PHA 5127
Homework 2
Fall 2002

Question 1

A 41 yr old, 60 kg female patient with gram-negative pneumonia infection, was treated with gentamicin and ampicillin. Gentamicin has been given as an iv bolus (2 mg/kg). The $AUC_{0-\infty}$ in this patient calculated from the first dose was 35.6 mg*h/L. Two weeks later, this patient was admitted to hospital again due to failure of compliance. Same medication was prescribed and the concentration-time profile of gentamicin in this patient this time was shown as following (Assume first-order elimination for gentamicin.).

Time (h)	Concentration (mg/L)
1	5.5
2	4.2
3	3.3
4	2.5
6	1.5
8	0.9

1. Calculate the CL for this patient from the first dose.
2. Calculate $AUC_{0-\infty}$, CL, Vd and $t_{1/2}$ for this patient after his second admission. Is there any change in CL in this patient? If there is a change in CL, what could be the possible reasons?

Question 2

A patient is to be started on two medications (A and B) administered by IV bolus injections. Blood samples were taken at 1 and 4 hours following the first injections of drug A or B alone in order to determine whether concentrations were in an appropriate range for each drug. See table below for these levels and additional information.

Drug	Dose (mg)	C_p at 1 h (mg/L)	C_p at 4 h (mg/L)	E_H	f_u
A	400	1.22	0.76	0.1	0.3
B	1200	0.92	0.51	0.8	0.1

Assume liver blood flow of 90 L/hr, where E_H is the extraction ratio and fu is the fraction unbound. Both drugs are metabolized by CYP 3A4.

1. Calculate $t_{1/2}$, V_d, CL_{hep}, CL_{total} and F (bioavailability) for
   (a) Drug A.
   (b) Drug B.

2. There is a drug-drug interaction between drug A and B wherein B displaces A from the binding sites on plasma proteins. If these two drug are administered at the same time, f_u for drug A will increase to 0.9. Also, drug B is a CYP3A4 inducer and the intrinsic hepatic clearance (CL_{int}) of drug A is increased by 30%.
   (c) Calculate new CL_{hep} for drug A.

Question 3

Select two drugs whose prescribing information indicates that the dose should be decreased with hepatic impairment. Describe the pharmacokinetics of these drugs and discuss why this drug's dose should be decreased. Finally, indicate specifically how you would go about decreasing this dose.