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Original Article

Evaluation of PK/PD Properties of Recommended Doses of Meropenem in Critically Ill Patients with Augmented Renal Clearance, A Prospective Observational Study

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Abstract

Augmented renal clearance (ARC) is a common phenomenon among critically ill patients and creates sub-therapeutic concentrations of antibiotics, due to an increase in renal clearance of them. We evaluated the Pharmacokinetic and Pharmacodynamic (PK/PD) properties of recommended doses of meropenem in critically ill patients with ARC. Adult critically ill patients with confirmed ARC, based on 12-hour Creatinine Clearance (CrCl) (≥130 ml/min/1.73 m^2), who received standard doses of meropenem enrolled in this study. Two blood samples were gathered from each participant, at the steady-state time, to determination of peak and trough concentrations. Serum concentrations of meropenem were measured by high-performance liquid chromatography (HPLC) with an ultra-violet (UV) detector. From eighteen paired samples (peak and trough concentrations) that were obtained from 16 critically ill patients, peak concentrations were significantly lower in group 1 (received meropenem 1g every 8 hours) than in group 2 (received meropenem 2g every 8 hours) (mean ±SD, 5.95 ±3.39 µg/mL vs. 11.93± 4.18 µg/mL, respectively, p=0.005). Trough concentrations were sub-threshold (< 2 µg/mL) in 10 patients of group 1 (83.3%) and 3 patients of group 2 (50%). ft > MIC ≥ 50% was achieved in 83.3% of patients in both groups whereas 16.6% of patients of group 1 and 33.3% of patients of group 2 had ft> MIC= 100%. Augmented renal clearance is an essential cause of sub-therapeutic concentrations of meropenem in critically ill patients, and higher than the recommended doses of meropenem administered as an intermittent infusion may be necessary to achieve the PD targets and improve efficacy.

Keywords: Augmented renal clearance; Critically ill patients; High-performance liquid chromatography; HPLC; Meropenem; Pharmacodynamic; Pharmacokinetic.

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1. Introduction

Augmented renal clearance (ARC) is a common phenomenon among critically ill patients [1, 2]. The incidence of ARC, based on the study population and definition of ARC, was reported

from 14 to 80% [3-5]. Augmented renal clearance refers to the enhanced renal elimination of solutes and is commonly defined as creatinine clearance (CrCl) ≥130 ml/min/1.73m^2 [3, 6]. An increase in the renal clearance of drugs due to ARC, especially hydrophilic ones like β-lactams, can lead to changes in the pharmacokinetic/ pharmacodynamics (PK/PD) properties [3, 7, 8] and create sub-therapeutic concentrations of antibiotics as a major reason of treatment failure in critically ill patients [8-11]. Nowadays, for the enhancement of drug efficacy, interventions such as therapeutic drug monitoring (TDM) have been suggested to achieve optimal antimicrobial concentration [12].

Meropenem is a broad-spectrum β-lactam. Meropenem bactericidal activity is time-dependent, and minimum plasma concentration must be maintained higher than the minimum inhibitory concentration (MIC) for an adequate percentage of time in the dosing interval (%ft >MIC) to reach optimal efficacy [13-15]. According to these PD properties, studies suggested prolonged infusion of meropenem rather than increasing the dose to maximize efficacy and minimize concentration-related adverse effects [16-18].

This study aimed to evaluate the PK/PD properties of meropenem in ARC patients, receiving recommended doses as a 4-hr intermittent infusion.

2. Materials and Methods

2.1. Settings

This single-center prospective observational study was conducted at a 30-bed medical-surgical intensive care unit (ICU) of Imam Hossein Medical Center, affiliated with Shahid Beheshti University of Medical Sciences (SBMU) in Tehran, Iran. This study was approved by the Institutional Review Boards of SBMU with the ethics committee code of IR.SBMU.PHARMACY.REC.1398.103.

2.2. Study population

Inclusion criteria were ICU-admitted adult patients with a confirmed ARC by 12-hour urine collection (12-hr CrCl ≥130 ml/min/1.73 m^2) who received meropenem 1g or 2g every 8 hours, as an intermittent infusion over 4-hr, according to physician decision. Patients who were pregnant or lactating, or had a serum creatinine (Scr) ≥ 1.3 mg/dL and hypersensitivity to β -lactams were excluded.

2.3. Interventions

All ICU patients were evaluated for the risk of ARC development, using ARC and augmented renal clearance in trauma intensive care (ARCTIC) scoring systems (**Table 1**) [3, 19] on the first day of admission. For patients who were categorized as high-risk based on scoring systems, 12-hour urine collection was requested. Patients with confirmed ARC, based on 12-hour urine CrCl, who received standard doses of meropenem (1g or 2g every 8 hours, infused over 4-hr) based on the physician in charge decision, enrolled in the study. After 48 hours, at the steady-state time, two blood samples were gathered from each participant. The first sample was obtained 60 minutes after the end of the meropenem infusion (peak

concentration (Cpeak)) and the second one attained 30 minutes before receiving the next dose (trough concentration (Ctrough)). Blood samples were immediately centrifuged for 15 min at 4000 g, and serum was stored at -80°C for later analysis.

2.4. Meropenem assay

The samples were analyzed at the clinical pharmacy laboratory of SBMU. The plasma concentration of meropenem was determined by validated high-performance liquid chromatography (HPLC) according to a previously reported procedure with some minor modifications [20]. In brief, sample preparation involves two-step plasma protein precipitation with acetonitrile and dichloromethane. Initially, 950 µl of plasma was added to 50 µl of acetaminophen (40 µg/mL) following the addition of 1000 µl of acetonitrile. After shaking for 10 min by Vortex Mixer and 10 min centrifugation at 1000 g respectively, a 1000 µl of supernatant was added to 1000 µl methylene chloride. Finally, a 20 µl of the aliquot of the upper aqueous layer was injected into the C18 analytical column (250×4.6 mm with 3.5 µm spherical particles) after 10 min shaking by Vortex Mixer and 10 min centrifugation at 1000 g in turn. The mobile phase consisted of 10.53 mmol/L ammonium acetate: acetonitrile (91:9, v/v) (pH=4) pumped at 1ml/min. The UV detector was adjusted at 298 nm. The meropenem calibration curve was linear over the concentration range of 0.25-20 mg/L with the correlation coefficient (r^2) =0.999. Intra-assay accuracy ranged from +1.38% to +8.50 % and precision was less than .3.06%. Inter-assay accuracy ranged from -1.28% to +2.17% and precision was less than .5.42%. The lower limit of quantification was 0.125 mg/L.

Table 1: The ARC risk-scoring systems.

	ARC Scoring System	**ARCTIC Scoring System**
Criteria	Age 50 or younger = 6 pts Trauma = 3 pts SOFA score ≤ 4 = 1 pt	SCr<0.7 mg/dL = 3 pts Male sex = 2 pts Age <56 years = 4 pts Age: 56–75 years = 3 pts
Interpretation	0–6 points= low ARC risk 7–10 points= high ARC risk	≤6 points= low ARC risk >6 points= high ARC risk

ARC = Augmented renal clearance (ARC); Augmented Renal Clearance in Trauma Intensive Care (ARCTIC); Sequential Organ Failure Assessment score (SOFA); Serum creatinine concentration (Scr); point (pt).

2.5. Definition and Endpoints

2.5.1. Formulas

Urinary creatinine clearance in a 12-hour urinary collection was calculated using the below equation:

$$\text{12-hour creatinine clearance (ml/min)} = \frac{urine\ volume\ (mL) \times urine\ creatinin\ (\frac{mg}{dL})}{serum\ creatinin\ (\frac{mg}{dL}) \times collectin\ time\ (min)}$$

The PK parameters of meropenem were calculated according to the following equations:

$$\text{CL (L/hr)} = \frac{[\text{Dose}/\text{T}]}{\text{Css ave}}$$

$$\text{K (min}^{-1}\text{)} = \frac{\ln[\text{Cpeak}/\text{Ctrough}]}{\text{t}}$$

$$\text{Vd (L)} = \frac{\text{CL}}{\text{K}}$$

$$\text{T1/2(hr)} = \frac{0.693}{\text{K}}$$

"CL" is the clearance of meropenem, "K" is the elimination rate constant, "Vd" is the volume of distribution, and" T1/2" is the terminal half-life. Css ave is the average steady-state concentration of meropenem. "T" is the dosing interval and "t" is the time interval between the measurements of Cpeak and Ctrough.

2.5.2. Endpoints

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) determined 2 µg/mL of meropenem as a susceptible breakpoint of meropenem for Gram-negative organisms (MIC). The primary pharmacodynamic endpoint of this study was the concentrations above the breakpoints for ≥50% of the dosing interval (ft>MIC ≥ 50%), and the secondary endpoint was ft>MIC= 100%.

2.6. Statistical analysis:

All statistical analyses were performed using SPSS for Windows (Version 21.0; SPSS Inc., Chicago, IL, USA). Quantitative data were tested for normality of distributions by Kolmogorov–Smirnov test, and then compared by Unpaired Student's *t*-test, and Mann-Whitney U test for normal and non-normal data, respectively. Qualitative data were analyzed by the Chi-square test, and a P-value of < 0.05 was considered significant.

3. Results and Discussion

From a total of 819 critically ill patients who were evaluated from August 23, 2019, to September 23, 2021, 79 patients were ARC positive, according to 12-hr CrCl, and 16 subjects received meropenem. A total of twelve patients received meropenem with a dose of 1g every 8 hours (group 1), and the remaining four subjects received 2g every 8 hours (group 2). During the treatment period, the dose of meropenem increased from 1g every 8 hours to 2g every 8 hours, according to their physician's decision, for two patients in group 1. We gathered blood samples of them after achieving a steady state based on the drug's half-life. Overall we collected 18 paired samples (peak and trough concentrations) for analysis 12 samples were for Group 1, and 6 samples were for Group 2. We were detailed data in **Figure 1**.

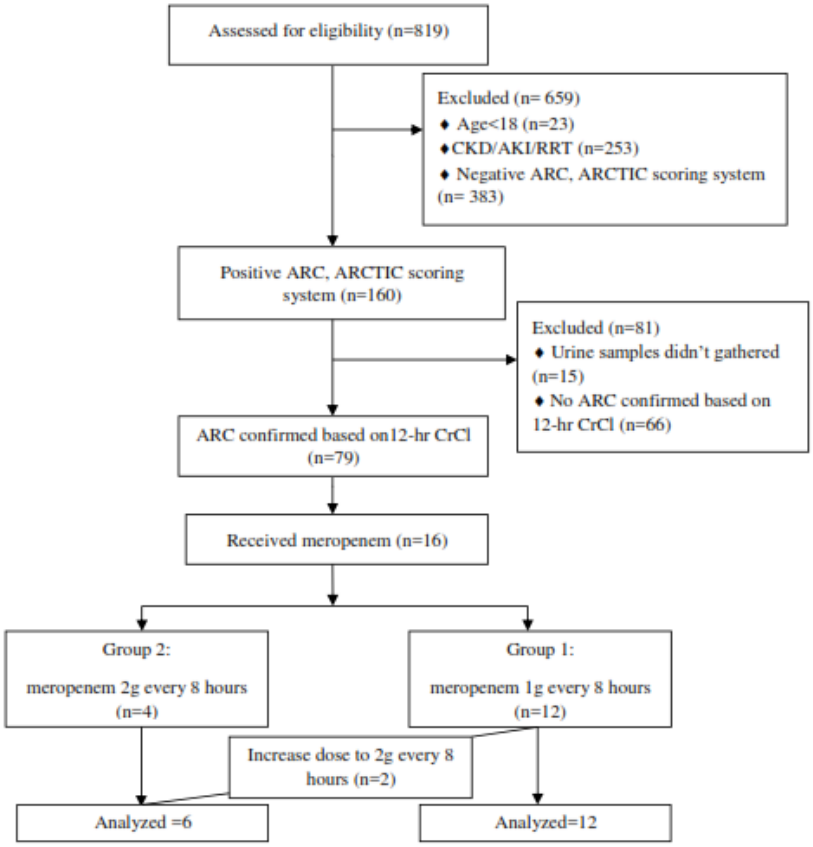

Figure 1. Participant inclusion process.
CKD: Chronic Kidney Disease; AKI: Acute Kidney Injury; RRT: Renal Replacement Therapy; ARC: Augmented Renal Clearance; ARCTIC: Augmented Renal Clearance in Trauma Intensive Care; CrCl: Creatinine Clearance.

Baseline characteristics including age, sex, ideal body weight (IBW), ICU diagnosis on admission based on International Classification of Diseases-10 (ICD10) codes, sequential organ failure assessment (SOFA), ARC and ARCTIC score, 12-hr CrCl were recorded for participants. There were statistically significant differences in sex, ICU diagnosis, and ARCTIC score between the two groups (p= 0.001, 0.017, 0.030, respectively). The results are shown in **Table 2**.

The mean ± SD of the PK parameters has been shown in **Table 3** and **Figure 2**. There were no statistically significant differences in the parameters between the two groups, except for Cpeak. The peak concentrations were significantly lower in group 1 than in group 2 (mean ± SD: 5.95 ± 3.39 µg/mL vs 11.93 ± 4.18 µg/mL, respectively); t (16) = - 3.273, *p*= 0.005 (**Figure 2B**). The mean ± SD of trough concentrations was 1.32 ± 1.01 µg/mL in group 1 and 2.37 ± 2.08 µg/mL in group 2 (**Figure 2A**).

In 13 out of 18 samples (72%), the trough level was less than <2 µg/mL (sub-therapeutic) 10 of them were in group 1 (83% of 12 trough concentrations), and 3 of them were in group 2 (50% of 6 trough concentrations) (**Figure 3A**). ft>MIC ≥ 50% was achieved in 10 patients of group 1 (83.3%) and 5 patients of group 2 (83.3%) whereas 2 patients of group 1 (16.6%) and 2 patients of group 2 (33.3%) had ft> MIC= 100% (**Figure 3B**).

Table 2: Aflatoxins in total samples.

		Groups				sig[a, b,c]
		(1) 1g every 8 hours		(2) 2g every 8 hours		
		Count	Mean ± SD[d]	Count	Mean ± SD[d]	
Sex	Male	10	--	6	--	0.001
	Female	2	--	0	--	
Age		12	36 ± 9.70	6	33.50 ± 10.73	0.625
IBW[e]			66.67 ± 9.30		72.73 ± 5.42	0.251
ICU diagnosis on admission day based on ICD10 code[f]	T	6	--	3	--	0.017
	G	1	--	0	--	
	I	3	--	1	--	
	B	2	--	1	--	
	K	0	--	1	--	
SOFA[g] score		--	4.50 ± 2.11	--	5.67 ± 0.52	0.095
ARC[h] score		---	7.42 ± 2.84	--	7.50 ± 1.64	0.208
ARCTIC[i] score			6.67 ± 1.15	--	7.50 ± 1.64	0.030
12-hr CrCl [j]			181.57 ± 57.97	--	188.48 ± 64.45	0.851

a unpaired t-test; b, Mann-Whitney U test; c, chi-square test; d, Standard Deviation;e, Ideal Body Weight(Kg); f, ICD 10 code definition: "B: Certain infections, G: Diseases of the nervous system, I: Disease of the circulatory system, K: Disease of the digestive system, T: Injury to a different part of the body region."; g, Sequential Organ Failure Assessment (SOFA); h, Augmented Renal Clearance (ARC); i, Augmented Renal Clearance in Trauma Intensive Care (ARCTIC); j, creatinine clearance of 12-hour urine collection(ml/min)

Table 3: Pharmacokinetic data.

	Groups		sig[a, b]
	1g every 8 hours	2g every 8 hours	
	Mean ± SD[c]	Mean ± SD[c]	
CL[d]	42.85± 18.3	41.25± 19.75	0.867
K[e]	0.0077 ± 0.0036	0.0090 ± 0.0031	0.465
Vd[f]	118.02 ± 92.47	77.15 ± 22.95	0.553
T1/2[g]	1.90 ± 1.20	1.45± 0.653	0.261
Ft [h]	72.80 ± 20.15	84.04 ± 21.16	0.288

a, unpaired t-test; b, Mann-Whitney U test; ; c, Standard Deviation (SD); d, Total clearance(L/hr); e, Elimination rate constant(min^{-1}); f, Volume of distribution (L);g, Elimination half-life (hr); h, Fraction of time>MIC(Mimimum Inhibitory Concentration,2µg/mL)(%).

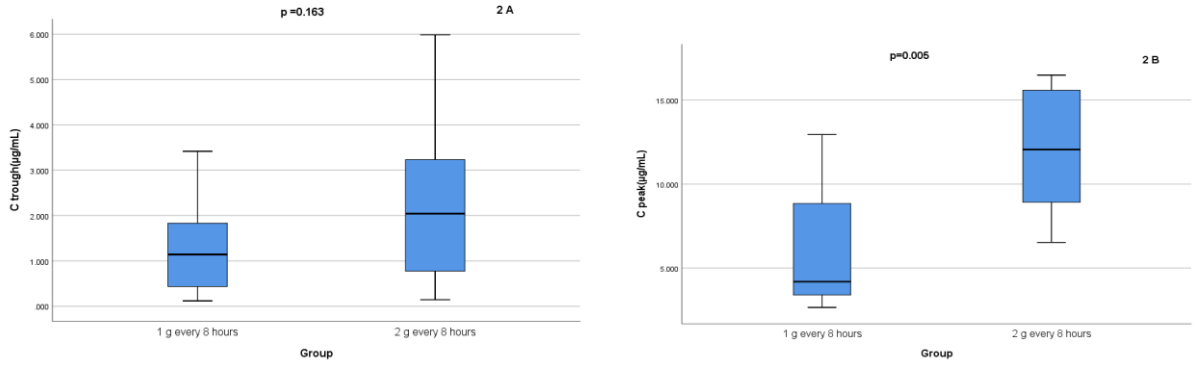

Figure 2. Comparison of meropenem blood levels in two groups. 2A: trough concentration (µg/mL), 2B: peak concentration (µg/mL).

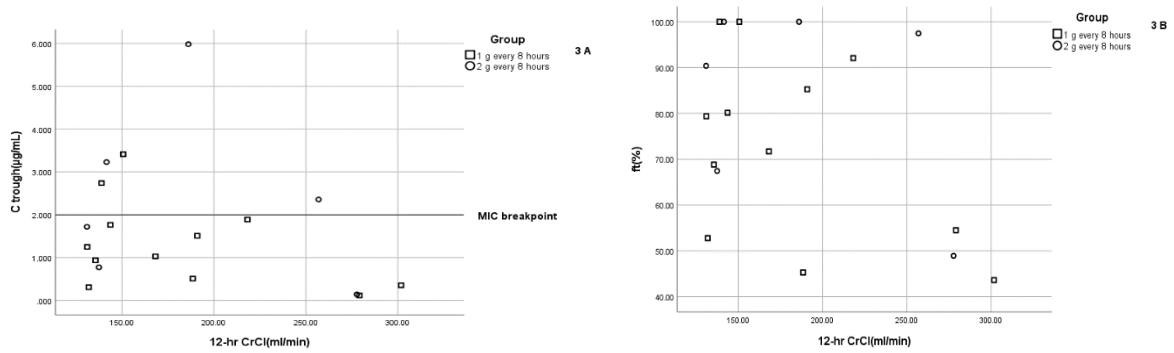

Figure 3. Creatinine Clearance (CrCl) and meropenem trough concentration (3A) and ft >MIC (3B).

This study has shown that ARC was associated with lower concentrations and a higher risk of not achieving PD targets in critically ill patients even when administering meropenem by intermittent infusion (infused over 4- hr) since that, 77.7% and 16.6% of all samples not attained to 100%ft> MIC and 50%ft>MIC, respectively. In group 1 (3g daily), 83.3% and 16.6 % of patients do not achieve 100%ft> MIC and 50%ft>MIC, respectively. By this consequence, previous studies with Carlier *et al*., have demonstrated that 76% and 37% of critically ill patients with ARC, who received meropenem 1g every 8 hours as a 3-hr infusion, did not achieve 100%ft> MIC and 50%ft>MIC, respectively [21].

In the prospective observational study, Ehmann and colleagues mentioned that target attained, 50%ft>MIC and 100%ft> MIC, for Gram-negative pathogens with MIC 2 µg/mL, was zero percent in critically ill patients with ARC with the administration of meropenem 1g every 8 hours infused over 30 minutes and concluded that increasing dose or increasing infusion time could increase the number of patients who achieved to therapeutic targets [22]. A comparison of our findings with the mentioned study confirmed prolonged infusion (4-hr vs. 30 minutes) and higher doses (6g daily vs. 3g daily) increase the likelihood of achieving the target plasma concentrations.

Studies have shown that 40 to 70% ft>MIC was necessary for time-dependent antibiotics such as meropenem to treat infections [23]. However, many studies in critically ill patients demonstrated that to maximize the effect of β-lactam antibiotics, it is better to increase the ft to 100% (100%ft>MIC) or to maintain the concentration four times the MIC for the entire dosing interval (100%ft>4MIC) [24, 25]. In our study, we did not achieve 100%ft>4MIC in all samples, even in group 2 (6g daily), with 4-hr infusion in critically ill patients with ARC. Vd of meropenem in critically ill patients with ARC increased in comparison with healthy volunteers (reported Vd in our study and healthy volunteers were 77.15-118.02 L vs. 15-20 L, respectively) [26]. This results were from other studies on critically ill patients [27, 28].

Also, clearance of meropenem obtained from healthy volunteers was 7.82 L/hr [16], but, in our study clearance increased due to augmented renal perfusion in patients with ARC (41.25-42.85 L/hr), this is higher than those reported by other studies on critically ill patients (4.7 to 15.4 L/hour) [27, 28].

Another finding of our study was increased Vd in our subjects, which could reduce the concentration of time-dependent antibiotics such as meropenem. Due to the relationship between Vd and the loading dose (LD), the use of aggressive LD suggested in critically ill patients with ARC to overwhelm increased Vd [29]. The correlation between the clearance of meropenem and renal clearance has been proven [28]. Therefore, increases in renal clearance can lead to a decrease in concentrations. Low serum concentrations of meropenem in our study confirm these results [21, 30], Therefore, because of the relationship between maintenance dose (MD) and clearance, MD can be initiated higher than the recommended doses of meropenem in critically ill patients with ARC [21, 31].

4. Conclusion

Augmented renal clearance is an essential cause of sub-therapeutic concentrations of meropenem in critically ill patients, and higher than the recommended doses of meropenem administered as an intermittent infusion may be necessary to achieve the PD targets and improve efficacy.

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Conflict of interest

The authors declare to have no conflict of interest.

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