

Name: _____

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PHA 5127

Second Exam

Fall 2011

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

Name

Put all answers on the bubble sheet

TOTAL _____/200 pts

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Question Set I (True or False)

(15 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). Mark **false** if there is not sufficient information given to provide answer. Increases and Decreases differences should be of clinical significance, otherwise state "F".

The lipophilic drug A (neither an acid nor a base) is cleared only by hepatic metabolism, crosses membranes quite easily, and dissolves in the GI tract. When given to Patient A, it has a f_u of 0.01, a f_{ut} of 0.3 and an intrinsic clearance of 300 ml/L. Patient B shows a plasma protein binding of 98 %; the only difference to Patient A.

1. T F The oral bioavailability of this drug is higher in Patient B.
2. T F The AUC of plasma concentration vs time curve in Patient B after iv bolus injection is higher than when the same dose is given as iv bolus to Patient A.
3. T F The AUC when expressed in free drug concentrations in plasma will be the same for both patients when the same dose is given.
4. T F Decrease in tissue binding will affect the half-life of the drug in both Patient A and B.
5. T F Increase in liver blood flow will affect the half-life of the drug in both patients.

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Question Set II

(10 points)

6. Consider a lipophilic unionized drug, eliminated only through renal elimination (no active transport). How will a decrease in the fraction unbound in plasma and a change in creatinine clearance (50% increase) affect the initial concentration (C_0), clearance (CL), AUC, and half-life ($t_{1/2}$) when given as an iv bolus, bioavailability (F) when given as tablet of a low-extraction drug? (Please note that \leftrightarrow means no clinically relevant change, \downarrow and \uparrow clinically relevant changes)
- A) $\downarrow C_0$, $\uparrow CL$, $\downarrow F$, $AUC \downarrow$, $\downarrow t_{1/2}$
 - B) $\leftrightarrow C_0$, $\leftrightarrow CL$, $\uparrow F$, $AUC \uparrow$, $\leftrightarrow t_{1/2}$
 - C) $\downarrow C_0$, $\leftrightarrow CL$, $\leftrightarrow F$, $AUC \leftrightarrow$, $\uparrow t_{1/2}$
 - D) $\uparrow C_0$, $\downarrow CL$, $\leftrightarrow F$, $AUC \uparrow$, $\leftrightarrow t_{1/2}$
 - E) none of above combinations.

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Question Set III (Matching)

(20 points)

For the physiological changes listed below, select the induced changes on the pharmacokinetic parameters for an aminoglycoside (assume renal elimination only). Some answers may be used more than once. However, only one answer per “physiological change”. Assume the drug is just given once.

Select the clinically relevant effect on pharmacokinetic parameters

(A) $Cl \uparrow$ (B) $Cl \downarrow$ (C) $k_e \downarrow$ (D) $F \uparrow$ (E) *nothing happens or effect is not listed*

Physiological change

- | | | |
|-----|------------------------------------|--------------|
| 7. | Decrease in plasma protein binding | <u> A </u> |
| 8. | Increase in tissue binding | <u> C </u> |
| 9. | Increase in liver blood flow | <u> E </u> |
| 10. | Increase in GFR | <u> A </u> |

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Question set IV

(20point)

A drug, stable in the GI tract and in GI membranes ($f_u=0.5$, $t_{1/2}=20$ h, not transported by transporters), given orally, is cleared only through renal clearance ($Cl_{ren}=0.75$ ml/min ;). After 5 months of treatment, the AUC is determined. It is half of what was found at the end of month one.

Indicate for this situation, a change in which of the following parameters explains this result

11. T F change in GFR
12. T F change in oral bioavailability
13. T F change in plasma protein binding
14. T F induction of the P450 system

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Question Set V

(20 points)

The following drugs (1-5) have been given at toxic doses. What methods (A-E) could be used to treat the patient if:

- 15) Drug 1 is eliminated mainly through hepatic metabolism (high extraction drug) D
- 16) Drug 2 is eliminated mainly through hepatic metabolism (low extraction drug) C
- 17) Drug 3 is lipophilic (not an acid, not a base) and eliminated solely through kidney. B
- 18) Drug 4, a lipophilic acid, $pK_a=13$, is eliminated solely through the kidney. B
- 19) Drug 5, a Lipophilic acid, $pK_a=7.4$, is eliminated solely through the kidney. A

Select for above drugs the best single choice for detoxification from the list below:

- A) Adjust urine pH.
- B) Increase urine flow.
- C) Give drug that induces liver enzymes.
- D) Perform dialysis, as nothing else will work.

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Question Set VI

(15 points)

20. A new hydrophilic drug is eliminated through renal and hepatic processes. Plasma protein binding is 10%. Urine flow is 2 ml. GFR is 120 ml/min. Liver blood flow is 60 L/h. E is 0.26, due to first pass metabolism in the liver.

What will be the oral bioavailability? You might have to round.

- A) 25 %
- B) 2.5 %
- C) 75 %
- D) 7.5%
- E) none of the above

Question Set VII

(15 points)

21. Robert is very sick and needs treatment with an aminoglycoside. In order to start him on the aminoglycoside you have to estimate Robert's creatinine clearance. Robert is 5 ft 10 inches tall, 64 years old, male, and weights 140 kg. His serum creatinine is 1.5 mg/dl.

What is Robert's creatinine clearance? You might have to round.

- A) 70 ml/min
- B) 80 ml/min
- C) 900 ml/min
- D) 110 ml/min
- E) 120 ml/min

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Question Set VIII (30 points)

A patient receives 400 mg of a drug as multiple iv bolus injections every 6 hours. Assume steady state is achieved. Just after the next dose is administered, a blood sample is taken to determine C_{peak} (14 mg/L). Then 4 hours later a second sample is taken (2.8 mg/L).

22. Calculate k_e .

A) 0.82 (1/hr)

B) 0.40 (1/hr)

C) 1.85 (1/hr)

D) None of the above

23) Calculate the trough concentration.

A) 2.5 mg/L

B) None of the above

C) 0.125 mg/L

D) 1.254 mg/L

24) What is the volume of distribution of this drug.

A) 60.5L

B) 80.67L

C) None of the above

D) 31.42L

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Question Set IX (True or False)

(15 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)

25. T F Assume steady state has been reached after having started multiple iv bolus injections. At steady state, the average steady state concentration will depend on the volume of distribution of the drug.
26. T F The time to reach steady state for multiple iv bolus injections is affected by volume of distribution of the drug.
27. T F The fluctuation is affected by the clearance and volume of distribution of the drug.
28. T F Consider: $\tau = \ln F / k_e$. F stands for degree of first pass.
29. T F Consider: $\tau = \ln(C_{\max} / C_{\text{trough}}) / k_e$ to determine the dosing interval for multiple iv bolus injection regimens. When this equation is used for oral forms of administration and C_{\max} is defined as the upper and C_{\min} is defined as the lower concentration of the therapeutic window, a safety factor is built into the resulting τ .

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Question Set X

(15 points)

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

Assume a multiple i.v. bolus dosing regimen.

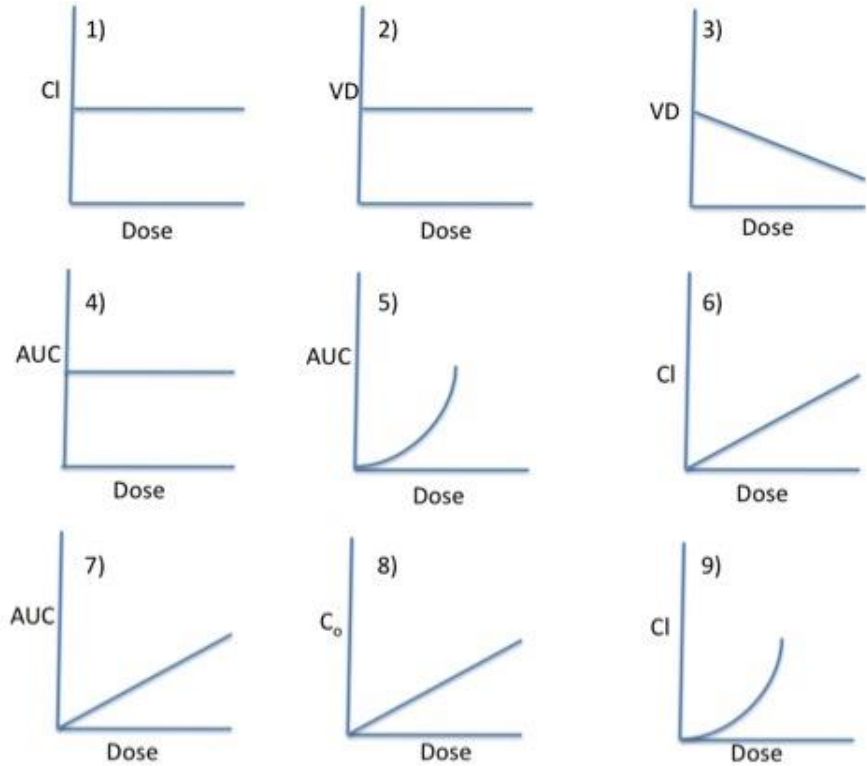
30. **T** **F** For a lipophilic drug whose clearance is constant under the given conditions, the following statement can be made: The stronger the plasma protein binding the less pronounced the degree of accumulation.
31. **T** **F** For a lipophilic drug whose clearance is constant under the given conditions, the following statement can be made: The stronger the stronger the tissue protein binding the more pronounced the fluctuation between peak and trough concentration.
32. **T** **F** For a lipophilic, low extraction drug, cleared mainly through liver metabolism, the following statement can be made when the drug is given through multiple iv bolus injections: The stronger the plasma protein binding the higher the average steady state concentration.

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Question Set XI (15 points)

33. Select the schemes that agree with linear pharmacokinetics?



- A) 5, 9
- B) 6, 7, 8
- C) 3, 6, 7
- D) 1, 3, 4, 6
- E) 1, 2, 7, 8

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Question Set XII (10 points)

Question set I (10 pts): Select whether the following statements are True (A) or False (B) concerning an orally administered drug that is absorbed by a first order process and eliminated by a first order process

34. **T** **F** The faster the absorption rate for a given dose, the earlier the highest concentration will be observed.
35. **T** **F** The unit for the absorption rate will be [1/h].
36. **T** **F** t_{max} depends only on k_a
37. **T** **F** All the drug has been absorbed when t_{max} is reached
38. **T** **F** For a sustained release formulation, clearance can be calculated from the terminal slope if V_d is known.