



Investigation of pharmacokinetic and clinical outcomes of various meropenem regimens in patients with ventilator-associated pneumonia and augmented renal clearance

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Received: 9 December 2021 / Accepted: 4 February 2022 / Published online: 16 February 2022
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Abstract

Introduction Augmented renal clearance (ARC) defined as creatinine clearance (Cl_{cr}) above 130 mL/min/1.73m² may lead to suboptimal antibacterial treatment. The aim of this study was to determine a strategy for meropenem administration to achieve both pharmacodynamic-pharmacokinetic (PK-PD) target (50%ft > MIC) and better clinical outcomes in patients with VAP and ARC.

Materials and methods In this randomized clinical trial, patients with VAP and high risk for ARC were recruited. An 8-h urine collection was performed on the 1st, 3rd, and 5th days of study to measure Cl_{cr}. Included patients were divided into three groups: (1) 1 g meropenem, 3-h infusion, (2) 2 g meropenem, 3-h infusion, (3) 1 g meropenem, 6-h infusion. On the 2nd, 3rd, and 5th days of treatment, peak and trough blood samples were collected to undergo HPLC assay. MICs were assessed using microdilution method. Patients were also clinically monitored for 14 days.

Results Forty-five patients were included. Group 3 showed significantly higher rate of patients achieving ft > MIC > 50% (100% for group 3 versus 40% for group 2 and 13% for group 1; $p = 0.0001$). Mean ft > MIC% was significantly higher in group 3 (78.77 ± 5.87 for group 3 versus 49.6 ± 7.38 for group 2 and 43.2 ± 7.98 for group 1; $p = 0.0001$). Statistical analysis showed no significant differences among groups regarding clinical improvement.

Conclusion According to the findings of this trial, prolonged meropenem infusion is an appropriate strategy compared to dose elevation among ARC patients.

Keywords Augmented renal clearance · Meropenem · Ventilator-associated pneumonia · PK-PD target · ft > MIC

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Introduction

ARC is a clinical phenomenon mostly detected among critically ill patients, defined as enhanced Cl_{cr} of greater than 130 mL/min/1.73m² [1, 2]. Further investigations demonstrated a significant impact on treatment outcome in ARC patients due to suboptimal plasma levels of drugs, especially time-dependent antibiotics [3–6]. Therefore, new dosing strategies in order to cope with ARC effects are strongly needed [4, 7].

Ventilator-associated pneumonia (VAP) is a life-threatening infection in the ICU. The mortality of VAP reaches 30%, and the adequacy of the initial empirical treatment greatly influences the prognosis [8]. ARC may increase the risk of suboptimal treatment and mortality in VAP patients. Meropenem being an important agent in empiric therapy for VAP, and as a time-dependent antibiotic, is particularly at risk of over-filtration in ARC patients [9–12].

The aim of this study was to determine a proper dosing strategy for meropenem administration, in order to achieve $FT > MIC > 50\%$ and to evaluate clinical outcomes in critically ill patients with VAP and ARC.

Materials and methods

Study design

This single-center study was conducted as a randomized clinical trial in Loghman Hakim Medical Center, affiliated with Shahid Beheshti University of Medical Sciences (SBMU), Tehran, Iran. Recruitment occurred from October 2019 to March 2021.

Study participants

The patients were considered eligible for inclusion if they met all of the following criteria: (1) a definite or highly probable diagnosis of VAP according to CPIS¹ (a score of more than 6 is considered high risk for pneumonia) [13], (2) high risk for developing ARC according to ARC score [14] or ARCTIC score [15], (3) receiving meropenem, (4) serum creatinine less than 1.3 mg/dL, (5) being at least 18 years old.

Patients were excluded (1) if measured Clcr was less than 130 mL/min/1.73m² on the 1st, 3rd, and 5th days of study; (2) if they developed AKI²; and (3) if meropenem administration was discontinued due to any reason.

The included patients were block-randomized into the three study groups: (1) receiving 1 g meropenem q8h during 3-h infusion, (2) receiving 2 g meropenem q8h during 3-h infusion, (3) receiving 1 g meropenem q8h during 6-h infusion. Time/concentration curves are shown in Figs. 1 and 2.

All patients initially received empiric antibiotic regimen for VAP including meropenem, vancomycin, and an aminoglycoside intravenously.

Study procedures

The patients diagnosed with VAP were included and assigned into one of the three study groups on the first day of suspicion of ARC based upon scoring systems [14, 15] (Table 1). On this day (day 1), meropenem was started as study protocol according to the intervention group that the patient was block-randomized into. At the same day, the patients underwent an 8-h urine collection for Clcr

¹ Clinical Pulmonary Infection Score.

² Acute kidney injury.

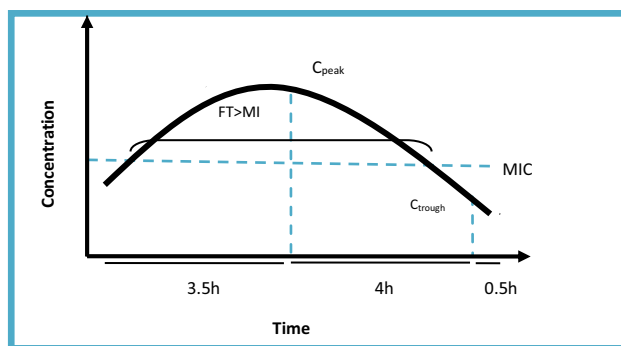


Fig. 1 Time/concentration curve for 3-h infusion (groups 1 and 2)

measurement in order to confirm ARC [4]. Clcr was measured using below equation [4]:

$$\text{Clcr} = \frac{[\text{urine creatinine } (\mu\text{g/mL}) \times \text{urine volume (mL)}]}{[\text{serum creatinine } (\mu\text{g/mL}) \times T \text{ (min)}]}$$

Cutoff point for Clcr was 130 mL/min/1.73m² based upon previous studies.

If ARC was not confirmed, the patient was excluded and meropenem administration was changed to the standard regimen. If ARC was confirmed, the patient persisted in the study and the protocol was continued for him. Blood sample (5 mL) collection took place on the next day (2nd day) from the arterial catheter of the patients. Peak blood samples were collected 30 min after the end of 3-h (groups 1 and 2) or 6-h (group 3) meropenem infusion. Trough blood samples were collected 30 min before the start of the next dose of meropenem infusion. Urine collection for ARC confirmation was repeated on the 3rd and the 5th days of study to ensure the persistence of ARC. Also on these days, blood samples were collected from the patients. Blood samples were immediately centrifuged for 10 min at 4000 rpm, and serum was separated and stored at -80°C for later analysis.

Meropenem assay

In order to analyze the serum samples, validated Agilent Infinity Lab High-Performance Liquid Chromatography

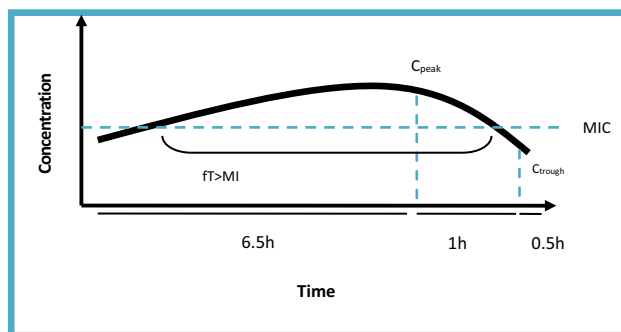


Fig. 2 Time/concentration curve for 6-h infusion (group 3)

Table 1 ARC and ARCTIC scoring system

ARC scoring system [6]		ARCTIC scoring system [23]	
Risk factors	No. of points	Risk factors	No. of points
Age \leq 50 y	6	Age < 56 y	4
Trauma admission	3	Age 56–75 y	3
Modified SOFA score \leq 4	1	Scr < 0.7 mg/dL	3
Low (0–3), intermediate (4–6), and high risk (7–10)		Male sex	2
		High risk, score \geq 6; low risk, score < 6	

(HPLC) system was used. Samples were separated on Agilent Infinity Lab 2.6 m C18 column (250 \times 4.6 mm with 3.5- μ m spherical particles). The mobile phase used for analysis was 10.53 mmol/L ammonium acetate:acetonitrile (91:9, v/v) (pH = 4). The mobile phase was delivered at a total flow rate of 1 mL/min. The UV detector was adjusted at 298 nm. C18 column temperature was maintained at 35 °C. The total run time was set for 10.0 min [16, 17].

Sample preparation involved plasma protein precipitation with acetonitrile and a wash step with dichloromethane. Acetaminophen was chosen as the internal standard due to structural and behavioral similarities to meropenem. Initially, 950 μ L of serum was added to 50 μ L of acetaminophen (800 μ g/mL) following the addition of 1000 μ L of acetonitrile. After shaking for 10 min by Heidolph vortex mixer and 10-min centrifugation by Hettich Micro 200 Centrifuge at 1000 g, a 1000 μ L of supernatant was added to 1000 μ L methylene chloride. After a 10-min shaking by vortex mixer and a 10-min centrifugation at 1000 g, 20 μ L of the aliquot of the upper aqueous layer was injected into the C18 analytical column [11].

The assay was linear from 0.25 to 20 μ g/mL with an imprecision and inaccuracy < 7% at high, medium, and low concentrations.

MIC assessment

MIC determination of strains isolated from tracheal aspiration cultures of the included patients was performed using broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI) [18]. The 96-well microplate contained Mueller–Hinton broth with varying concentrations of meropenem (ranging from 100 to 0.25 μ g/mL). The wells were inoculated with 50 μ L of suspended culture to inoculum density of 10^5 CFU/mL per well. The microplate was incubated at 37° for 24 h. Then it was visually evaluated and MIC was recorded as the lowest meropenem concentration, where no turbidity (visible growth) was observed.

PK-PD parameter analysis and clinical monitoring

Peak and trough serum concentrations from samples collected on the 2nd, 3rd, and 5th days of study were measured

through HPLC analysis. Then PK parameters consisted of clearance (Cl), elimination constant (K), and half-life ($T_{1/2}$) were calculated for each patient. Assuming one compartmental first-order kinetic, the time within the dosing interval where the concentration is maintained above MIC was calculated ($fT > MIC$).

PK-PD target attainment was evaluated through calculation of $fT > MIC\%$. Each patient was also monitored for clinical outcomes for 14 days following the start of antibacterial treatment. Clinical improvement factors included the days it took for fever resolution, secretion decrease, leukocytosis resolution, and also the duration of intubation, hospitalization in the ICU, and mortality rate.

Statistical analysis

The statistical analysis was performed using the statistical software package IBM-SPSS statistics version 26.0 (IBM Corp., New York, NY, USA). Qualitative variables were analyzed by chi-square method and presented as frequencies and percentages. Continuous variables with non-normal distribution were analyzed by Kruskal–Wallis method and expressed as mean \pm standard deviation and median values with interquartile ranges. Post-hoc analysis as Fisher's test was performed for significantly non-equal variances between groups. A P value < 0.05 was considered statistically significant.

Results

In this study, 195 patients were included. One hundred seventeen patients were excluded, because measured Clcr did not meet the cutoff point for ARC. Twenty-one cases expired during the first 5 days of treatment (7 cases in group 1 – 9 cases in group 2 – 5 cases in group 3). In 12 cases, urine was not properly collected. Forty-five patients were block-randomized into the three study groups. Demographic characteristics and the clinical factors are shown in Table 2. MIC results are illustrated in Table 3. Statistical analysis proved the variances to be normally distributed (P value > 0.05), except for peak and trough concentrations. PK factors are shown in Table 4.

Table 2 Patients' demographics and clinical characteristics

Variable	1 g, 3-h inf. (n = 15)	2 g, 3-h inf. (n = 15)	1 g, 6-h inf. (n = 15)	P
Age, mean ± SD	44.4 ± 10.87	40.07 ± 10.47	35.87 ± 9.22	0.078
Weight, mean ± SD	64 ± 7.12	67 ± 9.22	62.33 ± 10.33	0.393
Male/female sex, n (%)	10/5 (80/20)	9/6 (60/40)	10/5 (66.7/33.3)	0.908
mSOFA on admittance, median (IQR)	2 (1–3)	2 (1–3)	2 (2–3)	0.799
CPIs on admittance, median (IQR)	6 (6–6)	6 (6–6)	6 (6–6)	1
ARC score, median (IQR)	10 (9–10)	10 (10–10)	10 (10–10)	0.548
ARCTIC score, median (IQR)	9 (7–9)	9 (7–9)	9 (9–9)	0.412
Microorganism, n (%)				
<i>Acinetobacter baumannii</i>	12 (66.7)	11 (73.3)	10 (66.7)	0.711
<i>Klebsiella pneumoniae</i>	3 (33.3)	4 (26.7)	5 (33.3)	
Diagnosis, n (%)				
Multiple trauma	5 (33.3)	7 (46.4)	6 (40)	0.904
SAH	2 (13.3)	1 (6.6)	1 (6.6)	
Status epilepticus	1 (6.6)	0	0	
Myasthenia gravis	1 (6.6)	0	0	
Head trauma	3 (20)	4 (26.6)	5 (33.3)	
CVA	1 (6.6)	2 (13.3)	1 (6.6)	
Brain tumor	2 (13.3)	1 (6.6)	2 (13.3)	

Patients were monitored clinically for treatment outcomes for 14 days. Clinical factors are illustrated in Table 5. Statistical analysis showed no significant differences among groups regarding clinical improvement (P value > 0.05) although $fT > MIC\%$ proved to be significantly different among groups (P value < 0.05) (Table 5). Post-hoc analysis revealed group 3 (1 g meropenem q8h infused over 6 h) to show significantly higher levels of $fT > MIC\%$ compared to group 2 ($p = 0.0001$)

and group 1 ($p = 0.0001$). Mean $fT > MIC\%$ rates were significantly higher in group 3 (78.77 ± 5.87 for group 3 versus 49.6 ± 7.38 for group 2 and 43.2 ± 7.98 for group 1; $p = 0.0001$). Group 3 also showed significantly higher rate of patients achieving $fT > MIC > 50\%$ (100% for group 3 versus 40% (6/15) for group 2 and 13% (2/15) for group 1; $p = 0.0001$). A comparison between the three groups regarding $fT > MIC\%$ is illustrated in Fig. 3.

Table 3 MIC results

1 g, 3-h inf			2 g, 3-h inf			1 g, 6-h inf			P
No.	Microorganism	MIC	No.	Microorganism	MIC	No.	Microorganism	MIC	
1	<i>A. baumannii</i>	6.25	1	<i>A. baumannii</i>	6.75	1	<i>A. baumannii</i>	7.00	
2	<i>A. baumannii</i>	6.00	2	<i>A. baumannii</i>	5.75	2	<i>K. pneumoniae</i>	8.00	
3	<i>A. baumannii</i>	6.75	3	<i>A. baumannii</i>	5.00	3	<i>A. baumannii</i>	7.75	
4	<i>A. baumannii</i>	6.50	4	<i>K. pneumoniae</i>	8.50	4	<i>A. baumannii</i>	6.25	
5	<i>A. baumannii</i>	6.25	5	<i>K. pneumoniae</i>	7.50	5	<i>K. pneumoniae</i>	8.00	
6	<i>A. baumannii</i>	6.25	6	<i>A. baumannii</i>	6.00	6	<i>A. baumannii</i>	5.75	
7	<i>A. baumannii</i>	7.00	7	<i>A. baumannii</i>	5.75	7	<i>A. baumannii</i>	7.00	
8	<i>A. baumannii</i>	5.00	8	<i>A. baumannii</i>	6.00	8	<i>A. baumannii</i>	6.75	0.695
9	<i>K. pneumoniae</i>	7.50	9	<i>K. pneumoniae</i>	8.00	9	<i>A. baumannii</i>	5.25	
10	<i>A. baumannii</i>	6.00	10	<i>A. baumannii</i>	6.25	10	<i>K. pneumoniae</i>	8.50	
11	<i>A. baumannii</i>	6.75	11	<i>K. pneumoniae</i>	8.00	11	<i>K. pneumoniae</i>	8.75	
12	<i>A. baumannii</i>	6.25	12	<i>A. baumannii</i>	7.00	12	<i>A. baumannii</i>	6.00	
13	<i>K. pneumoniae</i>	8.25	13	<i>A. baumannii</i>	6.50	13	<i>K. pneumoniae</i>	7.50	
14	<i>A. baumannii</i>	5.75	14	<i>A. baumannii</i>	6.70	14	<i>A. baumannii</i>	5.25	
15	<i>K. pneumoniae</i>	8.00	15	<i>A. baumannii</i>	6.25	15	<i>A. baumannii</i>	6.25	

Table 4 Pharmacokinetic parameters

Variable, mean \pm SD	1 g, 3-h inf	2 g, 3-h inf	1 g, 6-h inf	P
Clcr day 1	162.47 \pm 26.21	151.13 \pm 16.07	146.13 \pm 14.39	0.163
Clcr day 3	148.87 \pm 17.04	145.80 \pm 13.68	139.67 \pm 7.41	0.220
Clcr day 5	139.07 \pm 8.96	137.53 \pm 8.85	134.53 \pm 5.19	0.286
Peak day 2	10.67 \pm 1.64	12.10 \pm 2.39	8.95 \pm 1.68	0.012
Peak day 3	9.55 \pm 1.6	12.15 \pm 2.44	8.90 \pm 1.46	0.011
Peak day 5	10.97 \pm 2.51	11.56 \pm 2.75	8.46 \pm 1.27	0.001
Trough day 2	0.92 \pm .85	1.56 \pm 1.07	4.34 \pm 1.55	0.030
Trough day 3	0.96 \pm .37	1.23 \pm 1.08	4.04 \pm 1.06	0.033
Trough day 5	0.94 \pm .47	1.60 \pm .87	4.24 \pm 1.36	0.010
K day 2	0.91 \pm 0.4	1.13 \pm 0.39	0.77 \pm .31	0.345
K day 3	0.85 \pm 0.34	.99 \pm 0.33	0.77 \pm .36	0.418
K day 5	0.87 \pm 0.44	.90 \pm 0.29	0.81 \pm .3	0.664
T1/2 day 2	0.98 \pm 0.39	.85 \pm 0.27	1.09 \pm .46	0.315
T1/2 day 3	1.03 \pm 0.37	.99 \pm 0.3	1.13 \pm .71	0.874
T1/2 day 5	1.11 \pm 0.38	1.01 \pm 0.37	1.07 \pm .54	0.556
Cl day 2	19.22 \pm 4.1	19.79 \pm 4.81	19.53 \pm 3.91	0.709
Cl day 3	21.77 \pm 3.27	22.85 \pm 7.26	19.64 \pm 4.08	0.214
Cl day 5	20.81 \pm 5.49	19.15 \pm 4.51	19.74 \pm 4.7	0.606

Discussion

In this randomized clinical trial on 45 ARC patients receiving meropenem, $ft > MIC\%$ and clinical factors were evaluated between three groups. This survey demonstrated the superiority of prolonged (6 h) infusion of meropenem in order to achieve $ft > MIC > 50\%$.

Previous studies mainly suggested two strategies to overcome ARC—(1) dose elevation to 6 g meropenem per day [11] and (2) infusion prolongation to 3–6 h [19]—however, the investigations were mostly observational and the results showed obvious inconsistency. Previous studies also proved the advantage of prolonged infusion of beta-lactams among critically ill patients regarding $ft > MIC\%$, which is similar to our conclusion, except for ARC identification [20–23]. However, no robust prospective controlled study investigating prolonged infusion of beta-lactams among ARC-identified population exists.

Previous studies mostly revealed that higher beta-lactam concentrations alone cannot significantly influence their

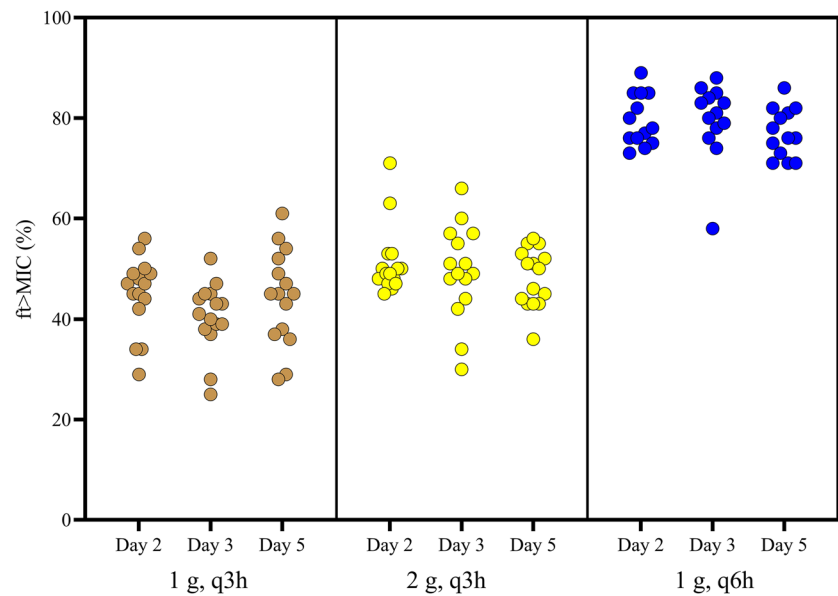
efficacy. Based on numerous in vitro and in vivo experimental data, it is the duration of effective exposure that is more important for these time-dependent antibiotics [24].

The patients were also monitored for clinical improvement for 14 days following VAP diagnosis. The comparison of all parameters among the three groups proved no significant differences. A possible explanation is the difference between plasma concentrations of antibiotic versus tissue penetration. Free concentrations in plasma are often viewed as an acceptable approximation for free concentrations at the site of infection, but this is not always the case [25, 26]. Tissue penetration of meropenem in respiratory tract (expressed as percentage of tissue vs. plasma concentration) is reported in literature as 40% in the lung. This relatively low concentration in pulmonary tissue might explain why attaining $ft > MIC > 50\%$ might not necessarily improve clinical outcomes [27]. Another explanation is the small study population which is inadequate to properly reflect the influence of dosing approaches. Therefore, further robust prospective investigations evaluating clinical outcomes among larger populations are suggested.

Table 5 Clinical outcomes and PD target attainments

Variable	1 g, 3-h inf	2 g, 3-h inf	1 g, 6-h inf	P
Fever resolution (days), median (IQR)	2 (2–2)	2 (2–2)	2 (2–2)	0.612
Secretion decrease (days), median (IQR)	3 (2–3)	3 (3–3)	3 (3–3)	0.446
Leukocytosis resolution (days), median (IQR)	3 (3–3)	3 (2–3)	3 (3–3)	0.552
Intubation days, median (IQR)	19 (14–23)	15 (10–30)	19 (10–24)	0.895
ICU days, median (IQR)	19 (16–23)	17 (11–30)	22 (12–25)	0.767
Mortality, % (n)	60 (9/15)	46 (7/15)	40 (6/15)	0.853
$ft > MIC\%$ day 2, mean \pm SD	44.87 \pm 7.48	51.27 \pm 6.93	79.62 \pm 5.11	0.0001
$ft > MIC\%$ day 3, mean \pm SD	40.40 \pm 6.86	49.40 \pm 9.42	79.62 \pm 7.63	0.0001
$ft > MIC\%$ day 5, mean \pm SD	44.33 \pm 9.5	48.20 \pm 5.81	77.08 \pm 4.89	0.0001

Fig. 3 A comparison between the three groups regarding $f_{t>MIC}$



Conclusion

According to the findings of this trial, prolonged meropenem infusion is an appropriate strategy compared to dose elevation among ARC patients.

Author contribution S. Razzazzadeh carried out sampling and calculations. I. Alavi Darazam evaluated clinical criteria. M. Hajiesmaeili provided administrative support for the clinical process. J. Salamzadeh performed statistical analysis. A. Mahboubi performed MIC assessments. E. Sadeghnezhad contributed to meropenem HPLC assay. Z. Sahraei conceived the original idea and the trial designing and was in charge of overall direction. All authors contributed to the final manuscript. All authors read and approved the final manuscript.

Funding HPLC was funded by Tarbiat Modares University.

Declarations

Ethics approval Institutional ethics approval was provided according to local protocols with the ethics committee code of IR.SBMU.PHARMACY.REC.1398.095. The trial was registered at the Iranian Registry of Clinical Trials with the registration number of IRCT20130917014693N12.

Conflict of interest The authors declare no competing interests.

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