Prospective Case

BJ is a 67 YO 5'5" woman with a cellulitis from *Staph aureus*. Her weight is 70 Kg (IBW = 57 Kg) and her serum creatinine is 1.3 mg/dl. Her measured CrCl was 44.7 ml/min. What dose (mg) of vancomycin would you recommend for initiation of therapy and what dosing interval to give you a target peak of about 36 mg/L and trough of 15 mg/L?

_________ mg Vancomycin Q____H

Answer: Population PK data for vancomycin estimates the elimination rate constant and half-life (Note when you have a measured CrCl don't use a population estimate, use the measured value.):

$$k_e = \frac{44 + (8.3 \cdot CrCl)}{10000} \qquad = \frac{44 + (8.3 \cdot 44.7)}{10000} = 0.0415 \ Hr.^{-1} \qquad \text{Eq. 1}$$

$$t_{1/2} = \frac{\ln 2}{k_e} \qquad = \frac{\ln 2}{0.0415} = 16.7\,Hr \qquad \text{Eq. 3}$$

Estimate the volume of distribution (from population estimates):

$$V_{ss} = V_d \ factor \cdot DWT \ = 0.7 L/Kg \cdot DWT \qquad \text{Eq. 4}$$

$$V_{ss} = 0.7\,L/Kg \cdot 70\ Kg = 49\,L$$

Estimate Tau (the 5th equation in the Sawchuk-Zaske list):

$$\tau = \frac{\ln\left(C_{\text{max/desired}} / C_{\text{min/desired}}\right)}{k_e} + t_{\text{inf}} \qquad = \frac{\ln(36/15)}{0.0415\ Hr^{-1}} + 1.5\,Hr = 22.6\,Hr \qquad \text{Eq. 5}$$

Select a practical Tau (e.g. Q4H, Q6H, Q8H, Q12H or Q24H) based on this estimate. Here Q24H.

Using the practical interval, estimate the new dose (the 6th equation in the Sawchuk-Zaske list):

$$R_0 = C_{\text{max,desired}} \cdot V_{ss} \cdot k_e \left[\frac{1 - e^{-k_e \tau}}{1 - e^{-k_e t_{\text{inf}}}}\right] \qquad \text{Eq. 6}$$

$$= 36\,mg/L \cdot 49\,L \cdot 0.0415\ Hr^{-1}\left[\frac{1 - e^{-0.0415\,Hr^{-1} \cdot 24 Hr}}{1 - e^{-0.0415\,Hr^{-1} \cdot 1.5\,Hr}}\right] = 765\,mg/Hr$$

$$Dose = R_0 \cdot t_{\text{inf}} \qquad = 765\,mg/Hr \cdot 1.5\,Hr = 1147\,mg$$

Make a practical recommendation (Vancomycin is usually dosed in 250 mg increments):

<u>1250 mg Q24H</u>

Verify that this will give you desirable steady state peak and trough concentrations:

$$C_{ss,pk} = \frac{R_0}{V_{ss} \cdot k_e} \bullet \frac{\left(1 - e^{-k_e t_{\text{inf}}}\right)}{\left(1 - e^{-k_e \tau}\right)} \qquad \text{Eq. 7}$$

$$C_{ss,pk} = \frac{1250mg / 1.5\,Hr.}{49\,L \cdot 0.0415\ Hr^{-1}} \bullet \frac{\left(1 - e^{-0.0415 \cdot 1.5}\right)}{\left(1 - e^{-0.0415 \cdot 24}\right)} = 39.2\,mg/L$$

$$C_{ss,tr} = C_{ss,pk} \cdot e^{-k_e(\tau - t_{\text{inf}})} \qquad = 39.2 mg/L \cdot e^{-0.0415\,(24-1.5)} = 15.4\,mg/L \qquad \text{Eq. 8}$$

Retrospective Case

RW is a 5' 6" 68 Kg. 19 Y.O. female burn victim that has been on vancomycin 1 Gm Q12H for 5 days. Levels are done and come back with a Pk/Tr = 17/4.1 mg/L. The skin grafts still show signs of cellulitis and the physician wants to increase the dose. What would you recommend? (The Pk was 60 minutes after a 90 minute infusion.)

_________ mg Vancomycin Q____H

Calculate the elimination rate constant:

$$k_e = \frac{\ln\left(C_{pk}/C_{tr}\right)}{t_{tr} - t_{pk}} = \frac{\ln\left(17/4.1\right)}{12 - 2.5} = \frac{\ln\left(17/4.1\right)}{9.5\ Hr.} = 0.15\ Hr^{-1} \qquad \text{Eq. 1}$$

(In terms of the dosing interval the infusion was started at t = 0, it stopped at 1.5 hr, and the pk was measured at 2.5 hr and the trough (extrapolated) was at 12 hours, therefore t_2 -t_1 is 12 -2.5 = 9.5. This is where most errors in calculations are made. Many prefer Tau (12 Hr) – Tinf (1.5 Hr.) – Tpinf (1 Hr.) = 12-1.5-1=9.5 Hr.)

$$t_{1/2} = \frac{\ln 2}{k_e} = 4.6\ Hr \qquad \text{Eq. 3}$$

Calculate the maximum concentration:

$$C_0 = \frac{C_{pk}}{e^{-k_e\left(t_{pk} - t_{\inf}\right)}} = \frac{17 mg/L}{e^{-0.15 Hr^{-1}\left(2.5\ Hr - 1.5\ Hr\right)}} = 19.75\ mg/L \qquad \text{Eq. 2}$$

Calculate the volume of distribution:

$$V_{ss} = \frac{R_0}{k_e} \cdot \frac{1 - e^{-k_e t_{\inf}}}{\left(C_0 - C_{tr} \cdot e^{-k_e t_{\inf}}\right)} \qquad \text{Eq. 4}$$

$$= \frac{1000mg / 1.5\ Hr}{0.15\ Hr^{-1}} \cdot \frac{1 - e^{-0.15 Hr^{-1} \cdot 1.5 Hr}}{\left(19.75\ mg/L - 4.1\ mg/L \cdot e^{-0.15\ Hr^{-1} \cdot 1.5 Hr}\right)} = 54.4\ L$$

Using C_o, k_e and V_{ss} estimate a dosing interval, a dose and predict the steady state peak and trough using a practical regimen using Eq 7, Eq. 8, Eq 9, Eq. 10 and Eq. 11.

$$\tau = \frac{\ln(36/15)}{0.15\ Hr^{-1}} + 1.5\ Hr = 7.34\ Hr \approx 8 Hr \qquad \text{Eq. 5}$$

$$R_0 = 36\ mg/L \cdot 54.4\ L \cdot 0.15\ Hr^{-1} \left[\frac{1 - e^{-0.15 Hr^{-1} 8 Hr}}{1 - e^{-0.15 Hr^{-1} 1.5 Hr}}\right] = 1018.8\ mg/Hr \qquad \text{Eq. 6}$$

$$Dose = 1018.8\ mg/Hr \cdot 1.5\ Hr = 1528\ mg \approx 1500\ mg$$

Make a practical recommendation and then verify:

1500 mg Q8H

$$C_{ss,pk} = \frac{1500mg / 2\,Hr.}{54.4\,L \cdot 0.15\,Hr^{-1}} \bullet \frac{\left(1 - e^{-0.15 \cdot 2}\right)}{\left(1 - e^{-0.15 \cdot 8}\right)} = 34.1\ mg/L \qquad \text{Eq. 7}$$

$$C_{ss,tr} = 35.3\,mg/L \cdot e^{-0.15(8-2)} = 13.9\,mg/L \qquad \text{Eq. 8}$$

(Note: for that dose adjust the infusion to 2 Hr)