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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