PHA 5127
Designing A Dosing Regimen
Answers provided by
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Mr. JM is to be started on aminophylline for the treatment of asthma. He is a non-smoker and weighs 60 kg. Design an oral dosing regimen for this patient such that the theophylline plasma levels are within the therapeutic window. Assume very fast absorption of the tablet. The following information is provided:

F(bioavailability) = 1	Aminophylline is 85% theophylline by weight
V_d = 0.5 L/kg	100 mg aminophylline tablets are available
Cl = 40 ml/hr/kg	therapeutic window is 10-20 mg/L

1) Determine V_d and Cl for this patient based on the normal values given above. Calculate k_e.

2) Determine the dosing interval using the relationship between τ and the fluctuation factor F. The dosing interval should be practical (i.e. some factor of a 24-hour period).

3) Use the average steady-state equation to determine the dose. Note that only 100 mg tablets of aminophylline are available here.

4) Calculate the steady-state peak and trough levels based on this dosing regimen to verify that the theophylline levels are within the therapeutic range.

5) What information is needed to better design a dosing regimen for this patient?

6) How many doses will it take to reach steady-state plasma levels? If the dose or the dosing interval is changed, how long will it take to again reach the steady-state?

7) Suggest a loading dose to decrease the amount of time required to reach a therapeutic level. What would be the peak concentration after this loading dose?

Working through this problem should help you understand where many of the equations we have seen come into play.

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1) V_d, Cl, and k_e may be estimated for this patient using the average values given as per kilogram.

$V_d = (0.5\ L/\cancel{kg})(60\ \cancel{kg}) = 30\ L$

$Cl = (40\ ml/hr/kg)(60\ kg) \times (1L/1000ml) = 2.4\ L/hr$

It is now possible to calculate k_e:

$Cl = k_e \cdot V_d$

Which rearranges to give

$$k_e = \frac{Cl}{V_d} = \frac{2.4L/hr}{30L} = 0.080hr^{-1}$$

2) The dosing interval τ can be determined using the equation:

$$\tau = \frac{\ln F}{k_e} \ ,$$

where F is the fluctuation factor that relates the Cp_{ss} (peak) and the Cp_{ss} (trough)

$$F = \frac{Cp_{ss}(\max)}{Cp_{ss}(\min)}$$

Since we want the dosing regimen to produce plasma levels within the therapeutic window, we can use

$Cp_{ss}(\max) = 20\ mg/L$

And

$Cp_{ss}(\min) = 10\ mg/L$

Then, $F = \frac{20mg/L}{10mg/L} = 2$

The dosing interval should be:

$$\tau = \frac{\ln F}{k_e} = \frac{\ln 2}{0.08hr^{-1}} = 8.66hr$$

We can round this number down to 8 in order to dose three thimes per day

τ = 8 hr

3) The average steady-state concentration for oral dosing is given by

$$\overline{C}p_{ss} = \frac{f \cdot D}{Cl_{TOT} \cdot \tau}$$

This equation may be solved for the dose, D

$$D = \frac{\overline{C}p_{ss} \cdot Cl_{TOT} \cdot \tau}{f} = \frac{\overline{C}p_{ss} \cdot k_e \cdot V_d \cdot \tau}{f}$$

To use this equation, we must assume some average concentration within the therapeutic window. A safe average concentration between 10 and 20 mg/L is 15 mg/L. However, $\overline{C}p_{ss}$ is <u>NOT</u> the mean of Cp_{ss}(max) and Cp_{ss}(min). We are simply stating that 15 mg/L is a good average concentration to reach. Thus, let

$$\overline{C}p_{ss} = 15 mg / L$$

The dose required to obtain this average steady-state level is

$$D = \frac{(15 mg / L)(2.4 L / hr)(8 hr)}{1} = 288 mg\ theophylline$$

Since we are administering aminophylline and not pure theophylline, we need to convert this to the amount of aminophylline.

$$D(\text{aminoph}) = 288 mg\ theoph \cdot \left(\frac{100 mg \text{ aminoph}}{85 mg \text{ theoph}} \right) = 338\ mg \text{ aminoph}$$

If only 100 mg tablets are supplied, this number must be rounded down to 300 mg, i.e. 3-100 mg tablets.

Thus the dosing regimen is <u>300 mg every 8 hours</u>

4) In determining the dosing regimen, we made two approximations:

8.66 ≈ 8 hours

and 338 ≈ 300 mg

(For drugs with narrow therapeutic windows, it is always safer to round <u>down</u> the dose).
It is a good idea to calculate Cp_{ss}(max) and Cp_{ss}(min) based on this dosing regimen to see how these values fit in the therapeutic window.

We are not given a value for k_a. Thus, we can not use the oral dosing equations for $Cp_{ss}(max)$ and $Cp_{ss}(min)$. If absorption takes place very fast, we may approximate these levels with the i.v. bolus equations.

First, we must calculate the amount of theophylline in the 300 mg dose of aminophylline:

$$D\,(\text{mg theoph}) = 300\text{ mg aminoph}\cdot\left(\frac{85\text{ mg theoph}}{100\text{ mg aminoph}}\right) = 255\,mg\ theoph$$

The i.v. bolus equation for $Cp_{ss}(max)$ is

$$Cp_{ss}(\max) = \frac{D}{V_d\cdot(1-e^{-k_e\tau})}$$

$$= \frac{255mg}{(30L)[1-e^{-(0.08hr^{-1})(8hr)}} = 17.98mg/L$$

The trough level is then

$$Cp_{ss}(min) = Cp_{ss}(max)\cdot e^{-k_e t}$$

$$= (17.98\text{ mg/L})\cdot e^{-(0.08hr^{-1})(8hr)} = 9.48\text{ mg/L}$$

5) If we were given two concentration-time points after a single dose, we could calculate k_e and V_d (if the i.v. bolus equations are sufficient) for this patient. The actual parameters could be used in these calculations rather than the population averages.

6) It takes roughly 5-7 half-lives of the drug to reach steady state. $t_{1/2}$ may be calculated from the k_e found in part (1):

$$t_{1/2} = \frac{\ln 2}{k_e} = \frac{0.693}{0.08hr^{-1}} = 8.7\ hr$$

The time required to reach steady-state is approximately

$5 \text{ x } t_{1/2} = (5)(8.7\text{ hr}) = 43.5$ hours

Thus, for $\tau = 8$ hrs, 6 doses are required to reach steady-state levels:

Dose =	1	2	3	4	5	6	43.5
	0	8	16	24	32	40	hours

Note: If any change is made in the dosing regimen, it will take roughly 5 half-lives to reach steady-state again. That is, it takes about 43.5 hours to reach the point where there is no significant change in the peak or trough concentrations.

7) The purpose of a loading dose is to achieve steady-state levels with a single dose and thereby eliminate the time factor required for accumulation. To determine the loading dose, we use the single dosing equation. This equation is solved for D (which will be the loading dose). This equation includes Cp_{ss}(max), the desired peak level at steady-state (see question 4).

$$LD = Cp_{ss}(\text{max}) \cdot V_d$$

$$= (17.99 mg / L \text{ theoph})(30\text{L})\left(\frac{100\text{mg aminoph}}{85 \text{ mg theoph}}\right)$$

$$= 635 \text{ mg}$$

For practical purposes, this is rounded down to 600 mg.