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Comparative evaluation of the accuracy and precision of pharmacokinetic equations to predict free meropenem concentrations in critically ill patients

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ABSTRACT

Objectives: Population pharmacokinetic analysis that quantify the effect of demographic, pathophysiological, and other drug-related factors on pharmacokinetic behavior are valuable for accurately predicting individualized and optimized doses for patients. The aim of this study was to establish the agreement between observed and population pharmacokinetic equations based predictions of concentrations to rank the predictive performance of available pharmacokinetic models.

Methods: Unbound meropenem concentrations were measured in critically ill patients as part of a clinical therapeutic drug monitoring (TDM) program. Published one and two compartment population models with covariate relationship were coded in the R language into Individually Designed Optimum Dosing Strategies (ID – ODS^{TM}) and were used to predict meropenem concentrations. Difference plots were produced to visually evaluate the agreement between the observed and predicted concentrations. Absolute and relative bias and precision of the models as predictors of of observed concentrations were determined. The clinical implications of the different results were evaluated according to whether the predicted concentration would have required dose adjustments for a target of 100% $\int$T > MIC (chosen MIC = 2mg/L).

Results: 157 free meropenem concentrations from 56 patients were available for analysis. Eight published pharmacokinetic models were evaluated using percentage difference plots. The models studied showed an absolute bias in predicting serum concentrations that ranged from a mean (95% CI) % difference of -108.6 (-119.91, -97.30) % to 19.86 (7.26, 32.47) %, while absolute precision ranged from -249.13 (-263.42, -234.84) % to 31.91 (17.62, 46.21) % and -178.93 (-196.93, -160.93) % to 175.04 (157.04, 193.04) %. A dose change prompted by individuals was required in 44 % to 64 % of the concentrations. When compared to an absolute standard, the one compartment model by Muro et al. developed in Japanese patients was found to be the least biased and most precise at predicting free merpenem concentrations.

Conclusion: Seven of the eight equations evaluated here are likely to under-predict free meropenem concentrations coupled with variable magnitudes of precision that prompted similar dosing decisions using four of the targeted models. When compared to th absolute standard, the model by Muro et al. ranked the highest at accurately and precisely predicting free meropenem concentrations. The calculated results of this dosing approach also led to similar choices of dose adjustments most often as compared to the results based on the observed concentrations. The best performed model thus may be adapted into a 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. Vital to these critically-ill patients is early and appropriate antibiotic therapy, which may be interfered by the complex pharmacokinetics in this subset of patients. The clinical and microbiological efficacy of meropenem is often linked to time dependent action, meaning it is based upon the percentage of the dosing interval in which free drug concentrations remain above the minimum inhibitory concentration of the pathogenic organism (fT> MIC) [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]. Pharmacokinetic analyses that quantify the effect of demographic, pathophysiological, and other drug-related factors on pharmacokinetic behavior are valuable for accurately predicting optimized doses for patients. In establishing therapeutic drug monitoring programs to provide optimal antimicrobial dosing the question arises as to which pharmacokinetic model would best predict meropenem concentrations in the critically-ill. The purpose of this study was to establish the agreement between observed and population pharmacokinetic models and equations based predictions of free meropenem concentrations to rank the predictive performance of eight available pharmacokinetic models using absolute and relative measures of bias and precision. The eight methods studied were the Crandon, Li, Doh with and without the presence of edema, Leroy, Christensson, Muro, and Roberts methods[3].

METHODS

Simulation and data analysis

- The ID – ODS^{TM} (Individually Designed Optimum Dosing Strategies) program was used to predict free plasma meropenem concentrations taking into account patient demographic and laboratory information.
- One and two compartment IV infusion models were 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.
- Protein binding of 2% was assumed to calculate the free meropenem concentrations.
- 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 predictions 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

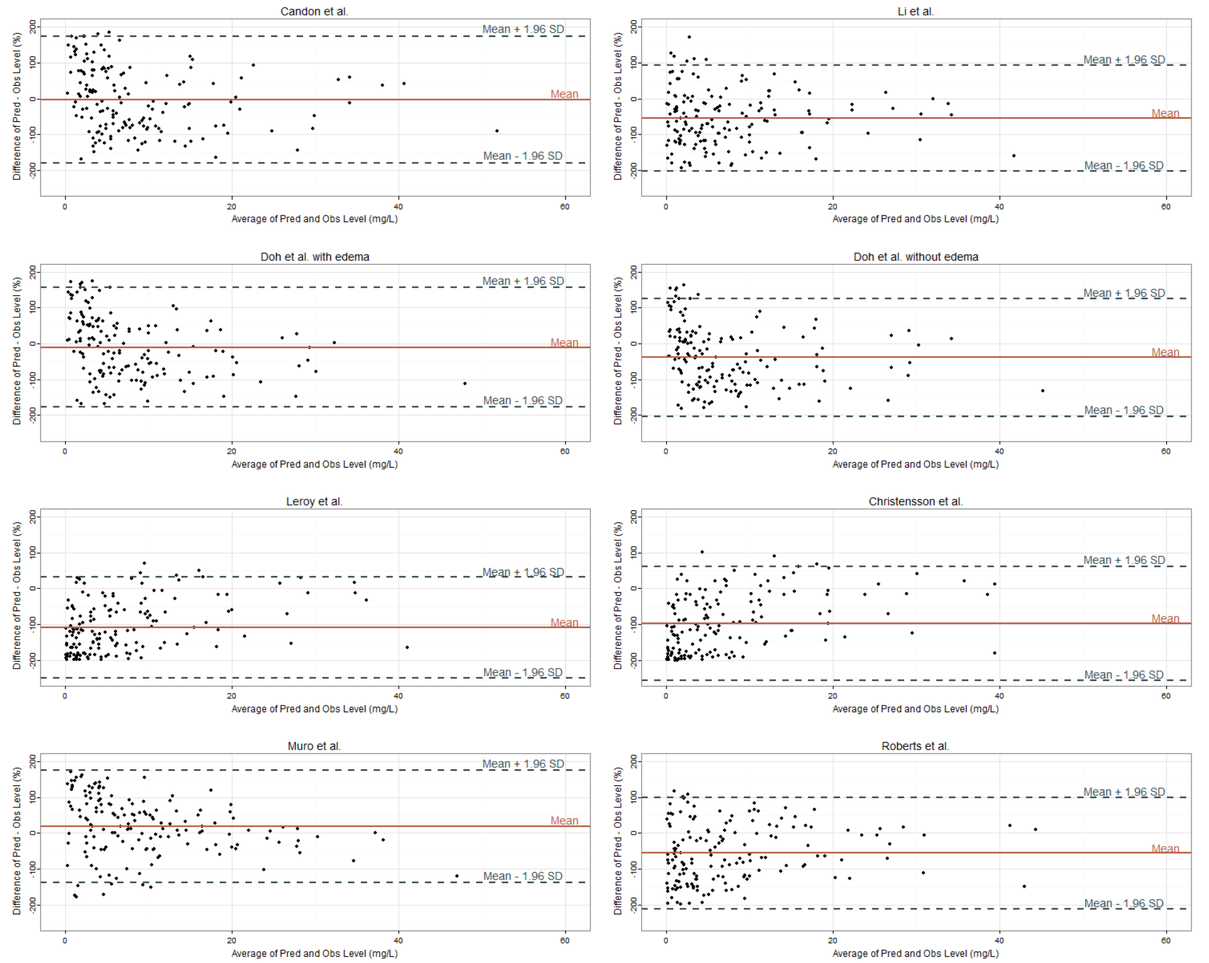

Figure 1. Percent difference Bland – Altman plots of observed versus predicted concentrations for the eight equations evaluated

RESULTS

Model	Δ ME		Δ MSE	
	Mean	95% CI	Mean	95% CI
Crandon	-1.82	-3.28 to -0.36	-26.27	-58.5 to 5.95
Li	-4.25	-5.55 to -2.95	-29.02	-49.95 to -8.01
Doh w ed.	-2.96	-4.29 to -1.63	-35.00	-58.4 to -11.58
Doh w/o ed.	-4.31	-5.69 to -2.93	-19.8	-39.02 to -0.57
Leroy	-5.34	-6.69 to -4	-13.13	-35.39 to 9.12
Christensson	-4.45	-5.85 to -3.05	-16.02	-40.13 to 8.09
Muro	0.02	-1.19 to 1.24	-55.04	-82.82 to -27.26
Roberts	-3.37	-4.66 to -2.08	-36.54	-57.37 to -15.7

Table 1. Summary statistics of relative performance indicators against a constant naïve predictor

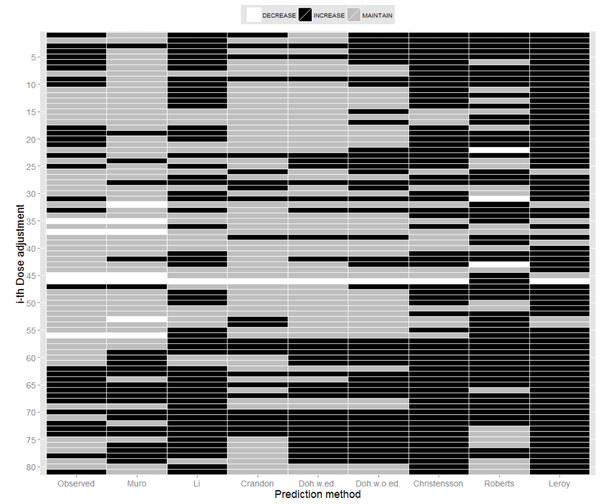

Figure 2. Tile plot of dose adjustments prompted by observed vs. model predicted concentrations

CONCLUSION

- Seven of the eight equations evaluated here are likely to under-predict free meropenem concentrations coupled with variable magnitudes of precision that prompted similar dosing decisions using four of the targeted models. When compared to the absolute standard, the model by Muro et al. ranked the highest at accurately and precisely predicting free meropenem concentrations.
- The calculated results of this dosing approach also led to similar choices of dose adjustments most often as compared to the results based on the observed concentrations.
- Based on these absolute and relative performance indicators, the best performed model thus may be adapted into a TDM program focusing on the optimal dosing of meropenem.

REFERENCES

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2. Roberts et al. Crit Care Med. 2009 Mar, 37(3) 840-51
3. Detailed list of references is available from the authors
4. http://www.R-project.org

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