An Introduction to the basic ideas of the mathematics behind Phamacokinetics.

By Tyeba Siddiqui

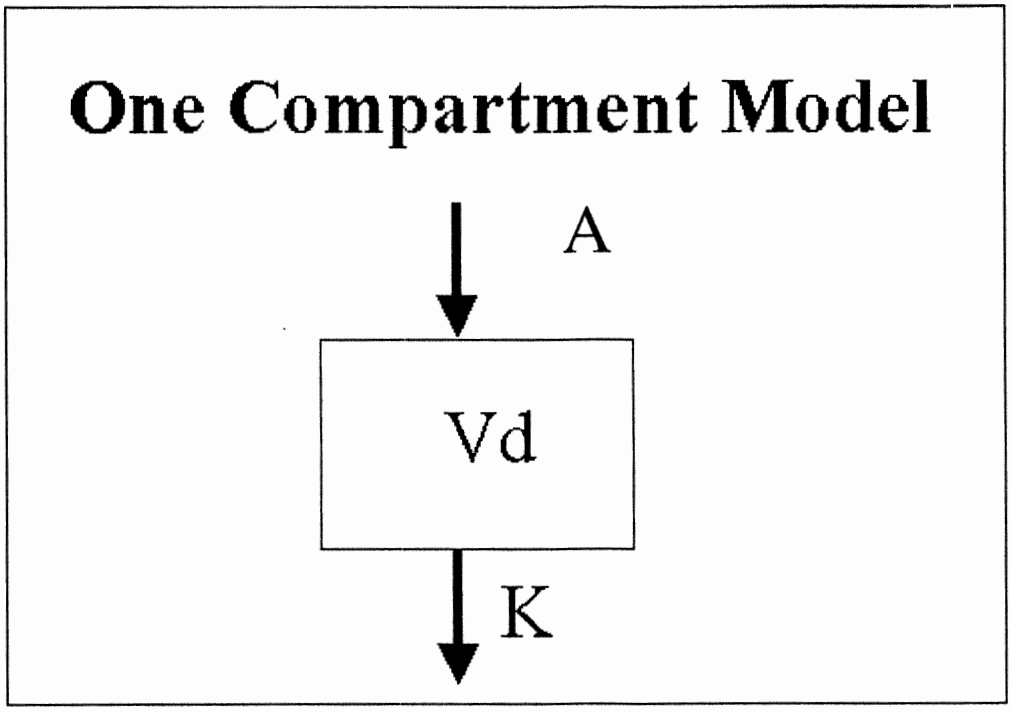
April 5 1999
Course 6.337 Berry

PHARMACOKINETICS is an essential study of how drugs are absorbed, metabolized and eliminated by the body over time. Without this type of analysis, the proper dosages and the management of drugs would not be as reliable as we need them to be. The main goal here is to obtain a therapeutic level of the drug in the patients body for a desired amount of time and therefor alleviate the ailment that plagues the patient.

Drugs can be administered in many different forms, some of which are intravenous administration, intramuscular, intranasal, intraarterial, and alas we cannot forget the most common type of self-administered drugs, orally! To keep it simple, I will only discuss one type of administration that is intravenous.

A drug administered by intravenous injection is also known as Bolus injection, where a high concentration of the drug is injected directly into the blood stream. In the one compartment open model with bolus intravenous injection, the drug administered is distributed rapidly throughout the body. The drug is eliminated by first order kinetics and the rate of loss of the drug from the body follows the Malthusian law and is given by

$$\mathbf{dA/dt = -kA}$$



- A is the amount of drug in the blood at time t after injection.
- k is the elimination rate constant for the drug.

Solving this equation by separating and then integrating will describe the time course of the amount of drug in the body after injection.

$$\int_{Ao}^{A} (1/A)\, dA = \int (-k)\, dt$$

$$\ln A/Ao = -k(t-to)$$

$$A(t) = Aoe^{(-k(t-to))}$$

assuming that to=0, the initial time that the first dose is administered at time t=0

$$A(t) = Aoe^{(-kt)}$$

To find out the concentration of drug in the plasma, right after administration we use the formula $C^{o}_{p} = Do/V_d$ where C^{o}_{p} is the concentration of drug in plasma

Do is the dose of drug given (mg), V_d is the volume of distribution of drug (L)

Every drug has a volume of distribution, which is dependent on such factors as:

- mass of the patient
- hydrophobicity or hydrophilicity of the drug
- amount of drug that is bound to proteins

explain

Generally speaking, the more lipophilic (hydrophobic) the drug is, the more it will bind to carrier proteins in the plasma, and the more it will concentrate in cells, giving it a greater volume of distribution.

Example

1. Dextrose(Glucose) - very hydrophilic, soluble in water

    - does not bind to plasma proteins very well

    V_d = 3L (mainly confined to plasma)

2. Imipramine(a tricyclic antidepressant) is very lipophilic (dissolves in tissues/lipid membranes and not in water) - binds very well to plasma proteins, V_d=2000L - concentrates greatly into cells

V_d is essential in helping to calculate blood levels of drugs in clinical studies, toxicology studies, overdose, etc. Also, generally the more that a drug is bound to plasma proteins, the longer its half life will be.

explain

Back to $A(t) = Aoe^{(-kt)}$, can be converted to concentrations by dividing by the distribution volume V_d to give

$$\mathbf{(A(t)/\ V_d\ ) = (Ao/\ V_d\ )e^{(-kt)}}$$

$$C(t) = Coe^{-kt}$$

where C is the concentration of the drug in the body, Co is the initial concentration of the drug at t=0. All the equation in terms of A can also be written in terms of the concentration, C, of drug in the blood.

ln C = ln Co -kt or logC = logCo - kt/2.303

The half life of the drug is used also to determine the value of k by the use of

$t_{1/2} = \ln 2/k$

so to estimate k we have **$k = \ln 2/t_{1/2}$**

The half life is found by finding the time it takes for the concentration **C=Co/2** in eqn7 we get **$k = \ln 2/t_{1/2}$**

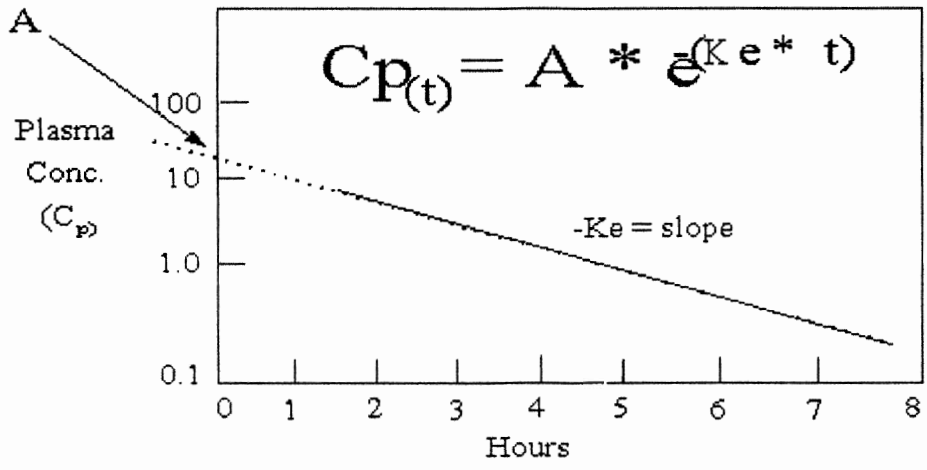
relationship between concentration C, volume V, and A amount of drug in blood is **A=VC** and gives

logC = logCo - kt/2.303

where Co is the drug concentration in plasma immediately after injection. If we plot logC versus time t we get a linear curve when plotted on logarithmic paper.

Co can be found by looking at the graph of logC Vs t. the y-intercept is Co, well actually the log of C, but sine the concentration values are plotted on log paper, the paper converts the actual values into log values.

One Compartment Model -- Plot



Obtained from intravenous data (in this case) is the area under the plasma level curve, AUC, integrating

$$C(t) = Coe^{-kt}$$

$$AUC = \int C = \int Coe^{-kt}\, dt = -Co/k\ (e^{-kt})|t=0..\infty$$

$$= -Co/k\ (e^{-k\infty} - e^{-k0}) = -Co/k\ (-1)$$

$$AUC = Co/k$$

The total area under the curve is the plasma concentration at time = 0, obtained by extrapolation, dividing the first order elimination rate constant k of the drug. This is also known as the bioavailability of the drug, the greater the value, the more available the drug is to the body.

ELIMINATION of a drug can be determined from urinary excretion data. This is only possible when some of the drug excreted is unchanged. Considering a drug being eliminated by both renal and non renal or biotransformation process leads to and elimination rate K where **K=kr+knr,**

- kr = constant rate for renal excretion
- knr = the sum of all the non renal elimination rate.

Let Au = amount of drug unchanged excreted through urine and Anr = the amount of drug eliminated through all non renal pathways.

The excretion rate of unchanged drug is **dAu/dt = krA**, A is amount of drug in the body at time t.

$$\mathbf{dAu/dt = kr\ A \rightarrow A=Ao\ e^{-kt}}$$

$$\mathbf{dAu/dt = kr\ Aoe^{-kt}}$$

separating and integrating both sides gives

$$\mathbf{Au = (kr/k)Ao\ e^{-kt}\ |t=0..t\ \ gives}$$

$$\mathbf{Au = (kr/k)\ Ao(1 - e^{-kt})} \quad \rightarrow \text{amount of drug in the urine at time t.}$$

The total amount of unmetabolized drug eliminated in the urine can be found by setting $t=\infty$ in the above equation to obtain

$$\mathbf{Au^{\infty} = (kr/k)\ Ao}$$

which can be substituted back into its original equation to obtain

$$\mathbf{Au = Au^{\infty}\ (1 - e^{-kt})}$$

which describes the continuous cumulative excretion of unchanged drug in the urine.

The amount of unmetabolized drug ultimately eliminated by the urine can be found by letting t approach ∞ infinity,

$$Au^{\infty} - Au = Au^{\infty} e^{-kt}$$

in log form $\log(Au^{\infty} - Au) = \log Au^{\infty} - kt/2.303$

Au^{∞}-Au is known as the amount of drug that has yet be excreted. This can also be given in terns of dosage given to the patient

$\log(Du^{\infty} - Du) = \log Du^{\infty} - kt/2.303$.

INTRAVENOUS INJECTION -drug concentration in plasma

Suppose a drug is administered intravenously at a constant rate, the change in the amount of drug in the body with respect to time is

$$dA/dt = R - kA$$

where R is the rate of drug infusion, amount per time. Solving this we obtain

$$\int (1/(R-kA))dA = \int dt$$

$$(-1/k)\ln|R - kA| = t + c1$$

$$\ln|R - kA| = -kt + c2$$

$$R - kA = e^{-kt} e^{c2} = Le^{-kt}, \text{ if we let } c2=L$$

$$\text{finally obtaining } A(t) = (R - Le^{-kt})/k$$

or by the use of Laplace transforms

$$sA = R/s - kA \rightarrow sA + kA = R/s$$

$A(s+k) = R/s \rightarrow A = R/s(s+k)$ using f(s) = A/s(s+a) and F(t) = A/a $(1-e^{-at})$

so we get $A = R/k\ (1 - e^{-kt})$

in terms of concentration

$$\mathbf{Cp= (R/V_dk) (1 - e^{-kt})}$$

this is the concentration of the drug in the plasma as time goes on indefinitely.

So we analyze Cp as t $\rightarrow\infty$ the term (e^{-kt}) $\rightarrow$ 0

so **Cp** $\rightarrow$ **$(R/V_dk)(1-0) = R/V_dk$** which is a constant.

This is known as the infusion equilibrium, at this concentration the

elimination rate = infusion rate and **dC/dt =0**, which is the steady state

concentration, **$Css= (R/V_dk)$**

the graph of log(Css-Cp)/Css versus time gives again a straight line with a slope of -k/2.303, the half life is once again ln2/k. K is the elimination rate constant which comes from dC/dt = -kC , solving this differential equation leads to

$$\mathbf{\int (1/dC)dC = -k\int dt}$$

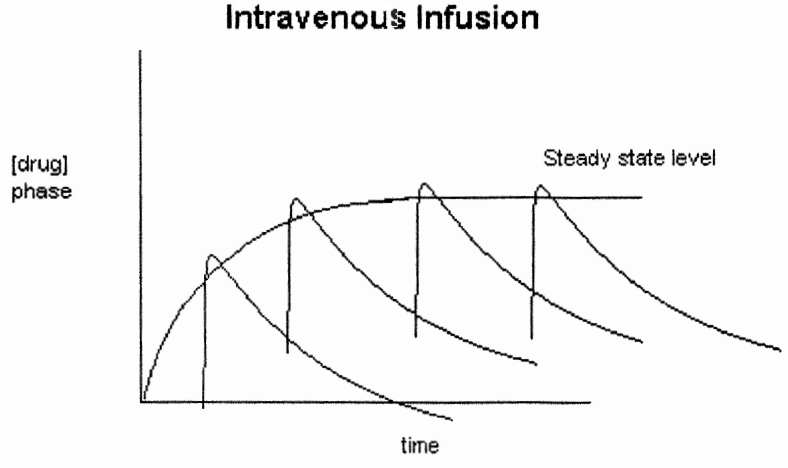
$$\mathbf{C = Coe^{-kt}}$$

where Co is the drug concentration in the plasma when infusion is stopped, i.e., the initial condition for the post infusion period, so let

Co = Cmax and **$C = Cmax*e^{-kt}$.**

INTRAVENOUS INFUSION

rate of input (infusion rate) = rate of output (elimination rate)



steady state dCp/dt =0

One compartment model drugs

$$\mathbf{dD_B/dt = R - kD_B}$$

R= infusion rate(zero order)

k = elimination rate (first order)

D_B = amount of drug in the body

at steady state $R - kD_B = 0$

$$\mathbf{Cp= (R/V_dk) (1 - e^{-kt})}$$

Examples:

1. We ultimately want to find the number of half lives that it will take to reach a certain percentage of Css.

Suppose that V_d = 10L , k=0.2hr^{-1} and we want Css=10μg/ml. How long will it take to reach Css when k changes?

First find R :

$R=Css*V_d*k$

$=10\mu g/ml(10000ml)(0.2hr^{-1}) = 20000\mu g/hr = 20mg/hr$

now k changes to k=0.1hr^{-1} and R=10mg/hr

How long does it take to reach Css when k changes?

$Css=R/V_d*k$ @ 99% of Css

$=99\%(R/V_dk) = (R/V_dk)(1-e^{-kt})$

$Cp=(R/V_dk)(1-e^{-kt})$ eqn26

$e^{-kt} = 1\%$ => $-kt = \ln 0.01$

$t_{99\%}= \ln 0.01/k = -4.61/(\ln 2/t_{1/2})$

$t_{99\%ss} = 6.65\ t_{1/2}$

at steady state

Number of half lives to reach a fraction of Css

% of Css reached	# of $t_{1/2}$
90	3.32
95	4.32
99	6.65

Calculating $t_{1/2}$ from infusions:

$Cp = (R/V_dk)(1-e^{-kt})$

$Css = R/V_dk$ → **$Cp = Css(1-e^{-kt})$**

$k = (-2.303/t)\log((Css-Cp)/Css)$

Example:

After the administration of a drug the ½ life of the drug in question is 3 to 6 hours, R = 15mg/hr. Blood is sampled at 8 and 24 hrs. Cp = 5.5 and 6.5mg/L. What is the ½ life of the drug in this patient.

$K = (-2.303/8)\log(-0.81) = 0.233$

$t\ ½ = 0.693/0.233 = 2.97$ hrs is the ½ life of the drug in this patient.

Example:

A patient is infused for 6hrs with drug X at R= 2mg/hr ($k=0.01hr^{-1}$, Vd = 10L)

Calculate Cp at 2hrs after stopping the infusion. t=8hrs, T=6hrs

$Cp = (R/V_dk)(1-e^{-kt})e^{-k(t-T)}$, T = time interval of infusion

t = total time of infusion (infusion + elimination times)

Plugging in the values into the equation leads to

Cp = 1.14μg/mL

INFUSION PLUS LOADING DOSE D_L

This is a method of administering a drug when it is desired to have immediate levels of concentration at steady state.

IV Bolus: $C1 = Coe^{-kt} = (D_L/V_d)\, e^{-kt}$ injection to get the concentration level in plasma in an effective therapeutic range.

Infusion: $C2 = (R/V_dk)(1-e^{-kt})$ infusion to maintain the level of drug in the body.

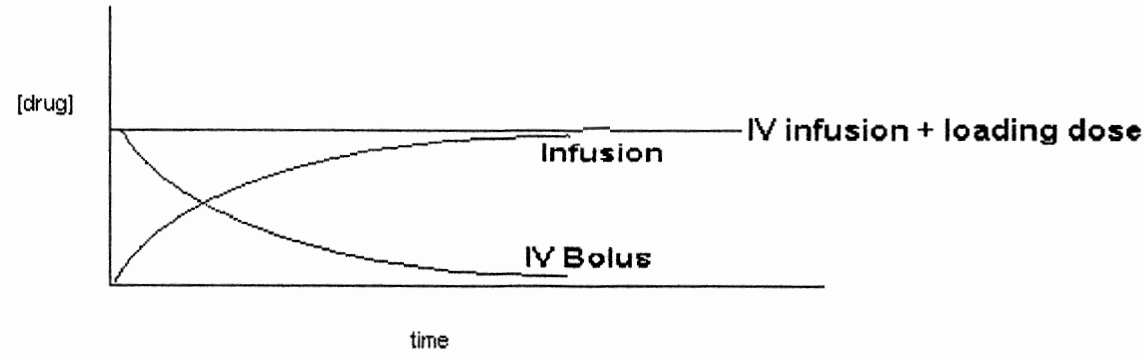
$$Cp = C1+C2$$

$$Cp = (D_L/V_d)\, e^{-kt} + (R/V_dk)(1-e^{-kt})$$

$$= (R/V_dk) + ((D_L/V_d)e^{-kt} - (R/V_dk)e^{-kt})$$

$$Cp = (R/V_dk)$$

IV Infusion plus Loding Dose



loading dose $D_L = R/k$

Example:

An anesthetic is administered at 2mg/hr by IV infusion: k =0.1hr^{-1} , Vd = 10L,

what is D_L?

At Cp = 2μg/mL,

D_L = R/k = (2mg/mL)/(0.1hr^{-1}) = 20 mg is the loading dose.

Example:

Find Cp at 6hrs after the loading dose (10mg) is given, and R=2mg/hr, t ½ = 3hrs, V_d = 10L.

Css=R/V_dk = (2000μg/hr) / [(10*10^3)(0.1)] = 2μg/mL

reach Cs instantly : D_L = R/k

k = (.693/3) = 0.231 hr^{-1}

Cp = (D_L/V_d) e^{-kt} + (R/V_dk)(1-e^{-kt})

Cp = (10000/10000) $e^{-0.231(6)}$ + (2000/10000*0.231)(1-$e^{-0.231(6)}$)

= 0.09μg/mL

MULTIPLE DOSE

Some drugs serve their purpose after just one dose, but often one dose is not enough to reach a desired effectiveness level. Most drugs are administered in a fixed dosage at a fixed time interval such as ever 4hrs or 3 times a day or every 8hrs. In this case no Css is present because of levels peaking and troughing with the time intervals.

If a drug is administered at a fixed time with a fixed dosage, it seems obvious that some of the drug will accumulate in the patients body. This however is

desirable within a certain extent. Most drugs have a range where the drug is most effective, this is called the therapeutic range of the drug. If the level of the drugs concentration in the plasma rises above this level, the patient can suffer severe organ damage due to toxicity. Our goal here is to find a safe level in the concentration of the drug in the plasma.

Let us assume that C=C(t) is the concentration of a drug into the plasma which is governed by the Malthusian law dC/dt = -kC, k is once again out elimination constant (k>0). Separating and integrating this equation leads to $C(t) = Co*e^{-kt}$, where Co is the initial concentration of the drug in the plasma at time t = 0, at C(to=0) = Co.

Keeping each dose administered to be of the same concentration as the initial Co, and if each injection is given at equal time intervals, T, at t = 0, T,2T,3T,... and so on. At each of these intervals the concentration of the drug is raised by the equal amount of Co.

Cn denotes the concentration of the drug in the plasma immediately after the nth dosage and Rn is the residual concentration of the drug in the plasma immediately after the (n+1)th dosage.

Concentration at time interval T	**Residuals at time T**
First interval:	
$\mathbf{C(t)=Co*e^{-kt}}$	$\mathbf{R_1 = C_o e^{-kt}}$
Second interval:	
$\mathbf{C_2 = R_1 + C_o}$	$\mathbf{R_2 = (R_1 + C_o)e^{-kT}}$

$C(t) = (R_1 + C_o)e^{-k(t-T)}$

Third interval:

$C_3 = R_2 + C_o$

$C(t) = (R_2 + C_o)e^{-k(t-2T)}$ $\qquad R_3 = (R_2 + C_o)e^{-kT}$

From this we see a pattern

$C_1 = Co$ $\qquad R_1 = C_o e^{-kt}$

$C_2 = R_1 + C_o$ $\qquad R_2 = (R_1 + C_o)e^{-kT}$

$= C_o e^{-kT} + C_o$ $\qquad = (C_o e^{-kT} + C_o)\, e^{-kT}$

$= C_o (e^{-kT} + 1)$ $\qquad = C_o (e^{-kT} + 1)\, e^{-kT}$

$C_3 = R_2 + C_o$ $\qquad R_3 = (R_2 + C_o)e^{-kT}$

$= C_o (e^{-kT} + 1)\, e^{-kT} + C_o$ $\qquad = C_o (1 + e^{-kT} + e^{-k2T})\, e^{-kT}$

$= C_o (1 + e^{-kT} + e^{-k2T})$

The pattern here is established for C_n, the concentration of the drug after n doses:

$C_n = C_o (1 + e^{-kT} + \ldots + e^{-k(n-1)T})$ $\qquad R_n = C_o (1 + e^{-kT} + \ldots + e^{-k(n-1)T})\, e^{-kT}$

$R_n = C_n e^{-kT}$

We would like to establish a safe tolerance concentration level, S, which is our therapeutic window, where the drug is effective.

If the concentration of the drug in plasma is above the desired peak levels the patient will endure toxicity. This is not known as a typical side effect because side effects occur often at normal concentration levels in plasma. To make sure that our patient does not suffer some sort of organ failure due to toxicity, we must find a time interval where the drug can be safely used for an indefinite amount of time and eliminated adequately to avoid excessive residual accumulation.

$S > C_o$ for S we want Cn and $\lim_{n \to \infty} Cn = S$. This is finding the maximum amount of Cn after $n \to \infty$ doses. $C_n = C_o(1 + e^{-kT} + \ldots + e^{-k(n-1)T})$ is a geometric series, therefor we obtain $C_n = C_o(1 + e^{-knT})/(1 - e^{-kT})$ which is the sum of the above geometric series.

$\lim_{n \to \infty} C_n = C_o/(1 - e^{-kT}) \leq S$, this level of concentration must be either less than or equal to S or our patient has the risk of organ failure due to toxicity.

$$C_o/S \leq (1 - e^{-kT}) \rightarrow (C_o/S) - 1 \leq (e^{-kT})$$

$$1 - (C_o/S) \geq (e^{-kT}) \rightarrow \ln(1 - (C_o/S)) \geq -kT$$

$$(-1/k)\ln(1 - (C_o/S)) \leq T$$

$$T_{min} = (-1/k)\ln(1 - (C_o/S))$$

This is the minimum amount of time between doses before a toxic level of the drug begins to accumulate.

ONE COMPARTMENT MODEL SCENARIO

The following is a scenario follows a one-compartment model, the goal here is to determine and adjust the patients dosage to attain an acceptable therapeutic window.

Question:

Bob is a 76 year old male patient, mass 95kg, admitted to the hospital for an acute myocardial infarction (sudden heart attack). He develops a fever and leukocytosis, and is diagnosed with and E.Coli pneumonia. His treatment is initiated on Gentamicin and Cefazolin. Recommend and initial Gentamicin dosage regimen to provide peak level of 8 - 10 mg/L and troughs < 1.5. At the recommended dosage, drug levels obtained pre and post third dose were 2.4 mg/L and 6 mg/L, respectively. What adjustment in dose would you make at this time? Note t ½ of Gentamicin = 2 - 4 hrs and V_d = 0.26L/kg

Solution:

We will use a standard dosing interval at first of 8 hrs, and a ½ life of 3 hrs because it is probably average for this 95kg male

Assumptions:

This person follows population kinetics, renal function and creatinine clearance is normal, protein binding is not a factor. Kinetics is not affected by concurrent administration of cefazolin.

Calculations:

We want our Cmax (peaks) to be 8 - 10 mg/L. We pick 8mg/L (lower dosage) because at higher peaks the dose administered can get quite toxic is some cases. Toxic levels are 10 - 12 mg/L, if at these levels for a good length of time. We want out Cmin (troughs) to be 1.5 mg/L or less.

$k = 0.693/t\ ½ = .693/3hrs = 0.231\ hr^{-1}$

$V_d = 0.26L/kg\ (95kg) = 24.7L$

$f = e^{-kt} = e^{-0.231*8} = 0.158$

Peak

$Cmax = Dmax/V_d$

therefore $Dmax = Cmax*(V_d) = 8mg/L(24.7L)$, $Dmax = 197.6mg$

also $Dmax = Do/(1 - f)$

so $Do = Dmax(1-f) = 197.6mg(1-0.158) = 166mg\ q8h$

$Do = 166mg$ every 8 hrs

Trough

$Cmin = Dmin/V_d$

therefore $Dmin = Cmin*V_d = 1.5mg/L(274.7L)$, $Dmin = 37.05mg$ or less

To check:

$Dmin = Dmax - Do = 197.6mg - 166.4\ mg$

$Dmin = 31.2mg$ (safe trough)

This is equivalent to 31.2mg/24.7L = mg/L, which is well below the desired trough level of 1.5mg/L. Therefore we would give Bob a dose of 166mg every 8 hours of gentamicin (which is 5.24 mg/kg/day - a high enough level for worrying about ototoxicity and nephrotoxicity - deafness and kidneys shutting down). Normal dosing levels for a life threatening infection can be up to 5mg/kg/day, divided into two or three doses (CPS 1997).

The second part of this question states that with the present dosing regimen, we are getting a trough of only 2.4 mg/L after the third dose. From the information given, we have concluded that the amount he is getting now is not enough to get him up to desired peak levels, and he is not clearing enough to get him up to desired trough levels that we want. We have hypothesized from this fact that his V_d is greater than we had expected, because a 166mg dose is raising his plasma levels by only 3.6mg/L instead of the 6.74mg/L that we had calculated. We can also factor in the probabilities that his renal function is lower, so that could help explain the higher than desired troughs. This can also cause the t ½ life of gentamicin to go up, since:

$C_{LT} = V_dk = V_d(0.693/t\ ½)$ → this is concentration of the drug cleared through the tissue , therefore as C_{LT} decreases, k decreases, and t ½ would increase.

To make sure that renal toxicity does not occur, this may be a problem, we will increase the dosage to distribute more into his increased V_d and get our peaks back up to 8mg/L and decrease the dosing frequency to every 12 hrs to allow for more clearance and lower troughs. Assume a t ½ of 4 hrs now. (this will help

lower already high doses being given as well as help account for the low renal function)

Assumptions:

To do the next part we have to make the following assumptions:

- This person is now not following population kinetics (his volume of distribution is now thought to be greater than normal)
- the renal clearance is probably depressed (but since we have no data that describe this, we cannot find any urinary excretion data, C_{LT} or a possible new t ½ for gentamicin)
- any other assumptions listed in the first part of this question

Calculation:

New V_d = Do/Cp, Do = 166mg given,

Cp = 3.6mg/L resulted

V_d = 166g/L = 46.1L

k = 0.693/4 hrs = 0.173 hr^{-1}

$f = e^{-kt} = e^{-0.173*12} = 0.125$

Peak

$C_{max} = D_{max}/V_d$

therefore $D_{max} = C_{max}*(V_d)$ = 8mg/L(46.1L) , Dmax = 368.8mg

also $D_{max} = D_o/(1 - f)$

so $D_o = D_{max}(1-f)$ = 368.8mg(1-0.125) = 322.7mg q12h

Do = 322.7mg every 12 hrs

Trough

$C_{min} = D_{min}/V_d$

therefore $D_{min} = C_{min} * V_d$ = 1.5mg/L(46.1L),

D_{min} = 69.15mg or less

To check:

$D_{min} = D_{max} - D_o$ = 197.368.8mg - 322.7 mg

D_{min} = 46.1 mg (safe trough)

This is equivalent to: 46.1mg/46.1L = 1.0 mg/L, well below our desired mark of 1.5mg/L. Therefore, we will administer this man a dose of 323mg every 12 hours of gentamicin in order to get our desired levels. This is equivalent to a dose of 6.8mg/kg/day, which is a very high, if not toxic, dose of gentamicin.

We can generalize the idea of compartmental models in Pharmacokinetics by comparing the body to sinks or tanks. In a one compartment model, the substance, or the drug in our case, is just stirred in the sink. The single compartment has input, the injection, from the outside and output to the outside, urinary excretion. The output will always be proportional to the concentration of the drug in the sink.

The equation $x'(t) + kx(t) = f(t)$ for $t>0$ describes the stirred sink reaction. Initial conditions for this are $x(0)=a$. The decay constant is $k>0$, this is how quickly the drug is eliminated from the sink. The use of Laplace transforms $X(s) = L\{x(t)\}$ to solve this ODE this gives us

$L\{x'(t)\} + kL\{x(t)\} = L\{f(t)\}$

$sX(s)-x(0)+kX(s)=F(s)$

substituting $x(0) = a$ and solving for $X(s)$ gives us

$$X(s) = \frac{F(s) + a}{(s+k)}$$ where a and F(s) are known values.

Invert the transform to obtain the solution of x(t)

$x(t) = L^{-1}\{X(s)\} = L^{-1}\{ (F(s) + a)/(s+k)\} + L^{-1}\{a/(s+k)\}$

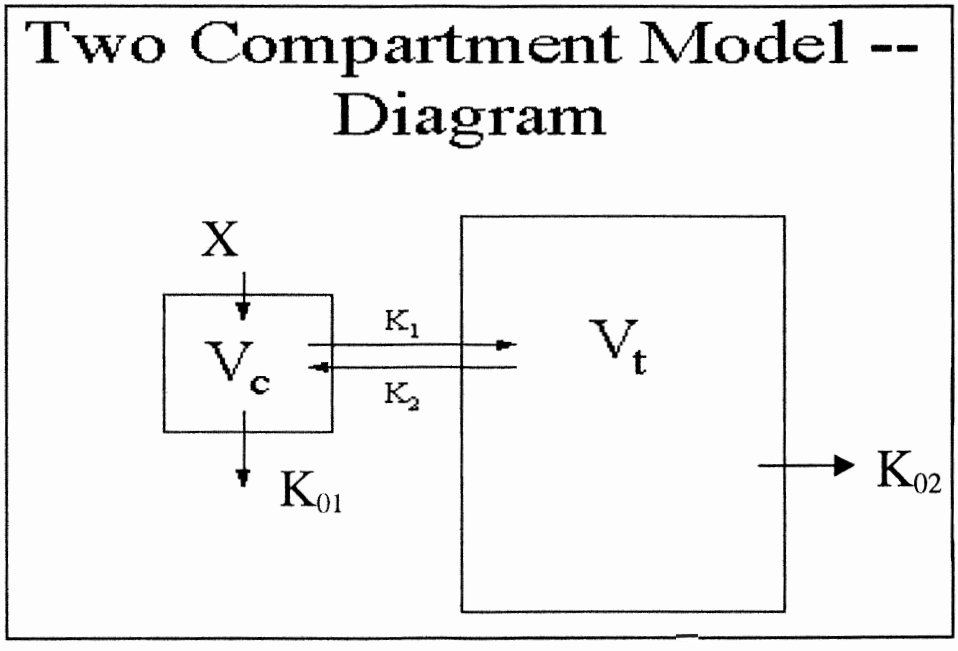
using this we then obtain $x(t) = ae^{-kt} + \int e^{-k(t-y)}f(y)dy$ the first part of this shows the effects of the initial condition, the second part of this equation reflects the effect of the input.

If we were to take a=0 the transform of the solution would become

X(s) = (1/(s+k)) F(s) = G(s)F(s), where G(s) is just (1/(s+k)) the transform of the input and F(s) is related to the transform of the output, X(s).

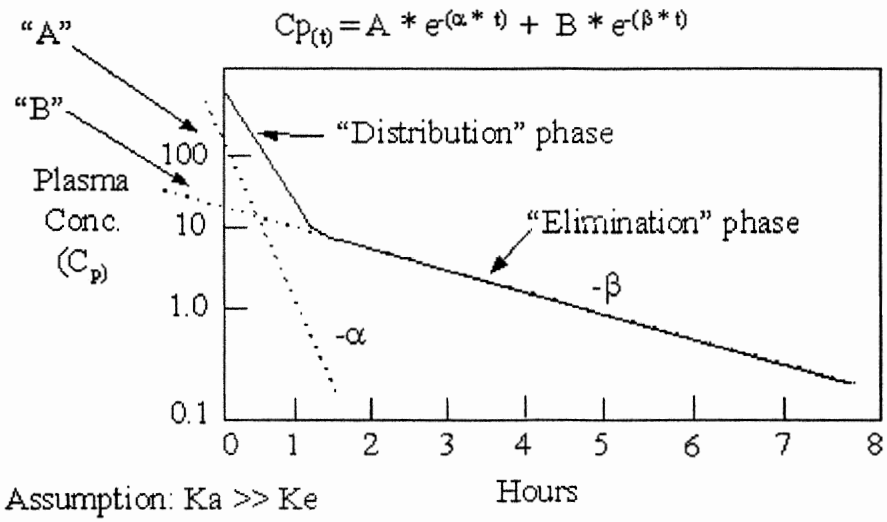
Suppose we have N compartments, somehow linked to each other, we can have 2 compartments liked to one another and both can have input functions and output functions, in other words the sinks both may eleminate some of the drug at a constant rate. The two sinks themeselves also have a constant rate of transfer between them.

Let k_{12} denote the flow into compartment 1 and out of 2, and k_{21} is into 2 and out of 1.

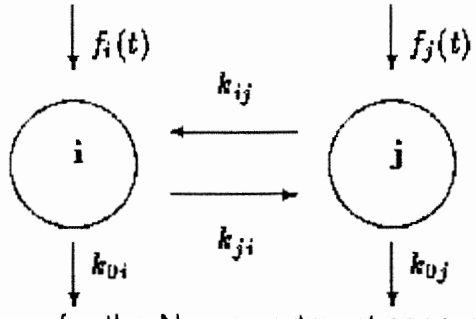


Let k_{01} denote the flow from compartment 1 to the outside, and the flow of substance out from 2 to the outside is denoted as k_{02}.

Two Compartment Model -- Plot



Two compartment general "sinks"



In the general ij case for the N compartment case, where $x_i(t)$ is the amount of substance in compartment i at time t, and T is the time interval between the change in $x_i(t)$

$$x_i(t+T) \approx xi(t) - \sum_{j=0}^{N} kijXiT + \sum_{j=1}^{N} kijXiT + fi(t)\cdot T \qquad \text{where } j \neq i \quad \text{for } 1 < i < N.$$

flow out of i flow into i

By rearraging the equation and dividing through by T, and taking the limit as $T \to \infty$ we obtain the ODE

$$x'(t) = -xi\cdot \sum_{j=0}^{N} kij + \sum_{j=1}^{N} kij\cdot xi + fi(t) \qquad \text{for } 1 < i < N$$

let $k_{ii} = -\sum_{j \neq i} k_{ji}$, $k_{ii} < 0$. Then x becomes the N-vector $(x_1, x_2, \ldots, x_N)^T$ and let f be the N-vector $(f_1, f_2, \ldots, f_N)^T$. The system of N ode's can written in matrix notation $x'(t) = \Lambda x(t) + f(t)$ where k_{ij} are the entries of matrix Λ. We can solve this using laplace transforms.

$(sI - \Lambda)X(s) = F(s) + a$

$X(s) = (sI - \Lambda)^{-1}F(s) + a(sI - \Lambda)^{-1}$ let 's look at this when a=0, this equation takes the form as one we have seen on the previous page where $G(s) = (sI - \Lambda)^{-1}$, the transfer matrix in this case.

This inverse matrix can be defined as $(sI - \Lambda)^{-1} = adj(sI - \Lambda)/det(sI - \Lambda)$

$det(sI - \Lambda)$ is the Nth degree polynomial of Λ, the roots of this are the eigenvalues, $\lambda_{1,\ldots,}\lambda_N$, of Λ.

The following equations can be derived from the above generalizations.

for a 2 compartment mode we have

$a+b = k_{12} + k_{21} + k$ → k is sometimes denoted as k_e.

$$C_p = Ae^{-at} + Be^{-bt}$$

$$A = \frac{D^\circ (a - k_{21})}{V_p(a-b)} \quad , \quad B = \frac{D^\circ (k_{21} - b)}{V_p(a-b)}$$

$$\frac{dC_t}{dt} = \underbrace{k_{12} C_p}_{\text{in.}} - \underbrace{k_{21} C_t}_{\text{out}}$$

$$C_p = \frac{D_p}{V_p} \qquad C_t = \frac{D_t}{V_t}$$

$$\frac{dC_p}{dt} = \underbrace{k_{21} \frac{D_t}{V_t}}_{\text{in}} - \underbrace{k_{12} \frac{D_p}{V_p} - k \frac{D_p}{V_p}}_{\text{out}}$$

$$\frac{dC_t}{dt} = k_{12} \frac{D_p}{V_p} - k_{21} \frac{D_t}{V_t}$$

$$C_p = \frac{D_p^\circ}{V_p} \left[\underbrace{\frac{a - k_{21}}{a-b} e^{-at}}_{\text{distribution phase}} + \underbrace{\frac{k_{21} - b}{a-b} e^{-bt}}_{\text{elimination phase}} \right]$$

$$C_t = \frac{D_p}{V_t} \left[\frac{k_{12}}{b-a} e^{-at} + \frac{k_{12}}{a-b} e^{-bt} \right]$$

$$K = \frac{ab(A+B)}{Ab+Ba} \quad , \quad k_{12} = \frac{AB(b-a)^2}{(A+B)(Ab-Ba)}$$

$$k_{21} = \frac{Ab+Ba}{A+B} \quad , \quad t_{1/2} = \frac{\ln 2}{b}.$$

Woks Cited

Gibaldi, M and Perrier D. Pharmacokinetics 2nd edition. Marcel Dekker Inc. New York 1982.

Wagner,J.G A safe method for rapidly achieving plasma concentration plateaus. Eur. J. Clinical. Pharmacology. 10:433(1976)

Lloyd, B et al. Pharmacokinetics and bioavailability of digoxin capsuls, solution and tablets after single and multiple doses. Am. J. Cardoilogy 42:129 (1978)