

Population pharmacokinetics suggests that an intraperitoneal daily dose of 750 mg meropenem is sufficient to treat peritonitis in patients undergoing automated peritoneal dialysis

Sami Ullah (1), Martin Ursli (2), Uwe Fuhr (1), Martin Wiesholzer (2), Manuel Kussmann (3), Wolfgang Peoppl (3,5), Markus Zeitlinger (4), Max Taubert (1)

(1) University of Cologne, Faculty of Medicine and University Hospital Cologne, Center for Pharmacology, Department I of Pharmacology, Cologne, Germany (2) Department of Internal Medicine I, University Hospital St. Poelten, Karl Landsteiner University of Health Sciences, St. Poelten, Austria (3,4) Department of Internal Medicine I and Department of Clinical Pharmacology, Medical University of Vienna, Vienna, Austria (5) Department of Dermatology and Tropical Medicine, Military Medical Cluster East, Austrian Armed Forces, Vienna, Austria

Background

Peritonitis is one of the most frequent complication of peritoneal dialysis (PD). Appropriate management of peritonitis is essential for the long term success of PD (ISPD guidelines 2016) including antibiotic therapy. In these patients, intraperitoneal (i.p.) application of antibiotics is preferred over the intravenous (i.v.); as the former delivers higher concentrations directly at the infection site. Dosing recommendations of many antibiotics including meropenem are based on limited clinical experience rather than formal pharmacokinetic studies. Therefore, this study was conducted to optimize i.v./i.p. dose of meropenem in automated PD patients and to evaluate the risk of accumulation after three-week meropenem therapy.

Methods

This analysis was performed on a data from a randomized, crossover, two period pharmacokinetic study conducted in six patients undergoing automated PD. Each patient was administered a single dose of 500 mg i.v. or i.p. meropenem and plasma / dialysate concentrations were determined using HPLC-MS. A Population pharmacokinetic model was developed for plasma and dialysate concentrations (n=360) using NONMEM 7.4.3. Based on the model, probability of target attainment (PTA) in plasma and dialysate were calculated using 3000 virtual subjects via Monte Carlo simulations (dose range 250-2500 mg daily). $T_{>MIC} \geq 40\%$ was defined as the pharmacokinetic/pharmacodynamic (PK/PD) target for simulations (MIC of 2 and 8 mg/L).

Results

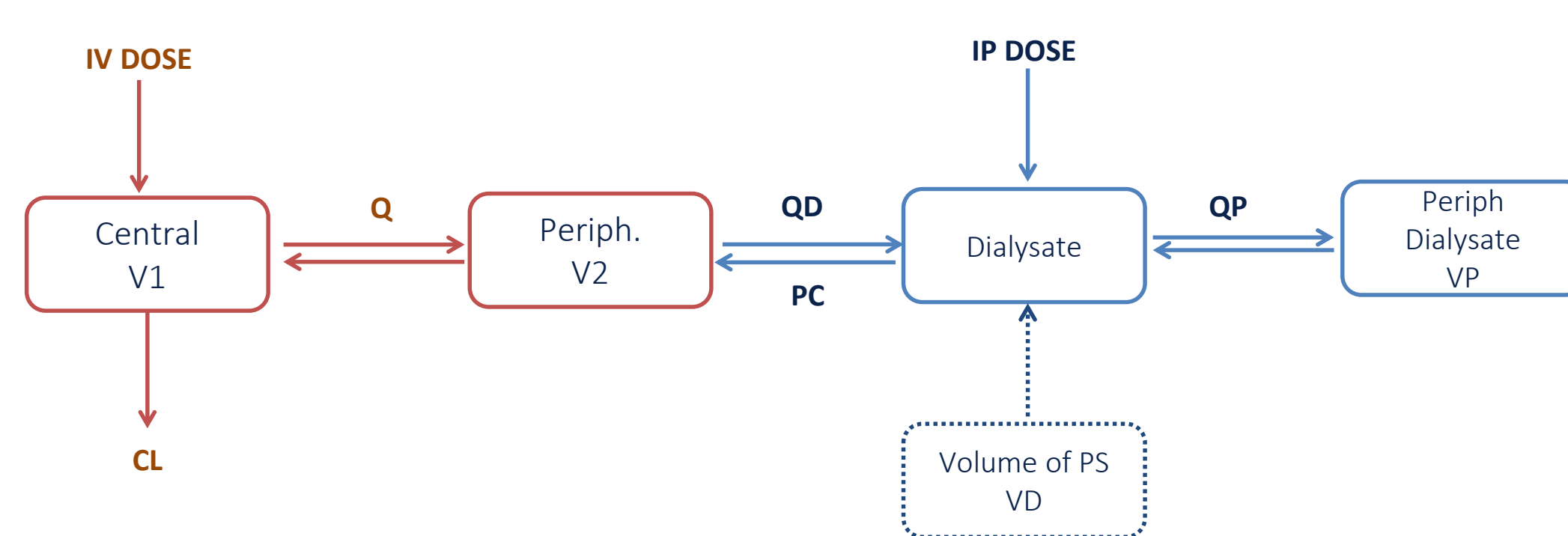


Figure 1. Model structure: A two-compartment model each for plasma and dialysate concentrations. PC; partition coefficient between dialysate fluid and plasma, QD; inter-compartmental CL between peripheral plasma and dialysate fluid cmt, QP; inter-compartmental CL between central plasma and peripheral dialysate cmt, VP; volume of peripheral dialysate cmt, Vbase; baseline volume of peritoneal solution. Changes in the volume of peritoneal dialysate cmt (VD) were incorporated in the dataset based on the actual volume of peritoneal solution (PS) infused or removed.

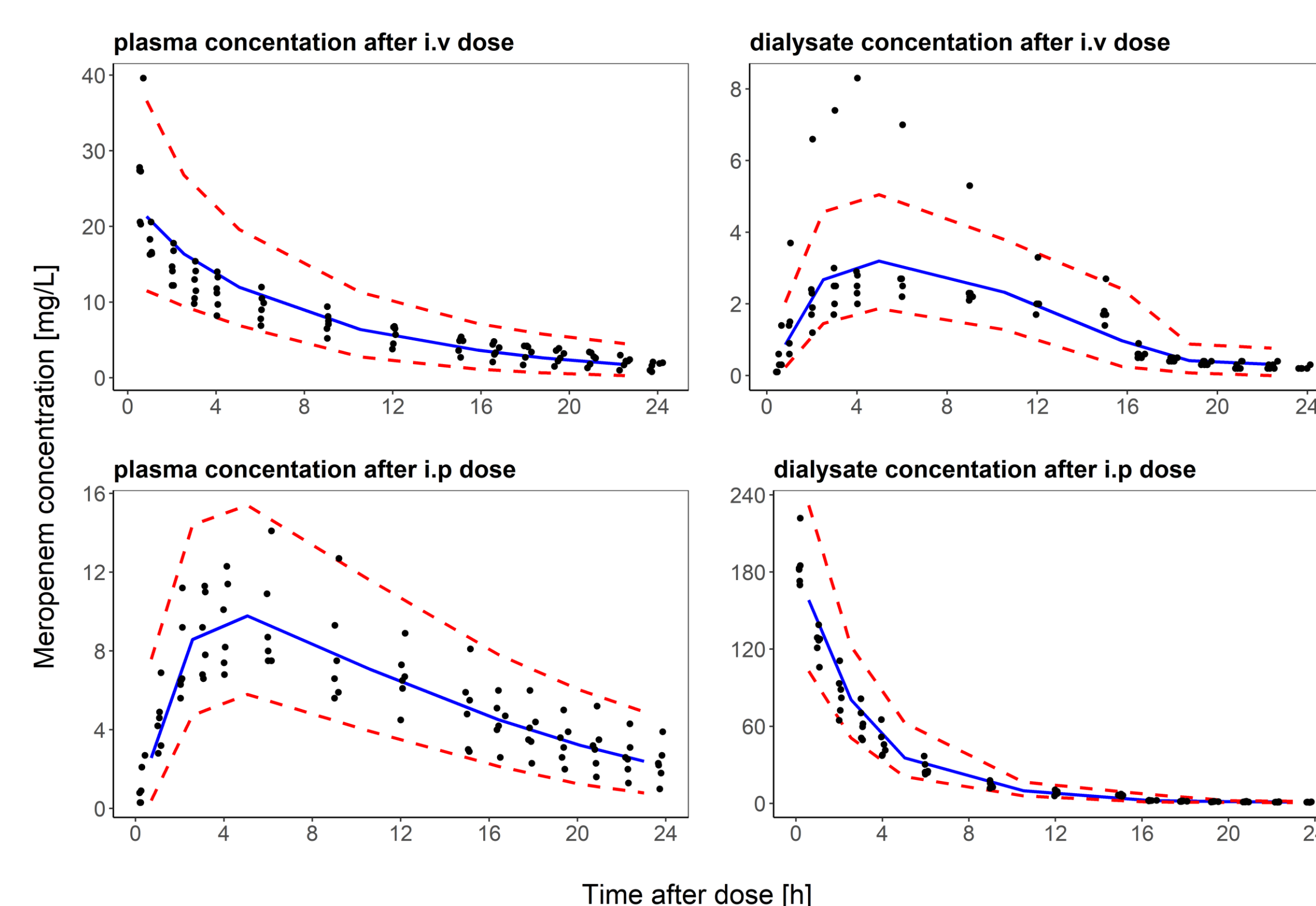


Figure 2. Visual predictive checks of meropenem plasma (left) and dialysate (right) concentrations. Black circles represent observed data, solid blue and dashed red lines show median and 5th and 95th percentile of the simulated predicted concentrations respectively.

Table 1: Parameter estimates obtained from bootstrap analysis (n=1000)

Parameter	Median (95 % CI)	IIV (CV %)
CL (L/h)	2.43 (1.96-3.10)	24.6 (6.35-37.4)
V1 (L)	2.79 (1.81-3.69)	
Q (L/h)	70.6 (44.4-86.3)	
V2 (L)	18.3 (14.3-23.7)	35.2 (6.74-49.5)
PC (Partition co-efficient)	2.99 (2.42-3.68)	
QD (L/h)	0.24 (0.17-0.32)	
QP (L/h)	0.19 (0.16-0.23)	
VP (L)	5.82 (3.67-8.62)	
VD_BASE (L)	0.86 (0.64-1.14)	
Proportional residual error (SD)	0.43 (0.38-0.47)	
Additive residual error (SD)	0.36 (0.27-0.48)	

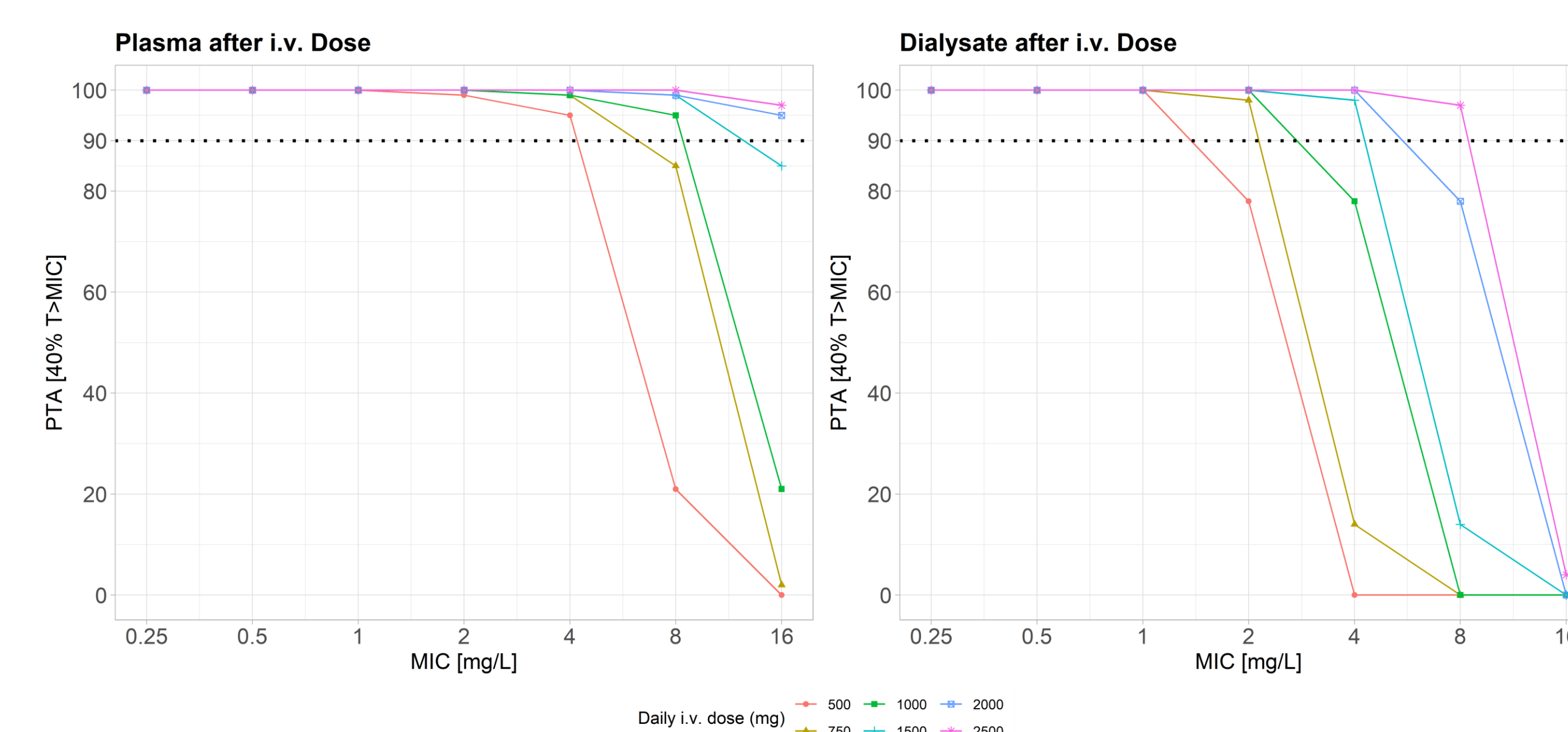


Figure 3: Probability of target attainment in plasma (left) and peritoneal dialysate fluid (right) after intravenous meropenem dosing during day 1 (0-24 h).

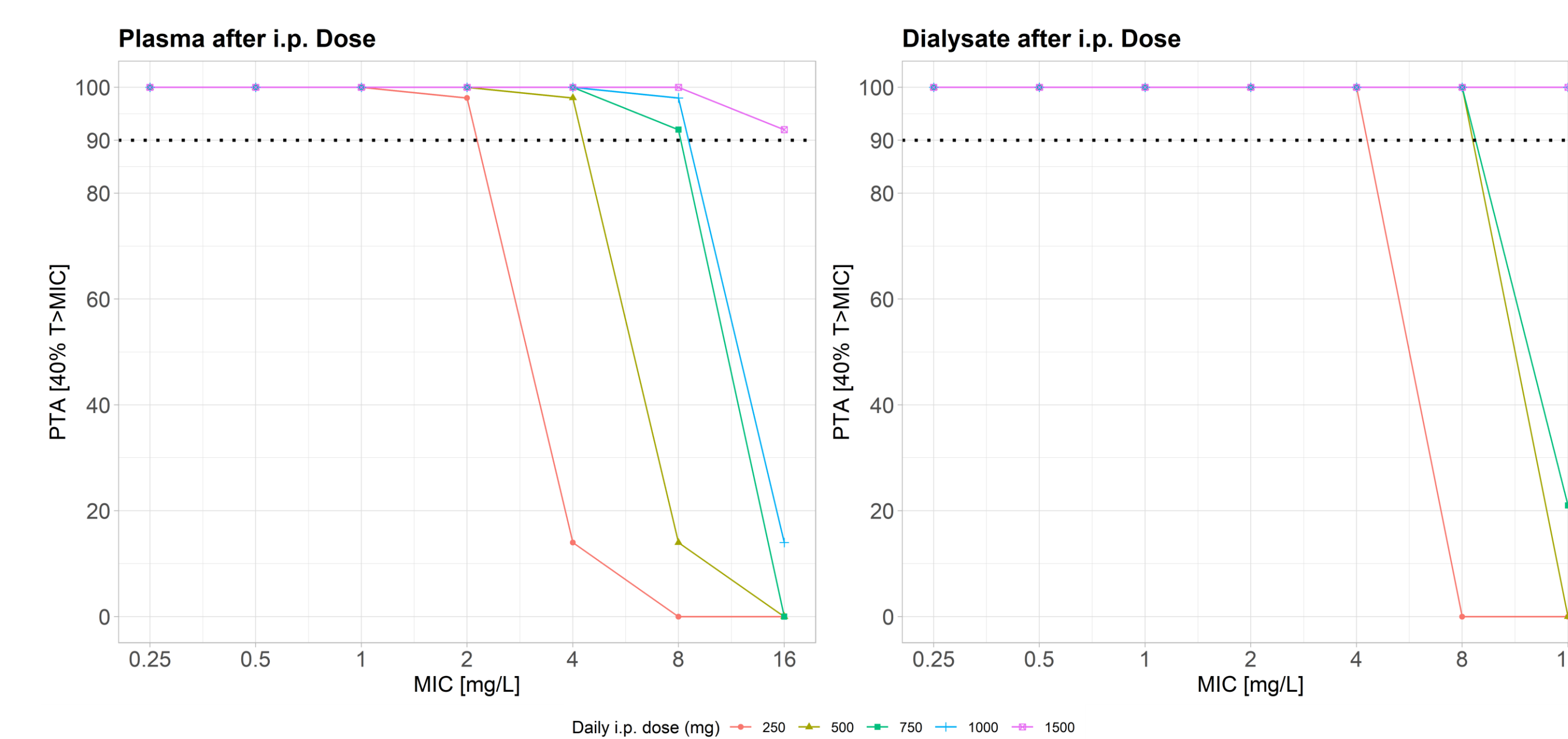


Figure 4: Probability of target attainment in plasma (left) and peritoneal dialysate fluid (right) after intraperitoneal meropenem dosing during day 1 (0-24 h).

Conclusions

Our results suggest that an i.p. dose of 750 mg per day is optimal for pathogens with an MIC ≤ 8 mg/L in automated PD patients, while this assumption needs to be reassessed in peritonitis patients.