

PHA 5127  
Homework 2 - Answer key  
(Total points: 10)  
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.).

1. Calculate the CL for this patient from the first dose.

$$CL = \frac{Dose}{AUC_{0-\infty}} = \frac{2 \cdot 60}{35.6} = \mathbf{3.4 \text{ L/hr}}$$

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?

Time (h)	Conc(mg/L)	$AUC_{t1-t2}$
0	<b>7.1</b>	
1	5.5	6.3
2	4.2	4.9
3	3.3	3.8
4	2.5	2.9
6	1.5	4.0
8	0.9	2.4
$AUC_{0-8}$		<b>24.3</b>

The sum of individual AUCs is **24.3 mg\*h/L**.

- (1) Calculate the  $AUC_{0-\infty}$ .

$$k_e = \frac{\ln(C_2/C_1)}{(t_1 - t_2)} = \frac{\ln(1.5/4.2)}{(2 - 6)} = 0.26 \text{ h}^{-1}$$

$$AUC_{8-\infty} = \frac{C_x}{k_e} = \frac{0.9}{0.26} = 3.5 \text{ mg*h/L.}$$

$$AUC_{0-\infty} = AUC_{0-8} + AUC_{8-\infty} = 24.3 + 3.5 = \mathbf{27.8 \text{ mg*h/L.}}$$

$$CL = \frac{Dose}{AUC_{0-\infty}} = \frac{2 \cdot 60}{27.8} = \mathbf{4.3 \text{ L/hr}}$$

$$V_d = \frac{CL}{K_e} = \frac{4.3}{0.26} = \mathbf{16.5 \text{ L}}$$

$$t_{1/2} = \frac{\ln 2}{k_e} = \frac{0.693}{0.26} = \mathbf{2.7 \text{ hrs}}$$

One of the possible reasons for the increase in CL is that the change in plasma protein binding of the drug. If the unbound fraction of the drug increases, the clearance through liver metabolism and/or renal excretion will increase.

### 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 <sub>p</sub> at 1 h (mg/L)	C <sub>p</sub> at 4 h (mg/L)	E <sub>H</sub>	f <sub>u</sub>
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<sub>H</sub> is the extraction ratio and f<sub>u</sub> is the fraction unbound. Both drugs are metabolized by CYP 3A4.

- Calculate t<sub>1/2</sub>, V<sub>d</sub>, CL<sub>hep</sub>, CL<sub>total</sub> and F (bioavailability) for
  - Drug A.

$$k_e = \frac{\ln(C_2 / C_1)}{(t_1 - t_2)} = \frac{\ln(0.76 / 1.22)}{(1 - 4)} = 0.16 \text{ h}^{-1}$$

$$t_{1/2} = \frac{\ln 2}{k_e} = \frac{0.693}{0.16} = \mathbf{4.33 \text{ hrs}}$$

$$C_t = C_0 \cdot e^{-k_e \cdot t}$$

$$C_0 = C_t \cdot e^{k_e \cdot t} = 1.22 \cdot e^{0.16 \cdot 1} = 1.43 \text{ mg/L}$$

$$V_d = \frac{\text{Dose}}{C_0} = \frac{400}{1.43} = \mathbf{280 \text{ L}}$$

$$CL_{\text{hep}} = Q \cdot E_H = 90 \cdot 0.1 = \mathbf{9 \text{ L/hr}}$$

$$CL_{\text{total}} = V_d \cdot k_e = 280 \cdot 0.16 = \mathbf{44.2 \text{ L/hr}}$$

$$F = 1 - E_H = \mathbf{0.9}$$

- Drug B.

$$k_e = \frac{\ln(C_2 / C_1)}{(t_1 - t_2)} = \frac{\ln(0.51 / 0.92)}{(1 - 4)} = 0.20 \text{ h}^{-1}$$

$$t_{1/2} = \frac{\ln 2}{k_e} = \frac{0.693}{0.20} = \mathbf{3.47 \text{ hrs}}$$

$$C_t = C_0 \cdot e^{-k_e \cdot t}$$

$$C_0 = C_t \cdot e^{k_e \cdot t} = 0.92 \cdot e^{0.20 \cdot 1} = 1.12 \text{ mg/L}$$

$$V_d = \frac{Dose}{C_0} = \frac{1200}{1.12} = \mathbf{1071 \text{ L}}$$

$$CL_{hep} = Q \cdot E_H = 90 \cdot 0.8 = \mathbf{72 \text{ L/hr}}$$

$$CL_{total} = V_d \cdot k_e = 1071 \cdot 0.20 = \mathbf{214 \text{ L/hr}}$$

$$\mathbf{F = 1 - E_H = 0.2}$$

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.

**Method 1 (safe way to do it, and this method is preferred)**

First, to find original  $CL_{int}$

Originally,

$$CL_{hep} = \frac{Q \cdot f_u \cdot CL_{int}}{Q + f_u \cdot CL_{int}}$$

$$9 = \frac{90 \cdot 0.3 \cdot CL_{int}}{90 + 0.3 \cdot CL_{int}} \quad \text{rearrange the equation to solve } CL_{int}$$

$$CL_{int} = 33.3 \text{ L/hr}$$

Then the new  $CL_{hep}$  is equal to

$$CL'_{hep} = \frac{90 \cdot 0.9 \cdot 1.3 \cdot 33.3}{90 + 0.9 \cdot 1.3 \cdot 33.3}$$

$$CL'_{hep} = \mathbf{27.2 \text{ L/hr}}$$

**Method 2 (simple way, but risky sometimes)**

For low extraction drugs

$$\text{Originally, } CL_{hep} = f_u \cdot CL_{int} = 9 \text{ L/hr}$$

The new  $CL'_{hep}$  is equal to

$$CL'_{hep} = f'_u \cdot CL'_{int} = 3 \cdot f_u \cdot 1.3 \cdot CL_{int} = 3.9 \cdot 9 = \mathbf{35.1 \text{ L/hr}}$$

### 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.

Any two drugs belong to high extraction class such as propranolol, lidocaine verapamil, nitroglycerin, etc (See textbook on page 134).

The elimination of these drugs is mainly dependent on metabolism by the liver. Therefore, the patients with impaired liver function should be given reduced dose. The change of the dose could be based on the target concentration and the new clearance since the clearance determines the steady state drug concentration (equation:  $C_{ss} = \text{Dose} / CL$ ).

(As for low extraction drugs, the major elimination of the drugs depends on renal excretion other than liver metabolism. The patients with impaired liver function could still stay with the same dose.)