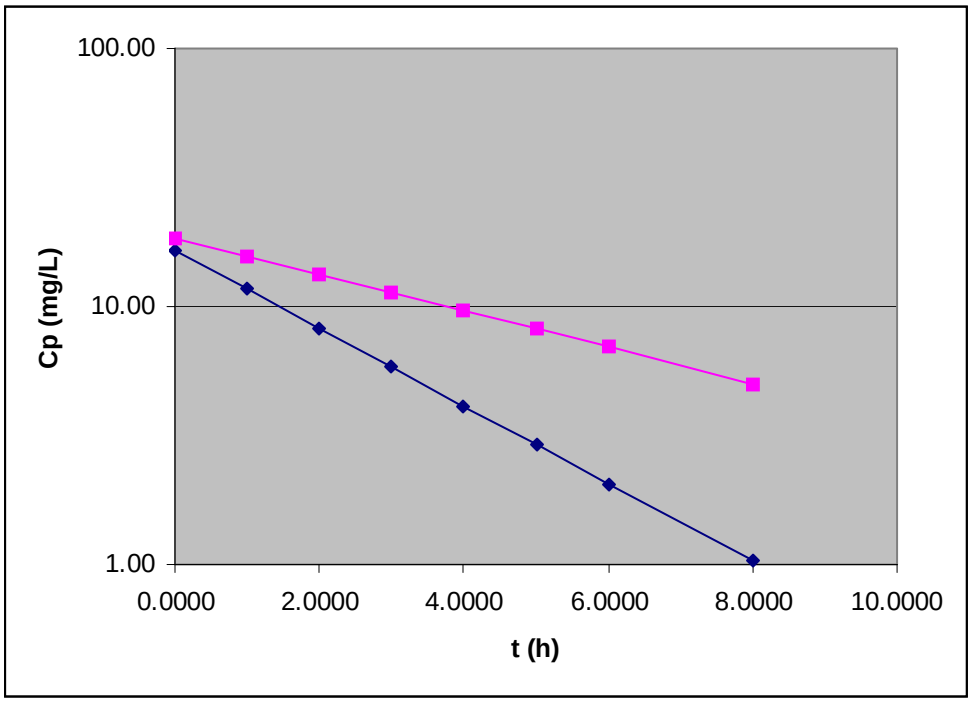
PHA 5128

Homework 1 (answers)

1. 1000 mg of a drug was given via intravenous bolus injection to two patients, one healthy subject and one suffering with cirrhosis. The following plasma concentrations were measured.

time (h)	Cp healthy (mg/L)	Cp cirrhosis (mg/L)	AUChealthy	AUC cirr
0.0000	16.47	18.25	14.06	16.89
1.0000	11.65	15.53	9.94	14.38
2.0000	8.24	13.22	7.03	12.24
3.0000	5.83	11.25	4.97	10.41
4.0000	4.12	9.58	3.52	8.86
5.0000	2.91	8.15	2.49	7.55
6.0000	2.06	6.94	3.09	11.97
8.0000	1.03	5.03	2.97	31.19

a. Prepare a semilogarihmic plot of the concentration of a drug versus time. Determine the elimination rate constants and half-lives, with cirrhosis and without, of the
drug



	Healthy	Cirrhosis
k(h-1)	0.347	0.161
t1/2(h)	2	4.3

b. Using the trapezoidal rule determine if there is a difference in the area under the curve for both. Is there a difference?

	Healthy	Cirrhosis
AUC 0-8(mg/L*h)	45.11	82.29
AUC 8-inf(mg/L*h)	2.97	31.19
AUC 0-inf(mg/L*h)	48.08	113.48

Yes there is a difference

c. Calculate the total clearance for both.

	Healthy	Cirrhosis
Cl (L/h)	20.8	8.8

d. Calculate the volume of distribution for both.

	Healthy	Cirrhosis
Vd (L)	60.7	54.8

2. A patient is admitted with an acute digoxin overdose. A serum level is measured at 10 ng/ml. Assuming a 48-hour half-life and no further drug absorption, how long does it take for the serum level to drop to the upper limit of the therapeutic range (2.0 ng/ml)?

$2 = 10\, e^{-(.693/48) * t}$

$\ln (2/10) = -(.693/48) * t$

$\frac{\ln (0.2)}{-0.0144} = t = 111.8$ hrs

3. A patient was given 1000 mg of vancomycin q36h over 30 min (i.v.) from 9:30 to 10:00 am. The following two serum levels were measured: 26.6 μg/ml at 11:00 am and 11.7 μg/ml at 10:00 am the following day. Calculate:

a. The elimination rate constant k

$$k = \frac{\ln (26.6/ 11.7)}{(24-1)} = 0.0357\ h^{-1}$$

b. The elimination half-life

$t_{1/2} = .693/0.0357 = 19.4$ h

c. The peak concentration at 10:00 am

$C_{max} = 26.2/e^{-0.0357*1} = 27.2\ \mu g/ml$

d. The concentration at 9:30 pm the following day.

$C_{min} = 11.7\ e^{-0.0357*11.5} = 7.8\ \mu g/ml$

e. The volume of distribution

$$Vd = \frac{1000\ (1 - e^{-0.0357*0.5})}{0.0357*0.5\ (27.2-7.8^{e-0.0357*0.5})} = 50.7L$$

f. The clearance

$CL = 0.0357*50.7 = 1.8\ L/h$

4. How would doubling the protein binding of a high extraction drug affect the resulting unbound and total serum levels? What recommendation would you make for dose adjustment? Assume constant rate infusion and steady state.

For a high extraction drug Cl = Q.
At steady state $C = R_0/Q$
$Cu = fu * C = fu*R_0/Q$
When the fb increases two fold, fu decreases resulting in a decrease in Cu by 50%. Dose should be doubled.

5. C. J. a 68 kg male epileptic is to be started on an oral regimen of phenobarbital. The pharmacokinetic parameters for this patient are Vd(0.65 L/kg), Cl (0.004 L/kg/h) and F (1.0). Design an oral dosage regimen of phenobarbital that will produce an average concentration of 20mg/L (16, 32, 65 and 100 mg mg tablets are marketed) for this patient, be sure to maintain a plasma concentration within the therapeutic range (15-40 mg/L). Assume the absorption of Phenobarbital is rapid and complete.

1. Calculate paients pk parameters
Cl = 0.272L/h Vd = 44.2L
$k = 0.272/44.2 = 0.0062h^-$

2. Calculate the appropriate dosing interval τ = ln(40/15)/0.0062 = 158.2 hr dosing intervals of up to 6 days are theoretically possible, for compliance reasons once daily is recommended

3. Making a dose to achieve an average concentration of 20 mg/L

D= 20*0.272*24 = 130mg or two 65mg tablets once a day.