MPAS 650 Pharmacotherapy I
Applied Pharmacokinetic Equations (May or may not be needed)

Adults: (≥ 17 years)

$$\text{CrCl}\,(\text{ml/min}) = \frac{(140\text{-Age}) \cdot CrClWt}{72 \cdot SrCr} \cdot (0.85 + Sex \cdot 0.15)$$

If the patient is < IBW, use Wt = ABW.
If the patient is > IBW and BMI < 25 Kg/m^2, Wt = IBW
If the patient has a BMI ≥ 25 Kg/m^2, Wt = AdjWT

Neonates: (<2 months)

$$CrCl(\text{ml/min}/1.73\text{m}^2) = \frac{0.45 \cdot (CmHt.)}{SrCr}$$

Pediatrics: (2 months – 16 years)

$$CrCl(\text{ml/min}/1.73\text{m}^2) = \frac{3.5 \cdot Age + 23.6}{SrCr}$$

IBW (males)
50 Kg + 2.3 Kg/inch over 5 feet
IBW (females)
45.5 Kg + 2.3 Kg/inch over 5 feet

BMI = Wt (Kg) / (Ht (In) * 0.0254)^2

If ActBW is > 30% over IBW, then
DWT = IBW + 0.4*(ActBW – IBW)
If BMI ≥ 25 Kg/m^2, then
CrCl-WT = IBW + 0.4*(ActBW – IBW)

$$BSA = Wt^{0.5378} \cdot Ht^{0.3964} \cdot 0.024265$$

CrCl Norm = CrCl * 1.73 /BSA

Population Estimates

Volume of distribution (V)

Vancomycin:
V_{ss} (L) = 0.7 L/Kg x ActWT

Elimination rate constant (k)

Vancomycin
Ke = [44 + (8.3 x CrCl)] / 10000

Peak and Trough:

1. Calculate the elimination rate constant.

$$k_e = \frac{\ln C_1 - \ln C_2}{t_2 - t_1} = \frac{\ln C_{pk} - \ln C_{tr}}{t_{tr} - t_{pk}} = \frac{\ln(C_{pk}/C_{tr})}{\tau - t_{inf} - t_{pi}}$$

2. Calculate C_o (t_{pk} = elapsed time from start of infusion)

$$C_0 = \frac{C_{pk}}{e^{-k_e (t_{pk} - t_{\text{inf}})}}$$

3. Calculate the half-life.

$$t_{1/2} = \frac{\ln 2}{k_e}$$

4. Calculate the volume of distribution.

$$V_{ss} = \frac{R_0}{k_e} \cdot \frac{1 - e^{-k_e t_{\text{inf}}}}{(C_0 - C_{tr} \cdot e^{-k_e t_{\text{inf}}})}$$

5. Calculate the dosing interval.

$$\tau = \frac{\ln(C_{Max,desired}/C_{Min,desired})}{k_e} + t_{\text{inf}}$$

6. Calculate the new infusion rate.

$$\boldsymbol{R_0 = C_{Max,desired} \cdot k_e \cdot V_{ss} \cdot \frac{(1 - e^{-k_e \tau})}{(1 - e^{-k_e t_{\text{inf}}})}}$$

7. Calculate the new peak.

$$C_{ss,pk} = \frac{R_0}{V_{ss} \cdot k_e} \cdot \frac{(1 - e^{-k_e t_{\text{inf}}})}{(1 - e^{-k_e \tau})}$$

8. Calculate the new trough.

$$C_{ss,tr} = C_{ss,pk} \cdot e^{-k_e (\tau - t_{\text{inf}})}$$

Single Level: $(\text{Dose}/\text{Tau})_{\text{new}} = (\text{Dose}/\text{Tau})_{\text{current}} * C_{\text{desired}}/C_{\text{measured}}$

Target Drug Concentrations

	Trough	Peak	Infusion Time
Vancomycin	10-20 mg/L	30 to 40 mg/L	1.5 Hr. (≤ 1.25 g) 2 Hr. (1.5 – 2 g)

Remember I said in lecture, the sample problem given in class with the vancomycin calculation was given to show you the calculations that will be done by someone. I will include the above equations on the exam, but you will **not** be expected to solve problems that require the use of all of these equations for a prospective or retrospective dose. However, several of these equations are necessary to ensure that you correctly order and interpret drug levels. The following sample problems show you the type of questions you might see on the exam.

It is easy enough for you to use a peak and trough measurement to calculate Ke, which is used to obtain the half-life. One of the biggest challenges is to make sure your use the right time in the denominator. Here are a couple practice problems to do this:

1. A drug that is given every 12 hours had a steady state trough that was measured at 7:45 am, the drug was infused from 8 am to 9:30 am and the peak was measured at 11:00 am. When computing the elimination rate the change in time was how many hours?

$$t_2 - t_1 = Tau - t_{inf} - t_{pinf} = 12 \text{ hr} - 1.5 \text{ hr} - 1.5 \text{ hr} = 9.0 \text{ hours}$$

2. A drug that is given every 8 hours had a trough that was measured at 11:45 pm, the drug was infused from midnight to 12:30 am and the peak was measured at 1:15 am. When computing the elimination rate the change in time was how many hours?

$$t_2 - t_1 = Tau - t_{inf} - t_{pinf} = 8 \text{ hr} - 0.5 \text{ hr} - 0.75 \text{ hr} = 6.75 \text{ hours}$$

It is important to know when are the appropriate times to order peaks and troughs. If levels are to be done they should be at steady state (5 times the elimination half-life) and a peak should be after distribution is complete (5 times the distribution half-life). Here are two more sample problems:

3. A new antibiotic has been developed and it has been determined that it will be given by an intermittent infusion. The drug can safely be infused over one hour. Pharmacokinetic studies have been done and elimination is characterized by a bi-exponential decline in concentration. Results from a large study indicate that the average distribution rate constant (alpha) is 2.77 $Hr.^{-1}$ ($t_{1/2}$= 0.25 Hr.). The average elimination rate constant (beta) is 0.156 Hr^{-1} ($t_{1/2}$= 4.4 Hr.). It will be necessary to monitor peak and trough values for this new antibiotic which will be dosed every 12 hours. When should you order the PK and TR to be done?

   The elimination half-life is 4.4 Hr., so SS is reached in 5x4.4 hours = 22 hours, so if the TR is measured at 24 hours, right before the 3rd dose you will be at steady state, and the PK should be 5x0.25 hr = 1.25 hr, so measure the PK 1.25 Hr after the 3rd infusion stops.

4. A new intravenous proton pump inhibitor has been developed and it has been determined that it will be given by an intermittent infusion. The drug can safely be infused over 30 minutes and it is important to maintain drug levels between 30-40 mg/L. The medication will be given every 8 hours. Pharmacokinetic studies have been done and elimination is characterized by a bi-exponential decline in concentration. Results from a large study indicate that the average distribution rate constant (alpha)

is 3.85 $Hr.^{-1}$ ($t_{1/2}$= 0.18 Hr.). The average elimination rate constant (beta) is 0.23 Hr^{-1} ($t_{1/2}$= 3.0 Hr.). When should you order the PK and TR to be done?

The elimination half-life is 3.0 Hr., so SS is reached in 5x3.0 hours = 15 hours, so if the TR is measured at 16 hours, right before the 3rd dose you will be at steady state, and the PK should be 5x0.18 hr = 0.9 hr, so measure the PK 1 Hr after the 3rd infusion stops.

5. It is important to look at kinetic data is available in the medical literature and interpret what is provided in a way that applies to your patient. Look at the data provided and make important applications for pseudoephedrine:

From Goodman & Gilman Appendix II, Table 1:

BioAVAIL-ABILITY (ORAL) (%)	URINARY EXCRETION (%)	BOUND IN PLASMA (%)	CLEARANCE (mL/min/kg)	VOL. DIST. (L/kg)	HALF-LIFE (hours)	PEAK TIME (hours)	PEAK CONC. (ng/ml)
Pseudoephedrine[a]							
~100	43-96[b]	96 ± 1	7.33[b,c]	2.64-3.51[c]	4.3-8[b,c]	IR: 1.4-2[d] CR: 3.8-6.1[d]	IR: 177-360[d] CR: 265-314[d]

[a] Data from healthy adult male and female subjects.

[b] At a high urinary pH (>7.0), pseudoephedrine is extensively reabsorbed; t1/2 increases, and CL decreases.

[c] CL/F, V/F, and t1/2 reported for oral dose.

[d] Range of mean values from different studies following a single 60-mg immediate-release tablet or syrup (IR), or 120-mg controlled-release capsule (CR) oral dose.

References:
Kanfer I, et al. Pharmacokinetics of oral decongestants. Pharmacotherapy,1993, 13:116S–128S.

- Pseudoephedrine is a good candidate for an oral dosage form, with nearly 100% absorbed, time to peak less than 1.5 hours (for the immediate release form) and a good concentration.
- There is a considerable variability with the half-life and it appears renal excretion could be a factor (footnote b), with urine pH > 7 would increase clearance.
- It appears that some of the pseudoephedrine is hepatic cleared and some of it is renal excreted.
- The half-life would indicate that pseudoephedrine would require fairly frequent dosing.
- This rapid clearance of the drug would suggest that a controlled or extended release product could be developed to allow less frequent dosing.
- It has fairly high protein binding, so there could be drug interactions with other highly protein bound drugs.