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Non-Linear Pharmacokinetic Models

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Student Objectives for this Chapter

- To draw the scheme and write the differential equations for compartmental pharmacokinetic models with non-linear metabolism elimination
- To understand the process of parallel pathways as it applies with one or more non-linear pathways
- To define and use the parameters Vm and Km
- To design and calculate appropriate dosage regimens when non-linear pharmacokinetics apply

All of the rate processes discussed so far in this course, except for the infusion process, follow first order kinetics. In particular the elimination process has been assumed to follow first order kinetics. In practice, occasionally it is observed that the elimination of a drug appears to be zero order at high concentrations and first order at low concentrations. That is 'concentration' or 'dose' dependent kinetics are observed. At higher doses, which produce higher plasma concentrations, zero order kinetics are observed, whereas at lower doses the kinetics are linear, that is first order.

This occurs especially with drugs which are extensively metabolized. A typical characteristic of enzymatic reactions and active transport is a limitation on the capacity of the process. There is only so much enzyme present in the liver, and therefore there is a maximum rate at which metabolism can occur. A further limitation in the rate of metabolism can be the limited availability of a co-substance or co-factor required in the enzymatic process. This might be a limit in the amount of available glucuronide or glycine, for example.

Most of our knowledge of enzyme kinetics is derived from *in vitro* studies where substrate, enzyme, and co-factor concentrations are carefully controlled. Many factors are involved *in vivo* so that each cannot be easily isolated in detail. However, the basic principles of enzyme kinetics have application in pharmacokinetics.

Dose dependent pharmacokinetics can often be described by Michaelis-Menten kinetics with the RATE of elimination approaching some maximum rate, Vm.

$$\text{The rate of metabolism } = \frac{Vm \bullet Cp}{Km + Cp}$$

Equation 21.1.1 Rate of Change for a Saturable Process

with Km a Michaelis-Menten constant. Km is the concentration at which the rate of metabolism is half the maximum rate, Vm

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References

- Table 14-1 Shargel, L. and Yu, A.B.C. 1985 **Applied Biopharmaceutics and Pharmacokinetics**, 2nd ed., Appleton-Century-Crofts, Norwalk, CT p254

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Scheme or Diagram

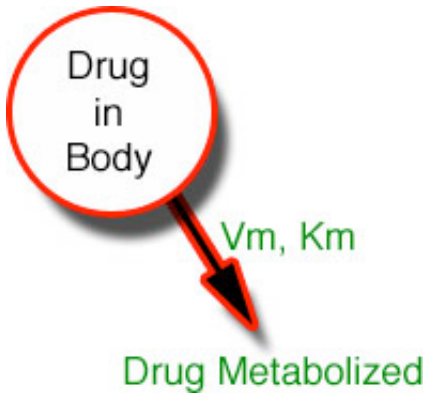

Diagram 21.2.1 Scheme for One Compartment Model with Michaelis-Menten Elimination

We can use Diagram 21.2.1, when M-M kinetics is included in a one compartment pharmacokinetic model as the only the route of elimination.

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Differential Equation

An equation for the rate of change of drug concentration with time can be derived using the techniques from Chapter 2, Writing Differential Equations.

$$\frac{dCp}{dt} = -\frac{Vm \bullet Cp}{Km + Cp}$$

Equation 21.3.1 Rate of Change of Drug Concentration with Time

Keeping track of units becomes even more important with non linear kinetics. In equation 21.3.1 the units for Vm are amount.volume^{-1}.time^{-1} for example mg.L^{-1}.day^{-1}. Another approach is to derive the equation for the rate of change of drug amount with time.

$$\frac{dX}{dt} = -\frac{Vm \bullet Cp}{Km + Cp}$$

Equation 21.3.2 Rate of Change of Drug Amount with Time

Equation 21.3.2 looks the same as Equation 21.3.1. The difference is the dX/dt on the left and the units for Vm on the right. The units for Vm are the same as dX/dt, i.e. amount.time^{-1} for example mg/day.

Dividing the rate of elimination (metabolism) by the drug concentration provides a value for the drug clearance.

$$Clearance = CL = \frac{dX/dt}{Cp} = -\frac{Vm \bullet Cp}{Km + Cp} \bullet \frac{1}{Cp} = -\frac{Vm}{Km + Cp}$$

Equation 21.3.3 Non linear Equation for Clearance

Notice that Equation 21.3.3 includes a concentration term on the right hand side (in the denominator). Clearance is not constant but varies with concentration. As the concentration increases we would expect the clearance to decrease. Calculations based on an assumption of constant clearance, such as the calculation of AUC are no longer valid. A simple increasing of dose becomes an adventure. No longer can we increase the dose by some fraction, for example 25%, and expect the concentration to increase by the same fraction. The calculations are more complex and must be done carefully.

It is not possible to integrate Equation 21.3.1 but by looking at low and high concentrations we can get some idea of the plasma concentration *versus* time curve.

Low Cp approximation to first order

At low concentrations, where Km > Cp, Km + Cp is approximately equal to Km

$$\text{therefore } \frac{dCp}{dt} = -\frac{Vm \bullet Cp}{Km + 0} = -\frac{Vm}{Km} \bullet Cp = -k' \bullet Cp$$

where the Vm/Km is a constant term and the whole equation now looks like that for first order elimination, with Vm/Km a pseudo first order elimination rate constant, k'.

Therefore at low plasma concentrations we would expect first order kinetics. Remember, this is the usual situation for most drugs. That is any Km is usually larger than the therapeutic plasma concentrations.

High Cp approximation to zero order

For some drugs, higher concentrations are achieved, that is Cp > Km, then Km + Cp is approximately equal to Cp.

$$\text{therefore } \frac{dCp}{dt} = -\frac{Vm \bullet Cp}{0 + Cp} = -\frac{Vm \bullet Cp}{Cp} = -Vm$$

and we now have zero order elimination of drug, that is the rate of elimination is INDEPENDENT of drug concentration (remaining to be eliminated). At high plasma concentrations we have zero order or concentration independent kinetics.

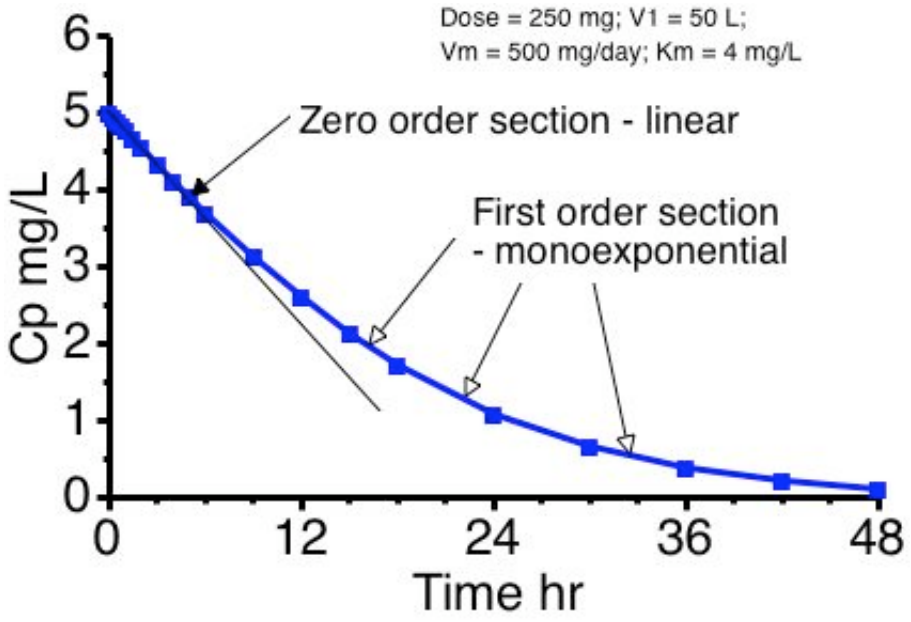

Figure 21.3.1 Linear Plot of Cp Versus Time Showing High Cp and Low Cp - Zero Order and First Order Elimination

Click on the figure to view the Java Applet window

In Figure 21.3.1 at high Cp, in the zero order part, the slope is fairly constant (straight line on linear graph paper) and steeper, that is, the rate of elimination is faster than at lower concentrations. [However, the apparent rate constant is lower. This is easier to see on the semi-log graph in Figure 21.3.2.]

At higher concentrations the slope is equal to -Vm. At lower concentrations we see an exponential decline in plasma concentration such as we see with first order elimination.

On semi-log graph paper we can see that in the zero order region the slope is more shallow, thus the rate constant is lower. The straight line at lower concentrations is indicative of first order kinetics.

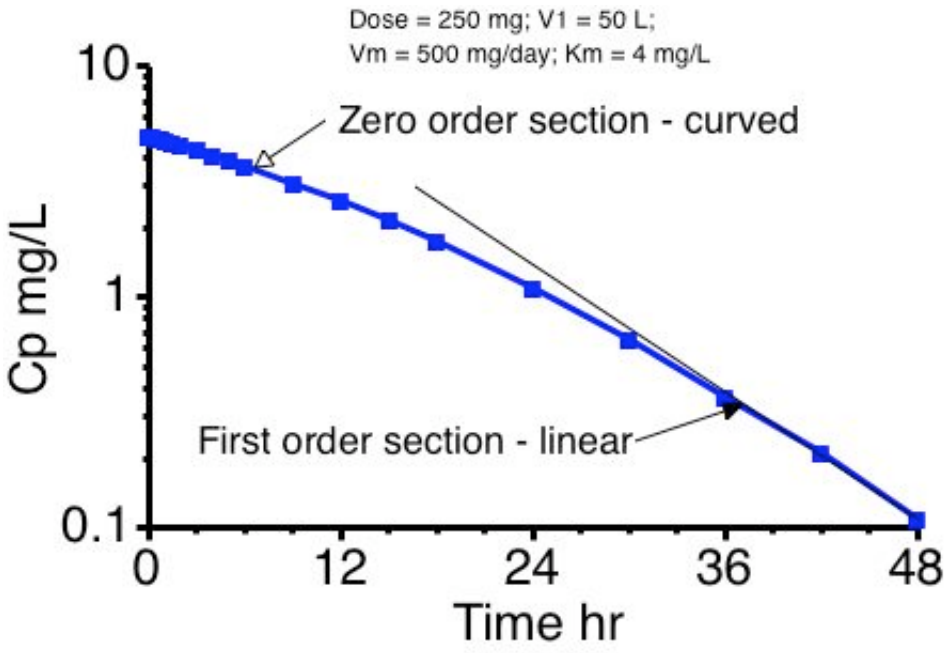

Figure 21.3.2 Semi-Log Plot of Cp Versus Time Showing High Cp and Low Cp

Click on the figure to view the Java Applet window

Another way to use or look at Figure 21.3.2 is to consider the slope of the line as a measure of a psuedo first order rate constant, k'. If we start with Equation 21.3.2 since this includes Vm with the more usual units of amount/time (mg/day) we can derive equation Eq 21.3.4 for this psuedo first order rate constant.

$$\frac{dX}{dt} = \frac{V \bullet dCp}{dt} = -k' \bullet V \bullet Cp = -\frac{Vm \bullet Cp}{Km + Cp}$$

$$k' = \frac{Vm}{V \bullet (Km + Cp)}$$

Equation 21.3.4 Psuedo First Order Rate Constant

As for the clearance described earlier (Equation 21.3.3) this pseudo rate of elimination changes with concentration. As the concentration increases the elmination process slows down. We can take this one step further by looking at a 'half-life' for the elimination.

$$t_{1/2} = \frac{0.693 \bullet V}{Vm} \bullet (Km + Cp)$$

Equation 21.3.5 Psuedo Half life for Elimination

Earlier when we talked about linear kinetics we talked about the time it takes to get to steady state concentrations. With linear kinetics this time was independent of concentration and could be calculated as 3, 4 or 5 half-lives. With non-linear kinetics, this time will increase with concentration just as this psuedo half-life increases with concentration. This is very important later when we use steady state concentrations to make parameter estimates. If we don't wait long enough our determination of steady state concentration will be in error and so will the parameter estimates. This time to steady state might change from a few days to weeks as the dose is increased.

Averaging Equation 21.3.1 over a dosing interval at steady state where the dose is equal to the drug metabolized during the interval leads to Equation 21.3.6

$$Dose = \frac{Vm \bullet \overline{Cp}}{Km + \overline{Cp}}$$

Equation 21.3.6 Dose Required to Achieve an Average Concentration

Rearrangement of Equation 21.3.6 to solve for $Cp_{average}$ can be used to illustrate the problem of arbitrarily increasing the dose for a drug that exhibits non linear, Michaelis-Menten (MM), kinetics.

$$\overline{Cp} = \frac{Dose \bullet Km}{Vm - Dose}$$

Equation 21.3.7 Average Concentration at Steady State

The presence of saturation kinetics can be quite important when high doses of certain drugs are given, or in case of over-dose. In the case of high dose administration the effective elimination rate constant is reduced and the drug will accumulate excessively if saturation kinetics are not understood.

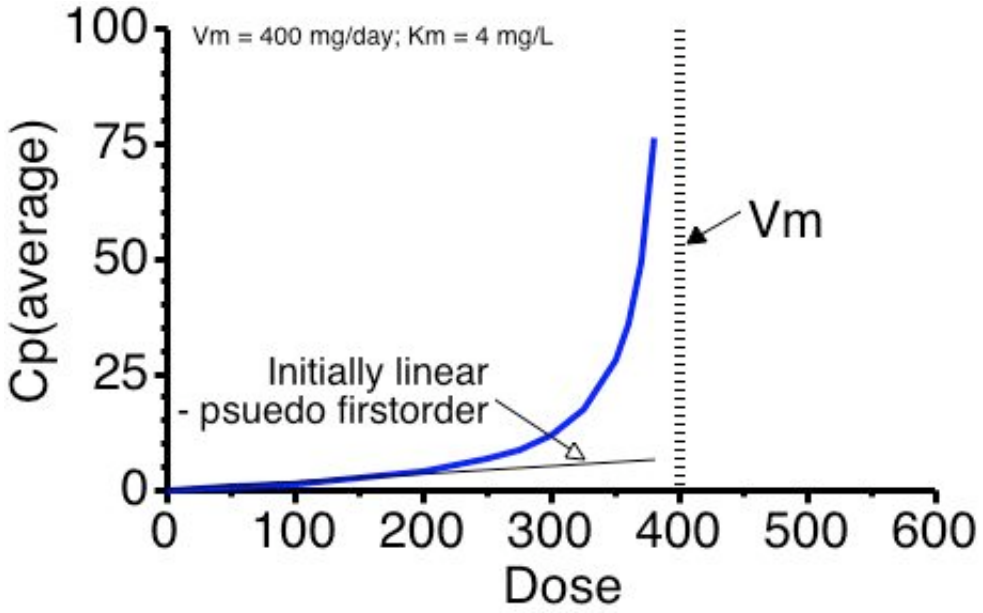

Figure 21.3.3 Linear Plot of $Cp_{average}$ Versus Dose Per Day

Click on the figure to view the Java Applet window

Phenytoin is an example of a drug which commonly has a Km value within or below the therapeutic range. The average Km value about 4 mg/L. The normally effective plasma concentrations for phenytoin are between 10 and 20 mg/L. Therefore it is quite possible for patients to be overdosed due to drug accumulation. At low concentration the apparent half-life is about 12 hours, whereas at higher concentration it may well be much greater than 24 hours. Dosing every 12 hours, the normal half-life, can rapidly lead to dangerous accumulation. At concentrations above 20 mg/L elimination maybe very slow in some patients. Dropping for example from 25 to 23 mg/L in 24 hours, whereas normally you would expect it to drop from 25 -> 12.5 -> 6 mg/L in 24 hours. Typical Vm values are 300 to 700 mg/day. These are the maximum amounts of drug which can be eliminated by these patients per day. Giving doses approaching these values or higher would cause dangerous accumulation of drug. Figure 21.3.3 is a plot of $Cp_{average}$ versus dose calculated using Equation 21.3.7.

Calculator 21.3.1 Calculate $Cp_{average}$ with Non-linear Elimination

Dose Rate:	350
Km:	5.0
Vm:	500
	Calculate
$Cp_{average}$ is:	

Error Message Value is not a numeric literal probably means that one of the parameter fields is empty or a value is inappropriate.

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Parallel Pathway

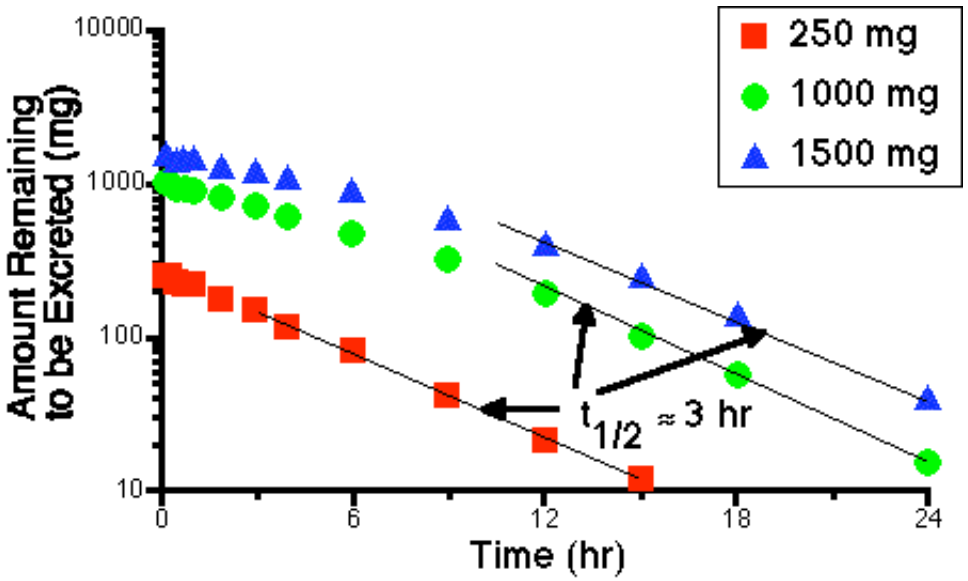

Figure 21.4.1 Plot of Salicylate Amount in the Body Versus Time. Similar $t_{1/2}$ at Lower Concentrations Only (Levy, 1965)

Another drug with saturable elimination kinetics is aspirin or maybe more correctly salicylate. In the case of aspirin or salicylate poisoning the elimination maybe much slower than expected because of Michaelis-Menten kinetics as shown in Diagram 21.4.1.

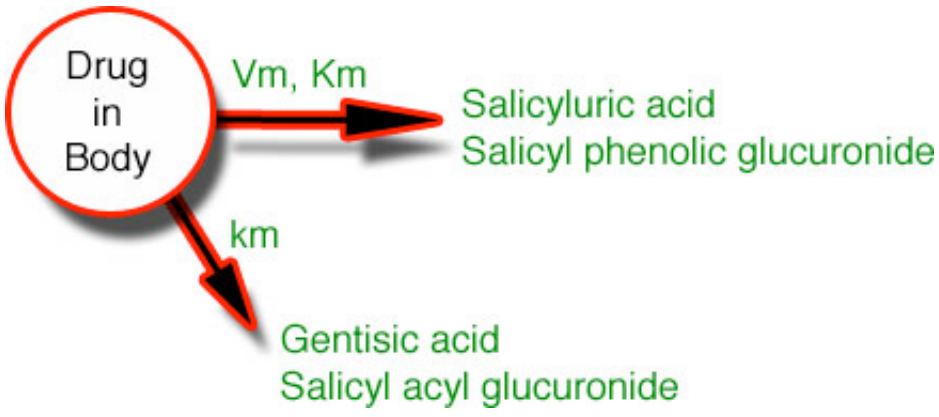

Diagram 21.4.1 Scheme for Aspirin/Salicylate Elimination

In the case of aspirin we have parallel first order process with the Michaelis-Menten kinetics. Therefore as dose and consequently the concentrations increase proportionally more drug would be removed by the first order processes rather than the saturable one. This is shown in the figure below (Figure 21.4.2).

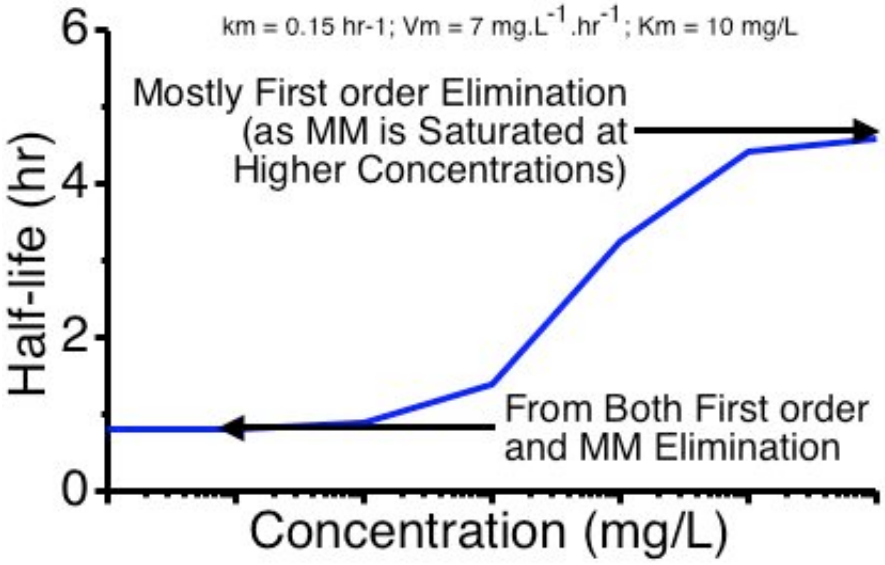

Figure 21.4.2 Plot of Apparent $t_{1/2}$ Versus log(DOSE) (Niazi, 1979)

The phenomena of non-linear pharmacokinetics is of great importance in multiple dose therapy in which more significant changes in the plateau levels are produced by the accumulation of drug in the body than can be expected in single dose studies. This accumulation will result in toxic responses especially when the therapeutic index of the drug is low.

References

- Levy, G. 1965. *J. Pharm. Sci.,* **54**, 959
- Niazi, S. 1979 **Textbook of Biopharmaceutics and Clinical Pharmacokinetics**, Appleton-Century-Crofts, New York, NY, Fig 7.14 p 181

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Dosing Approaches

First dose

One approach is to use the population values for Vm and Km. For phenytoin we would use the population values of Vm = 7 mg/kg/day and Km = 5 mg/L. Aiming at 15 mg/L for $Cp_{average}$ with a patient weight of 80 kg Equation 21.5.1. can be used to estimate the 'first' dose.

$$Dose_1 = \frac{Vm \bullet \overline{Cp_1}}{Km + \overline{Cp_1}} \text{ AND } Dose_2 = \frac{Vm \bullet \overline{Cp_2}}{Km + \overline{Cp_2}}$$

Equation 21.5.1 Dosing Rate versus $Cp_{average}$

$$Dose = \frac{Vm \bullet \overline{Cp}}{Km + \overline{Cp}} = \frac{7 \times 80 \times 15}{(5 + 15)} = 420 \text{ mg/day}$$

Probably better to start out low since toxicity is more probable above 20 mg/L.

Second dosing regimen

That is after giving a continuous dose regimen to steady state, measure plasma concentration and adjust dose. For example if after 420 mg/day, $Cp_{average}$ is 20 mg/L then a downward adjustment would be necessary. If we assume that the Km is close to the average value of 5 mg/L we can estimate Vm from the equation above

$$Vm = Dose + \frac{Dose \bullet Km}{\overline{Cp}} = 420 + \frac{420 \times 5}{20} = 420 + 105 = 525 \text{ mg/day}$$

thus a new dose rate can be calculated

$$Dose = \frac{Vm \bullet \overline{Cp}}{Km + \overline{Cp}} = \frac{525 \times 15}{5 + 15} = 394 \text{ mg/day}$$

approximately 400 mg/day. **Note**: A reduction in dose of 20 mg/day (5 %) is calculated to give a 5 mg/L change (25 %) in $Cp_{average}$.

Another approach at this point could be the use of the "Orbit Graph" method described by Tozer and Winter, 1992, redrawn from Vozeh, S. 1981. This method uses data previously derived from a patient population to construct shapes, orbit representing 50, 75, 90,95 and 97.5% of the population values of Vm and Km. Plotting this information with one data point allows the estimation of a

second doing regimen.

Third dosing regimen

If we already have two steady state plasma concentrations after two different dose rates we can solve Equation 21.5.1 for the two parameters, Vm and Km. This assumes that the patient is fully compliant.

$$Dose_1 = \frac{Vm \bullet \overline{Cp_1}}{Km + \overline{Cp_1}} \text{ AND } Dose_2 = \frac{Vm \bullet \overline{Cp_2}}{Km + \overline{Cp_2}}$$

using simultaneous equations.

With $Cp_{average,\ 1}$ = 8.0 mg/L and $Cp_{average,\ 2}$ = 27.0 mg/L for R1 = 225 mg/day and R2 = 300 mg/day

$$225 = \frac{Vm \bullet 8}{Km + 8} \text{ and } 300 = \frac{Vm \bullet 27}{Km + 27}$$

225 • Km + 225 • 8 = 8 • Vm (1)

and

300 • Km + 300 • 27 = 27 • Vm (2)

or multiplying (1) x 300

300 • 225 • Km + 300 • 225 • 8 = 300 • 8 • Vm (3)

and multiplying (2) x 225

300 • 225 • Km + 300 • 225 • 27 = 225 • 27 • Vm (4)

subtracting (4) - (3)

300 • 225 • (27 - 8) = (225 • 27 - 300 • 8) • Vm

$$Vm = \frac{1282500}{3675} = 349 \text{ mg/day}$$

and

$$Km = \frac{8 \bullet Vm - 225 \bullet 8}{225} = \frac{992}{225} = 4.4 \text{ mg/L}$$

With these Vm and Km values we can now calculate a new, better dosing regimen.

Calculator 21.5.1 Calculate Vm and Km from Two Steady State $Cp_{average}$ Values

First Dose Rate:	225
First Average Cp:	8.0

Second Dose Rate:	300
Second Average Cp:	27
	Calculate
Km is:	
Vm is:	

Error Message Value is not a numeric literal probably means that one of the parameter fields is empty or a value is inappropriate.

Graphical methods

There are a number of graphical methods which have been described for when you have data from two or more dosing intervals. Basically these rely on converting the equations mentioned above into a straight line form which can be plotted to give the Vm and Km as a function of the intercept and/or slope. Again, steady state, average concentrations are required with the patient fully compliant. Some of these methods have been reviewed by Mullen and Foster, 1979. They found that iterative computer analysis was the best method, followed by a plot of $Cp_{average}$ versus $Cp_{average}$/Dose (Equation 21.5.2), and this was followed by a direct linear plot method. Since the direct linear plot method was the least complicated and required no calculations these authors thought it should be quite useful.

$$\overline{Cp} = Vm \bullet \frac{\overline{Cp}}{Dose} - Km$$

Equation 21.5.2 Equation for $Cp_{average}$ versus $Cp_{average}$/Dose

Direct Linear Plot Method

This method, described by Mullen, 1978, involves plotting Dose and $Cp_{average}$ data points on linear graph paper. The y-axis represent Dose and Vm while the x-axis represents Km in the positive direction and $Cp_{average}$ in the negative direction. This is shown in Figure 21.5.1.

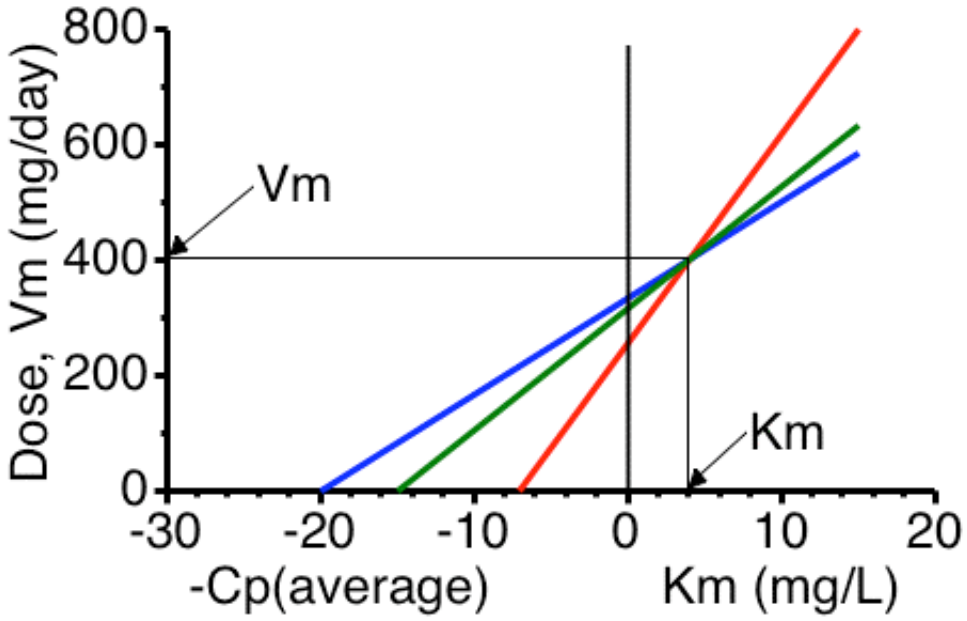

Figure 21.5.1 Linear plot of Dose, Vm versus Km, $Cp_{average}$

After a dose of 256 mg/day and 333 mg/day the steady state $Cp_{average}$ values were measured to be 7 and 20 mg/L, respectively. These data are represented as the red and blue lines, respectively. These lines intercept at 4,400 which provide a value of Km and Vm of 4mg/L and 400 mg/day, respectively. If we were aiming for a $Cp_{average}$ value of 15 mg/L this point on the x-axis could be connected with the intersection of the red and blue lines by drawing the green line. The intersection of the green line with the y-axis provides the required dose of 316 mg/day. Various dose and expected $Cp_{average}$ could be estimated from the intersection of the red and blue lines.

Want more practice with this type of problem!

References

- Tozer, T.N. and Winter, M.E. 1992 Chapter 25, "Phenytoin" in **Applied Pharmacokinetics**, 3rd. ed., Evans, W.E., Schentag, J.J., and Jusko, W.J. ed., Applied Therapeutics, San Francisco, CA Figure 25-11, p 25-31
- Vozeh, S. et al. 1981 Predicting individual phenytoin dosage, *J. Pharmacokin. Biopharm.*, **9**, 131-146
- Mullen, P.W. and Foster, R.W. 1979 Comparative evaluation of six tehniques for determining the Michaelis-Menten parameters relating phenytoin dose and steady-state serum concentrations, *J. Pharm. Pharmacol.*, **31**, 100-104

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