

PHA 5128
Corrected answers HW 4
Spring 2006

1 A 40 year old, 62.5 kg female will receive carbamazepine regimen, please calculate a daily dose to achieve average steady plasma concentration of 5mg/L

$$Dose = \frac{Cl \cdot \overline{C_{pss}} \cdot \tau}{S \cdot F} = \frac{0.064 \times 62.5 \times 5 \times 24}{0.8} \text{ mg/day} = 600 \text{ mg (2pt)}$$

2 A.C., a 9-year old, 27 kg male, is being treated for a seizure disorder. He has been receiving 100 mg/day of Phenobarbital (50mg BID) for the past 20days. The Phenobarbital serum concentration just before the morning dose on the 21th Day (at the trough of the 40th and just prior to the 41th dose) was reported to be 25 mg/l. Calculate the Phenobarbital concentration on that day and assuming A.C. has average pharmacokinetic parameters for Phenobarbital.

$$Cl = 0.008 \text{ L/h/kg} \times \text{weight} = 0.216 \text{ L/h}$$

$$Vd = 0.7 \text{ L/kg} \times \text{weight} = 18.9 \text{ L}$$

$$Ke = Cl/Vd = 0.216/18.9 = 0.011 \text{ h}^{-1} = 0.27 \text{ days}^{-1} \text{ (1pt)}$$

$$C_{ssmin} = [(S \cdot F \cdot Dose / Vd) / (1 - e^{-ke \cdot \tau})] \cdot e^{-ke \cdot \tau} = 18 \text{ mg/L (1pt)}$$

3 H.L., a 42 year-old, 68 kg male, had been taking 300 mg/day of sodium phenytoin. However, his dose was increased to 400 mg/day because his seizure were poorly controlled and his plasma concentration of the drug was only 7 mg/L. Now he complain of minor CNS side effects and his reported plasma phenytoin concentration is 23 mg/L. Renal and hepatic function are normal. Assumed that both of the reported plasma concentrations represent steady-state levels and that H.L. has complied with the prescribed dosing regimens

- a. Calculate H.L.'s apparent Vm and Km and a new daily dose of phenytoin that will result in a steady-state level of about 15 mg/L
- b. Estimate the phenytoin clearance, volume of distribution and half-life at 23mg/L

$$a. Vm = \frac{300 \times 400 \times (23 - 7)}{23 \times 300 - 7 \times 400} = 468 \text{ mg sodium phenytoin} = 430 \text{ mg phenytoin}$$

$$Km = \frac{7 \times (468 - 300)}{300} = 3.92 \mu\text{g/mL}$$

$$D = \frac{468 \times 15}{3.92 + 15} = 371 \text{ mg} = 375 \text{ mg sodium phenytoin (1pt)}$$

$$b. Cl = \frac{Vm}{Km + C_{pss}} = \frac{430}{3.92 + 23} = 16L/day$$

$$V_d = 0.65 \times 68 = 44.2L \quad t_{1/2} = 2days(1pt)$$

4 a. Phenytoin follows non-linear pharmacokinetics, Please draw a concentration-time profile that best describes non-linear pharmacokinetics.

b. Recommend a loading dose with a target of $C_{peak} = 20$ mg/L for a 26 year old 50 kg female.

$$V_d = 0.65 \times 50 = 32.5L$$

$$LD = \frac{V_d \cdot C_{p_0}}{S \cdot F} = (32.5 \times 20) / 0.92 = 700mg(1pt)$$

5 D.W., a 68-year-old, 74-Kilogram, alcoholic, epileptic patient, has been taking phenobarbital (200 mg at bedtime) for three years. He has been free of seizures for at least one year. He was admitted to the hospital on January 10 with ataxia and general central nervous system depression, without alcohol on his breath. A plasma phenobarbital concentration of 56 milligrams/liter was measured in a blood sample drawn at 11:00 of that day. The drug was discontinued (including no dose on January 10) and another blood sample was obtained on January 16 at 10:00 to determine if the patient was metabolizing the drug more slowly than expected, as the patient had signs of hepatic cirrhosis. The second concentration was 16 milligrams/liter.

- Estimate the values of clearance, volume of distribution and expected half-life in this patient.
- Estimate the expected concentrations at the times of sampling and compare with the observed concentrations.
- Given that clearance of this drug is much more variable than volume of distribution, state the likely cause of the observations made and provide a recommendation for his future antiepileptic therapy with phenobarbital.

$$a. k = \ln(56/16) / 143 = 0.00876h^{-1}$$

$$t_{1/2} = 0.693 / 0.00876 = 79h$$

$$V_d = 0.7 \times 74 = 51.8L$$

$$Cl = 0.0876 \times 51.8 = 0.454 L/h(0.5pt)$$

$$b. Cl = 4mL/kg/h = 0.296L/h$$

$$V_d = 51.8L$$

$$t_{1/2} = 121h$$

$$C_{pss} = 200 / (0.296 \times 24) = 28 \mu g/mL(0.5pt)$$

$$Ke = 0.00573h^{-1}$$

$$C = 28e^{-0.0573(143)} = 12.4mg/L$$

c. *Patients levels are higher than expected, however, his clearance and half-life are higher and shorter than expected.*

Most likely explanation: Patients took more than prescribed.

Recommendation: Patient counseling:

$D = C_p \times 0.385 = 7.7 \text{mg/h} = 185 \text{mg/day}$, so keep the dose.(1pt)