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

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Question Set I

1. Forced diuresis is likely to significantly enhance the clearance of which of the following drugs (5 points)
   
a) a drug which is both polar and predominantly cleared by the kidney.
b) a drug mainly cleared via liver metabolism.
c) a drug predominantly cleared by the kidney, for which most of the filtered and secreted drug is reabsorbed
d) a drug for which the renal clearance is close to fu*GFR

2. Two patients receive the **high extraction drug A** which is mainly metabolized by the P450 system. One patient also took a drug which is an enzyme inducer of the P450 system. As a result, the intrinsic clearances between the patients differed by a factor of 10. Which of the following statements is/are correct (5 points).
   
a) Differences in the total clearance observed for the two patients will be clinically relevant
b) The oral bioavailability of this drug in the two patients will be of no clinical relevance.
c) Assume that the plasma protein binding in both patients increases, the t_{1/2} of the drug will be reduced in both patients.
d) Assuming that the plasma protein binding in both patients increases during treatment, the t_{1/2} of the drug will be increased in both patients.

3. (10 points) How will the increase in both tissue binding and liver blood flow, assuming that both increased by the same factor, affect the initial concentration
(C₀), clearance (CL), AUC, and half-life (t₁/₂) of a drug predominantly eliminated through liver metabolism (low extraction drug). Determining the resulting change in AUC, CL, AUC and t₁/₂. Assume the drug is given as an iv bolus injection. Also determine the effect on oral bioavailability F when the drug is given as a tablet. (Please note that ↔ means no change)

A) ↓C₀, ↑CL, ↓F, AUC↓, ↓ t₁/₂
B) ↔ C₀, ↔ CL, ↑F, AUC↑, ↔ t₁/₂
C) ↓C₀, ↔CL, ↔ F, AUC↔, ↑ t₁/₂
D) ↑C₀, ↓ CL, ↔ F, AUC↑, ↑ t₁/₂
E) none of above combinations.
Question Set II. (20 points)

For the physiological changes listed below, select the effect on the pharmacokinetic parameters for a lipophilic, protein bound, very weak acidic drug (pKa=13.8) that is only eliminated through renal elimination. Answers may be used more than once.

Select the effect on pharmacokinetic parameters

(A) $\text{Cl} \uparrow$  
(B) $\text{Cl} \downarrow$  
(C) $V_D \downarrow$  
(D) $F \downarrow$  
(E) nothing happens or effect is not listed

Physiological change

4. Decrease in plasma protein binding  
   ____

5. Increase in tissue binding  
   ____

6. pH adjustment of urine from 7.4 to 6.3  
   ____

7. Increase in GFR  
   ____
Question set III (20 points):

Assume that drug A (cleared through hepatic metabolism) is given to patient s1 and 2. The graph depicts the concentration-time profiles for patient 1 and 2. Which of the following statements might explain (True) or not explain (False) the differences in the concentration-time profiles in the two patients after iv bolus injection? Only one parameter (CL, Dose, Vd) will differ between patient 1 and 2. On the bubble sheet mark A for true or B for false

8. T F Tissue binding of drug A differs in the two patients.
9. T F If $C_l$ is 0.08 L/h in both patients, plasma protein binding is higher in patient 1 than in patient 2.
10. T F If $C_l$ of drug A is 80,000 l/h in both patients, plasma protein binding in patient 1 has to be higher than in patient 2.
11. T F If $C_l$ of drug A is 80,000 l/h in both patients, liver blood is lower flow in Patient 1 than in patient 2.
A lipophilic drug (not an acid, not a base) is cleared through renal and hepatic clearance ($Cl_{\text{ren}}=0.75 \text{ mL/min}$; $Cl_{\text{hep}}= 8 \text{ mL/min}$). Plasma protein binding suddenly doubles. 

Indicate for this situation whether the following parameters would

(A) increase

(B) decrease

(C) stay unchanged

(D) insufficient information is provided

12. oral bioavailability
13. hepatic clearance
14. renal clearance
15. $Cl_{\text{int}}$
Question Set V (True or False)

(20 points)

True (A) or False (B). On the bubble sheet mark A for true or B for false

Mark whether the following statements are true (A) or False (B) for a drug given as iv bolus

16. T F The renal clearance of a drug is always smaller than the drugs hepatic clearance.
18. T F clearance = ke*dose/Cpo.
19. T F Assume that an acidic drug whose unionized form is lipophilic and whose pkₐ is 7.0. The drug is predominantly cleared by renal elimination. Adjustment of the urine pH within physiological ranges will significantly change the renal clearance.
20. T F Assume that an acidic drug whose unionized form is lipophilic and whose pkₐ is 13.0. The drug is predominantly cleared by renal elimination. Adjustment of the urine pH within physiological ranges will significantly change the renal clearance.
Question Set VI (15pts)

21. Which of the following are correct statements for an IV bolus dosing regimen. 
   (t_{1/2}=24 h, once daily dosing regimen)

   1) Peak and trough concentrations are the same after the first dose and at steady state
   2) The accumulation factor is the same after 2 doses and at steady state
   3) The higher the elimination rate constant of a drug, the longer it will reside in the body
   4) The AUC_{0-infinity} following a single dose and the AUC_{0-tau} at steady state are the same for the same drug, assuming linear pharmacokinetics

   (A)  1 & 3
   (B)  1, 2 & 3
   (C)  4
   (D)  2,4
   (E)  3, 4
Question Set VII 10 pts

22. A 55-year male patient (80 kg, 5'6'' height) was given multiple IV bolus injections of 1000 mg of drug Z every 8 hours. His serum creatinine level was determined to be 1.3 mg/dL. Given that drug Z is completely eliminated via the kidneys and that its volume of distribution is 50L please compute the respective average steady-state concentration for this patient. (10 points)

(A) 32.6 \( \mu g/\text{mL} \)
(B) 35.9 mg/L
(C) 287 \( \mu g/\text{mL} \)
(D) 35.9 mg/mL
(E) 38.3 mg/L
Question Set VIII

Mark whether the following statements are true (A) or false (B) for a drug that is given as an i.v. bolus to a patient. Note that the drug follows linear kinetics and its concentration-time profile is best described by a one-compartment body model. (15 points)

23. T F It is assumed that membranes do represent significant barriers
24. T F The rate of elimination is described by a first-order rate constant
25. T F Drug metabolism is saturable
26. T F The amount of drug eliminated per unit time is constant
27. T F It is assumed that the drug distributes instantly throughout the body
Question Set IX

28. Which of the following statements are correct. (5 points)

1) Following multiple IV injections, maximum concentrations in plasma depend only on dose and volume of distribution
2) The extraction ratio changes significantly for high extraction drugs once liver blood flow changes
3) Renal clearance can exceed the glomerular filtration rate
4) The Cockroft-Gault equation is used to compute hepatic clearance
5) Highly ionized substances tend to remain in the urine, unless substrate of a transport system.

(A) 1,2,3
(B) 2,3,5
(C) 2,3,4
(D) 3,5
(E) None of the above