Westfälische Wilhelms-Universität Münster

PharmaCampus
Institut für Pharmazeutische und Medizinische Chemie

Muhammad Usman, Georg Hempel
Institute of Pharmaceutical and Medicinal Chemistry - Clinical Pharmacy, Corrensstr. 48, 48149 Muenster, Germany.

Population Pharmacokinetics of Meropenem in Elderly Patients: Dosing Simulations based on Renal Function

Introduction

Meropenem is a potent carbapenem antibiotic active against a wide variety of bacteria [1]. It is commonly prescribed for the empirical treatment of life-threatening infections. As it exhibits time-dependent antimicrobial activity, the most important PK/PD index is the percentage of time interval for which the plasma concentration of meropenem remains above MIC (%T>MIC) of pathogenic microorganism. For optimal antibacterial activity 40% T>MIC should be achieved [2]. However, in case of severe bacterial infections a higher %T>MIC even up to 100% is suggested [3]. Meropenem is eliminated mainly through the kidney via glomerular filtration (GFR). Because GFR progressively decreases with increasing age [4], the kidney status must be considered for maintaining the plasma concentration of meropenem above the MIC of target pathogens on the one side and to ensure safety and cost-effectiveness on the other side.

The aim of this investigation was to develop a population pharmacokinetic (popPK) model of meropenem in elderly patients in order to observe the influence of different covariates on meropenem clearance (CL). Moreover, simulations of different dosage regimens were performed to observe the percentage probability of target attainment (PTA %) for maintaining the plasma concentration of meropenem above MIC in relation with creatinine clearance (CL_{CR}).

Methods

Data Collection

Data of patients above 65 years of age treated with meropenem were collected from different sources (Table 1). A two-compartment model was developed in NONMEM® by using first order conditional estimation method with interaction (FOCE-I). The influence of different covariates on meropenem clearance was observed by using stepwise covariate modelling (scm).

Table 1: Patient characteristics

Patient's demographics	Dr. Otto Frey	Isla et al [5]	Doh et al [6]	Pooled data
No of patients (M/F)	159 (96/63)	10 (6/4)	9 (4/5)	178 (106/72)
No of samples	363	69	61	493
Age (Years)	75 (65-94)	74 (69-83)	73 (65-86)	75 (65-94)
Weight (Kg)	77 (37-147)	75 (59-80)	56 (42-78)	75 (37-147)
CL_{CR} (mL/min)	36.4 (6.2-213.8)	14.7 (3-118)	74.96 (8.83-231.4)	36.5 (3-231.4)

Simulations

Monte Carlo simulations of different dosage regimens with daily dose of 3000 mg were performed to observe the probability of target attainment (PTA %) for maintaining the plasma concentration of meropenem for 40% T>MIC, 60% T>MIC and 80% T>MIC between dosage intervals. The MIC breakpoints described by European committee of anti-microbial susceptibility testing (EUCAST) for plasma concentration of meropenem are ≤ 2 mg/L, 4-8 mg/L and > 8 mg/L, respectively against susceptible, intermediate and resistant strains of *Enterobacteriaceae, Acinetobacter* spp., *Pseudomonas* spp. and *Gram-positive & Gram-negative* anaerobes.

Results

The final parameter estimates of meropenem along with 1000 bootstrap results are shown in table 2. During scm, CL_{CR} and body weight had a significant influence while age had no additional influence on meropenem CL. The basic goodness-of-fit plots of final model are shown in Figure 1. The results for Monte Carlo simulations of different dosage regimens are shown in Figure 2. As CL_{CR} is a covariate for clearance, 5000 patients were simulated in order to observe the effect of CL_{CR} on maintaining the plasma concentration of meropenem above MIC of susceptible, intermediate and resistant strains of target bacteria (Figure 3).

Table 2: Population parameter estimates with bootstrap estimates

Parameter	Final Estimate	RSE (%)	Bootstrap Estimate	95 % CI
CL (L/h)	5.71	3	5.72	5.42-6.05
V_1 (L)	14.2	12	13.4	5.3-17.6
Q (L/h)	11.8	33	16.1	5.83-76.5
V_2 (L)	11.2	13	12.0	7.64-20.5
IIV CL (%)	33.5	15	33.1	27.5-37.3
Prop. Error (%)	22	6	22	18-25
Additive Error (mg/L)	0.27	28	0.34	0.19-1.54

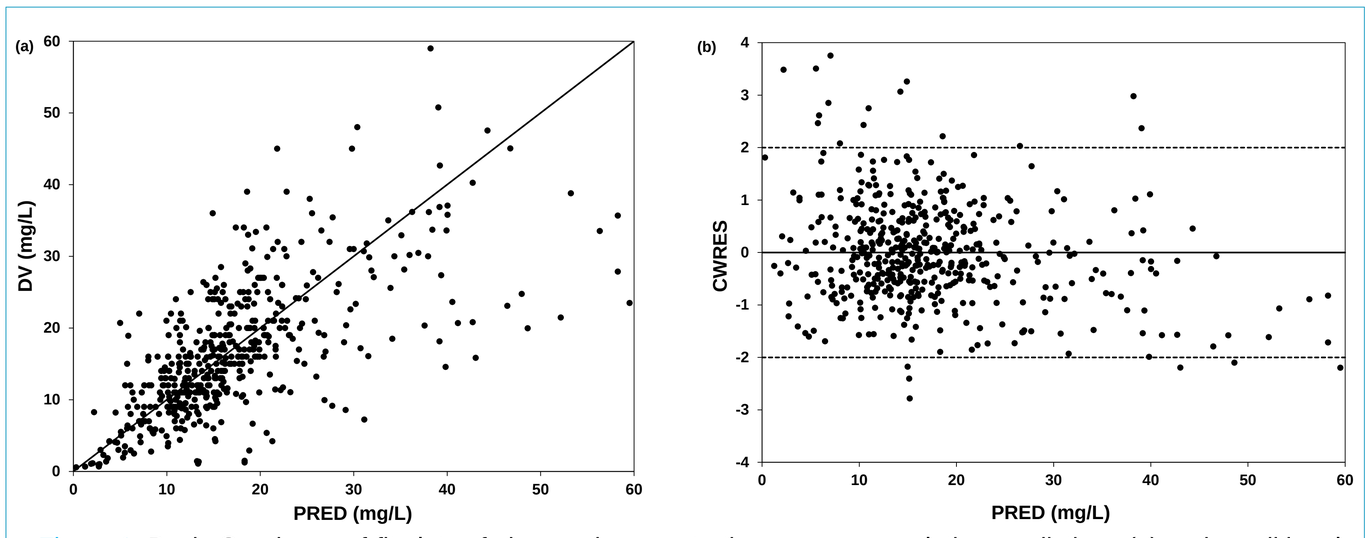

Figure 1: Basic Goodness-of-fit plots of observed concentrations versus population predictions (a) and conditional weighted residuals versus population predictions (b) of meropenem.

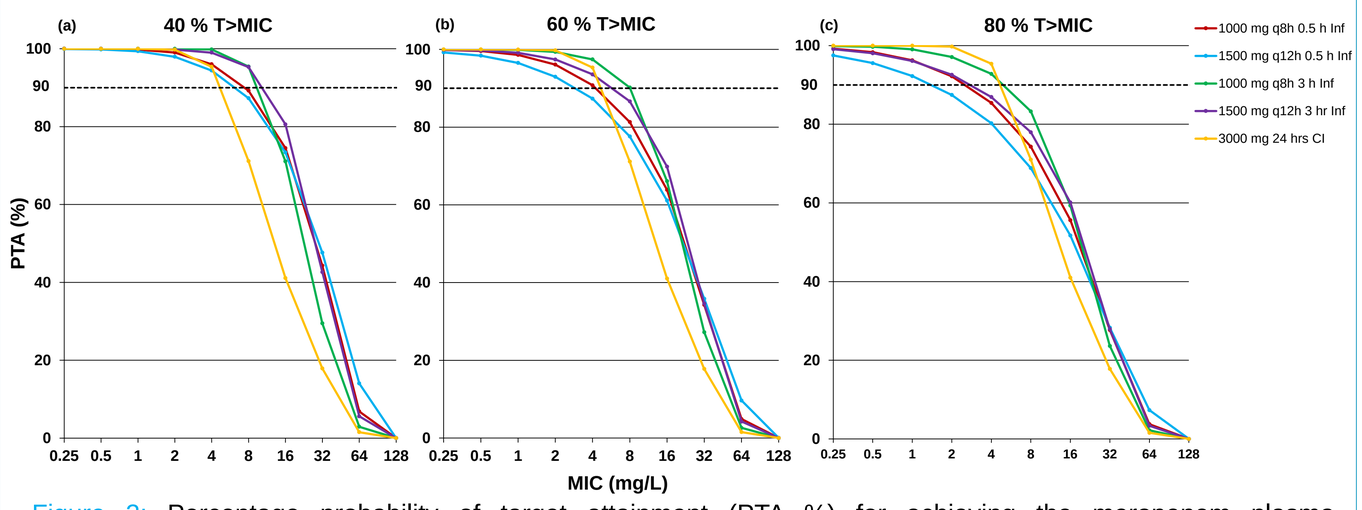

Figure 2: Percentage probability of target attainment (PTA %) for achieving the meropenem plasma concentrations of different dosage regimens for 40% T>MIC (a), 60% T>MIC (b) and 80% T>MIC (c) between dosage intervals. Dashed line indicates 90% probability of target attainment.

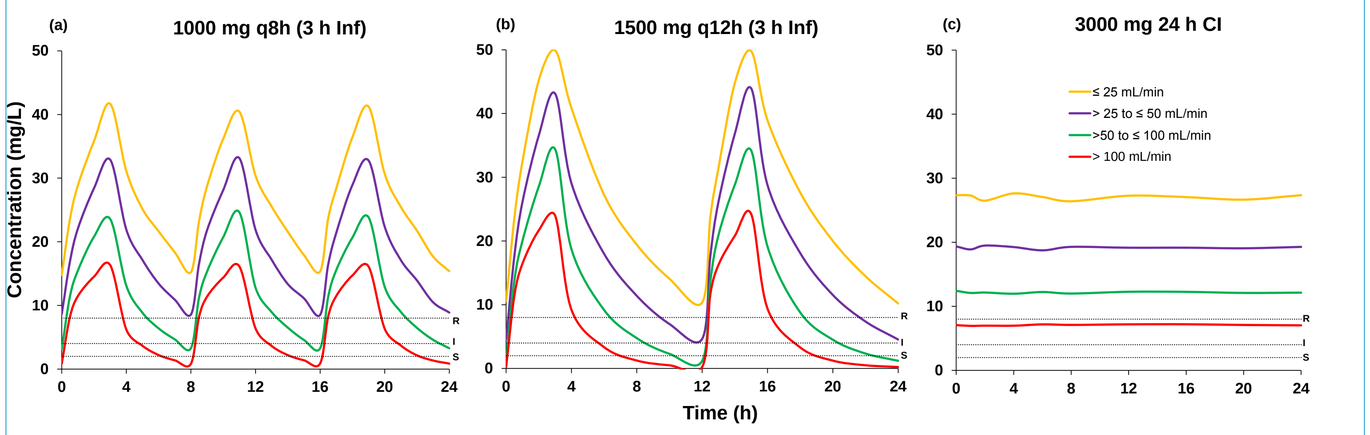

Figure 3: The simulated median plasma concentration-time profiles of meropenem administered as 3 h infusion of 1000 mg every 8 h (a), 1500 mg every 12 h (b) and a 24 h continuous infusion of 3000 mg (c) at different levels of CL_{CR} (mL/min) against susceptible (S), intermediate (I) and resistant (R) strains of *Enterobacteriaceae, Acinetobacter* spp., *Pseudomonas* spp. and Gram-positive & Gram-negative anaerobes.

Conclusions

Meropenem CL was significantly lower in the elderly compared to the CL reported in younger patients due to reduced renal function. An extended infusion of 1000 mg q8h can be considered for empirical treatment of infections in elderly patients when CL_{CR} is ≤ 50 mL/min. A continuous infusion of 3000 mg daily dose is preferred if CL_{CR} > 50 mL/min. However, a higher daily dose of meropenem would be required for resistant strains (MIC > 8 mg/L) of bacteria if CL_{CR} is > 100 mL/min.

Acknowledgement: We are highly thankful to Dr. Otto Frey, Dr. Dong-Soek Yim and Dr. Arantxazu Isla for sharing their meropenem data with us.

wissen.leben
WWU Münster

References

[1] Wiseman, L.R., et al., Drugs, 1995. **50**(1): p. 73-101.
[2] Nicolau, D.P., Clin Infect Dis, **2008**. **47 Suppl 1**: p. 32-40.
[3] Roberts, J.A., et al., Clin Infect Dis, **2014**. 58(8): p. 1072-83.
[4] Verhave, J.C., et al., Am J Kidney Dis, **2005,** 46(2): p. 233-41.
[5] Isla, A., et al., J Clin Pharmacol, **2005**. 45(11): p. 1294-304.
[6] Doh, K., et al., J Antimicrob Chemother, **2010**. 65(11): p. 2428-35.

Contact:
muhammad.usman@uni-muenster.de

Supported by:
HEC Pakistan and DAAD Germany.