PHA 5128
Spring 2001
Final Exam

TYPED KEY

1. Joy is a 25 year old 60 kg chronic asthmatic who is hospitalized with severe asthma. She is treated there with aerosol albuterol, but has a poor response. She is then given 375 mg if IV aminophylline over 30 minutes. Thirty minutes after the loading dose was administered (60 minutes from time zero) the theophylline concentration was 10 μg/ml. She has normal liver, kidney, and cardiac function and is afebrile. After the loading dose, Joy was started on an IV aminophylline constant infusion of 60 mg/hr, solu-Medrol 40 mg IV q6h, and albuterol nebulization q1h. Eight hours after the first serum level, a second level was 19 μg/ml.

a. Using Joy's actual volume of distribution, calculate her expected steady state theophylline concentration for this infusion rate.

$$Vd = \frac{D}{C_0} = \frac{375 \cdot 0.85}{10} = 31.9L$$

$$CL = \frac{2 \cdot 60 \cdot 0.85}{(10+19)} + \frac{2 \cdot 31.9 \cdot (10-19)}{(10+19) \cdot 8} = 3.52 - 2.48 = 1.04 L/h$$

$$C = \frac{60 \cdot 0.85}{1.04} = 49 \mu g/mL$$

b. Make a recommendation for a dose adjustment

-Immediately stop the infusion!
-New Dose

$$R_0 = \frac{15 \cdot 1.04}{0.85} = 1.84 \rightarrow 20 mg/hr$$

-Keep monitoring

2. A 3 month old infant, born at full- term gestational age, is admitted to Shands Hospital for possible pneumonia. The infant weighs 3.5 kg. Ampicillin 175 mg iv q 6 hr and Gentamicin 5 mg iv (30 min. infusion) tid (06-14-22) is started. On day 3 of therapy, Gentamicin serum concentrations are drawn as listed below:
gentamicin serum conc. 0.9 μg/ml drawn at 0530
Gentamicin serum conc. 5.5 μg/ml drawn at 1500

a. Determine the k_e, $t_{1/2}$, V_d and CL of gentamicin in this patient.

$$K = \frac{ln\frac{5.5}{0.9}}{6.5} = 0.28h^{-1}$$

$t_{1/2}$ = 2.5 h

$$C_{max} = \frac{5.5}{e^{-0.28\cdot 0.5}} = 6.3\mu g / mL$$

$$C_{min} = 0.9 \cdot e^{-0.28\cdot 0.5} = 0.78 g / mL$$

$$Vd = \frac{5}{0.28 \cdot 0.5} \cdot \frac{\left(1 - e^{-0.28\cdot 0.5}\right)}{\left(6.3 - 0.78 \cdot e^{-0.28\cdot 0.5}\right)} = 35.7 \cdot \frac{0.131}{5.62} = 0.83L$$

CL = 0.28 · 0.83 = 0.23 L/h

b. Calculate the dose and dosage schedule necessary to achieve a measured peak serum gentamicin concentration (30 min. after the end of the infusion) of 8 μg/ml and a measured trough (30 min. before the end of the dosing interval) of 1 μg/ml.

$$C_{max} = \frac{8}{e^{-0.28\cdot 0.5}} = 9.2 g / mL$$

$$C_{min} = 1 \cdot e^{-0.28\cdot 0.5} = 0.87\mu g / mL$$

$$\tau = \frac{ln\frac{9.2}{0.87}}{0.28} = 8.4 \Rightarrow 8h$$

$$D = 9.2 \cdot 0.28 \cdot 0.83 \cdot 0.5 \cdot \frac{\left[1 - e^{-0.28\cdot 8}\right]}{\left[1 - e^{-0.28\cdot 0.5}\right]} = 7.3 \Rightarrow 7mg$$

7mg q8h

c. Gentamicin is sent to the floor in syringes, with 8 mg giving a volume of 0.5 ml per syringe. What volume needs to be administered?

0.5 · (7/8) = 0.438 mL

3. Cyclosporine has an average volume of distribution of 4.5 L/kg and clearance of 7 ml/min/kg. Currently, the recommended therapeutic range in whole blood is 150-400 ng/ml for the trough concentration. The average absorption half-life is 30 minutes. Recent studies have reported that the cyclosporine peak concentration may be a better correlate for therapeutic efficacy.

a. For a 500 mg bid treatment in a 70 kg patient and an oral bioavailability of 30%, calculate the expected peak and trough concentrations.

$$k_a = \frac{0.693}{0.5} = 1.39h^{-1}$$

CL = 490 mL/min = 29.4 L/h

V_d = 4.5 · 70 = 315 L

$$k_e \frac{29.4}{315} = 0.093h^{-1}$$

$$t_{max} = \frac{ln\left[\frac{1.39\cdot\left(1-e^{-0.093\cdot 12}\right)}{0.093\cdot\left(1-e^{-1.39\cdot 12}\right)}\right]}{1.39-0.093} = \frac{ln\left(\frac{1.39-0.672}{0.093\cdot 1}\right)}{1.297} = 1.8h$$

$$C_{max} = \frac{0.3\cdot 500\cdot 1.39}{(1.39-0.093)\cdot 315}\cdot\left[\frac{e^{-0.093\cdot 18}}{1-e^{-0.093\cdot 12}} - \frac{e^{-1.39\cdot 1.8}}{1-e^{-1.39\cdot 12}}\right]$$

$$= 0.51\cdot\left(\frac{0.846}{0.672} - \frac{0.082}{1} = 0.6 \Rightarrow 600ng/mL\right)$$

$$C_{min} = 0.51\cdot\left(\frac{0.328}{0.672} - 0\right) = 0.249 \Rightarrow 250ng/mL$$

b. Give a therapeutic range for the peak concentrations that is equivalent to the 150-400 ng/ml range based on trough values.

Based on linear PK $\rightarrow \frac{C_{max}}{C_{min}} = \frac{600}{250} = 2.4$

Range for peak levels: $150 \cdot 24 = 360$
$400 \cdot 2.4 = 960$ } 400-1000 ng/mL

4. F.R. a 38 year-old, 70 kg male, had been taking 300 mg/day of sodium phenytoin; however, his dose was increased to 400 mg/day because his seizures were poorly controlled and because his plasma concentration was only 7 mg/L. Now he complains of minor CNS side effects and his reported plasma phenytoin concentration is 23 mg/L. Renal and hepatic function are normal. Assume that both of the reported plasma concentrations represent steady-state levels and that F.R. has complied with the prescribed dosing regimens.

a. Calculate F.R.'s apparent Vm and Km and a new daily dose of phenytoin that will result in a steady-state level of about 15 mg/L.

$$Vm = \frac{300 \cdot 400 \cdot (23-7)}{23 \cdot 300 - 7 \cdot 400} = 468 mg\ sodium\ phenytoin = 430\ mg\ phenytoin$$

$$Km = \frac{7 \cdot (468-300)}{300} = 3.92 \mu g / mL$$

$$D = \frac{468 \cdot 15}{3.92 + 15} = 371\ mg \rightarrow 375 mg\ sodium\ phenytoin$$

b. Estimate the phenytoin clearance, volume of distribution and half-life at 23 mg/L.

$$CL = \frac{R_0}{C} = \frac{Vm}{Km + C} = \frac{430}{3.92 + 23} = 16 L / d$$

$V_d = 0.65 \cdot 70 = 45.5$ L

$t_{1/2} = 2$ days

5. Depakene Syrup (Valproic Acid) is to be given to a 70 kg female. In a previous trial of a single dose of Depakene (500 mg) in the same patient, it was noted that after 24 hours of elimination an initial concentration of 45 μg/ml had been reduced to 12.8 μg/ml.

a. Calculate the volume of distribution, clearance and half-life in this patient and compare with the population averages.

$$k = \frac{ln\frac{45}{12.8}}{24} = 0.052h^{-1}$$

$$V_d = \frac{500}{45} = 11.1L$$

CL = 0.58 L/h

$t_{1/2}$ = 13.2 h

Pop. Average

V_d = 0.14 · 70 = 9.8 L

CL = 0.008 · 70 = 0.56 L/h

$t_{1/2}$ = 11h

Good agreement

b. Suggest a dosing regimen for chronic treatment.

$$\tau = \frac{ln\frac{100}{50}}{0.052} = 13.3 \rightarrow 12h$$

MD = 75 · 0.58 · 12 = 522 mg → 500 mg

500 mg bid

6. Jeff is a 50 kg 14 year old adolescent with chronic asthma who has been taking SloBid 400 mg (2x200 mg slow-release theophylline) Q12h for over a year. On this regimen a 4 hour serum theophylline concentration was 15.2 μg/ml and his asthma was well controlled. However, he has been depressed and this morning he took 50 capsules in an attempt at suicide. About 2 hours later he begins projectile vomiting and has a pounding headache. He gets scared and calls 911. At the emergency department, he is given droperidol to control the vomiting and is started on oral activated charcoal by nasogastric tube, 20 mg Q 2h. A stat theophylline serum concentration measurement was 50 μg/ml, his heart rate was 140 bpm and his blood pressure was 100/60. He is able to hold down the charcoal.

a. Calculate the theophylline clearance for this patient.

$$CL = \frac{400}{15.2 \cdot 12} = 2.2 L/h$$

b. How long will they have to treat the patient with charcoal to lower the serum concentration to 12.5 mcg/ml?

$V_d = 0.5 \cdot 50 = 25L$

$K = 0.088\ h^{-1}$

$$t = \frac{ln\frac{50}{12.5}}{0.088} = 15.8h \quad \text{(2 half-lives)}$$

7. A patient (35 years old, 65 kg) is to be started on phenobarbital sodium.

a. Calculate a loading dose to yield a C_{p0} of 30 mg/L.

$$LD = \frac{30 \cdot 0.65 \cdot 65}{0.9} = 1408mg \Rightarrow 1.4g$$

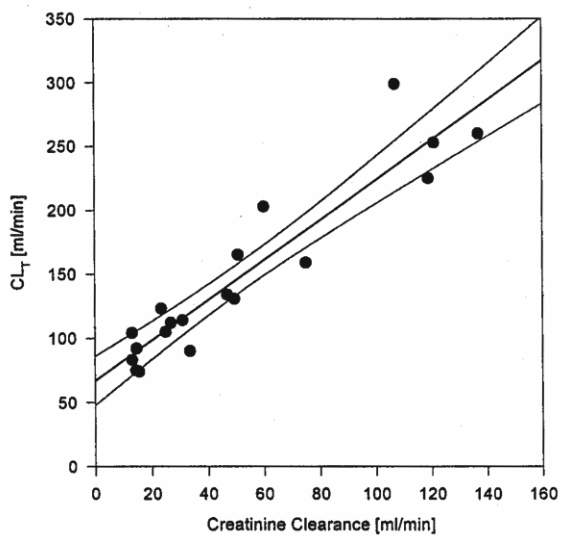
b. Calculate a daily maintenance dose to produce an average steady state concentration of 20 mg/L.

$$MD = \frac{20 \cdot 0.004 \cdot 65 \cdot 24}{0.9} = 139mg \Rightarrow 140mg / day$$

c. The same patient is to be treated simultaneously with carbamazepine. Propose an oral maintenance dosing regiment for carbamazepine for this patient to achieve a carbamazepine level of 6 μg/mL.

$$MD = \frac{6 \cdot 0.1 \cdot 65 \cdot 24}{0.8} = 1170mg \Rightarrow 600mgbid$$

8. In a study in patients with various degrees of renal impairment the following relationship was found for piperacillin:



The volume of distribution in the elimination phase (Vd_{area}) was 19 L and independent of renal function.

a. For a patient with normal renal function and a patient with impaired renal function (CL_{CR} 25 ml/min), estimate the clearance, half-life and the percentage of the dose excreted into the urine.

	Normal	**Impaired**
CL	250 mL/min	100 mL/min
$t_{1/2}$	0.9 h	2.2 h
CL_{NR}	70 mL/min	70 mL/min
CL_R	180 mL/min	30 mL/min
F_R	72%	30%
k	0.79 h^{-1}	0.32 h^{-1}

b. Design an intravenous bolus multiple dosing regimen for both patients to achieve steady state peak and trough concentrations of 100 and 5 μg/ml, respectively.

	Normal	**Impaired**
τ	$\frac{ln\frac{100}{5}}{0.79} = 3.8 \Rightarrow 4h$	$\frac{ln\frac{100}{5}}{0.32} = 9.4 \Rightarrow 8h$
D	52.5·0.25·60·4=3150	52.5·0.1·60·8=2520
	3 g q4h	2.5 or 3g q8h

c. The volume of distribution at steady state (Vd_{ss}) for piperacillin is 14 L. Explain the difference between Vd_{area}

$Vd_{area} = V_d$ during elimination phase,

$Vd_{ss} = V_d$ at steady state,

Lower Cp $\Rightarrow$larger V_d $\rightarrow$ $Vd_{area} > Vd_{ss}$