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PHA 4123

Clinical Pharmacokinetics

Spring 1998

On my honor, I have neither given nor received unauthorized aid in doing this assignment.

TYPED KEY

NAME

Question	**Points**
1.	_____/15
2.	_____/15
3.	_____/15
4.	_____/15
5.	_____/15
6.	_____/15
7.	_____/10

TOTAL. _____/100

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1. *Digoxin.* Mrs D.H., a 53-year-old, 82-kilogram patient with congestive cardiac failure for the past three years, was admitted on April 16 to the hospital at 16:00 because of a worsening of her congestive cardiac failure symptoms. Her admission history indicated that she had taken her digoxin tablet (0.25 mg) that morning at the usual time (8:00-9:00), but had failed to take a tablet on Sunday (April 15). A plasma sample (blood withdrawn at 17:00) was obtained to see if the symptoms were consistent with noncompliance. A plasma digoxin concentration of 0.9 microgram/liter and a serum creatinine of 0.9 milligram/ deciliter were reported.

1) From the information available, conclude if noncompliance is likely.

<u>Not likely</u>
Expected and measured concentrations are close

2) What concentration would you expect?

$$CL_{cr} = 0.85 \cdot \frac{(140-53)\cdot 82}{72 \cdot 0.9} = 93.6 mL/min$$

CL = 0.33 · 82 + 0.9 -· 93.6 = 111.3 mL/min = 6.7 L/h

$$Cp_{ss} = \frac{F \cdot D}{CL \cdot \tau} = \frac{0.7 \cdot 0.25}{6.7 \cdot 24} = 1.1 ng/mL$$

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2. *Theophylline. J.T.,* a 6-year-old, 22-kilogram boy suffering from asthma and epilepsy, was taking 100-milligram aminophylline tablets (S = 0.85) four times a day at 8:00, 12:00,16:00, and 20:00. Because of poor control of both his asthma and his seizures, a blood sample was obtained at 8:00, just before the next dose, for determination of theophylline and phenobarbital concentrations. The theophylline concentration was 6.3 milligrams/liter.

1) Assuming a normal volume of distribution, estimate the clearance and half-life in this patient.

V_d = 0.5L/kg = 11L

$t_{1/2}$ = 3.5 h

CL = k · V_d = 2.2 L/h

2) Estimate the peak theophylline concentrations in this patient.

$$C_{max} = \frac{0.85 \cdot 100}{11} = \left(\frac{e^{-0.2 \cdot 12} + e^{-0.2 \cdot 8} + e^{-0.2 \cdot 4} + 1}{1 - e^{-0.2 \cdot 24}} \right) = 7.7 \cdot \left(\frac{0.091 + 0.202 + 0.449 + 1}{0.992} \right) = 13.5 \mu g / mL$$

3) Make a dose recommendation for this patient.

The estimated C_{min} is 13.5 · e-0.2 · 12 = 1.2 μg/mL
The measured C_{min} is 6.3 μg/mL
Two potential explanations:

1. Patient has a lower CL than expected (unlikely in presence of phenobarbital)
2. Measured level was erroneous

⇒ Switch to sustained release product 200 mg Q12H, repeat plasma level monitoring.

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3. *Gentamicin.* Mr. B.G., a 23-year-old, 58-kilogram patient with a gram-negative pneumonia, was being treated with gentamicin and ampicillin. Gentamicin had been given as an intravenous infusion (80 mg) over 45 minutes every 8 hours. Blood samples were obtained just before and 30 minutes after the end of the fourth infusion to prevent toxicity and to evaluate his therapy. The gentamicin concentrations reported were 0.4 and 4.9 milligrams/liter. The serum creatinine in the patient was 1.2 milligrams/deciliter.

1) Compare the measured results with the population average.

$$CL_{cr} = \frac{(140-23)\cdot 58}{72\cdot 1.2} = 78.5 mL/min = 4.7 L/h$$

$V_d = 0.25 \cdot 58 = 14.5L$

$$k = \frac{CL}{V_d} = 0.324 h^{-1}$$

$$C_{max} = \frac{80}{4.7\cdot 0.5}\cdot\frac{\left(1-e^{-0.324\cdot 0.5}\right)}{\left(1-e^{-0.324\cdot 8}\right)} = 5.5 \mu g/mL$$

$$C^*_{max} = 5.5\cdot e^{-0.324\cdot 0.5} = 4.7 \mu g/mL$$

$$C^*_{min} = 5.5\cdot e^{-0.324\cdot 7} = 0.6 \mu g/mL$$

Good agreement of measured and calculated levels.

2) Make a dosing adjustment to achieve a peak concentration of 8 mg/L.

Dose proportional:

$$\frac{5.5}{8} = \frac{80}{x} \Rightarrow = 116 \approx 120\ mg\ Q8H$$

3) Would this patient be a good candidate for once-a-day dosing? What daily dose would you recommend?

5 mg/kg Q24H → 300 mg

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4. *Gentamicin.* An 85-kilogram, 42-year-old female patient is receiving 120-milligram doses of gentamicin in short-term, constant-rate infusions over 45 minutes every 8 hours. The patient has a serum creatinine of 1.2 milligrams/deciliter. Plasma samples were obtained just before and 45 minutes after the end of the fourth dose.

1) Estimate the values of clearance, volume of distribution, and half-life expected in this patient.

$$CL_{cr} = \frac{(140-42)\cdot 85}{72\cdot 1.2}\cdot 0.85 = 82.0\ mL/min = 4.9\ L/h$$

$V_d = 0.25 \cdot 85 = 21.3$ L

$$k = \frac{4.9}{21.6} = 0.23\ h^{-1}$$

$$t_{1/2} = \frac{0.693}{0.23} = 3\ h$$

2) Estimate the gentamicin concentration in plasma expected at the two sampling times**.**

$$C_{max} = \frac{120}{4.9\cdot 0.75}\cdot\frac{\left(1-e^{-0.23\cdot 0.75}\right)}{\left(1-e^{-0.23\cdot 8}\right)} = 32.7\cdot\frac{0.158}{0.841} = 6.1\mu g/mL$$

$$C^*_{max} = 6.1\cdot e^{-0.23\cdot 0.75} = 5.1\mu g/mL$$

$$C^*_{min} = 6.1\cdot e^{-0.23\cdot 7.25} = 1.2\mu g/mL$$

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5. *Phenobarbital.* Mr: 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.

1) Estimate the values of clearance, volume of distribution and expected half-life in this patient.

$$k = \frac{ln\left(\frac{56}{16}\right)}{143} = 0.00876\ h^{-1}$$

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

$V_d = 0.6 \cdot 74 = \underline{44\ L}$

$CL = 0.00876 \cdot 44 = \underline{0.385\ L/h}$

2) Estimate the expected concentrations at the times of sampling and compare with the observed concentrations.

$CL = 4\ mL/kg/h = \underline{0.296\ L/h}$

$V_d = 0.6 \cdot 74 = \underline{44\ L}$

$t_{1/2} = \underline{103\ h}$

$$C_{ss} \frac{200}{0.296 \cdot 24} = 28 \mu g / mL$$

$C = 28 \cdot e^{-0.0067 \cdot 143} = 11\ \mu g/mL$

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3) 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.

Patients levels are <u>higher</u> than expected, however, his clearance and half-life are higher and shorter than expected.

Most likely explanation: Patient took more than prescribed

Recommendation: Patient counseling

$D = Cp \cdot 0.385 = 7.7$ mg/h = 185 mg/day $\rightarrow$ keep the dose.

6. Describe the mechanism of activated charcoal use in the treatment of overdose and the rationale(s) for administering it on a repeated basis. (Example: 1 gm/kg every 6 hours).