

Problem Set "Multiple Dosing"

A new intravenous antihypertensive drug is effective at plasma concentrations above 50 ng/mL. For plasma concentrations above 150 ng/mL serious side effects have been reported. The drug has a half-life of 6 hours and a volume of distribution of 40 L.

1. What doses have to be given once a day, b.i.d., t.i.d. and q.i.d. to keep the plasma levels above 50 ng/mL at all times?
 - a. What would be the maximum concentrations observed in these treatments?
 - b. What are appropriate loading doses?

$$D = Cp_{ss(\min)} \times Vd \times \left(\frac{1 - e^{-k_e t}}{e^{-k_e t}} \right)$$

$$Ld = Cp_{ss(\max)} \times Vd$$

$$Cp_{ss(\max)} = \frac{D}{Vd} \times \frac{1}{1 - e^{-k_e t}}$$

τ [h]	D[mg]	$Cp_{ss(\max)}$ [ng/ml]	LD[mg]
24	30	800	32
12	6	200	8
8	3	126	5
6	2	100	4

2. What doses have to be given once a day, b.i.d., t.i.d. and q.i.d. to keep the plasma levels below 150 ng/mL at all times?

a. What would be the minimum concentrations observed in these treatments?

b. What are appropriate loading doses?

$$D = C_{p_{ss(max)}} \times V_d \times (1 - e^{-k_e \tau})$$

$$LD = C_{p_{ss(max)}} \times V_d$$

$$C_{p_{ss(min)}} = \frac{D}{V_d} \times \frac{e^{-k_e t}}{1 - e^{-k_e t}}$$

τ [h]	D[mg]	$C_{p_{ss(max)}}$ [ng/ml]	LD[mg]
24	5.6	9	6
45	4.5	38	6
8	3.6	60	6
6	3.0	75	6

3. What doses have to be given once a day, b.i.d., t.i.d. and q.i.d. to maintain an average plasma level of 100 ng/mL and what would be the respective maximum and minimum concentrations?

$$D = C_{p_{ss}} \times Cl_{tot} \times t$$

$$LD = C_{p_{ss(max)}} \times V_d$$

$$C_{p_{ss(max)}} = \frac{D}{V_d} \cdot \frac{1}{1 - e^{-k_e t}}$$

$$C_{p_{ss(min)}} = \frac{D}{V_d} \cdot \frac{e^{-k_e t}}{1 - e^{-k_e t}}$$

τ [h]	D[mg]	$C_{p_{ss(max)}}$ [ng/ml]	$C_{p_{ss(min)}}$ [ng/ml]	LD[mg]
24	11.1	296	18	11.8
12	5.5	185	46	7.4
8	3.7	153	61	6.1
6	2.8	139	69	5.5

4. What dosing interval would be needed to keep the plasma levels between 50 and 150 ng/mL at all times?

Answer:

$$t = \frac{\ln F}{k_e}$$

$$F = \frac{150}{50} = 3$$

$$\tau = 9.5 \text{ hours}$$

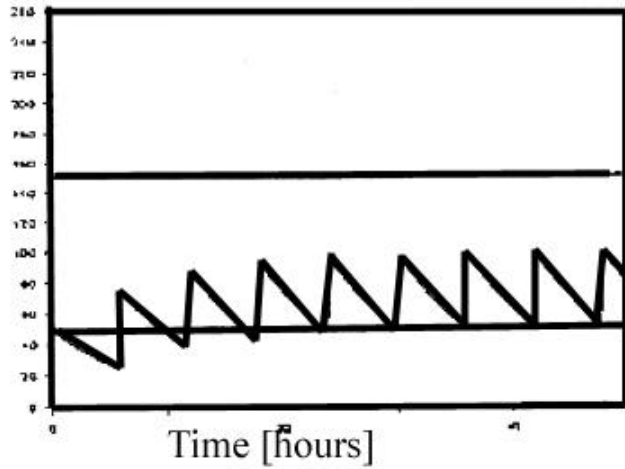
5. Make a dosing recommendation for repetitive i.v. administration.

Answer

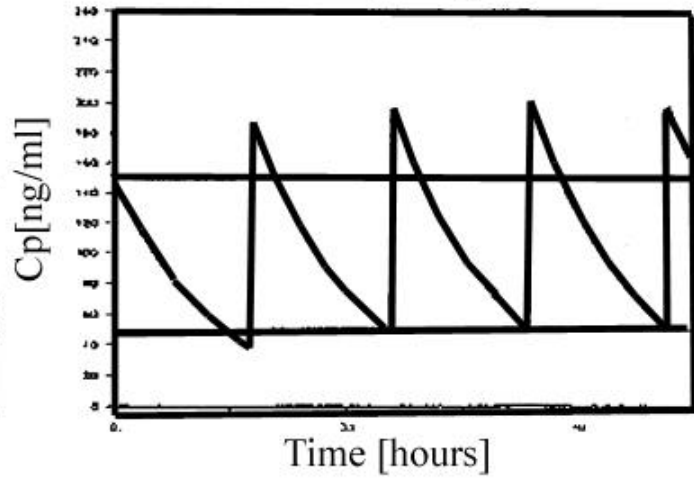
$$2.5 \text{ q.i.d.} \quad \rightarrow C_{p_{ss(max)}} \quad 125 \text{ ng/ml}$$

$$\rightarrow C_{p_{ss(min)}} \quad 63 \text{ ng/ml}$$

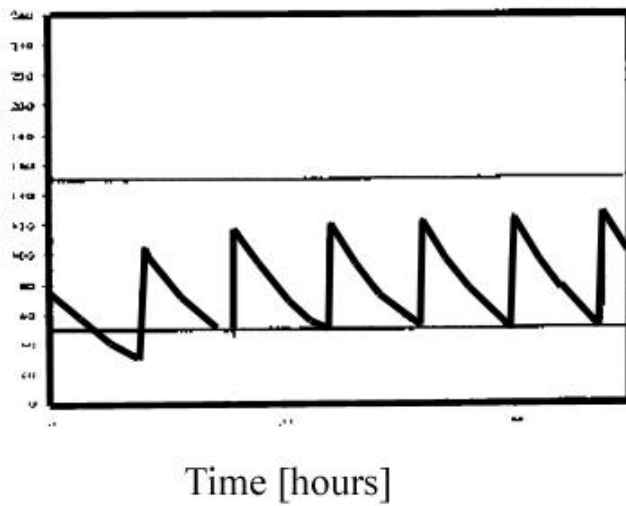
Problem 1, 2mg quid



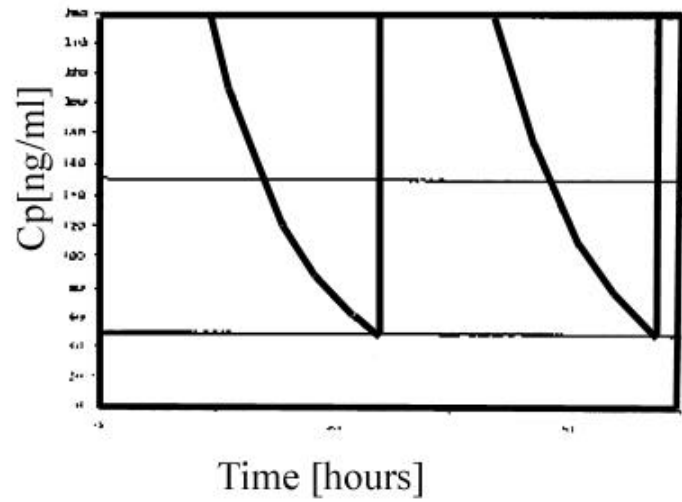
Problem 1, 6 mg bid

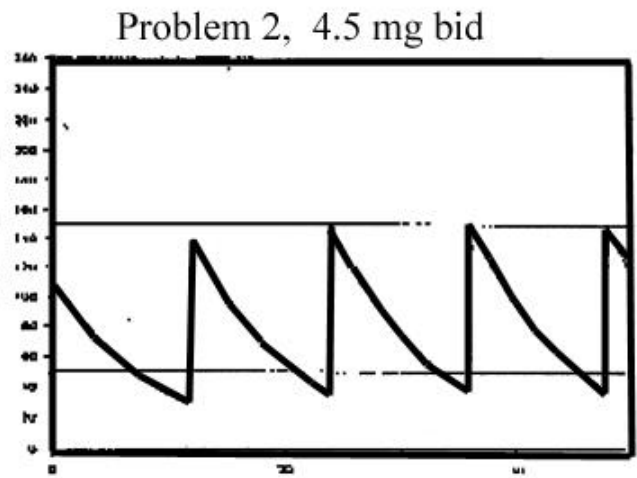
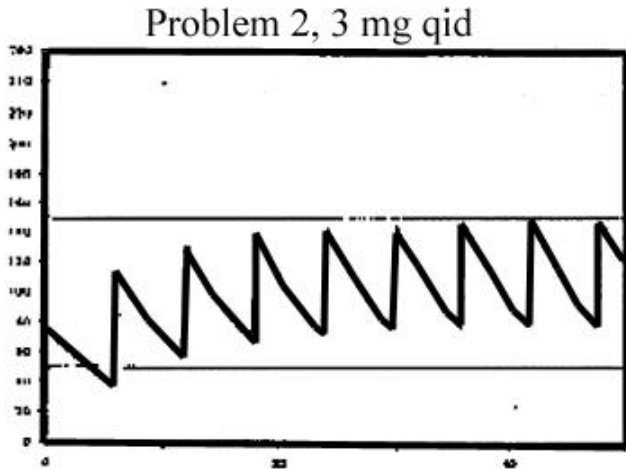


Problem 1, 3mg bid

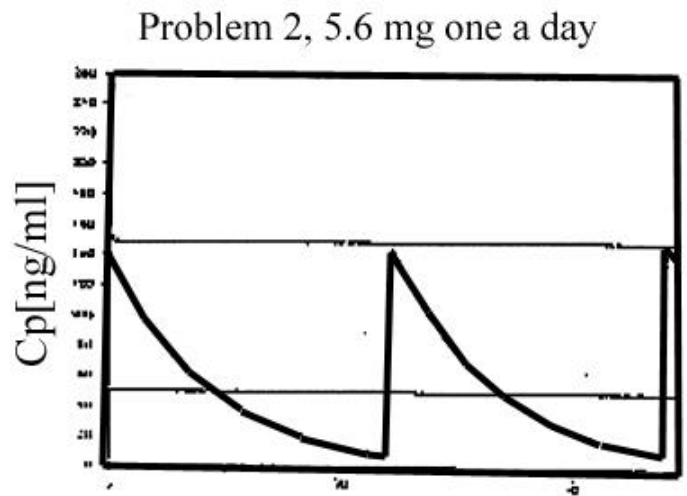
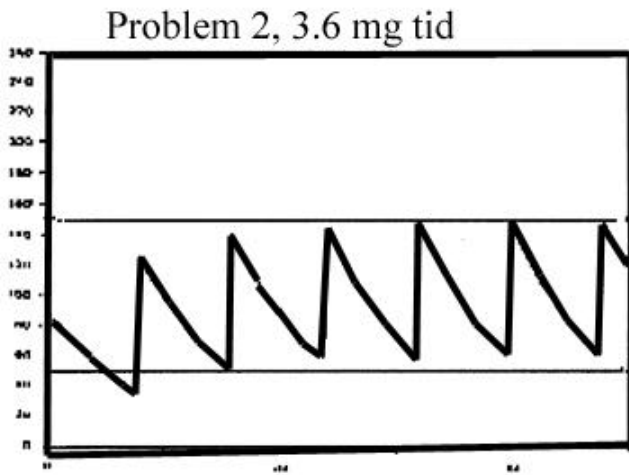


Problem 1, 30 mg once a day



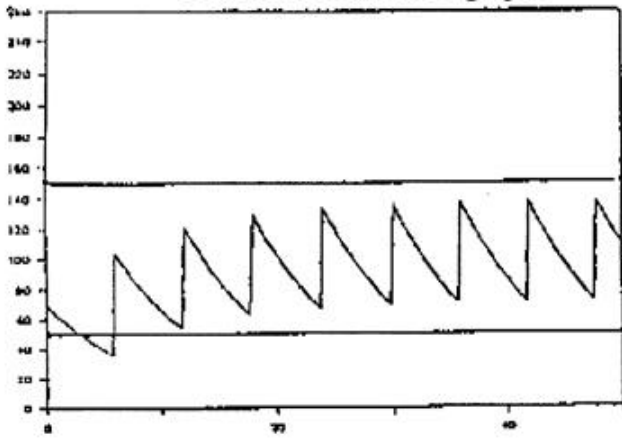


Time [hours]

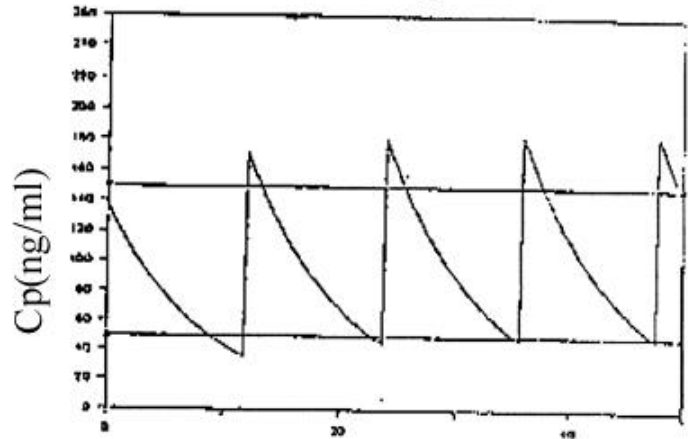


Time [hours]

Problem 3, 2.8 mg qid

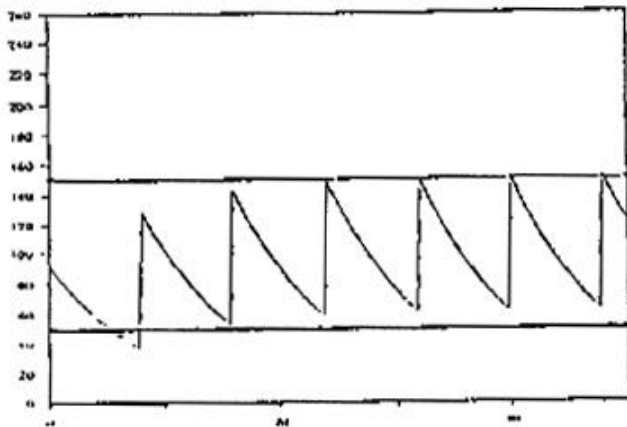


Problem 3, 5.5 mg bid

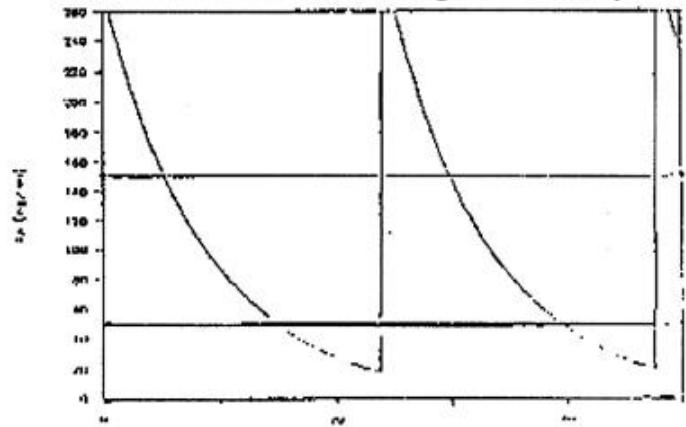


Time [hours]

Problem 3, 3.7 mg tid



Problem 3, 11 mg once a day



Time [hours]