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Use of Bayesian Pharmacokinetic Models to Predict Plasma Meropenem Concentrations in Critically Ill Patients – Application to Therapeutic Drug Monitoring

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ABSTRACT

Objectives: Therapeutic Drug Monitoring (TDM) is an efficient tool for optimizing the therapeutics of drugs. Applying Bayesian feedback to TDM is a method that can accurately describe patient pharmacokinetics based with only minimal data. The goal of this study was to establish the agreement between observed pharmacokinetic data with a Bayesian feedback as well as a non-Bayesian model of meropenem in critically ill patients.

Methods: Total meropenem concentrations were measured in critically ill patients as part of a clinical TDM program. Meropenem was administered by either intermittent or extended infusion. A two compartment population pharmacokinetic model incorporating body weight and creatinine clearance as covariates was coded in the R language into Individually Designed Optimum Dosing Strategies (ID-ODS^{TM}) and was used to calculate the meropenem concentrations, allowing for the change in model parameters from dose to dose. Difference plots of observed versus predicted concentrations (with or without feedback) were constructed to evaluate the agreement between the observed and predicted concentrations. Bias and precision of the two models as predictors of observed concentrations were determined by the mean differences,95% limits of agreement and their corresponding 95% confidence intervals (95%CI).

Results: 290 meropenem concentrations from 34 patients were available for analysis. Relative percentage difference plots were constructed to increase the normality of the data. Here observed versus model predicted concentrations with or without feedback showed non-significant bias with a mean (95%CI) % difference of 1.81 (-1.82, 5.45) % and -0.93 (-8.17, 6.30) %, respectively. Predictions with as compared to without feedback showed improved precision illustrated by a narrower range of 95% (95%CI) lower and upper limits of agreements of -59.89 (-66.17, -53.61) % to 63.52 (57.25,69.80) % and -123.65 (-136.13, -111.17) % to 121.78 (109.30,134.26) %, respectively.

Conclusion: Model based simulations with and without Bayesian feedback were found to be similarly accurate, while the method with Bayesian feedback resulted in better precision of predicted meropenem concentrations in this group of critically ill patients. These highly individualized Bayesian models further enable practitioners to correctly describe the pharmacokinetics of meropenem in their patients, which in turn ensures more accurate dose adjustments in a clinical TDM program focusing on the optimal dosing of meropenem.

INTRODUCTION

Meropenem is a β-lactam antibiotic commonly used for the treatment of serious gram-negative infections in the critically ill. It is well established that efficacy of β-lactams correlates best with the percentage of the dosing interval where their unbound concentrations are maintained above the MIC ($fT_{>MIC}$). Studies in animal models of infection have shown that maximum bactericidal activity is reached at 40% $fT_{>MIC}$ for meropenem, while a higher target of at least 100% $fT_{>MIC}$ was suggested in treating severe infections in humans[1].

Achieving these pharmacokinetic/pharmacodynamic (PK/PD) targets in the critically ill can be difficult due to the variable pharmacokinetics secondary to the complex pathophysiologic changes that these patients undergo[2]. TDM is a potentially useful tool in aiding achievement of PK/PD targets in this special patient population, while the best method for optimizing dosing regimens based on TDM data is yet to be established. Methods to improve target attainment rates for time dependent antibiotics with the use of Monte Carlo simulations are well documented[3]. On the contrary, implementing Bayesian methods for meropenem dose optimization is limited because of a lack of lack of readily available commercial assays to measure blood concentrations and computerized decision support algorithms.

The aim of this study was to describe the correlation between observed meropenem concentrations in critically ill patients with predicted concentrations using a non-Bayesian model and separately with Bayesian feedback.

METHODS

Simulation and data analysis

- The ID – ODS^{TM} (Individually Designed Optimum Dosing Strategies) program was used to predict plasma meropenem concentrations taking into account patient demographic and laboratory information.
- The 2-compartment IV infusion model by Crandon et al. was coded using the R® language into ID - ODS^{TM} where meropenem concentration-time profiles were calculated using the published mean population pharmacokinetic parameter estimates for drug clearance, volume of distribution and transfer rate constants[4]. The Flexible Modeling Environment for Inverse Modeling, Sensitivity, Identifiability, Monte Carlo Analysis (FME) package was utilized to carry out the Bayesian analysis via the Markov Chain Monte Carlo method using the Metropolis – Hastings algorithm[5].
- The published mean ± SD from the Crandon et al. model was applied as the prior probability of the parameters assuming a normal distribution.
- Change in calculated pharmacokinetic parameters were allowed from dose to dose to ensure the incorporation of changing physiologic variables during the time course of therapy to grant the way for better tracking of observed concentrations.
- Analysis of prediction errors was based on evaluating measures of absolute and relative bias and precision.
  - Absolute bias and precision were described using the Bland-Altman method using the calculated percentage mean difference and 95% limits of agreement and their 95% confidence intervals, respectively.
  - Relative bias and precision were established by calculating delta mean prediction errors (ΔME) and delta mean squared prediction errors (ΔMSE) against a naïve predictor and their 95% confidence intervals, respectively.
- The R® software environment for statistical computing and graphics was used for statistical analysis and to generate plots[6].

RESULTS

Model	Difference [%]		95% Limits of Agreement [(95%CI),%]
	Mean	95% CI	
Crandon	-0.93	-8.17, 6.30	-123.65 (-136.13, -111.17) to 121.78 (109.30,134.26)
Bayesian	1.81	-1.82, 5.45	-59.89 (-66.17, -53.61) to 63.52 (57.25,69.80)

Model	Δ ME		Δ MSE	
	Mean	95% CI	Mean	95% CI
Crandon	-2.11	-4.03 to -0.19	-417.19	-580.29 to 254.09
Bayesian	-1.15	-2.58 to 0.28	-541.61	-727.46 to -355.77

Table 1. Summary statistics of absolute and relative performance indicators

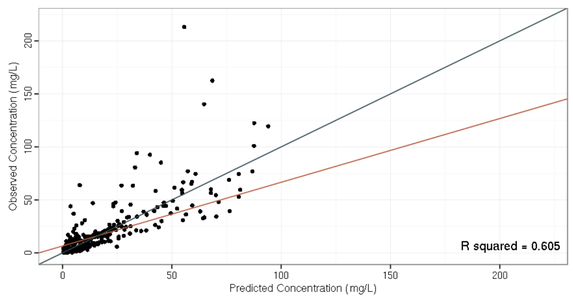

Figure 1 A. Observed versus population predicted concentrations (red: regression line, blue: unity)

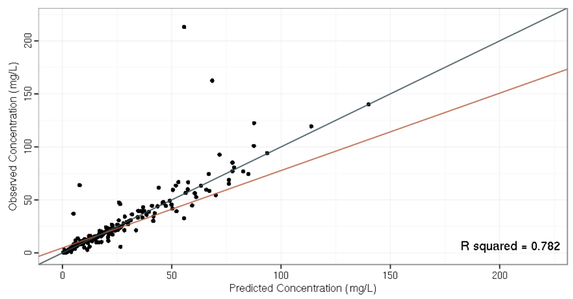

Figure 1 B. Observed versus individual Bayesian model predicted concentrations (red: regression line, blue: unity)

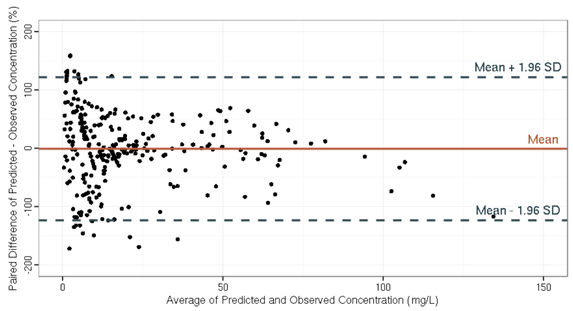

Figure 2 A. Percent difference Bland – Altman plot of observed versus predicted concentrations

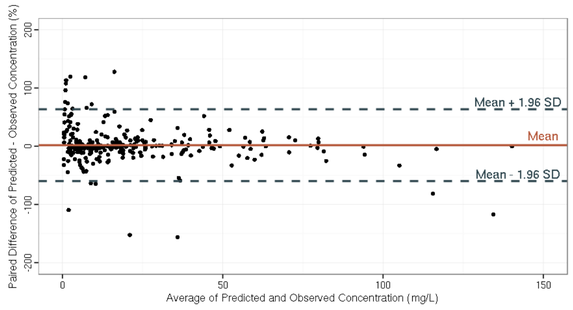

Figure 2 B. Percent difference Bland – Altman plot of observed versus Bayesian model predicted concentrations

RESULTS

Patient Characteristics	
Age (years)	51 (18, 76)
Height (cm)	167 (150, 197)
Weight (kg)	75 (45, 120)
Sex (% male)	45.6
Serum creatinine (μmol/L)	71 (< 30, 299)
Sepsis/shock (%)	52.1

Table 2. Patient demographic information (data shown as median (min,max), unless otherwise noted)

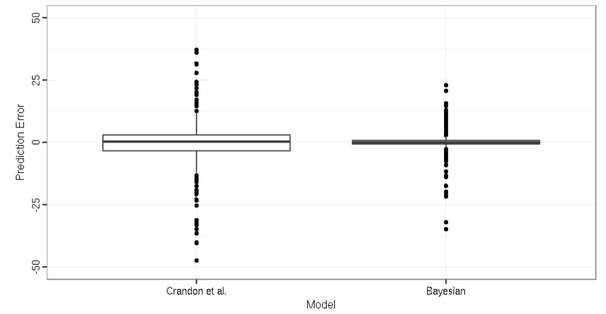

Figure 3. Box plot of calculated prediction errors against the naïve predictor

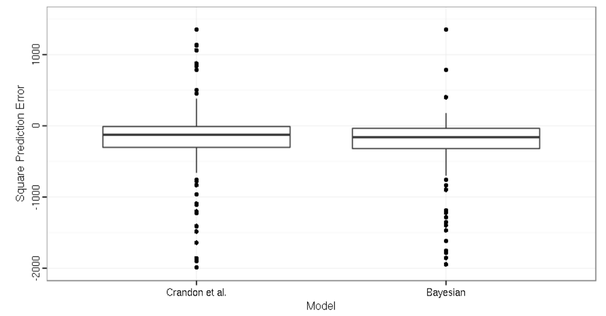

Figure 4. Box plot of calculated square prediction errors against the naïve predictor

CONCLUSION

- Using absolute and relative performance, model based simulations with and without Bayesian feedback were found to be similarly accurate, while the method with Bayesian feedback resulted in better precision of predicted meropenem concentrations in this group of critically ill patients.
- These highly individualized Bayesian models further enable practitioners to correctly describe the pharmacokinetics of meropenem in their patients, which in turn ensures more accurate dose adjustments in a clinical TDM program focusing on the optimal dosing of meropenem.

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