Nonlinear pharmacokinetics

CH9

1. Define *nonlinear pharmacokinetics*. How do drugs that follow nonlinear pharmacokinetics differ from drugs that follow linear pharmacokinetics?

      a. What is the rate of change in the plasma drug concentration with respect to time, dC_p/dt, when $C_p \ll K_M$?
      b. What is the rate of change in the plasma drug concentration with respect to time, dC_p/dt, when $C_p \gg K_M$?

2. What processes of drug absorption, distribution, and elimination may be considered "capacity limited," "saturated," or "dose dependent?"

3. Drugs, such as phenytoin and salicylates, have been reported to follow dose-dependent elimination kinetics. What changes in pharmacokinetic parameters, including $t_{1/2}$, V_D, AUC, and C_p, could be predicted if the amounts of these drugs administered were increased from low pharmacologic doses to high therapeutic doses?

4. A given drug is metabolized by capacity-limited pharmacokinetics. Assume K_M is 50

g/mL, V_{max} is 20   g/mL per hour, and the apparent V_D is 20 L/kg.

      a. What is the reaction order for the metabolism of this drug when given in a single intravenous dose of 10 mg/kg?
      b. How much time is necessary for the drug to be 50% metabolized?

5. How would induction or inhibition of the hepatic enzymes involved in drug biotransformation theoretically affect the pharmacokinetics of a drug that demonstrates nonlinear pharmacokinetics due to saturation of its hepatic elimination pathway?

6. Assume that both the active parent drug and its inactive metabolites are excreted by active tubular secretion. What might be the consequences of increasing the dosage of the drug on its elimination half-life?

7. The drug isoniazid was reported to interfere with the metabolism of phenytoin. Patients taking both drugs together show higher phenytoin levels in the body. Using the basic principles in this chapter, do you expect K_M to increase or decrease in patients taking both drugs? (*Hint:* see .)

8. Explain why K_M is often seen to have units of mM/mL and sometimes mg/L.

9. The V_{max} for metabolizing a drug is 10 mmol/hr. The rate of metabolism (v) is 5

mol/hr when drug concentration is 4   mol. Which of the following statements is/are true?

a. K_M is 5   mol for this drug.
b. K_M cannot be determined from the information given.

c. K_M is 4   mol for this drug.

10. Which of the following statements is/are true regarding the pharmacokinetics of diazepam (98% protein bound) and propranolol (87% protein bound)?

a. Diazepam has a long elimination half-life because it is difficult to be metabolized due to extensive plasma–protein binding.
b. Propranolol is an example of a drug with high protein binding but unrestricted (unaffected) metabolic clearance.
c. Diazepam is an example of a drug with low hepatic extraction.
d. All of the above.
e. a and **c.**
f. b and **c.**

11. Which of the following statements describe(s) correctly the properties of a drug that follows nonlinear or capacity-limited pharmacokinetics?

a. The elimination half-life will remain constant when the dose changes.
b. The area under the plasma curve (AUC) will increase proportionally as dose increases.
c. The rate of drug elimination $= C_p \times K_M$.
d. All of the above.
e. a and **b.**
f. None of the above.

12. The hepatic intrinsic clearances of two drugs are

Drug A: 1300 mL/min
Drug B: 26 mL/min
Which drug is likely to show the greatest increase in hepatic clearance when hepatic blood flow is increased from 1 L/min to 1.5 L/min?
a. Drug A
b. Drug B
c. No change for both drugs