Name: J Stark

SS#: Solutions

PHA 5127

First Exam
Fall 2000

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

_____

Name

Question/Points

1. _____/ 7.5pts
2. _____/7.5 pts
3. _____/5 pts
4. _____/10 pts
5. _____/10 pts
6. _____/10 pts
7. _____/10 pts
8. _____/10 pts
9. _____/10 pts
10. _____/20 pts

TOTAL _____/100 pts

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1.) Forced diuresis is likely to significantly enhance the clearance of...
(7.5 points)

a) a drug which is both polar and slowly removed from the body. – no signif. reabsorp
b) a drug mainly cleared via metabolism. – N/A for renal processes
c) a drug for which most of the filtered and secreted drug is reabsorbed
d) a drug for which the ratio of its renal clearance to creatinine clearance is 1.0 – possibly

List correct answer(s):

C – diuresis will limit reabsorption

2.) Pharmacokinetic studies have shown that a new centrally active drug entity (works in the brain) designed for headaches has a very slow onset of action when compared to other headache drugs. Indicate what possible statements might agree with this observation.(7.5 points)

a) The drug is hydrophilic
b) The plasma protein binding is too low.
c) Distribution is controlled by perfusion rate limitations
d) Distribution into the brain shows permeability-rate limitations
e) The drug is a strong base.

List correct statement(s):

A - hydrophilic drugs have difficulty crossing the BBB.

D - Since other headache drugs work more quickly, it is very possible that this drug has limited permeability

E - A strong base will be charged at physiological pH values.

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3.) Two patients receive the **high extraction drug Anonymous** which is mainly metabolized by the P450 system. One patient also takes a drug which is an enzyme inducer of the P450 system. As a result, the intrinsic clearances between the patients differ by a factor of 10. What 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 different and this difference will be of clinical relevance.
c) Assume that the plasma protein binding in both patients increases, the $t_{1/2}$ of the 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.

For high E, $Cl_H \approx Q_H$

$F_H \approx \frac{Q_H}{Clint \cdot fu}$

List the correct answer(s)

B – depends on Cl_{int}

C – due to changes in Vd not Cl

$\downarrow t_{1/2} = \frac{\ln 2 \cdot Vd \downarrow}{Cl}$

$\downarrow Vd = V_p + V_t \cdot \frac{fu \downarrow}{fut}$

4.) For the physiological changes listed below, select the induced change on the pharmacokinetic parameters for a lipophilic, protein bound, low extraction drug cleared by liver and kidney. (10 points)

$Cl_H = Clint \cdot fu$

$Cl_{Ren}(fu\,H) = GFR \cdot fu$

Physiological change	Effect on kinetics
1. Increase in plasma protein binding B	a. Cltot ↑
2. Increase in liver blood flow G	b. Vd ↓
3. Decrease in metabolic liver enzymes E	c. Vd ↑
4. Decrease in creatinine clearance D	d. GFR↓
5. Increase in the number of fat cells C	e. Clint ↓
	f. Clhep ↑
	g. none of the above effect

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5.) An aminoglycoside has a normal elimination half-life of 100 minutes in young adults. In patients 70-90 years old, the elimination half-life of this aminoglycoside is 300 minutes. The normal dose of the aminoglycoside is 15 mg//kg per day divided into two doses. Assume that the volume of distribution per body weight is not changed by the patient's age. What should be the daily dose for a 75-year-old patient when the dosing frequency is unchanged (10 points).

$t_{1/2}(young) = 100$ min

$t_{1/2}(old) = 300$ min

Dose = 15 mg/kg for normal patients

For steady state dosing,

$$\bar{C}_{pss} = \frac{D}{CL \cdot \tau}$$

The 3-fold difference in $t_{1/2}$ is due to CL (it was stated that Vd is the same).

$$t_{1/2} = \frac{\ln 2 \cdot Vd}{CL}$$

Thus, the Cl for older patients must be 3 times lower than that for younger patients.

The dose to provide the same average concentration is

$$D = \bar{C}_{pss} \cdot CL \cdot \tau$$

For an older patient, the appropriate dose is

$$D = \bar{C}_{pss} \cdot \frac{CL(normal)}{3} \cdot \tau$$

So, $\frac{15 \text{ mg/kg}}{3} = \boxed{5 \text{ mg/kg}}$

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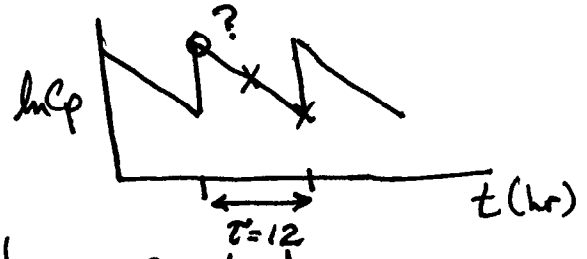
6.) A drug was given as an i.v. bolus twice a day. Steady state was reached.
6 hours after the last dose a serum concentration of 10.5 µg/ml was measured.
12 hours after the last dose a concentration of 6.4 µg/ml was observed (10 points).

Calculate C_{max}?



Since steady state has been reached, we may use simple 1st order elimination expressions for all calculations within a dosing interval. To find C_{max}, we must back extrapolate after determining k_e:

$$k_e = -m = -\frac{\ln Cp_1 - \ln Cp_2}{t_1 - t_2} = -\frac{(\ln 10.5 - \ln 6.4)}{(6-12)\,hr} = 0.08\ hr^{-1}$$

$$Cp(t) = Cp_0 \cdot e^{-k_e \cdot t} \longrightarrow Cp_0 = Cp(t) \cdot e^{+k_e \cdot t} = 10.5\,\mu g/ml \cdot e^{(0.08\,hr^{-1} \cdot 6\,hr)}$$

$$= \boxed{17.0\ \mu g/ml}$$

What will be the C_{min}?

No calculation needed as this was given (concentration 12 hrs after the dose and τ = 12 hr),

$$\boxed{6.4\ \mu g/ml}$$

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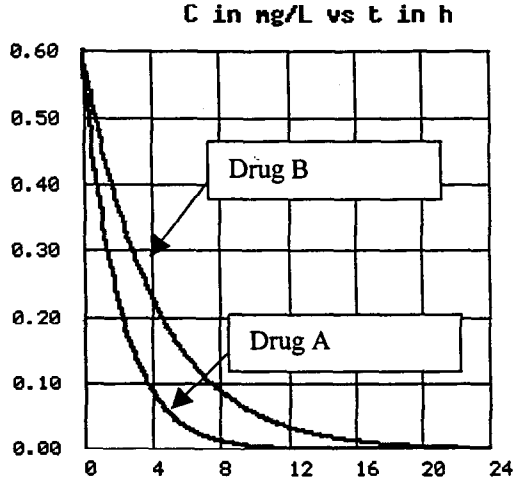
7.) The concentration time profiles of a certain drug differ in two patients, as shown in the graph. The dose was the same. What is the reason for this difference? (10 points)



C_{p_0}: Initial concentration depends on

$$C_{p_0} = \frac{D}{V_d} \Rightarrow \text{same for both}$$

If the same dose were given, we may conclude that V_d is the same for both patients.

Slope/Elimination: Rate of elimination is different between these two patients. Recall that

$$k_e = \frac{CL}{V_d}$$

Therefore, since Patient A is eliminating the drug more quickly, we know that CL is greater for patient A.

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8.) Assume a drug is predominantly cleared via the kidney. What factors (**drug properties**) determine its renal clearance (10 points)

Size
f_u
GFR
polarity / ionization / pka

9.) How is the volume of distribution of digoxin likely to change if a patient who is on digoxin also gets started on quinidine. Assume that plasma volume, tissue volume and unbound fraction of drug in plasma are unchanged. Brief explanation! (10 points)

$$\downarrow V_d = V_p + V_t \cdot \frac{f_u}{f_{u_t}\uparrow}$$

If V_p, V_t, and f_u are the same for digoxin upon coadministration of quinidine, a change in V_d must be due to tissue binding (f_{u_t}).

Quinidine may displace digoxin in tissues resulting in a lower V_d for digoxin. (Lower V_d since digoxin is not being retained in the tissues to the same degree as without quinidine).

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10.) Peter Pan is a non-smoker (60 kg) asthmatic. He is to be started on an oral regimen of aminophylline (85% of which is theophylline). The population pharmacokinetic parameters for theophylline are: F (bioavailability)=1, V=0.5 L/kg, Cl=40ml/hr/kg).

Assume that the absorption of this tablet is so fast, so that we can use i.v. model for describing plasma levels. Design an oral dosage form of aminophylline (100 mg or 200 mg tablets are available) to maintain a plasma concentration between 10 and 20 mg/L at steady state. (20 points)

$$\tau = \frac{\ln\left[C_{pss(max)}/C_{pss(min)}\right]}{k_e}$$

k_e may be determined from the population parameters given:

$$k_e = \frac{Cl}{V_d} = \frac{40\,ml/hr/kg}{0.5\,L/kg} \cdot \frac{1L}{1000\,ml} = 0.08\,hr^{-1}$$

The appropriate dosing interval is

$$\tau = \frac{\ln\left[20/10\right]}{0.08\,hr^{-1}} = 8.66\,hrs \sim \boxed{8\,hours}$$

For oral dosing, the dose may be calculated using average steady state equations. We may assume $\bar{C}_{pss} = 15\,mg/L$ is the desired average concentration at steady state (this is not exactly true mathematically).

$$\bar{C}_{pss} = \frac{D \cdot F}{Cl \cdot \tau}$$

Solving for dose D gives

$$D = \frac{\bar{C}_{pss} \cdot CL \cdot \tau}{F}$$

10) Cont'd.

$$D = \frac{(15\ mg/L)(40\ ml/hr/kg)(8\ hr)}{1} \cdot \frac{60\ kg}{1} \cdot \frac{1\ L}{1000\ ml}$$

$$= 288\ mg\ theophylline$$

Since we are administering aminophylline,

$$288\ mg\ theoph \cdot \frac{100\ mg\ aminoph}{85\ mg\ theoph} = \underline{338\ mg\ aminophylline}$$

Using the dosage forms available, we would administer

300mg aminophylline every 8 hours