PHA 5128
Spring 2010
Final Exam Key

1	**Renal Disease**
2	**Digoxin**
3	**Cyclosporine**
4	**Methotrexate**
5	**Phenobarbital**
6	**Carbamazepine**
7	**Valproic Acid**
8	**Phenytoin**
9	**Phenytoin**
10	**Theophylline**
11	**Lidocaine, Procainamide**
12	**Geriatrics**
13	**Aminoglycosides**
14	**Drug-Drug-Interactions**

1.)

The recommended dose for drug X for people with a normal renal function (Cp_{creat} = 0.6 mg/dl) is 10mg/kg/day. A patient (male, 50 year old, 60 kg, not obese) has Cl_{Cr} of 25 ml/min. Calculate an individual dose for this patient. Assuming drug X is only eliminated by the kidneys (only filtration, no active secretion, and no reabsorption).

A 1200mg/day
B 600mg/day
C 240mg/day
D 120mg/day
E 60mg/day

Cl_{cr} normal = [(140-50)*60]/ (72*0.6) =125(ml/min)

Dose $_{patient}$ = 600 mg * 25/125 = 120 mg/day

2.)

A patient (50 years old, IBW = 50 kg, Sr_{Cr} = 2.5 mg/dL, female) was diagnosed with congestive heart failure. She had been taking 0.25 mg digoxin qd for 3 months. The digoxin plasma concentration was determined to be 5μg/L. How long will it take for the concentration to fall back to 1 μg/L?

A 8 hours
B 8 days
C 6 days
D 6 hours
C 7 days

Cl_{Cr}=(female) = (140-50)*50/85/2.5 = 21.2 ml/min

$CL_{(CHF\ patient)}$ =0.33*50+0.9 * 21.2 = 35.6(ml/min) =35.6 *60 *24 /1000= 51.26(L/day)

Vd =3.8*50+3.1*21.2=255.7(L)

K = CL/Vd= 51.26/255.7= 0.2 1/day
T = ln(C_1/C_2)/ K = ln (5/1)/0.2=8 days

3.)

A 70 kg liver transplant patient, is receiving 450 mg cyclosporine QD as an IV infusion. Currently, his hepatic function tests appear to be stable, and for the past three days he has been improving clinically with steady-state trough cyclosporine concentrations of approximately 220 µg/L. What would be an appropriate oral cyclosporine dose for him?

A 1300 mg/day
B 1500 mg/day
C 900 mg/day
D 500 mg/day
E 300 mg/day

Dose new= $\frac{Cp_{ssdesired}}{Cp_{sscurrent}} * \frac{F_{current}}{Fnew} * Dose_{current} = \frac{220}{220} * \frac{1.0}{0.3} * 450 = \mathbf{1500(mg/day)}$

4.)

S.V., a 34 year-old female patient (54 kg, SeCr 1.1 mg/dl) received a 30 mg methotrexate loading dose (IV bolus) followed by a 30 mg/h infusion over 36 hours. Her plasma concentration levels at 24h and 48h were 12.8 µM and 0.80 µM, respectively. Calculate the anticipated methotrexate level at 70 hours.

A 0.04 µM
B 0.14 µM
C 0.24 µM
D 0.34 µM
E 0.44 µM

$\mathbf{K_1} = \frac{\ln(C1/C2)}{t} = \frac{\ln(12.8/0.80)}{12} = 0.231\mathbf{(h^{-1})}$

$t_{1/2\,1}$ = 0.693/0.231=3 (h)

t at 0.5 µM

t= $\frac{\ln(C1/C2')}{K1} = \frac{\ln(12.8/0.5)}{0.231}$ **=14.0 (h)**

$t_{1/2\,1}$ = 3h $t_{1/2\,2}$= 10h

K_2 =0.693/10= 0.0693(h^{-1})

T= 70-14.0-36=20(h)
Cp_{70h}=0.5*$e^{-0.0693*20}$= 0.125(µM)

5.)

Mr. B.K., a 68-year-old, 75-kilogram, alcoholic, epileptic patient, has been taking phenobarbital; (200 mg at night before sleeping time) for three years. He has been diagnosed free of seizures for at least one year. He recently was admitted to the hospital with ataxia and general central nervous system depression. There was no trace of alcohol in his breath. A plasma phenobarbital concentration of 50 milligrams/liter was measured in a blood sample drawn at 11:00 A.M. of that day. The drug was discontinued (including no dose on the day he was admitted to the hospital). Another blood sample was obtained on day 5 at 10:00 A.M.to determine if the patient was metabolizing the drug more slowly than expected**,** as the patient had signs of hepatic cirrhosis. The second concentration was 12 milligrams/liter. Assume: Vd = 0.7 L/kg

Estimate the values of clearance, volume of distribution and expected half-life in this patient.

$$k_e = \frac{\ln\left(\frac{50}{12}\right)}{120-1} = 0.01199 \ \mathbf{h^{-1}}$$

$t_{1/2}$ = $\frac{0.693}{0.01199}$ **= 57.798 h or ~ <u>58 h</u>**

V_d = 0.7 * 75 = <u>52.5 L</u>

CL = 0.01199 * 52.5 = <u>0.6295 L/h</u>

A 0.36 L/h; 52.5 L, 58 h
B 0.54 L/h; 45.5 L; 58 h
C 0.63 L/h; 52.5 L; 58 h
D 0.39 L/h; 44.5 L; 79 h

6.)

A patient (35 years old, 55 kg) is to be started on phenobarbital sodium.

a. Calculate a loading dose to yield a C_{p0} of 30 mg/L
b. Calculate a daily maintenance dose to produce an average steady state concentration of 22 mg/L.
c. The same patient is to be treated simultaneously with carbamazepine. Propose an oral maintenance dosing regimen for carbamazepine for this patient to achieve a carbamazepine level of 6 µg/mL.

A (a) LD 1.3g; MD (b) 130 mg/day; MD (c) 500 mg bid
B (a) LD 1191 g; MD (b) 500 mg/day; MD(c) 130 mg bid
C (a) LD 1091 g; MD (b) 130 mg/day; MD (c) 500 mg bid
D (a) LD 1.3g; MD (b) 130 mg/day; MD(c) 990 mg bid

LD = Cp0*VD/S = 30 * 0.7 * 55 / 0.9 = 1.3 g

MD = $\frac{22*0.004*55*24}{0.9} = 129.07$ **mg or 130 mg/day**

MD = $\frac{6*0.1*55*24}{0.8} = 990$ **mg or 500 mg bid**

7.)

What is his expected trough concentration in this the following case:

R.M, a 10 year old 30 kg male receives 250 mg valproic acid every 12 hours via IV bolus injection for his absence seizures. But his seizures are only partially controlled. He reports no adverse effects at this dosing, and his renal and hepatic functions are normal.

CL=13ml/kg/h *BW=13ml/kg/h * 30 kg = 390 ml/h or 0.390 l/h
Vd = 0.14*L/kg *BW=0.14*L/kg * 30kg = 4.2 L
Using this we can calculate his ke:

Ke = Cl/Vd = 0.0928 h^{-1}
and
t1/2 = ln2 / ke = 7.5 h

Assuming steady state has been achieved and S and F = 1

Cssmin= [(S*F*Dose / Vd) / (1-$e^{-ke*tau}$**)] *** $e^{-ke*tau}$ **= 29.12 mg/l**

A 30 mg/L
B 25 mg/L
C 35 mg/L
D 30 µg/L
E 35 µg/L

8.) **10 points will be given to each student**

Which of following statement is correct about phenytoin?

1) The metabolism of phenytoin is capacity–limited which means that the clearances values increase with increasing plasma concentrations (at high concentrations).
2) The bioavailability of phenytoin is difficult to evaluate because of the drug's capacity–limited metabolism.
3) The steady state of the phenytoin is approximately reached after 5 times the apparent half-life.
4) The side effect of nausea and vomiting usually can be lowered or avoided by dividing loading dose of phenytoin into three separate doses.
5) Phenytoin shows nonlinear pharmacokinetics, we can use AUC=D/CL to calculate its AUC.

A 1, 2, 5
B 2, 3, 4
C 1, 2, 4
D 2, 3, 5
E) All of the above are correct

9.)

For patient L.T, a 70kg male, 300mg/day IV phenytoin was given as maintenance dose, the steady state concentration was found to be 8 mg/L. Then the maintenance dose was increased to 400 mg/day, the steady state concentration was later found to be 23 mg/L. This level was considered to be too high for this patient, so the maintenance dose was discontinued. How long would it take for the concentration to drop to 15 mg/L after discontinuation of dose?

A) 12h
B) 17h
C) 23h
D) 33h
E) 1h

$$t = \frac{\left[Km \times ln\left(\frac{C_1}{C_2}\right) + C_1 - C_2\right] \times Vd}{Vmax}$$

$$V_{max} == \frac{D_1 \cdot D_2 \cdot (C_2 - C_1)}{C_2 \cdot D_1 - C_2 \cdot D_2} = \frac{300 \cdot 400 \cdot (23-8)}{23 \cdot 300 - 8 \cdot 400} = 486.5 mg/day$$

$$K_m = \frac{C_1(V_{max} - D_1)}{D_1} = \frac{8 \times (486.5 - 300)}{300} = 4.97 mg/L$$

Vd=0.65L/kg*70kg=45.5L

$$t = \frac{\left[Km \times ln\left(\frac{C_1}{C_2}\right) + C_1 - C_2\right] \times Vd}{Vmax} = \frac{\left[4.97 \times ln\left(\frac{23}{15}\right) + 23 - 15\right] \times 45.5L}{486.5}$$
$$= 0.947day \approx 23h$$

10.)

D.P. is a 45 year old male, 75 kg, 6'1", intermittent asthmatic who shows symptoms of severe dyspnea, coughing, and wheezing. He is treated there with aerosol albuterol, but only partially clears. He is then given 500 mg of IV aminophylline (S = 0.85) over 30 minutes. Thirty minutes after finishing the IV infusion loading dose, the theophylline concentration was 15 µg/mL. After the loading dose, D.P. was started on an IV theophylline constant infusion of 50 mg/hr, Solu-Medrol IV and albuterol nebulization. Eight hours after the first serum level, a second level was 8 µg/ml. Calculate D.P.'s total body clearance, a second IV loading dose to increase his level from 8 µg/ml to 15 µg/ml, and the IV aminophylline infusion rate to maintain the concentration at 15 µg/ml.

A) CL=12L/h, LD=380mg, MD=150mg
B) CL=108mL/min, LD=230ug, MD=115ug
C) CL=6.5L/h, LD=230mg, MD=115mg
D) CL=3L/h, LD=200ug, MD=90ug
E) CL=50L/h, LD=200mg, MD=90mg

$$Vd = \frac{Dose \times F \times S}{Cp} = \frac{500mg \times 1 \times 0.85}{15mg/L} = 28.33L$$

Chiou: $CL = \frac{2 \times R_0}{(C_1 + C_2)} + \frac{2 \times Vd \times (C_1 - C_2)}{(C_1 + C_2) \times (t_2 - t_1)} = \frac{2 \times 50mg/h}{(8+15)} + \frac{2 \times 28.33 \times (15-8)}{(15+8) \times 8h} = 4.348 + 2.156 = 6.5L/h$

$$LD = \frac{\Delta Cp \times Vd}{S \times F} = \frac{7mg/L \times 28.33L}{0.85 \times 1} = 233.3mg \approx 230mg$$

$$MD = \frac{Cpss \times CL}{S \times F} = \frac{15mg/L \times 6.5Lh}{0.85 \times 1} = 114.7mg \approx 115mg$$

11.)

Lidocaine was given as bolus dose follow by infusion at 2 mg/min to a 50 year-old female (5'4", 125 lbs) who has just been admitted to the emergency room with ventricular tachycardia and chest pain consistent with an evolving myocardial infarction. Routine laboratory analyses reveal a serum creatinine and BUN of 3.0 and 48 mg/100 ml, respectively. Although lidocaine eliminates ventricular tachycardia, frequent hemodynamically significant ventricular ectopy is still present 12 hours later. Procainamide is given first as a loading dose of 17 mg/kg over one hour and then followed by a maintenance infusion of 120 mg/hour. Serum concentrations of procainamide and NAPA at the end of the loading infusion are 7 and 4 mg/L, respectively. Serum concentrations of procainamide one, six, and 24 hours following initiation of maintenance infusion are 7, 8 and 9 mg/L, respectively. Corresponding values for NAPA are 4, 9, and 14 mg/L, respectively. Ventricular ectopy is completely abolished beginning about 30 minutes after the loading infusion was administered and no further arrhythmias are noted. The physician now wants to dose procainamide orally. Make an appropriate dose recommendation for use of oral procainamide in this patient dose (Cp_{ss} = 9mg/L, tau = 6h)

A. 1400 mg
B. 250 mg
C. 1200 mg
D. 830 mg
E. 360 mg

$$weight/kg = 125lbs. \cdot 0.454 = 56.75kg$$

$$CL = \frac{R_0 \cdot F \cdot S}{Cp_{ss}} = \frac{120mg/h \cdot 1 \cdot 0.85}{9mg/L} = 11.33L/h$$

$$Vd = \frac{LD \cdot F \cdot S}{Cp_0} = \frac{17mg/kg \cdot 56.75kg \cdot 1 \cdot 0.85}{7mg/L} = 117.15L$$

$$t_{1/2} = \frac{0.693 \cdot Vd}{CL} = \frac{0.693 \cdot 117.15L}{11.33L/h} = 7.17h \approx 7h \Rightarrow k_e \frac{0.693}{t_{1/2}} = \frac{0.693}{7h} = 0.099h^{-1}$$

Dose = Cpss*CL*tau/(F*S) = 9*11.33*6/(.85*.87) = 830 mg

12.)

Please choose the right answer for tissue distribution in Elderly:

1. decreased total body water
2. increased intracellular water
3. little change in extracellular water
4. less fat tissue
5. less lean body mass (muscle)

A) 1, 2, 5
B) 1, 3, 5
C) 2, 3, 4, 5
D) 3, 4, 5
E) All of the above

13.)

A male patient receives amikacin via IV infusion at a rate of 2600 mg/h over 30 minutes at a dosing interval of 12 hours. Plasma concentrations at steady state were determined as 28 mg/L (30 minutes after stop of the infusion) and 4 mg/L (30 minutes before the next infusion was started). Calculate the apparent volume of distribution of the patient.

$$\boldsymbol{Vd = \frac{Dose}{k * T}\frac{\left(1 - e^{-kT}\right)}{(C_{max} - C_{min} * e^{-kT})}}$$

$$\boldsymbol{k = \frac{ln\left(\frac{C_{max}{}^{*}}{C_{min}{}^{*}}\right)}{\Delta t} = \frac{ln\left(\frac{28}{4}\right)}{10.5h} = 0.185\frac{1}{h}}$$

$$\boldsymbol{C_{max} = \frac{C_{max}{}^{*}}{e^{-kt_{max}{}^{*}}} = \frac{28\frac{mg}{L}}{e^{-0.185\frac{1}{h}*0.5h}} = 30.71\frac{mg}{L}}$$

$$\boldsymbol{C_{min} = C_{min}{}^{*}e^{-kt_{min}{}^{*}} = 4\frac{mg}{L} * e^{-0.185\frac{1}{h}*0.5h} = 3.65\frac{mg}{L}}$$

$$\boldsymbol{Vd = \frac{1300mg}{0.185\frac{1}{h} * 0.5h}\frac{\left(1 - e^{-0.185\frac{1}{h}*0.5h}\right)}{\left(30.71\frac{mg}{L} - 3.65\frac{mg}{L} * e^{-0.185\frac{1}{h}*0.5h}\right)} =}$$

$$\boldsymbol{14054.054mg\frac{(0.0884)}{\left(27.38\frac{mg}{L}\right)} = 45.37L}$$

A 30 L

B 35 L

C 40 L

D 45 L

E 50 L

14.)

Drug A, which is known to be a low-extraction drug, is given as an IV infusion. How would simultaneous administration of drug B that is known to significantly induce the main metabolic enzymes of drug A affect the plasma concentration at steady state (Cp_{ss}) of drug A?

Recall:

$$Cp_{ss,total} = \frac{Dose}{CL * \tau}$$

$$CL = f_u * CL_{int}$$

$$\downarrow Cp_{ss,total} = \frac{Dose}{f_u * CL_{int} \uparrow * \tau}$$

A Cp_{ss} increases

B Cp_{ss} does not change

C Cp_{ss} decreases

Digoxin

Vd [L]	3.8·IBW [kg] +3.1·CL_{Cr}[mL/min]
CL [mL/min]	0.8·IBW + CL_{Cr} [mL/min]
(CHF)	0.33·IBW + 0.9· CL_{Cr} [mL/min]
$t_{1/2}$ [h]	40
% renal	60
F	0.7 (T), 0.8 (E), 1.0 (C)
S	1
C_{max} [ng/mL]	< 2
C_{min} [ng/mL]	> 0.8

Clearance-Factor:

Quinidine	0.5
Amiodarone	0.5
Verapamil	0.75
Hyperthyroidism	1.3
Hypothyrodism	0.7

Vol.Distribution-Factor

Quinidine	0.7
Hyperthyroidism	1.3
Hypothyrodism	0.7

Cyclosporine

Vd [L/kg]	4.5 L/kg
CL [L/h/kg]	0.5
$t_{1/2}$ [h]	7
% renal	-
F	0.3
S	-
f_u	0.1
C_{max} [ng/mL]	<400
C_{min} [ng/mL]	>150

Dosing Weight: TBW

Available oral doses: 25 mg, 100 mg

Methotrexate

Vd [L/kg]	0.2 (V_c) 0.7 (Vd)
CL [L/h/kg]	1.6·CL_{Cr}
$t_{1/2}$ [h]	3 > 0.5 µM 10 < 0.5 µM
% renal	80
F	1 (<30mg/m²)
S	1
f_u	0.5

µM = mg/L/0.454

MTX

LD and 36h-Infusion

Leucovorin-Rescue

10 mg/m² Q6h for 72h or MTX<0.1 µM

If MTX > 1 µM at 48h, increase Leucovorin to 50-100 mg/m² Q6h

Body Surface Area

$$BSA = \left(\frac{TBW}{70}\right)^{0.73} \cdot 1.73m^2$$

Phenobarbital

Vd [L/kg]	0.7
CL [L/h/kg]	0.004 (ad.) 0.008 (ch.)
$t_{1/2}$ [h]	120 (ad.) 60 (ch.)
% renal	25
F	1
S	0.9 (sodium)
C_{max} [mg/L]	<40
C_{min} [mg/L]	>15

BW	TBW
f_u	0.5

Carbamazepine

Vd [L/kg]	1.4 (variable)
CL [L/h/kg]	0.064 (mono)
	0.1 (poly)
$t_{1/2}$ [h]	30 (first dose)
	15 (mono)
	10 (poly)
% renal	0
F	0.8 IR (0.7 XR)
S	1
C_{max} [mg/L]	< 12
C_{min} [mg/L]	> 4

Autoinduction

BW	TBW
f_u	0.25

Valproic Acid

Vd [L/kg]	0.14 (variable)
CL [L/h/kg]	0.008 (adults)
	0.013 (children)
$t_{1/2}$ [h]	11 (adults)
	7 (children)
% renal	2
F	1
S	1
C_{max} [mg/L]	< 100
C_{min} [mg/L]	> 50

BW	TBW
f_u	0.1 (saturable)

Phenytoin

Vd [L/kg]	0.65
V_{max} [mg/kg/day]	7
K_M [mg/L]	4
% renal	2
F	1
S	0.92
C_{max} [mg/L]	<20
C_{min} [mg/L]	>10

Oral Products: 30, 50, 100 200, 300

Bid or qd (Sustained Release)

$$C = \frac{K_M \cdot R_0}{V_{max} - R_0}$$

$$R_0 = \frac{V_{max} \cdot C}{K_M + C}$$

$$R_0 = \frac{S \cdot F \cdot D}{\tau}$$

$$V_{max} = \frac{D_1 \cdot D_2 \cdot (C_2 - C_1)}{C_2 \cdot D_1 - C_1 \cdot D_2}$$

$$C_{normal} = \frac{C'}{(1 - 0.1) \cdot \frac{[Album.]}{4.4} + 0.1}$$

Intravenous bolus

One compartment model

$$t = \frac{\left(K_M \cdot \ln \frac{C_0}{C} + C_0 - C \right) \cdot Vd}{V_{max}}$$

Phenytoin

Theophylline

Vd [L/kg]	0.5
CL [L/h/kg]	0.04 (ad.)
	0.08 (ch.)
$t_{1/2}$ [h]	8 (ad.)
	4 (ch.)
% renal	18
F	1
S	0.8 (A)
C_{max} [mg/L]	<20
C_{min} [mg/L]	>10

Clearance-Factor:	
Smoking	1.6
CHF	0.4
Cystic Fibrosis	1.5
Cirrhosis	0.5
Pulmonary Edema	0.5
Viral Illness	0.5
Erythromycin	0.75
Ciprofloxacin	0.7
Cimetidine	0.6
Influenza vaccine	0.5
Phenobarbital	1.3
Rifampin	1.3
Phenytoin	1.6

Lidocaine

V_c, Vd [L/kg]	0.5, 1.3 0.3, 0.9 (CHF) 0.6, 2.3 (Cir.)	TBW
CL [L/h/kg]	0.6 0.36 (CHF) 0.36 (Cir.)	IBW
$t_{1/2}$ [h]	0.1 (α) 1.7 (β)	
% renal	2	
F	0.4	
S	0.87	
C_{max} [mg/L]	< 5	
C_{min} [mg/L]	> 1	

Procainamide

Vd [L/kg]	2
CL [L/h]	$3 \cdot CL_{Cr} + 0.23*BW$
	↓(0.5) in CHF
$t_{1/2}$ [h]	0.1 (α) 3 (β)
% renal	70
F	0.85
S	0.87
C_{max} [mg/L]	< 8
C_{min} [mg/L]	> 4

N-acetylprocainamide (NAPA)

Vd [L/kg]	1.5
CL [L/h]	$1.6 \cdot CL_{Cr} + 0.025*BW$
$t_{1/2}$ [h]	6

Aminoglycosides

Vd [L/kg]	0.25
CL [L/h/kg]	CL_{Cr}
$t_{1/2}$ [h]	2-3
% renal	100
F	-
S	-
C_{max} [mg/L]	>8-10·MIC
C_{min} [mg/L]	<2 (G, T)
	<10 (A)

Dosing Weight

if TBW>1.2·IBW: IBW + 0.4·(TBW-IBW)

Third Space Fluids: Add to Vd (1L/kg)

Dettli Equation:
$k=0.00293 \cdot CL_{cr}[ml/min]+0.014\ [h^{-1}]$