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Research article

Dose optimization of meropenem for critically ill patients by pharmacokinetic/ pharmacodynamic simulation

Le Dinh Van[a], Nguyen Thi Cuc[a], Nguyen Hoang Anh (Jr) [a], Nguyen Tran Nam Tien[a], Nguyen Dang Minh Vuong[b], Bui Van Cuong[c], Pham The Thach[c], Do Ngoc Son[c], Nguyen Hoang Anh[a,b,*], Vu Dinh Hoa[a]

[a]*National DI & ADR Centre, Hanoi University of Pharmacy, 15 Le Thanh Tong, Hanoi, Vietnam*
[b]*Clinical Pharmacy and Drug Information Unit, Department of Pharmacy, Bach Mai Hospital, 78 Giai Phong, Hanoi, Vietnam*
[c]*Department of Intensive Care, Bach Mai Hospital, 78 Giai Phong, Hanoi, Vietnam*

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ABSTRACT

Recent pharmacokinetic/pharmacodynamic (PK/PD) studies revealed that prolonged infusion, especially continuous infusion could improve probability of target attainment (PTA) of meropenem. However, the implementation of continuous meropenem infusion in the clinical environment can be limited due to the solution's instability, which results in a diminished effectiveness of the drug. The two-step infusion approach has been expected as a promising novel approach to address this issue. The aim of this study was to assess the probability of target attainment for finding the optimal dosage regimens of meropenem in critically ill patients. Monte Carlo simulation using Ehmann population pharmacokinetic model was performed to evaluate the following different intravenous infusion regimens including extended infusion (EI), continuous infusion (CI) and two-step infusion (TS) with three total daily doses (3 g, 4.5 g and 6 g). The PK/PD target was defined as the probability of achieving a fractional time above the MIC of ≥ 98% on the first day of therapy. Subsequently, dosing regimens were suggested based on renal function which was estimated by the Cockcroft & Gault creatinine clearance (Clcr =10-30, 31-50, 51-70, 71-90, 91-130, and over 130 mL/min). Simulations also revealed that the 1000 mg q8h EI regimen is suitable to reach MICs of 1 mg/L, regardless of the patient's renal function. For higher MICs and up to 16 mg/L, continuous infusion therapy with a loading dose of 0.5 g and a maintenance dose of 3 g to 6 g per day should be considered in clinical practice. The two-step infusion approach did not demonstrate superior PTA compared to extended infusion therapy and was significantly lower than that of continuous infusion at the same dosage level.

**Corresponding author: Nguyen Hoang Anh; e-mail address: anhnh@hup.edu.vn*

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Introduction

Meropenem is a broad-spectrum carbapenem antibiotic which is commonly prescribed for treatment of severe infections caused by multidrug-resistant bacteria [1]. In critically ill patients, pathophysiological changes, and the frequent use of invasive interventions for therapy might substantially influence pharmacokinetics of meropenem, leading to an increased risk of inadequate antibiotic exposure [2]. Moreover, the emergence of antimicrobial resistance creates a significant challenge for clinicians in selecting an optimal dosing regimen to improve clinical outcomes.

As meropenem exhibits time-dependent bactericidal activity, the PK/PD index describing its antimicrobial efficacy is the percentage of the time during dosing interval that the free plasma concentration exceeds the minimum inhibitory concentration (MIC) value of the pathogens *(%fT >MIC*) [1]. Optimizing the dosing strategy is crucial for rapidly achieving effective concentrations and prolonging the period of time above MIC from the very first day of therapy. Previous PK/PD studies have shown that prolonged infusion, especially continuous infusion of meropenem could improve *%fT >MIC* index [3-5]. However, meropenem solution is stable for only approximately 6 hours at room temperature, meropenem may be considered an inappropriate agent for the implementation of continuous intravenous infusion [4]. Eguchi et al. had suggested that the utilization of two-step infusion method (rapid first-step infusion and slow second-step infusion) not only ensures the drug stability but also enhances the probability of PK/PD target attainment of meropenem (PTA) [6]. Therefore, this study aimed to assess the PTA in order to identify the optimal dosing regimens and infusion method for meropenem in critically ill patients.

Materials and Methods

Pharmacokinetic model

A published two compartment model with first-order elimination from Ehmann's research was selected for simulation (7). This model was developed based on a prospective observational study in a heterogeneous population of 48 critically ill patients with a total of 1376 blood samples over 4 days at an Intensive Care Units (ICU) in Germany. The summary of the Ehmann model is presented in ***Table 1***.

Table 1 - Population pharmacokinetic parameters of meropenem from Ehmann popPK model (7)

Parameter	Typical value (IIV, IOV)
CL (L/h)	9.25 (IIV: 27.1%, IOV: 12.5%)
V1 (L)	7.89 (IIV: 31.5%)
Q (L/h)	28.4
V2 (L)	16.1 (IIV: 16.7%)

CL: total clearance; Q: intercompartmental clearance; V1: central volume of distribution; V2: peripheral volume of distribution; IIV: inter-individual variability; IOV: inter-occasion variability

Methods

Monte Carlo simulations ($n_{simulations}$ = 1000) were performed to assess the PTA value of various dosage regimens. The patient characteristics in the simulated population are established according to the covariates identified in Ehmann model including creatinine clearance (ClCr) estimated using the Cockcroft-Gault equation, total body weight (WT) and serum albumin (ALB) [7].

Pharmacokinetic/pharmacodynamic target

In an effort to optimize treatment efficacy for the first day, a target of 98% fT > MIC over 24 hours was selected to evaluate for investigated dosage regimen [7]. A PTA threshold of ≥ 90% was considered optimal [2].

Three infusion strategies including extended infusion (EI), continuous infusion (CI) and two-step infusion (TS) (rapid first-step infusion and slow second-step infusion) were investigated with three total daily doses (3 g, 4.5 g, 6 g), as detailed in Table 2. Patients receiving CI therapy were administered an initial loading dose of 500 mg infusing over 0.5 hours [1].

Table 2 - Intravenous dosing regimens of meropenem

Daily dose	Extended infusion	Continuous infusion*	Two-step infusion
3000 mg	**EI1:** 1000mg EI3h q8h	**CI1:** 3000mg q24h	**TS1:** (500 mg SI0.5h + 500mg EI3h) q8h
4500 mg	**EI2:** 1500mg EI3h q8h	**CI2:** 4500mg q24h	**TS2:** (500 mg SI0.5h + 1000mg EI3h) q8h
6000 mg	**EI3:** 2000mg EI3h q8h	**CI3:** 6000mg q24h	**TS3:** (500 mg SI0.5h + 1500mg EI3h) q8h

SI: short-term infusion, EI: extended infusion, CI: continuous infusion, TS: two-step; EI3h: infusing over 3 hours, SI0.5h: infusing over 0.5 hours; q8h: every 8 hours;

**: for CI treatment at day 1, the initial loading dose of 500mg is infused over 0.5h.*

Probability of target attainment analysis

First, the impact of different infusion therapies on the PTA were investigated (Table 2). For each patient characteristic, simulations were performed for fixing covariate values with creatinine clearance, total body weight, and serum albumin fixed to 86.5 mL/min, 50 kg and 2.57 g/dL, respectively (this information represents the typical characteristics observed in critically ill patients at a tertiary hospital in Vietnam from Quan A. Truong research (27 patients, 2022)) [2].

Second, PTA analysis based on six simulations (1000 virtual patients per simulation) was performed for three total daily doses by varying creatinine clearance (ClCr) ranges, including 10-30, 31-50, 51-70, 71-90, 91-130 and over 130 mL/min (augmented renal clearance, ARC) while fixing the remaining ones to the covariate values stated above.

Finally, we recommended a meropenem dosing regimen for each patient group at various MIC values based on the following criteria, in order of preference: [1] PTA ≥ 90%; [2] lower total daily dose; [3] the complexity of the intravenous infusion therapy, in order of EI, TS, CI.

Data analysis and processing

The RsSimulx package (R version 4.2.2) was employed for Monte Carlo simulation. Additionally, the ggplot2 R-package (R version 4.2.2) was used for data visualization purposes.

Results and Discussions

Results

PK/PD analysis and treatment outcomes

Figure 1 illustrates the PTAs of 98% fT >MIC for different meropenem regimens (Table 2) in a typical patient with creatinine clearance, total body weight, and serum albumin fixed to 86.5 mL/min, 50 kg and 2.57 g/dL, respectively [2]. In the same level of total daily dose, the PTAs of two-step infusion therapy (TS) was not apparently different to that of extended infusion therapy (EI) for all MIC values, and significantly lower than that of continuous infusion therapy (CI) for MICs of ≥ 4 mg/L. Consequently, TS dosing regimens were excluded from further simulation analysis.

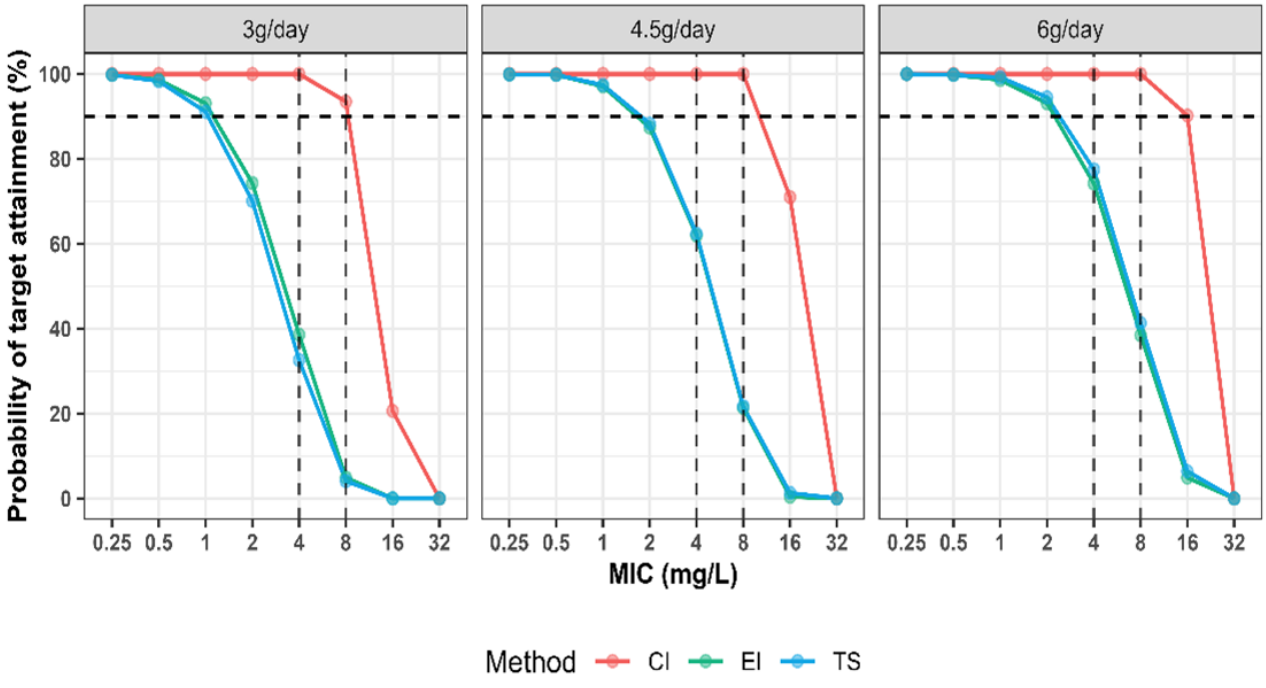

Figure 1. PTA of 98% fT >MIC for meropenem regimens in the typical patient with Clcr = 86.5 mL/min, WT = 50 kg, ALB = 2.57 g/dL.

The PTA values regarding creatinine clearance of CI dosing regimens and EI dosing regimens were depicted in Figure 2. Overall, PTA was dependent on the level of creatinine clearance, or more precisely, decreasing with increasing Clcr. For the isolates belonging to the R category (resistant, i.e., MIC = 32 mg/L), none of dosing regimens resulted in effective exposure (PTA ≥ 90%). However, for isolated pathogens belonging to the I category (intermediate, MIC ≤ 8 mg/L) and the S category (susceptible, MIC

≤ 4 mg/L), a dose of 3 g/day CI achieved PTA ≥ 90% in non-ARC groups and ARC group, respectively. Meanwhile, 6g/day EI would only cover isolates with MICs of ≤ 8 mg/L in patients with renal insufficiency (Clcr ≤ 50 mL/min). Neither the dose of 3 g/day EI nor the dose of 4.5 g/day EI is effective in almost less susceptible bacteria with MICs of ≥ 4 mg/L.

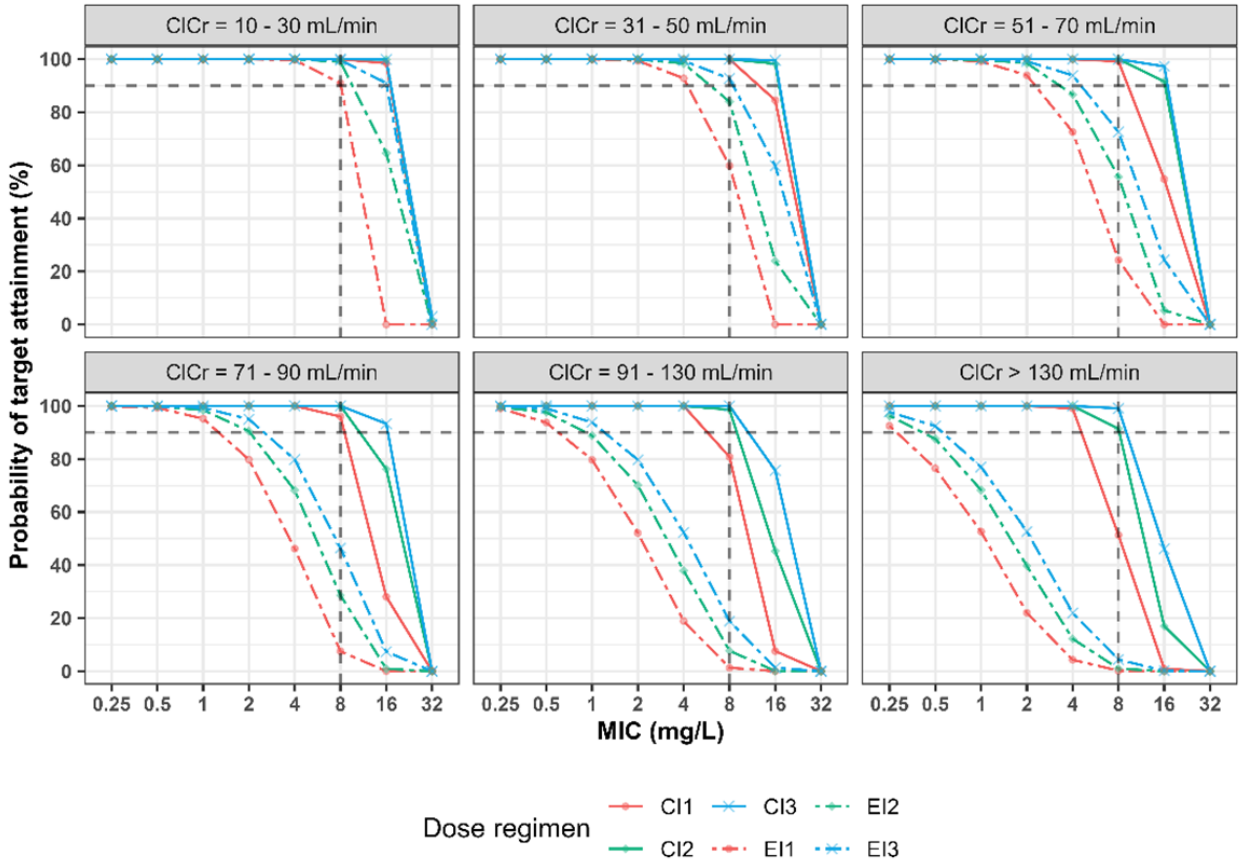

Figure 2. PTA of 98% fT >MIC for meropenem regimens in six renal function groups (EI1: 1000mg EI3h q8h, EI2: 1500mg EI3h q8h, EI3: 2000 mg EI3h q8h, CI1: 3000mg q24h, CI2: 4500mg q24h, CI3: 6000mg q24h)

Table 3. The recommended dosing regimen in critically ill patients based on PTA analysis

ClCr *(mL/min)*	MIC *(mg/L)*							
	0.25	*0.5*	*1*	*2*	*4*	*8*	*16*	*32*
10 – 30	**EI1**	**EI1**	**EI1**	**EI1**	**EI1**	**EI1**	**CI1 (EI3)**	-
31 – 50	**EI1**	**EI1**	**EI1**	**EI1**	**EI1**	**CI1 (EI3)**	**CI2**	-
51 – 70	**EI1**	**EI1**	**EI1**	**EI1**	**CI1 (EI3)**	**CI1**	**CI2**	-
71 – 90	**EI1**	**EI1**	**EI1**	**CI1 (EI2)**	**CI1**	**CI1**	**CI3**	-
91 – 130	**EI1**	**EI1**	**CI1 (EI3)**	**CI1**	**CI1**	**CI2**	-	-
> 130	**EI1**	**CI1 (EI3)**	**CI1**	**CI1**	**CI1**	**CI2**	-	-

EI1: 1000mg EI3h q8h, EI2: 1500mg EI3h q8h, EI3: 2000mg EI3h q8h, CI1: 3000mg q24h, CI2: 4500mg q24h, CI3: 6000mg q24h
***(Dosing regimen):** recommended regimen based on the criteria of prioritizing simpler infusion over lower dosing levels*

Recommended dosing regimens

A tabular dosing overview was generated considering Clcr of the patients and MIC value of pathogens, as shown in Table 3. None of the investigated dosing regimens could meet the predefined criteria in patient subgroups with ClCr > 90 mL/min for treating pathogen isolates with MICs of ≥ 16 mg/L. Notably, the dose of 3 g/day EI was recommended for isolates with MICs of ≤ 1 mg/L in most of renal function groups. For higher MIC values (MIC = 4, 8 mg/L) and high renal function, continuous infusion therapy should be considered to attain PTA ≥ 90%.

Discussions

Due to more challenges in treating serious life-threatening infections, the judicious selection of meropenem dosing regimen is vastly important to optimize the probability of achieving the PK/PD target [1]. Previously published studies have investigated the bacteriostatic and bactericidal activity of meropenem linked to fT > MIC of 20% and 40%, respectively [8]. To significantly increase clinical cure and bacteriological eradication in critically ill patients with serious bacterial infections, a target of 100% fT > MIC should be required [7]. Additional, in vitro and in vivo studies have even suggested a more intensive target of 100% fT > 4xMIC to improve antimicrobial efficacy in ICU settings with high rates of resistant pathogens [1], [2]. However, it is impossible to achieve 100% fT >MIC on the first day of infusion, since meropenem takes time to reach the MIC concentration after starting infusion. Thus, we utilized the target of 98% fT > MIC (ignoring the first 30 minutes infusion ~ equivalent to a 2% period within 24 hours for drug distribution in systemic circulation) according to proposal of Ehmann et al. with the goal of dosing optimization from the early stage of therapy [7].

The Ehmann popPK model was developed based on data from a heterogeneous population of 48 critically ill patients with severe infections [7]. Notably, this study applied a dense plasma sampling strategy (mean = 28 samples per patient), and these arterial blood samples were collected both in the steady state and across all three dosing intervals in the first day of therapy [7]. This intensive sampling enabled this model to describe accurately the complex pharmacokinetic changes in critically ill patients. Furthermore, this model might be also useful for minimizing errors in evaluation of dosing regimens stratified by Clcr based on PK/PD simulation, as the renal function observed in this study's population ranged widely (Clcr = 24.8-191 mL/min). Given these advantages of the Ehmann popPK model to other published studies [9-12], we selected this model for simulation. In addition, our study also incorporated typical characteristics of critically ill Vietnamese patients to increase the similarity to simulated population [2].

The present study aimed to evaluate the PTAs of nine meropenem dosing regimens with three different daily doses and two infusion methods. The results demonstrated that PTA of *98% fT > MIC* for two-step infusion dosing regimen (TS) bears the similarity to that of extended infusion dosing regimen (EI) at all MIC values (Figure 1). Conversely, Eguchi's study reported that the PTA of TS was apparently superior to that of EI at high MIC values (4 mg/L, 8 mg/L) [6]. The PTA of TS dosing regimen *([500mg SI0.5h + 500mg EI4h] q8h)* stood at 98.1%, compared to 29.5% of prolonged infusion therapy *(1000mg EI4h q8h)* for pathogen isolates with an MIC of 4 mg/L [6]. This discrepancy could be attributed to the different PK/PD targets chosen in two studies. In our study, the PK/PD target was set at *98% fT >MIC*, whereas Eguchi et al. employed a target of *50% fT > MIC*. Furthermore, although the two-step method utilizing a short infusion demonstrates a rapid attainment of target plasma concentration, it tends to a lower meropenem concentration than the extended infusion method in the subsequent stages due to the reduction in infusion rate.

Our study has reaffirmed the superiority of continuous infusion (CI) therapy in achieving the PK/PD target. Specifically, in non-ARC groups, the dose of 3 g/day CI could cover bacterial strains isolated with MICs ≤ 8 mg/L (Figure 1,2). This finding is consistent with the study of Mattioli et al. on Italian ICU patients with sepsis or septic shock [5]. Another PK/PD study *(Zhao et al. 2017)* in which meropenem using the dose of 3 g/day CI could lead to shorter treatment duration and better bactericidal effects compared to the intermittent infusion of 1g every 8 hours [4]. Furthermore, the efficacy of CI had been recognized in the guidelines about optimization of treatment with beta-lactam antibiotics in critically ill patients issued by the French Society of Pharmacology and Therapeutics and the French Society of Anesthesia and Intensive Care Medicine [3]. However, a recent RCT study has reported that the dose of 3 g/day CI did not improve the 28-day mortality, the 90-day mortality and emergence of drug-resistant bacteria in critically ill patients with sepsis [13]. To date, the clinically relevant outcome of continuous infusion meropenem has been controversial, the intensive trials about this issue need to be promoted in the future [13].

Meropenem is predominantly eliminated by the kidneys, leading its pharmacokinetics highly depend on creatinine clearance [2, 11]. Our study aimed to establish appropriate dosing regimens based on the patient's creatinine clearance index as an important clinical determinant of PK/PD target attainment (Table 3). The dose of 3 g/day EI could cover most bacteria isolates with MICs ≤ 1 mg/L in non-ARC groups, which is quite consistent with Ehmann et al. study [7]. However, for higher MIC values, clinicians should consider using a higher dose or continuous infusion therapy (Table 3). Notably, our study did not suggest an optimal dosing regimen for severe infections caused by pathogens with MICs of ≥ 32 mg/L. Therefore, it is necessary to consider the dosage increase of meropenem or the implementation of combination regimens as potential measures to achieve a clinical efficacy against these bacterial strains.

Although our study incorporated characteristics of critically ill Vietnamese patients into the simulation flow, results should be carefully interpreted and extrapolated due to the use of the popPK model developed from a distinct population. In the future, an external validation study about the predictive performance of this popPK model in Vietnamese ICU patients should be done to warrant the appropriateness of the recommended dosing regimen.

Conclusions and perspectives

Our study had elucidated that two-step infusion therapy of meropenem did not offer any advantage over the conventional prolonged infusion in achieving the target of *98% fT>MIC*. Clinicians should consider using high doses of meropenem (4.5-6 g/day) or continuous infusion therapy, depending on the bacterial MIC values and the patient's renal function. The findings have provided valuable information in selecting the appropriate meropenem dosing regimen to apply best clinical practices.

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