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Optimizing intermittent vancomycin therapy using C-reactive protein: investigating the role for AUC:EC50 in secondary care

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Background: C-reactive protein (CRP) pharmacodynamic (PD) models have the potential to augment minimum inhibitory concentration (MIC) data in antimicrobial pharmacokinetic (PK)-PD targets. We investigated a CRP PD model linked to a vancomycin PK model using routinely collected data from non-critical care adults in secondary care. The aim was to explore the role exposure-response for vancomycin therapy using time course of CRP as a quantified PD index.

Material/methods: Data from 30 in-patients receiving vancomycin for suspected or confirmed staphylococcal infections were selected. Data were analysed in a Non-Parametric Adaptive Grid (NPAG) using p-metrics within R and ADAPT software. One- and two-compartment pharmacokinetic

models were tested to describe vancomycin PK. Serial CRP measurements were extracted and a CRP PD model was developed linking the CRP response to the 2-compartment vancomycin PK model. Individual Bayesian PK estimates were fixed in the PK-PD model to avoid bias in parameter estimation. This allowed for PD parameter estimation, including posterior individual EC50 values. EC50 describes the concentration of vancomycin (mg/L) that produces half the maximal effect of CRP reduction for the individual. Exposure-response relationships were explored with 24-hour vancomycin area-under-the-curve (AUC) and the index, AUC:EC50, fitted to CRP data using a sigmoidal Emax model.

Results: Sixty percent (18/30) of individuals were male, with median age 60 (21-87) years. PK and PD models were adequately fitted to the data with R-squared values of 0.81 and 0.80, respectively. Population PK parameters for vancomycin were, volume of distribution of the central compartment (SD), 31 (14)L; clearance (SD) 3.2 (1.7)L/hr; Kcp (SD) 1.2 (1.2); Kpc (SD) 3.9 (4.0). Population PD parameters for the CRP response model were, rate constant for the maximum rate of CRP production (SD) 0.029 (0.022)mg · h/L; population max for CRP 550 (212)mg/L; rate constant for the maximum rate of CRP inhibition (SD) 0.059 (0.028)mg · h/L; H slope function (SD) 41 (3.7); and EC50 (SD) 16.9 (9.9)mg/L.

There was a wide variation observed in individual Bayesian posterior EC50 estimates (2.5-35.1mg/L), with mean (SD) AUC:EC50 of 33 (22). AUC:EC50 was fitted using a sigmoidal Emax model to terminal CRP which demonstrated an association with increasing AUC:EC50 and lower terminal CRP values on completion of vancomycin therapy (**Figure 1**).

Conclusions: The use of AUC:EC50 using CRP as a PD quantity has the potential to facilitate in-vivo exposure-response predictions for situations where in-vitro MIC data is currently used as the gold standard PD index. Future work must focus on validating this method for a number of in-vivo markers, including the role of PD models for predicting host toxicity, as well as developing mechanisms to translating precision dosing into accessible platforms suitable for use by clinicians.

Figure 1. Association of AUC:EC50 values to terminal CRP