KEY
PHA 5128
First Exam
Spring 1999

1. (20 pt.) The following table shows the pharmacokinetic properties of cefuroxime:

	cefuroxime
CL [L/h]	6.8
Vd L	14
F_{oral}	0.68
F_b	0.33
F_{ren}	0.96

Calculate the total daily oral dose necessary to maintain an average unbound concentration of 20 mg/L in plasma and urine. Assume a urine flow of 1 ml/min.

$$C - \frac{F \cdot D}{CL \cdot 24} = \frac{Cu}{fu}$$

$$D = \frac{Cu \cdot CL \cdot 24}{F \cdot fu} = \frac{20 \cdot 6.8 \cdot 24}{0.68 \cdot 0.67} = 7.2g$$

<u>urine</u>

$$\frac{dE}{dt} = 20\mu g / min = 1.2mg / h$$

$$CL_{ren} = 0.96 \cdot 6.8 = 6.5 \text{ L/h} = \frac{\frac{dE}{dt}}{C}$$

$$C = \frac{1.2}{6.5} = 0.18mg / L$$

$$D = \frac{C \cdot CL \cdot 24}{F} = \frac{0.18 \cdot 6.8 \cdot 24}{0.68} = 43mg$$

2. (25pts) A patient was given 100 mg gentamicin over 30 minutes (i.v.) from 6:00 to 6:30 am. During the elimination phase, two serum levels were measured:

At 8:00 am	9.3 pg/mL
At 5:00 pm	0.5 p.g/mL

Calculate:

a. The elimination rate constant k

$$k = \frac{ln\left(\frac{9.3}{0.5}\right)}{9} = \underline{0.325h^{-1}}$$

b. The elimination half-life

$$t_{1/2} = \frac{0.693}{0.325} = \underline{2.1h}$$

c. The peak concentration at 6:30 am

$$C_{max} = \frac{9.3}{e^{-0.325 \cdot 1.5}} = \underline{15.1 \mu g / mL}$$

d. The trough concentration at 6:00 pm

$$C_{min} = 0.5 \cdot e^{-0.325 \cdot 1} = \underline{0.3 \mu g / mL}$$

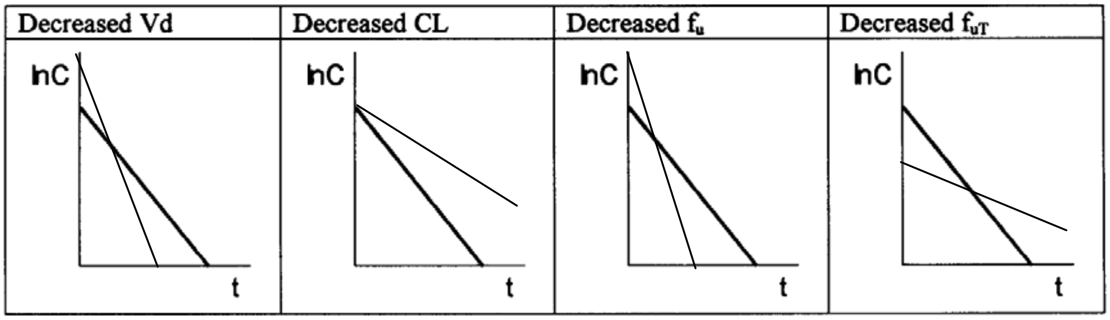
e. The volume of distribution

$$V_d = \frac{100}{0.325 \cdot 0.5} \cdot \frac{\left(1 - e^{-0.325 \cdot 0.5}\right)}{\left(15.1 - 0.3 \cdot e^{-0.325 \cdot 0.5}\right)} = \underline{6.2L}$$

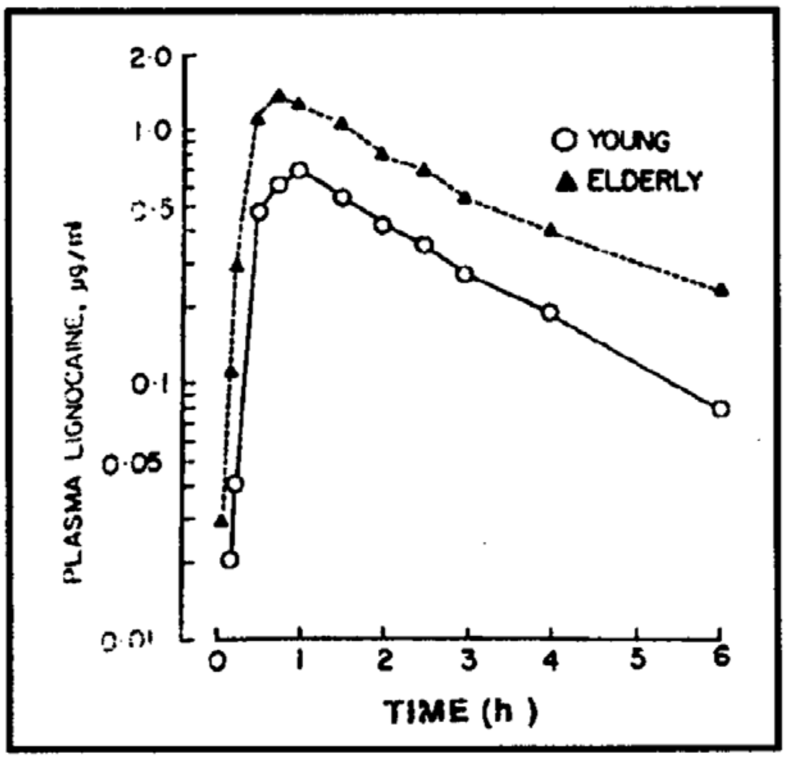
f. The clearance

CL = 0.325 · 6.2 = <u>2 L/h</u> or 34 mL/min

3. (10 pts) A high-extraction drug was given by i.v. bolus injection. Sketch the profiles for the following changes (all other primary parameters remaining constant):



4. (10 pts) In a study to compare the pharmacokinetics of 250 mg lignocaine after oral administration in old and young subjects, the following results were obtained:



Lignocaine is a high-extraction drug. Interpret the results.

Difference is due to <u>first-pass effect</u>, not clearance. First-pass effect depends on intrinsic clearance, whereas clearance is dependent on liver blood flow.

5. (20 pt.) Ciprofloxacin has a total body clearance of 6 mL/min/kg. 65% of the absorbed drug is renally eliminated, the remainder is hepatically eliminated. The plasma protein binding is 40%. The oral bioavailability is 60%. The volume of distribution is 1.8 L/kg.

For a 70 kg patient, calculate

a. the total body clearance

CL = 6.70 = 420 mL/min = <u>25.2 L/h</u>

b. the renal clearance

CL_{ren} = 0.65 · 25.2 = <u>16.4 L/h</u> or 273 mL/min

c. the elimination half-life

V_d = 1.8 · 70 = 126 L

$$t_{1/2} = \frac{0.693 \cdot V_d}{CL} = \frac{0.693 \cdot 126}{25.2} = \underline{3.5h}$$

d. the hepatic extraction ratio

CL_H = 0.35 · 25.2 = 8.8 L/h

$$E_H = \frac{CL_H}{Q} = \frac{8.8}{90} = \underline{0.1}$$

e. the intrinsic hepatic clearance

$$0.1 = \frac{0.6 \cdot CL_{int}}{90 + 0.6 \cdot CL_{int}}$$

$9 + 0.06 \cdot CL_{int} = 0.6 \cdot CL_{int}$

$$CL_{int} = \frac{9}{0.54} = \underline{16.7 L/h}$$

f. the fraction of the absorbed drug excreted by tubular secretion

CL_{ren} = 273 mL/min

GFR = 125 mL/min

$$F_{TS} = \frac{11.9}{25.2} = 0.47$$

CL_{TS} = 273-75 = 198 mL/min = 11.9 L/h

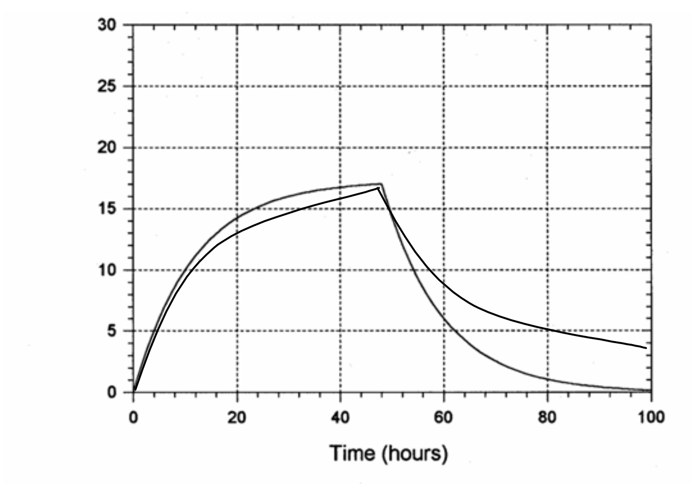
CL_{GFR} = 125 · 0.6 = 75

g. the expected oral bioavailability assuming complete absorption and first-pass effect

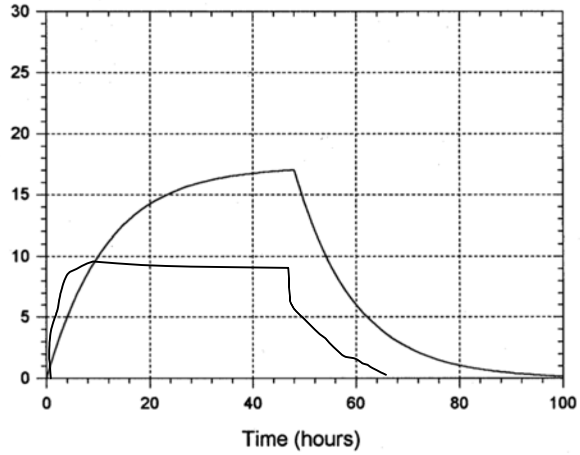
F = 1 - E_H = 0.9

6. (10 pts) Theophylline is administered as a constant rate infusion over 2 days. A plasma concentration profile is obtained which is shown in the two figures below.

a. In the graph below, add the expected curve for a patient with equal clearance but twice the volume of distribution



b. In the graph below, add the expected curve in a smoker with equal volume of distribution but twice the clearance.



7. (5 pts) In a study the volume of distribution for diazepam was found to be 13 L in a group of normal weight subjects (average weight 55 kg) and 19 L in a group of obese subjects (average weight 104 kg).

Discuss the results.

<u>Normal</u>

$$Vd = \frac{13}{55} = 0.24 L/kg$$

<u>Obese</u>

EBW = 105-55 = 49 kg

Additional $Vd = \frac{6}{49} = 0.12 L/kg$ (only 50% of IBW)

$\rightarrow$the uptake is 50% of that in IBW

$$Vd = 0.24 \cdot (IBW + 0.5 \cdot EBW)$$