Supplement 1: Validated 2-compartment population pharmacokinetic models of vancomycin.

Validated 2-compartment population pharmacokinetic models of vancomycin for critically ill and non–critically ill patients were used to obtain pharmacokinetic parameters as described below.[1,2] Critical illness was defined by admission to an intensive care unit (ICU).

Clearance

$$[1]\ CL = (\theta_1 \times CL_{Cr}) + (\theta_2 \times TBW)$$ [for critically ill patients][1]

$$[2]\ CL = (0.0322 \times CL_{Cr}) + 0.32$$ [for non–critically ill patients][2]

CL = vancomycin clearance (mL/min), CL_{Cr} = creatinine clearance (as determined using the Cockroft–Gault equation; mL/min), TBW = total body weight (kg), $\theta_1 = 0.034$, $\theta_2 = 0.015$.

Volume of distribution

$$[3]\ V_D = (\theta_3 + \theta_4) \times TBW$$ [for critically ill patients]

$$[4]\ V_D = (0.478 \times TBW) + 60.6$$ [for non–critically ill patients]

V_D = volume of distribution for both central and peripheral compartments (L), $\theta_3 = 0.414$, $\theta_4 = 1.32$.

Upon determining vancomycin CL and V_D, the k_e (elimination rate constant) was calculated according to the following equation:

$$[5]\ k_e = \frac{CL}{V_D}$$

k_e = elimination rate constant.

$$[6]\ C_{max} = \frac{C_{trough}}{e^{-k_e(t-t_i)}}$$

C_{trough} = measured trough level, t_i = time from the end of the infusion period, t = time of the measured trough level, C_{max} = calculated maximum serum vancomycin level following infusion.

$$[7]\ C_{min} = C_{trough} \times e^{-k_e(t_d - t)}$$

C_{trough} = measured trough level, t = time from the measured trough level, t_d = time at the end of the dosing interval, C_{min} = calculated minimum serum vancomycin level during the dosing interval.

Finally, the 24-h area under the curve (AUC_{24}) was calculated according to the following equation[3]:

$$[8]\ AUC = \frac{t_v(C_{max} + C_{min})}{2} + \frac{C_{max} - C_{min}}{k_e}$$

AUC = area under the curve for dosing interval, t_v = time over which vancomycin is infused.

The AUC_{24} was determined based on the vancomycin dosing interval. For example, if the dosing interval was scheduled as every 12 h, the AUC determined using equation 8 was multiplied by 2 to obtain the AUC_{24}.

AUC/MIC Determination Using 2 Levels

The AUC/MIC using 2 vancomycin levels was determined based on methods described by Pai and others.[3] Cases with 2 levels within one dosing interval were identified, with one level at least 2 h after the end of the infusion (C_1) and a trough level (C_2). The k_e was calculated using a first-order rate equation, where Δt is the time (h) between the 2 levels:

$$[9]\ C_2 = C_1 \times e^{-k_e \times \Delta t}$$

The extrapolated C_{min} and C_{max} values were then calculated according to the following equation:

$$[10]\ C_{max} = \frac{C_2}{e^{-k_e \times \Delta t}}$$

(where Δt = time between the end of infusion and trough level)

$$[11]\ C_{min} = C_2 \times e^{-k_e \times \Delta t}$$

(where Δt = time between trough level and the end of the dosing interval)

Finally, the AUC was calculated according to the following equation:

$$[12]\ AUC = \frac{t_{infusion} \times (C_{max} + C_{min})}{2} + \frac{C_{max} - C_{min}}{k_e}$$

(where $t_{infusion}$ = the duration of the vancomycin infusion)

The calculated AUC was then divided by the MIC. The AUC/MIC values calculated using 2 levels reflect various time intervals (i.e., the values were not all necessarily AUC_{24}/MIC). These AUC/MIC values were not included in the discordance analysis.

References

1. Llopis-Salvia P, Jimenez-Torres NV. Population pharmacokinetic parameters of vancomycin in critically ill patients. *J Clin Pharm Ther*. 2006;31(5):447-54.
2. Yamamoto M, Kuzuya T, Baba H, Yamada K, Nabeshima T. Population pharmacokinetic analysis of vancomycin in patients with gram-positive infections and the influence of infectious disease type. *J Clin Pharm Ther*. 2009;34(4):473-83.
3. Pai MP, Neely M, Rodvold KA, Lodise TP. Innovative approaches to optimizing the delivery of vancomycin in individual patients. *Adv Drug Deliv Rev*. 2014;77:50-7.