Nonlinear Pharmacokinetic Models

Objectives:

- To understand the schemes and differential equations associated with nonlinear pharmacokinetic models
- To understand the effect of parallel pathways
- To estimate the parameters Km and Vm
- To design appropriate dosage regimen for drugs with nonlinear elimination

Nonlinear Processes

- Lower concentration > first order
- Higher concentration > zero order
- Concentration or dose dependent kinetics
- Enzyme reaction associated with metabolism may be saturable
- Enzyme reaction may have a maximum rate limited by substrate
- Basic enzyme kinetics have application to pharmacokinetics

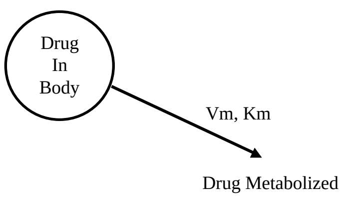
Michaelis-Menten Kinetics

$$\text{Rate of Elimination} = \frac{Vm \bullet Cp}{Km + Cp}$$

- where Vm is the maximum rate of metabolism
- and Km is Michaelis constant, the concentration (or amount) of drug at which the rate is 1/2 maximum

Scheme

- MM only elimination pathway



Differential Equation

- Single elimination pathway

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

Equation at Low Concentrations

- Km > Cp
- Km + Cp ≈ Km
- Therefore

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

- pseudo first order elimination

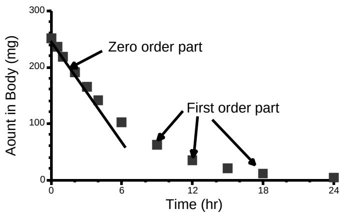
Equation at High Concentration

- Cp > Km
- Km + Cp ≈ Cp
- Therefore

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

- zero order elimination

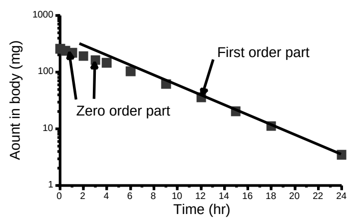
Linear Plot



High Dose - Concentration

- Slope constant on linear graph == zero order
- Slope approaches -Vm

Semi-log Plot



Low Dose - Concentration

- Slope constant on semi-log graph == first order
- Slope approaches -Vm/Km

Example - Phenytoin

- Average Km ≈ 4 mg/L (1 - 15 mg/L)
- Average Vm = 500 mg/day (100 - 1000 mg/day)
- Therapeutic window 10 - 20 mg/L (total Cp)
- Overdose possible if dose adjustment is not appropriate
- Half-life at low doses ≈ 12 hr, maybe greater than 24 hr at higher doses
- From 25 to 23 mg/L in 24 hours (cf. 25 > 12.5 > 6 mg/L when $t_{1/2}$ is 12 hr)

Evans, Schentag, Jusko, **Applied Pharmacokinetics**, Applied Therapeutics, Vancouver, WA 1992

Effect of MM Kinetics on $t_{1/2}$

- $t_{1/2}$ larger as concentration increases; i.e. slower elimination

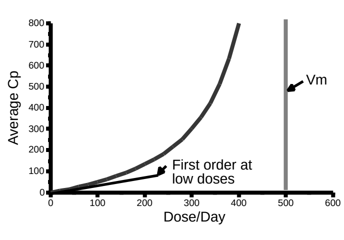
$$\frac{dC}{dt} = -kel \bullet C = -\frac{Vm \bullet C}{Km + C}$$

$$\text{since } kel = \frac{0.693}{t_{1/2}}$$

$$\frac{0.693}{t_{1/2}} = \frac{Vm}{Km + C}$$

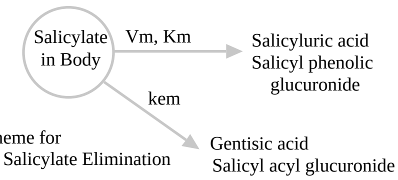
$$t_{1/2} = \frac{0.693 \bullet (Km + C)}{Vm}$$

Effect of MM Kinetics on $\overline{Cp}$



Parallel Pathways

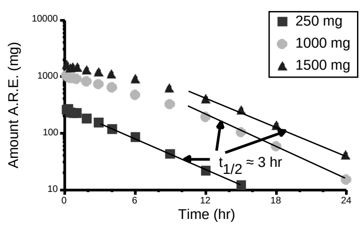
- Linear and Nonlinear Elimination



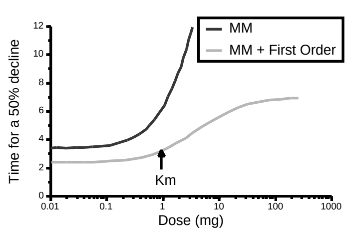
Scheme for Salicylate Elimination

from G. Levy 1965 J. Pharm. Sci., **54**, 959

Salicylate Elimination



Parallel Pathways



Adapted from Niazi, S. 1979 "Textbook of Biopharmaceutics and Clinical Pharmacokinetics, Appleton-Century Croft, New York, NY Fig 7.14, page 181

Parallel Pathways

- At low dose kem and Vm/Km is larger, thus $t_{50\%}$ is smaller
- At higher doses effective (pseudo first order) rate constant for MM process is small, thus $t_{50\%}$ is larger

Dosing Approaches

First Dose

- Use population (average) values for phenytoin
- Vm ≈ 7 mg/kg/day and Km ≈ 5 mg/L
- Aim for Cp = 15 mg/L in 80 kg patient
- Equation: $\text{Dose Rate} = \frac{Vm \bullet \overline{Cp}}{Km + \overline{Cp}}$

$$= \frac{7 \times 80 \times 15}{(5 + 15)} = 420 \text{ mg/day}$$

PDR Recommends 300 mg/day - probably better to start low

Determine Second Dose Regimen

Give an initial dosage regimen and measure Cp

- For example if after 420 mg/day, $\overline{Cp}$ is 20 mg/L
- Assume Km = 5 mg/L and calculate Vm

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

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

Change in Dose

- Note 420 mg/day >> 20 mg/L
- and 394 mg/day >> 15 mg/L
- 6% increase in dose results in 25% increase in concentration

A Nomogram

From Winter, M.E. and Tozer, T.N. 1986 Ch 16 "Phenytoin" in Applied Pharmacokinetics, Ed Evans, W.E., Schentag, J.J., and Jusko, W.J., 2 nd, Applied Therapeutics, Fig 16-12, page 525

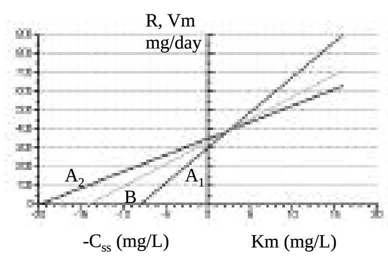
Using a Nomogram

- Line A from Cpss = 8 mg/L at 4.3 mg/kg/day (= 300 mg/day for 70 kg)
- Line B from midpoint of shape to new Cpss = 15 mg/L
- New Dose Rate is 5.2 mg/kg/day (= 364 mg/day)

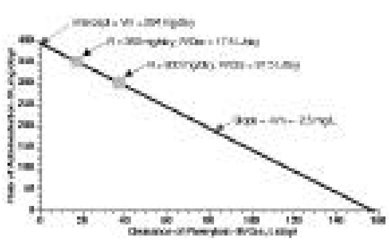
After Two or More Concentrations

- Determined at Steady State (note extended half-life
- For Both (All) Concentrations
  - Good patient compliance
  - Steady State is Achieved
  - Protein Binding is unchanged
- Example
  - 300 mg/day -> 8 mg/L
  - 350 mg/day -> 20 mg/L

Graphical Method - 1



Graphical Method - 2



A Third Method

- After two previous dosage regimen
- For example, Cp_1 = 8 mg/L Cp_2 = 20 mg/L, R_1 = 300 mg/day, and R_2 = 350 mg/day

$$DR_1 = \frac{Vm \cdot \overline{Cp_1}}{Km + \overline{Cp_1}}$$

$$300 = \frac{Vm \cdot 8}{Km + 8} \text{ and } 350 = \frac{Vm \cdot 20}{Km + 20}$$

Solve Simultaneous Equations

$$300 \cdot Km + 300 \times 8 = Vm \cdot 8$$
$$350 \cdot Km + 350 \times 20 = Vm \cdot 20$$
$$300 \times 350 \cdot Km + 300 \times 350 \times 8 = 350 \times 8 \cdot Vm$$
$$300 \times 350 \cdot Km + 300 \times 350 \times 20 = 300 \times 20 \cdot Vm$$
$$300 \times 350 \times (20 - 8) = (300 \times 20 - 350 \times 8) \cdot Vm$$
$$Vm = \frac{1260000}{3200} = 394 \text{ mg/day}$$
$$Km = \frac{8 \cdot Vm - 300 \times 8}{300} = \frac{750}{300} = 2.5 \text{ mg/L}$$

Graphical Methods

- With more than two previous dosage regimens the graphical methods can be used with more data points or lines plotted.

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