Vancomycin Example

Prospective Case

A 65 Y.O. male with a Sr.Cr. of 1.4 mg/dl develops a cellulitis. The patient has a measured CrCl of 52.0 ml/min. The Gram stain shows a Gram + cocci. The physician suspects *Staph. aureus* and wants to start vancomycin. The patient is 5' 4" and weights 86 Kg. What would be the appropriate dose to use?

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. Also, prospectively C_0 is the target peak concentration (Eq. 2)]:

$$k_e = \frac{44 + (8.3 \cdot CrCl)}{10000} \qquad = 0.0476\ Hr.^{-1} \qquad \text{Eq. 1}$$

$$t_{1/2} = \frac{\ln 2}{k_e} \qquad = 14.6\ Hr \qquad \text{Eq. 3}$$

Estimate the volume of distribution:

$$V_{ss} = V_d\, factor \cdot ActWT \qquad V_{ss} = 0.7 L/Kg \cdot 86\ Kg = 60.2\ L \qquad \text{Eq. 4}$$

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

$$\tau = \frac{\ln\left(C_{\text{max/desired}}/C_{\text{min/desired}}\right)}{k_e} + t_{\text{inf}} \qquad = \frac{\ln(36/15)}{0.0476\ Hr^{-1}} + 1.5\ Hr = 19.9\ Hr \qquad \text{Eq. 5}$$

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):

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

$$= 36 mg/L \cdot 60.2\ L \cdot 0.0476\ Hr^{-1} \left[\frac{1 - e^{-0.0476\ Hr^{-1} 24 Hr}}{1 - e^{-0.0476\ Hr^{-1} 1.5 Hr}}\right] = 1019.4\ mg/Hr$$

$$Dose = R_0 \cdot t_{\text{inf}} \qquad = 1019.4\ \ mg/Hr \cdot 1.5\ \ Hr = 1529\ mg$$

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

<u>1500 mg Q24H</u>

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

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

$$C_{ss,pk} = \frac{1500\ mg / 2\ Hr.}{60.2\ L \cdot 0.0476\ Hr^{-1}} \bullet \frac{\left(1 - e^{-0.0476 \cdot 2}\right)}{\left(1 - e^{-0.0476 \cdot 24}\right)} = 34.9\ mg/L$$

$$C_{ss,tr} = C_{ss,pk} \cdot e^{-k_e(\tau - t_{\text{inf}})} \qquad = 34.9\ mg/L \cdot e^{-0.0476\,(24-2)} = 12.25\ mg/L \qquad \text{Eq. 8}$$

Vancomycin Example

Retrospective Case

TW is a 5' 6" 68 Kg. 19 Y.O. female burn victim has been on vancomycin 1 Gm Q12H for 5 days. Levels are done and come back with a Pk/Tr = 17/4.1 mg/dl. 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.)

Calculate the elimination rate constant:

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

(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.)

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

Calculate the maximum concentration:

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

Calculate the volume of distribution:

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

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

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.

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

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

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

Make a practical recommendation and then verify:

<u>1500 mg Q8H</u>

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

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

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

1/21/20