1 - e^{-nk_e\tau})/(1 - e^{-k_e\tau})]$	$C = (D/V)[e^{-k_e t}/(1 - e^{-k_e\tau})]$
Continuous intravenous infusion	$C = [k_0/(k_e V)](1 - e^{-k_e t})$	N/A	$Css = k_0/Cl = k_0/(k_e V)$
Intermittent intravenous infusion	$C = [k_0/(k_e V)](1 - e^{-k_e t'})$	$C = [k_0/(k_e V)](1 - e^{-k_e t'})[(1 - e^{-nk_e\tau})/(1 - e^{-k_e\tau})]$	$C = [k_0/(k_e V)][(1 - e^{-k_e t'})/(1 - e^{-k_e\tau})]$
Extravascular (postabsorption, postdistribution)	$C = [(FD)/V]e^{-k_e t}$	$C = [(FD)/V]e^{-k_e t}[(1 - e^{-nk_e\tau})/(1 - e^{-k_e\tau})]$	$C = (FD/V)[e^{-k_e t}/(1 - e^{-k_e\tau})]$
Average steady-state concentration (any route of administration)	N/A	N/A	$Css = [F(D/\tau)]/Cl$

Symbol key: C is drug serum concentration at time = t, D is dose, V is volume of distribution, k_e is the elimination rate constant, n is the number of administered doses, τ is the dosage interval, k_0 is the infusion rate, Cl is clearance, t' is infusion time, N/A is not applicable.

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

- n is the number of doses administered
- k_i is the rate constant found in the exponential of the single dose equation
- τ is the dosage interval.

Multiple-Dose at steady state

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

n is ↑ → $(-nk_i\tau)$ will be larg negative number → $e^{-nki\tau}$ approaches zero

The state version of the multiple dosing factor becomes

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

- ***Intravenous bolus:***

A patient with tonic-clonic seizures is given phenobarbital 100 mg intravenously daily until steady-state occurs. Pharmacokinetic constants for phenobarbital in the patient are: $k_e = 0.116\ d^{-1}$, V = 75 L.

Calculate The steady-state concentration 23 hr after the last dose

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

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

$$= 10.9\ mg/L$$

- ***Intermittent intravenous infusion:***

A patient with gram-negative pneumonia is administered tobramycin 140 mg every 8 hours until steady state is achieved. Pharmacokinetic parameters for tobramycin in the patient are: V = 16 L, $k_e = 0.30\ h^{-1}$

Calculate steady-state concentration immediately after a 1 hour infusion

$$C = [k_0/ (k_eV)][(1 - e^{-ket'}) / (1 - e^{-ke\tau})]$$

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

$$= 8.3\ mg/L.$$

- ***Extravascular***.

A patient with an arrhythmia is administered 250 mg of quinidine orally (as 300 mg quinidine sulfate tablets) every six hours until steady state occurs. Pharmacokinetic constants for quinidine in the patient are: V = 180 L, k_e = 0.0693 h^{-1}, F = 0.7

Calculate steady-state concentration (postabsorption, postdistribution C_{ss}) just before the next dose

1 hr before next dose

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

5 hr (τ -1)

$$=[(0.7 \cdot 250 \text{ mg}) /180 \text{ L}][e^{(-0.0693 \text{ h}-1 \cdot 6 \text{ h})} /(1 - e^{(-0.0693 \text{ h}-1 \cdot 6 \text{ h})})]$$

$$= 1.9 \text{ mg/L}.$$

Volume of distribution in multiple dosing

We need to subtract predose concentration:

IV bolus dose: $V = D/(C_0 - C_{predose})$

Extravascular: $V/F = D/(C_0 - C_{predose})$

Intermittent IV infusion $$V = \frac{k_0(1 - e^{-k_e t'})}{k_e[C_{max} - (C_{predose} e^{-k_e t'})]}$$

Average Steady-State Concentration Equation

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

- works for any single or multiple compartment model: model independent equation.
- C_{ss} = Conc if the dose (adjusted for bioavailability) was given as a continuous IV infusion.
- Useful when the $t_{1/2} > \tau$

  SR dosage form is used

Michaelis-Menten Equations For Saturable Pharmacokinetics

- When the dose of a drug is increased and steady-state serum concentrations do not increase in a proportional fashion, but instead increase more than expected, e.g phenytoin.

$$D = (V_{max} \cdot C_{ss}) / (K_m + C_{ss})$$

D: dose

C_{ss}: steady-state drug concentration

V_{max}: maximum rate of drug metabolism

K_m: concentration where the rate of metabolism equal $V_{max}/2$.

Michaelis-Menten Equations For Saturable Pharmacokinetics

HW: rearrange Michaelis-Menten Eq to straight line eq

$D = (V_{max} \cdot C_{ss}) / (K_m + C_{ss})$

Rearranged to straight line eq

$D = V_{max} - [K_m (D/C_{ss})]$..... (1)

y-intercept

$Slop = \frac{-\Delta y}{\Delta x}$

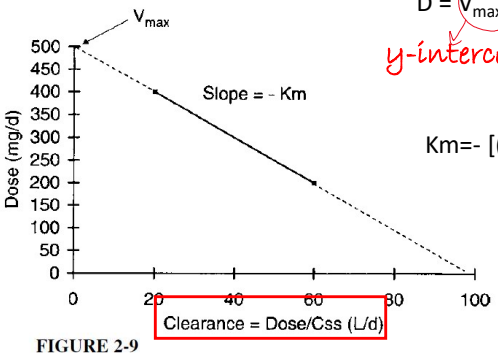


FIGURE 2-9

Km=- [(D 1 - D 2)]/ [(D1/Css1) - (D2/Css2)].... (2)

Vmax= D + [Km (D/Css)] .....(3)

Designing individualized dosage regimens using one compartment model equations

Therapeutic drug monitoring goal: **customize** drug doses to provide safe effective therapy

use _population PK parameters to calculate initial drug doses

→ administer dose

→ obtain serum conc

→ Calculate patient's unique PK parameters

→ individualize dosage regimens for that patient

Designing individualized dosage regimens using one compartment model equations

- **Mathematically,**
- **Linear pK**
  - ✓ get Css or Cp at time t after a given D
  - ✓ calculate the actual PK parameters (Cl, $t_{1/2}$, Vd)
  - ✓ use actual PK parameter to calculate new dose

Patient specific — based on measured Cp

- **Michaelis-Menten PK**
  - ✓ get 2 Css after 2 doses of drug
  - ✓ calculate the actual PK parameters (Km, Vmax)
  - ✓ use actual PK parameters to calculate new dose

Example: A patient receiving phenytoin for the treatment of tonic clonic seizures. The patient received a dose of 300 mg/d with a SteadyState concentration of 8 mg/L and a dose of 500 mg/d with a SteadyState concentration equal to 22 mg/L. calculate patient's PK parameters and phenytoin dose required to reach Css of 13 mg/L.

Km=- [(D1 - D2)]/ [(D1/Css1) - (D2/Css2)]

=- [(300mg/d-500mg/d)]/[(300mg/d/8mg/L)-(500mg/d/22mg/L)]

= 13.5 mg/L

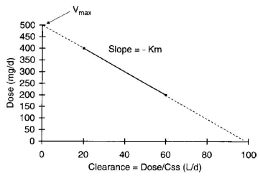
Vmax= D + [Km (D/Css)]

= 500 mg/d + [13.5 mg/L (500 mg/d / 22 mg/L)] = 807 mg/d

The phenytoin dose to reach a Css= 13 mg/L

D = (Vmax • Css)/(Km + Css) = 400 mg/d

We can also solve this question graphically



Calculation of clearance, volume of distribution, and half-life in pharmacokinetic research studies

- Clearance (Cl):
  - For IV administered drugs $Cl = D/AUC$
  - For extravascularly administered drugs $Cl = (FD)/AUC$
- Volume of distribution (V)

$Cl = K_e V$, $Cl = D/AUC$ or $Cl = FD/AUC$

$V = D/(K_e AUC)$ or $V = (FD)/(K_e AUC)$

oral

TABLE 2-3 Equations to Compute Individualized Dosage Regimens for Various Routes of Administration

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.