Renal clearance:

1. Explain why plasma protein binding will prolong the renal clearance of a drug that is excreted only by glomerular filtration but does not affect the renal clearance of a drug excreted by both glomerular filtration and active tubular secretion.

2. Explain the effect of alkalization or acidification of the urine on the renal clearance of dextroamphetaminesulfate. Dextroamphetaminesulfate is a weak base with a pK_a of 9.4.

3. Theophylline is effective in the treatment of bronchitis at a blood level of 10–20

g/mL. At therapeutic range, theophylline follows first-order kinetics. The average $t_{1/2}$ is 3.4 hours, and the range is 1.8 to 6.8 hours. The average volume of distribution is 30 L.

a. What are the average, upper, and lower clearance limits for theophylline?
b. The renal clearance of theophylline is 0.36 L/hr. What are the k_m and k_e, assuming all nonrenal clearance (Cl_{NR}) is due to metabolism?

4. A single 250-mg oral dose of an antibiotic is given to a young man (age 32 years, creatinine clearance 122 mL/min, 78 kg). From the literature, the drug is known to have an apparent V_D equal to 21% of body weight and an elimination half-life of 2 hours. The dose is normally 90% bioavailable. Urinary excretion of the unchanged drug is equal to 70% of the absorbed dose.

a. What is the total body clearance for this drug?
b. What is the renal clearance for this drug?
c. What is the probable mechanism for renal clearance of this drug?

5. A drug with an elimination half-life of 1 hour was given to a male patient (80 kg) by intravenous infusion at a rate of 300 mg/hr. At 7 hours after infusion, the plasma

drug concentration was 11 g/mL.

a. What is the total body clearance for this drug?
b. What is the apparent V_D for this drug?
c. If the drug is not metabolized and is eliminated only by renal excretion, what is the renal clearance of this drug?
d. What is the probable mechanism for renal clearance of this drug?

6. In order to rapidly estimate the renal clearance of a drug in a patient, a 2-hour postdose urine sample was collected and found to contain 200 mg of drug. A midpoint plasma sample was taken (1 hr postdose) and the drug concentration in plasma was found to be 2.5 mg%. Estimate the renal clearance for this drug in the patient.

7. According to the manufacturer, after the antibiotic cephradine (Velosef), given by IV infusion at rate of 5.3 mg/kg per hour to 9 adult male volunteers (average weight,

71.7 kg), a steady-state serum concentration of 17 g/mL was measured. Calculate the average total body clearance for this drug in adults.

8. Cephradine is completely excreted unchanged in the urine, and studies have shown that probenecid given concurrently causes elevation of the serum cephradine concentration. What is the probable mechanism for the interaction of probenecid with cephradine?

9. Why is clearance used as a measurement of drug elimination, rather than the excretion rate of the drug?

10. What is the advantage of using total body clearance as a measurement of drug elimination compared to using the elimination half-life of the drug?

11. A patient was given 2500 mg of a drug by IV bolus dose, and periodic urinary data was collected. **(a)** Determine the renal clearance of the drug using urinary data. **(b)** Determine total body clearance using the area method. **(c)** Is there any nonrenal clearance of the drug in this patient? What would be the nonrenal clearance, if any? How would you determine clearance using a compartmental approach and compare that with the area method?

Time (hr)	**Plasma Urinary Concentration (g/mL)**	**Urinary Volume (mL)**	**UrinaryConcentration (g/mL)**
0	250.00	100.00	0.00
1	198.63	125.00	2880.00
2	157.82	140.00	1901.20
3	125.39	100.00	2114.80
4	99.63	80.00	2100.35
5	79.16	250.00	534.01
6	62.89	170.00	623.96
7	49.97	160.00	526.74
8	39.70	90.00	744.03
9	31.55	400.00	133.01
10	25.06	240.00	176.13

HEPATIC CLEARANCE:

1. A drug fitting a one-compartment model was found to be eliminated from the plasma by the following pathways with the corresponding elimination rate constants.

Metabolism: $k_m = 0.200\ hr^{-1}$
Kidney excretion: $k_e = 0.250\ hr^{-1}$
Biliary excretion: $k_b = 0.150\ hr^{-1}$

a. What is the elimination half-life of this drug?
b. What would be the half-life of this drug if biliary secretion were completely blocked?
c. What would be the half-life of this drug if drug excretion through the kidney were completely impaired?
d. If drug-metabolizing enzymes were induced so that the rate of metabolism of this drug doubled, what would be the new elimination half-life?

2. A new broad-spectrum antibiotic was administered by rapid intravenous injection to a 50-kg woman at a dose of 3 mg/kg. The apparent volume of distribution of this drug was equivalent to 5% of body weight. The elimination half-life for this drug is 2 hours.

a. If 90% of the unchanged drug was recovered in the urine, what is the renal excretion rate constant?
b. Which is more important for the elimination of the drugs, renal excretion or biotransformation? Why?

3. Explain briefly:

a. Why does a drug that has a high extraction ratio (eg, propranolol) demonstrate greater differences between individuals after oral administration than after intravenous administration?
b. Why does a drug with a low hepatic extraction ratio (eg, theophylline) demonstrate greater differences between individuals after hepatic enzyme induction than a drug with a high hepatic extraction ratio?

4. A drug is being screened for antihypertensive activity. After oral administration, the onset time is 0.5–1 hour. However, after intravenous administration, the onset time is 6–8 hours.

a. What reasons would you give for the differences in the onset times for oral and intravenous drug administration?
b. Devise an experiment that would prove the validity of your reasoning.

5. Calculate the hepatic clearance for a drug with an intrinsic clearance of 40 mL/min in a normal adult patient whose hepatic blood flow is 1.5 L/min.

a. If the patient develops congestive heart failure that reduces hepatic blood flow to 1.0 L/min but does not affect the intrinsic clearance, what is the hepatic drug clearance in this patient?
b. If the patient is concurrently receiving medication, such as phenobarbital, which increases the $Cl_{int}$to 90 mL/min but does not alter the hepatic blood flow (1.5 L/min), what is the hepatic clearance for the drug in this patient?

6. Calculate the hepatic clearance for a drug with an intrinsic clearance of 12 L/min in a normal adult patient whose hepatic blood flow is 1.5 L/min. If this same patient develops congestive heart failure that reduces his hepatic blood flow to 1.0 L/min but does not affect intrinsic clearance, what is the hepatic drug clearance in this patient?

a. Calculate the extraction ratio for the liver in this patient before and after congestive heart failure develops.
b. From the above information, estimate the fraction of bioavailable drug, assuming the drug is given orally and absorption is complete.

7. Why do elimination half-lives of drugs eliminated primarily by hepatic biotransformation demonstrate greater intersubject variability than those drugs eliminated primarily by glomerular filtration?

8. A new drug demonstrates high presystemic elimination when taken orally. From which of the following drug products would the drug be most bioavailable? Why?

a. Aqueous solution
b. Suspension
c. Capsule (hard gelatin)
d. Tablet
e. Sustained release

9. For a drug that demonstrated presystemic elimination, would you expect qualitative and/or quantitative differences in the formation of metabolites from this drug given orally compared to intravenous injection? Why?

10. The bioavailability of propranolol is 26%. Propranolol is 87% bound to plasma proteins and has an elimination half-life of 3.9 hours. The apparent volume of distribution of propranolol is 4.3 L/kg. Less than 0.5% of the unchanged drug is excreted in the urine.

a. Calculate the hepatic clearance for propranolol in an adult male patient (43 years old, 80 kg).
b. Assuming the hepatic blood flow is 1500 mL/min, estimate the hepatic extraction ratio for propranolol.
c. Explain why hepatic clearance is more important than renal clearance for the elimination of propranolol.
d. What would be the effect of hepatic disease such as cirrhosis on the (1) bioavailability of propranolol and (2) hepatic clearance of propranolol?
e. Explain how a change in (1) hepatic blood flow, (2) intrinsic clearance, or (3) plasma protein binding would affect hepatic clearance of propranolol.
f. What is meant by first-pass effects? From the data above, why is propranolol a drug with first-pass effects?

11. The following pharmacokinetic information for erythromycin was reported by , p. 1679):

Bioavailability: 35%
Urinary excretion: 12%
Bound in plasma: 84%
Volume of distribution: 0.78 L/kg
Elimination half-life: 1.6 hours

An adult male patient (41 years old, 81 kg) was prescribed 250 mg of erythromycin base every 6 hours for 10 days. From the data above, calculate the following:
a. Total body clearance
b. Renal clearance
c. Hepatic clearance

12. Why would you expect hepatic clearance of theophylline in identical twins to be less variable compared to hepatic clearance in fraternal twins?

13. 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 proportionately with an increase in dose.
c. The rate of drug elimination = $C_p x K_M$.
d. At maximum saturation of the enzyme by the substrate, the reaction velocity is at V_{max}.
e. At very low substrate concentrations, the reaction rate approximates a zero-order rate.

14. The V_{max} for metabolizing a drug is 10 m/hr. The rate of metabolism (v) is 5 m/hr when drug concentration is 4 m. Which of the following statements is/are true?

a. K_M is 5 m for this drug.
b. K_M cannot be determined from the information given.
c. K_M is 4 m for this drug.

15. 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 due to its lack of metabolism and its extensive plasma protein binding.
b. Propranolol is a drug with high protein binding but unrestricted (unaffected) metabolic clearance.
c. Diazepam exhibits low hepatic extraction.

16. The hepatic intrinsic clearance of two drugs are as follows:

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 mL/min? Which drug will likely be blood-flow limited?