Name:_____

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1. Mark whether the following statements concerning bioequivalence are true (T) or false (F). (8 pts)

T F C_{pmax} and t_{max} are suitable for the assessment of bioequivalency

T F A 90% confidence that the generic product is within 90-110% of reference standard needs to be shown in bioequivalence studies

T F The Orange Book indicates products which are bioequivalent as AB

T F Sustained release products do not need to be tested, as they will show zero order release kinetics.

2. A drug is given in i.v. bolus multiple-dosing regimen. Mark the following statements true (T) or false (F):(12 pts)

T F The shorter the half-life of a drug, the less pronounced the differences between peak and trough values.

T F The accumulation is increased in patients with reduced clearance.

T F The time to reach steady state depends on the dosing interval.

T F At plateau (steady state) the amount of drug lost within a dosing interval equals the maintenance dose.

T F The larger the Vd, the lower the average steady state concentration.

T F The average steady state concentration depends on the oral bioavailability.

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3. Mark whether the following statements are true (T) or false (F) (10 pts)

T F A lowering of a drug's plasma and tissue binding might increase the effect of the drug.

T F Assuming linear pharmacokinetics, the rate of hepatic drug metabolism (not clearance) is directly related to the free drug concentration.

T F In highly perfused organs such as the liver, the rate of drug distribution is relatively high; for most agents, therefore, the drug in that tissue slowly equilibrates with the drug in plasma.

T F For high extraction drugs, the diffusion into the hepatocyte is always fast.

T F The elimination of drugs with non-linear pharmacokinetics may exhibit first-order characteristics at low concentrations and zero-order characteristics as the plasma concentration increases.

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4. When clearance is decreased but the volume of distribution is unchanged, the following dose adjustments might be possible (10 pts.):

   a) Lower maintenance dose and longer dosing interval

   b) Same maintenance dose and shorter interval

   c) Same maintenance dose and longer interval

   d) Lower maintenance dose and same interval

   e) Increase loading dose

List possible answers:_____.

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5.

a) Select the correct answer(s). Due to the nature of biological membranes, drugs with the following properties are more likely to cross most membrane barriers by diffusion: (8 pts, no partial credit)

a) nonionized and hydrophilic

b) ionized and hydrophilic

c) nonionized and lipophilic

d) ionized and lipophilic

ANSWER: :_____.

6) Which of the following factors affect glomerular filtration of a drug: (5 pts, no partial credit)

a) Molecular size

b) Plasma protein binding

c) Lipid solubility

d) Acid-base characteristics

e) Tissue binding

ANSWER: :_____.

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7.

A renal clearance of 500 ml/min may suggest: (5 pts)

T F elimination by glomerular filtration

T F high protein binding

T F extensive metabolism

T F elimination by tubular secretion

T F reabsorption in renal tubules.

8.

The volume of distribution in a 70 kg man is observed to be 7 liters. Indicate which one (or more) of the following statements is (are) consistent with the observation when you consider that albumin has a volume of distribution of about 7 liters. (8 pts)

a) highly bound to plasma proteins

b) does not pass membranes very well

c) highly bound to tissue proteins

d) low extraction drug.

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9. Select for the following pharmacokinetic phenomena, the relevant optical representation for a drug with predominantly metabolic clearance (15 pts)

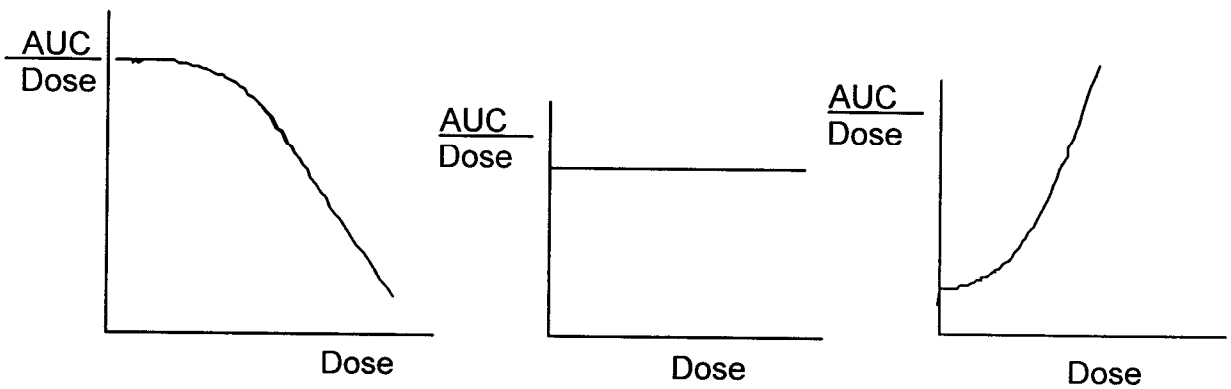
a) drug with linear pharmacokinetics _____

b) high extraction drug with saturable tissue binding _____

c) low extraction drug with saturable protein binding _____

d) saturable metabolism _____

e) orally given drug, G.I. absorption via active transport _____



1) 2) 3)

4) none of the previous graphs

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10. List factors contributing to pharmacokinetic variability (at least 4). Give only factors, no sentences (12 pts).

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11. Comment on the following statement: Interchange of brand name products with generic drugs should be generally done for drugs with broad therapeutic window, but should be carefully evaluated for drugs with narrow therapeutic window (10pts). The shorter your answer the better.

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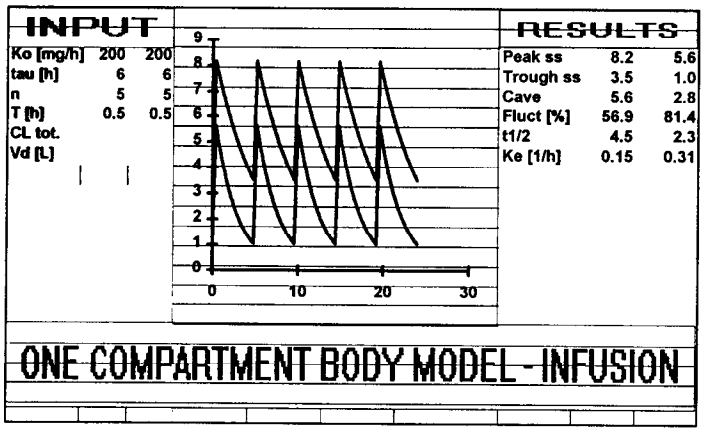
12. The following plasma-concentration time profiles have been observed for two patients after multiple short term infusions. (9 pts)



a) Please state whether clearance or volume of distribution differs in these patients (only one is possible). Explain for full credit.

b) What would you do to for the patient with the lower levels to increase to the same average steady state concentrations? Give hard quantitative (numbers) data for full credit.

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13.)

A 43 year old patient (70 kg develops a wound infection (found to be Staphylococcus aureus). Since this bacteria is resistant to penicillins, the patient is treated with vancomycin.

For a patient with normal renal function, the half-life is generally 6 hours. The volume of distribution is 0.9 hours/kg. For systemic infections, vancomycin is given intravenously and shows a pronounced distribution phase (up to one hour for the initial phase). Vancomycin is usually given via short term infusion. The desired steady-state concentration is 20 mg/L (1 hr post-infusion) and 5-10 mg/L at the end of the dosing interval. Also remember that vancomycin has a wide therapeutic margin.

a) Why is it possible to use a one compartment body model equations for this drug

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b) Explain why it is might be feasible to use an i.v. bolus equation for calculating the loading dose for this patient, despite the fact that a short term infusion was used.

c) What equation should be used for calculating the peak (one hour after post-infusion) observed at steady state for this patient. Give only the equation, do not calculate).

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d) If the actual peak (1 hr after post-infusion) and trough values (11 hours post infusion) are 23 mg/L and 14 mg/L (giving 500 mg every 12 hours, steady state reached) explain how you would calculate ke and Vd. No calculations, just words or equations.

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14. Give the relationship between Vd and time for a two compartment body model drug by drawing a graph.

(12 pts.)