TDM/CH 2

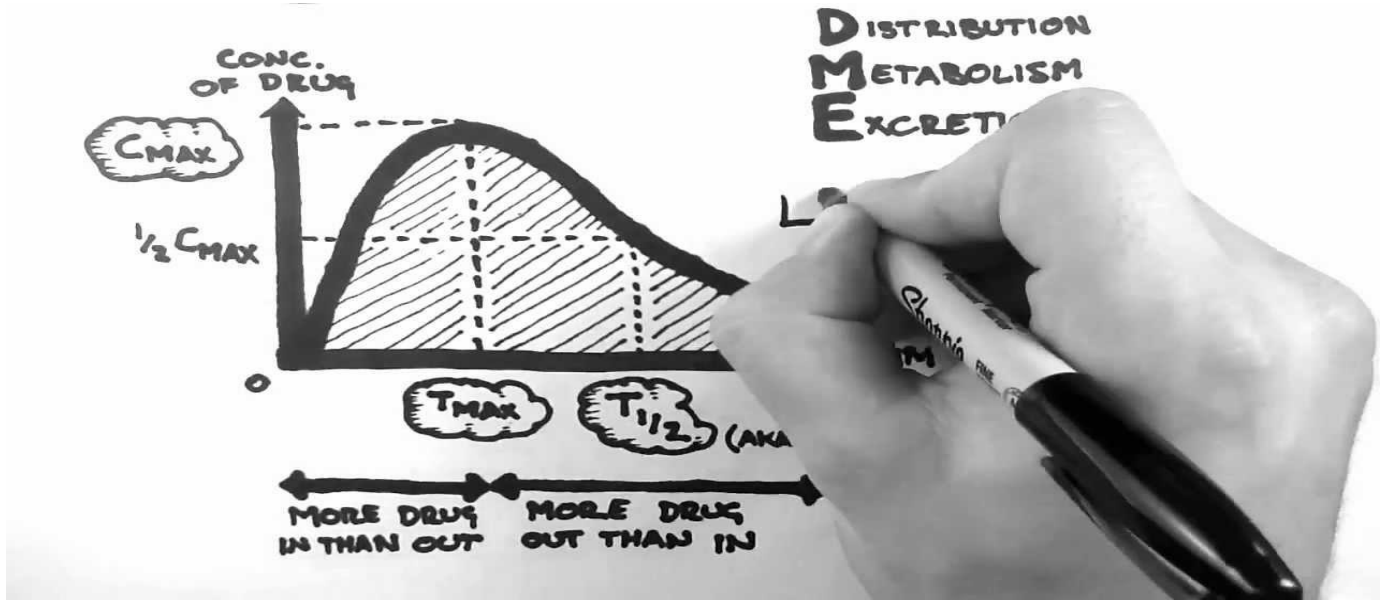

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TABLE 2-1 Single-Dose, Multiple-Dose, and Steady-State One-Compartment Model Equations

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.

TABLE 2-2 Single-Dose, Multiple-Dose, and Steady-State Pharmacokinetic Constant Computations Utilizing a One Compartment Model

ROUTE OF ADMINISTRATION	SINGLE DOSE	MULTIPLE DOSE	STEADY STATE
Intravenous bolus	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = D/C_0$ $Cl = k_e V$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = D/(C_0 - C_{predose})$ $Cl = k_e V$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = D/(C_0 - C_{predose})$ $Cl = k_e V$
Continuous intravenous infusion	N/A	N/A	$Cl = k_0/Css$
Intermittent intravenous infusion	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = [k_0(1 - e^{-k_e t'})]/\{k_e[C_{max} - (C_{predose} e^{-k_e t'})]\}$ $Cl = k_e V$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = [k_0(1 - e^{-k_e t'})]/\{k_e[C_{max} - (C_{predose} e^{-k_e t'})]\}$ $Cl = k_e V$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = [k_0(1 - e^{-k_e t'})]/\{k_e[C_{max} - (C_{predose} e^{-k_e t'})]\}$ $Cl = k_e V$
Extravascular (postabsorption, postdistribution)	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V/F = D/C_0$ $Cl/F = k_e(V/F)$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V/F = D/(C_0 - C_{predose})$ $Cl/F = k_e(V/F)$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V/F = D/(C_0 - C_{predose})$ $Cl/F = k_e(V/F)$
Average steady-state concentration (any route of administration)	N/A	N/A	$Cl/F = (D/\tau)/Css$

Symbol key: C_1 is drug serum concentration at time = t_1, C_2 is drug serum concentration at time = t_2, k_e is the elimination rate constant, $t_{1/2}$ is the half-life, V is the volume of distribution, k_0 is the continuous infusion rate, t′ is the infusion time, V/F is the hybrid constant volume of distribution/bioavailability fraction, D is dose, C_0 is the concentration at time = 0, Cl is drug clearance, Cl/F is the hybrid constant clearance/bioavailability fraction, $C_{predose}$ is the predose concentration, Css is the steady-state ··centration, N/A is not applicable.

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.

Q1. PZ is a 35-year-old, 60-kg female with a *Staphylococcus aureus* wound infection. While receiving vancomycin 1 g every 12 hours (infused over one hour), the steady state peak concentration (obtained one-half hour after the end of infusion) was 35 mg/L, and the steady-state trough concentration (obtained immediately predose) was 15 mg/L. (A) Using one compartment IV bolus equations, compute the pharmacokinetic parameters for this patient. (B) Using the patient-specific pharmacokinetic parameters calculated in part A, compute a new vancomycin dose that would achieve Css_{max} = 30 mg/L and Css_{min} = 7.5 mg/L.

Answer/

D = 1000 mg, C predose = 15 mg/mL, Ct = 35 mg/mL, t1 = 1.5 h, t2 = 12 h

A) One compartment IV bolus dose equations;

$$Ke = -\left(\frac{Ln\ C1 - LnC2}{t1 - t2}\right) \rightarrow Ke = -\left(\frac{Ln\ 35mg/mL - Ln15mg/mL}{1.5\ h - 12\ h}\right) \rightarrow Ke = 0.081\ h^{-1}$$

$$t½ = \frac{0.693}{Ke} \rightarrow t½ = \frac{0.693}{0.081h^{-1}} \rightarrow t½ = 8.6\ h$$

$$C_{\circ} = \frac{Ct}{e^{-Ket}} \rightarrow C_{\circ} = \frac{35mg/mL}{e^{-0.081\ h^{-1} * 1.5\ h}} \rightarrow C_{\circ} = 39.5\ mg/L$$

$$V = \frac{D}{C_{\circ} - Cpredose} \rightarrow V = \frac{1000mg}{39.5\frac{mg}{L} - 15\frac{mg}{mL}} \rightarrow V = 41\ L$$

B)

$$\tau = \frac{Ln\ Css_{max} - Ln\ Css_{min}}{Ke} \rightarrow \tau = \frac{Ln\ 30\frac{mg}{L} - Ln7.5\frac{mg}{L}}{0.081h^{-1}} \rightarrow \tau = 17.1\ h \approx 18\ h$$

$$D = Css_{max}V(1 - e^{-Ke\tau}) \rightarrow D = 30mg/L * 41\ L(1 - e^{-0.081\ h^{-1} * 18\ h})$$

$$\rightarrow D = 944\ mg \approx 1000mg$$

Recommended dose: 1000 mg every 18 h

Q2. Negamycin is a new antibiotic with an average volume of distribution of 0.35 L/kg and a half-life of 2 hours in patients with cystic fibrosis. Compute a dosage regimen for JM, a 22-year-old, 45-kg female cystic fibrosis patient with Pseudomonas aeruginosa in her sputum, that will achieve steady-state peak concentrations of 10 mg/L and trough concentrations of 0.6 mg/L using one-compartment model IV bolus equations (assume that the drug is given as an IV bolus).

Answer:

V = 0.35 L/kg, t½ = 2 h, wt = 45 Kg, Css_{max} = 10 mg/L, Css_{min}= 0.6 mg/L

V = 0.35 L/Kg *45 Kg→ V = 15.8L

$$t½ = \frac{0.693}{Ke} \rightarrow \quad Ke = \frac{0.693}{t½} \rightarrow \quad Ke = \frac{0.693}{2\ h} \rightarrow Ke = 0.347\ h^{-1}$$

$$\tau = \frac{Ln\ Css_{max} - Ln\ Css_{min}}{Ke} \rightarrow \tau = \frac{Ln\ 10\frac{mg}{L} - Ln\ 0.6\frac{mg}{L}}{0.347\ h^{-1}} \rightarrow \tau = 8.1\ h \approx 8\ h$$

$$D = Css_{max} V(1 - e^{-Ke\tau}) \rightarrow D = 10\frac{mg}{L} * 15.8\ L(1 - e^{-0.347\ h^{-1} * 8\ h}) \rightarrow$$

$$D = 148\ mg \approx 150\ mg$$

Recommended dose: 150 mg every 8 h

Q3. KL is a 65-year-old, 60-kg female being treated for septic shock. Among other antibiotics, she is being treated with tobramycin 60 mg every 8 hours (infused over 1 hour). Steady-state serum concentrations are: Css max = 7.1 mg/L, Css min = 3.1 mg/L. Using one compartment intermittent intravenous infusion equations, compute the pharmacokinetic parameters for this patient and use them to individualize the tobramycin dose to achieve Css max = 8 mg/L and Css min = 1.0 mg/L.

Answer/
Using one compartment intermittent IV infusion equation:

$$Ke = -\left(\frac{Ln\ C1 - LnC2}{t1 - t2}\right) \rightarrow Ke = -\left(\frac{Ln 7.1\frac{mg}{L} - Ln 3.1\frac{mg}{L}}{1\ h - 8\ h}\right) \rightarrow Ke = 0.118\ h^{-1}$$

$$V = \frac{K_{\circ}\ (1 - e^{-Ket'})}{\text{Ke}\ ((\ C_{max} - (C_{predose} e^{-Ket'}))} \rightarrow V = \frac{60\ \text{mg/1 h}(1 - e^{-0.188\ \bar{h}^{1} * 1h})}{0.118\ \text{h}^{-1}((\frac{7.1mg}{L} - \frac{3.1mg}{L} e^{-0.188\ \bar{h}^{1} * 1\ h}))} \rightarrow \text{V} =$$

13 L

$$\tau = \frac{Ln\ Css_{max} - Ln\ Css_{min}}{Ke} + t' \rightarrow \tau = \frac{Ln\ 8\ mg/L - Ln 1\ mg/L}{0.118\ h^{-1}} + 1\ \text{h} \rightarrow \tau = 18.6\ \text{h} \approx 18\ \text{h}$$

$$K_{\circ} = Css_{max}\text{Ke.V}\frac{(1 - e^{-Ke\tau})}{(1 - e^{-Ket'})} \rightarrow K_{\circ} = 8\ \text{mg/L} * 0.188\ \text{h}^{-1} * 13\ L\frac{(1 - e^{-0.118\ \bar{h}^{1} * 18\ h})}{(1 - e^{-0.188\ \bar{h}^{1} * 1\ h})}$$

$\rightarrow K_{\circ} = 97\ \text{mg} \approx 100\ \text{mg}$

Recommended dose: 100 mg every18 h

Q4. JB is a 52-year-old, 72-kg male being treated for gram-negative pneumonia. Assuming a V = 18 L and a t1/2 = 8 h, design a gentamicin dosage (infused over 1 hour) to achieve Css max = 10 mg/L and Css min = 1.2 mg/L using one compartment intermittent intravenous infusion equations.

Answer/

V =18 L, t½ = 8 h, Css_{max} = 10 mg/L, Css_{min}= 1.2 mg/L

Using one compartment intermittent IV infusion equation:

$$t½ = \frac{0.693}{Ke} \rightarrow Ke = \frac{0.693}{t½} \rightarrow Ke = \frac{0.693}{8\ h} \rightarrow Ke = 0.087\ h^{-1}$$

$$\tau = \frac{Ln\ Css_{max} - Ln\ Css_{min}}{Ke} + t' \rightarrow \tau = \frac{Ln\ 10 mg/L - Ln 1.2\ mg/L}{0.087\ h^{-1}} + 1\ h \rightarrow \tau = 25.4\ h \approx 24\ h$$

$$K_{\circ} = Css_{max} \text{Ke.V} \frac{(1 - e^{-Ke\tau})}{(1 - e^{-Ket'})} \rightarrow K_{\circ} = 10\ \text{mg/L} * 0.087\ \text{h}^{-1} * 18\ L \frac{(1 - e^{-0.087\ h^{-1} * 24\ h})}{(1 - e^{-0.087\ h^{-1} * 1\ h})}$$

$$\rightarrow K_{\circ} = 165\ \text{mg}$$

Recommended dose : 165 mg every 24 h

Q5.EV is a 42-year-old, 84-kg male suffering from an acute asthmatic attack. Using one compartment model equations, compute a theophylline IV bolus loading dose (to be administered over 20 minutes) and continuous infusion to achieve a Css = 12 mg/L. Assume a V = 40 L and t1/2 = 5 h.

Answer/

V = 40 L, t½ = 5 h, Css = 12 mg/L

$t½ = \frac{0.693}{Ke} \rightarrow \quad Ke = \frac{0.693}{t½} \rightarrow \quad Ke = \frac{0.693}{5\ h} \rightarrow Ke = 0.139\ h^{-1}$

$Ke = \frac{Cl}{V} \rightarrow Cl = Ke.V \rightarrow Cl = 0.139\ h^{-1} * 40\ \text{L} \rightarrow Cl = 5.56\ L/h$

$LD = Css\ V \rightarrow LD = 12\ mg/L * 40\ \text{L} \rightarrow LD = 480\ mg \approx 500\ mg\ IV\ over\ 20\ min$

$K_{\circ} = Css\ Cl \rightarrow K_{\circ} = 12\ mg/L * 5.56\ \text{L/h} \rightarrow K_{\circ} = 67\ mg/h \approx 70\ mg/h$

Q6. BJ is a 62-year-old, 70-kg female with a ventricular arrhythmia. Assuming a V = 33 L and Cl = 0.5 L/min, use one-compartment model equations to compute a lidocaine IV bolus loading dose (to be administered over 1–2 minutes) and continuous infusion to achieve a Css = 3 mg/L.

Answer/

V = 33 L , Cl = 0.5 L/min, Css = 3 mg/L
Using one compartment IV bolus dose and continuous infusion equation:

$LD = Css\ V \rightarrow LD = 3\ mg/L$ * 33 L$\rightarrow LD = 99\ mg\ \approx 100\ mg\ IV\ over\ 2\ min$

$K_{\circ} = Css\ Cl \rightarrow K_{\circ} = 3\ mg/L$ * 0.5 L/h $\rightarrow K_{\circ} = 1.5 mg/h \approx 70\ mg/h$

Q7. MM is a 54-year-old, 68-kg male being treated with procainamide 750-mg regular release capsules every 6 hours for an arrhythmia. The following steady-state concentration is available: Css min = 1.5 mg/L (obtained immediately predose). Calculate a dose that will achieve a Css min = 2.5 mg/L.

Answer/
D1 = 750 mg cap, Css min1 = 1.5 mg/L (predose)
D2=?, Css min2 = 2.5 mg/L

750 mg	1.5 mg/L
X	2.5 mg/L

X = 1250 mg (the recommended dose every 6 h)

Q8. LM is a 59-year-old, 85-kg male needing treatment with oral quinidine for an arrhythmia. Assuming F = 0.7, Tmax = 2 h, V = 200 L, and t1/2 = 8 h, compute Css min for a dose of oral quinidine 400 mg every 6 hours.

Answer/

F = 0.7, Tmax = 2 h, V = 200 L, t½ = 8 h, D = 400 mg, Css min = ?

$$t½ = \frac{0.693}{Ke} \rightarrow \quad Ke = \frac{0.693}{t½} \rightarrow \quad Ke = \frac{0.693}{8\ h} \rightarrow Ke = 0.087\ h^{-1}$$

$$Css_{max} = \frac{FD}{V} * \frac{(e^{-Ke\,T\,max})}{(1 - e^{-Ke\tau})} \rightarrow Css_{max} = \frac{0.7 * 400\ mg}{200\ L} * \frac{(e^{-0.087\ h^{-1} * 2h})}{(1 - e^{-0.087\ h^{-1} * 6\ h})} \rightarrow Css_{max} = 2.9 \text{ mg/L}$$

$$Css_{min} = Css_{max}\ e^{-Ke\ (\tau - T\ \max)} \rightarrow Css_{min} = 2.9\ mg/L\ e^{-0.087\ h^{-1}\ (6h - 2h)} \rightarrow Css_{min} = 2 \text{ mg//L}$$

Q9. JB is a 78-year-old, 100-kg male being treated with digoxin for heart failure. While receiving digoxin tablets 125 μg daily, a steady-state digoxin concentration equal to 0.6 μg/L is obtained. (A) Assuming F = 0.7, compute digoxin clearance for the patient using the average steady-state concentration equation. (B) Compute a new digoxin tablet dose for the patient that will achieve Css = 1.2

Answer/

D =125 μg, Css = 0.6 μg/L, F = 0.7, Cl = ?

D new (for Css = 1.2 μg/L) = ?

Using average steady state equation:

A)

$$Css = \frac{DF}{Cl\tau} \rightarrow Cl = \frac{DF}{Css\,\tau} \rightarrow Cl = \frac{125\ \mu g * 0.7}{0.6\frac{\mu g}{L} * 1\ d} \rightarrow \quad Cl = 146\ L/d$$

B)

125 μg	0.6 μg/L
D new	1.2 μg/L

D new = 250 μg (Recommended dose daily)

Q10. QJ is a 67-year-old, 80-kg male being treated for chronic obstructive pulmonary disease. Sustained-release oral theophylline is being added to his drug regimen. Assuming F = 1.0, V = 40 L, and t1/2 = 5 hours, compute an oral theophylline dose to be administered every 12 hours that would achieve a Css = 8 mg/L using the average steady-state concentration equation

Answer/
F = 1.0, V = 40 L, and t½ = 5 h, Css = 8 mg/L, D = ?
Using average steady state concentration equation:

$$t½ = \frac{0.693}{Ke} \rightarrow \quad Ke = \frac{0.693}{t½} \rightarrow \quad Ke = \frac{0.693}{5\ h} \rightarrow Ke = 0.139\ h^{-1}$$

$$Ke = \frac{Cl}{V} \rightarrow Cl = Ke.V \rightarrow Cl = 0.139\ h^{-1} * 40\ \text{L} \rightarrow Cl = 5.56\ L/h$$

$$Css = \frac{DF}{Cl\tau} \rightarrow D = \frac{Css.Cl.\tau}{F} \rightarrow D = \frac{8mg/L * 5.56L/h * 12\ h}{1} \rightarrow D = 534\ mg \approx 500\ mg$$

Recommended dose : 500 mg every 12 h

Q11. TD is a 32-year-old, 70-kg male with generalized tonic-clonic seizures. Assuming Michaelis-Menten parameters of Vmax = 500 mg/d and Km = 4 mg/L, calculate a dose of phenytoin that will achieve Css = 15 mg/L.

Answer/
Vmax = 500 mg/d, Km = 4 mg/L, Css = 15 mg/L, D = ?
Using Michaelis-Menten equation:

$$D = \frac{Vmax.Css}{Km+Css} \rightarrow \mathrm{D} = \frac{500\mathrm{mg/d} * 15\ \mathrm{mg/L}}{4\ \mathrm{mg/L}+15\ \mathrm{mg/L}} \rightarrow \mathrm{D} = 395\ \mathrm{mg} \approx 400\ mg$$

Recommended dose: 400 mg daily at bedtime

Q12. OP is a 28-year-old, 55-kg female with complex partial seizures. She has the following information available: Css = 8 mg/L while receiving phenytoin 300 mg at bedtime and Css = 22 mg/L while receiving phenytoin 400 mg at bedtime. Compute the patient's Michaelis-Menten parameters for phenytoin, and the phenytoin dose that would achieve Css = 15 mg/L.

Answer/
Css1 = 8 mg/L, D1 = 300 mg,
Css2 = 22 mg/L, D2 = 400 mg,
Vmax = ?, Km = ?, D (for Css = 15 mg/L) = ?
Using Michaelis-Menten equation:

$$Km = -\left(\frac{D1-D2}{\frac{D1}{Css1}-\frac{D2}{Css2}}\right) \rightarrow Km = -\left(\frac{300\ mg-400\ mg}{\frac{300\ mg}{8\ mg/L}-\frac{400\ mg}{22\ mg/L}}\right) \rightarrow \ Km = 5.2\ mg/L$$

$$Vmax = D + \left(\frac{Km.D}{Css}\right) \rightarrow Vmax = 300\ mg + \left(\frac{5.3\ mg/L * 300mg}{8\ mg/L}\right) \rightarrow \text{Vmax} = 495\ \text{mg/d}$$

$$D = \frac{Vmax.Css}{Km+Css} \rightarrow \text{D} = \frac{495\ \text{mg/d} * 15\ \text{mg/L}}{5.2\ \text{mg/L} + 15\ \text{mg/L}} \rightarrow \ \text{D} = 367\ \text{mg} \approx 375\ mg$$

Recommended dose: 375 mg daily at bedtime