



Concentration of meropenem in patients with sepsis and acute kidney injury before and after initiation of continuous renal replacement therapy: a prospective observational trial

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Received: 21 August 2019 / Revised: 13 November 2019 / Accepted: 17 December 2019 / Published online: 4 January 2020
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Abstract

Background The effect of renal replacement therapy on drug concentrations in patients with sepsis has not been fully elucidated because the pharmacokinetic properties of many antimicrobials are influenced by both pathophysiological and treatment-related factors. The aim of this study was to determine meropenem concentrations in patients with sepsis before and after the initiation of continuous venovenous hemodialysis with regional citrate anticoagulation (RCA-CVVHD).

Methods The study included 15 critically ill patients undergoing RCA-CVVHD due to sepsis-induced acute kidney injury. All participants received 2 g of meropenem every 8 h in a prolonged infusion lasting 3 h. Meropenem concentrations were measured in blood plasma using high-performance liquid chromatography coupled with tandem mass spectrometry. Blood samples were obtained at six-time points prior to and at six-time points after introducing RCA-CVVHD.

Results The median APACHE IV and SOFA scores on admission were 118 points (interquartile range [IQR] 97–134 points) and 19.5 points (IQR 18–21 points), respectively. There were no significant differences in the plasma concentrations of meropenem measured directly before RCA-CVVHD and during the first 450 min of the procedure. The drug concentration reached its peak 2 h after initiating the infusion and then steadily declined.

Conclusions The concentration of high-dose meropenem (2 g every 8 h) administered in a prolonged infusion was similar before and after the introduction of RCA-CVVHD in patients with sepsis who developed acute kidney injury.

Keywords Continuous venovenous hemodialysis · Meropenem · Regional citrate anticoagulation · Sepsis · Therapeutic drug monitoring

Introduction

Optimal antibiotic dosing is crucial in the therapeutic process, especially in critically ill patients with sepsis. These patients are at a significantly higher risk of antibiotic underdosing due to pathophysiological changes associated with large fluid shifts, resulting in an increased volume of distribution, alterations in both renal and liver clearance, as well as decreased

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s43440-019-00056-3>) contains supplementary material, which is available to authorized users.

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concentrations of plasma proteins [1, 2]. Acute kidney injury (AKI) is a common life-threatening complication of sepsis, which often requires an introduction of continuous renal replacement therapy (CRRT).

Meropenem displays time-dependent antibacterial activity, that is, its efficacy is associated with the percentage of time in which the free drug concentration exceeds the minimum inhibitory concentration (MIC), referred to as $\%fT_{>MIC}$ [3]. The drug has been shown to exert bacteriostatic effects at an $fT_{>MIC}$ of 20% and bactericidal effects at an $fT_{>MIC}$ of 40% [4]. However, the latest evidence on patients with sepsis undergoing CRRT suggests that clinicians should aim at an $fT_{>MIC}$ of 100% [5]. Antibacterial activity of meropenem may be maximal when the antibiotic concentration exceeds the MIC for the specific type of bacteria four- to five-fold for the entire duration of the dosing interval [6].

The degree of antibiotic clearance varies depending on the physicochemical and pharmacokinetic properties of the drug [7]. Hydrophilic antibiotics, including carbapenems, have a small volume of distribution, low molecular weight, and are bound to proteins to a minimal degree, which facilitates their rapid elimination during CRRT [8, 9]. However, their pharmacokinetic properties are known to be influenced by extracorporeal blood purification procedures, including CRRT. Moreover, an additional use of anticoagulation required for CRRT may cause unpredictable drug interactions [10]. Drug concentrations may also vary depending on the type of solute removal during CRRT (e.g., diffusion, convection), properties of the semipermeable membrane of the filter, the rate of ultrafiltration, as well as the dose of dialysis. Finally, drug clearance is also influenced by CRRT settings and the patient's demographic and clinical characteristics, including age, urine output, and countercurrent dialysate flow rates [11].

Several authors have suggested that drug doses should be carefully adjusted based on its blood concentration [12]. Continuous renal replacement therapy with regional citrate anticoagulation (RCA-CRRT) is becoming increasingly widely used in the management of critically ill patients with AKI [13]. However, there are no evidence-based recommendations on the dosing of drugs commonly used in patients with severe sepsis and septic shock treated with RCA-CRRT. Therefore, we aimed to assess whether there are significant differences in the plasma concentrations of meropenem administered in a prolonged infusion before and during RCA-CRRT among patients with sepsis who developed AKI.

Materials and methods

Patients

This prospective observational cohort study was conducted in the Intensive Care Unit (ICU) at University Hospital in

Krakow, Poland, between January 2014 and January 2017. All procedures involving human participants were conducted in accordance with the ethical standards of the institutional and national research committees as well as with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of Jagiellonian University (ul. Grzegórzecka 20, Kraków; protocol number, KBET/262/B/2013; date of approval, 27 January 2014).

This report conforms to the STROBE guidelines; the checklist with specific pages where each requirement was addressed can be found in Supplementary Table 1.

The inclusion criteria were as follows: (1) age older than 35 years and younger than 85 years; (2) diagnosis of severe sepsis or septic shock (according to the criteria of the Surviving Sepsis Campaign Consensus) [14]; (3) clinical indications for CRRT due to AKI, determined in accordance with the criteria adopted by Kidney Disease Improving Global Outcomes (KDIGO) recommendations: hyperkalemia (serum potassium concentration >6.5 mmol/L or rapidly rising), refractory fluid overload, metabolic acidosis, and signs of uremia (such as pericarditis or encephalopathy) [15]; (4) use of regional citrate anticoagulation (RCA) during CRRT; and (5) treatment with high doses of meropenem (2 g every 8 h) in prolonged infusions (lasting 3 h).

The exclusion criteria were lack of patient consent, pregnancy, bilirubin concentrations exceeding 150 $\mu\text{mol/L}$, blood transfusion of more than 50% of the circulating volume in the past 8 h, and the use of other extracorporeal techniques (such as plasmapheresis) in the past 24 h.

Methods

Patients' medical records were analyzed and relatives were interviewed to obtain demographic and clinical data such as age, sex, weight, height, comorbidities, site of infection, and laboratory parameters at baseline and during CRRT (i.e., complete blood count, coagulation parameters, serum concentrations of creatinine, urea, bilirubin, albumin, total protein, levels of inflammatory biomarkers including C-reactive protein, and procalcitonin).

The severity of clinical condition was assessed with the Acute Physiology and Chronic Health Evaluation (APACHE) IV score on admission and the Sequential Organ Failure Assessment (SOFA) score on the 1st, 3rd, and 7th day of ICU stay.

Continuous renal replacement therapy

Continuous renal replacement therapy was initiated according to the local practice and study protocol. Continuous venovenous hemodialysis with RCA (RCA-CVVHD) was used. The main indications for CRRT were metabolic

acidosis, oliguria with fluid overload, and hyperkalemia. For CRRT, commercially available equipment and solutions were used: MultiFiltrate[®] with the integrated Ci-Ca[®] system, 1.8-m² capillary hemofilters Ultraflux[®] AV 1000S with membrane Fresenius Polysulfone[®], Dialysate K2 or K4 (Fresenius Medical Care, Bad Hamburg, Germany). Anticoagulation was performed using 4% trisodium citrate (citrate flow rates were subsequently adjusted based on postfilter ionized calcium levels) and calcium chloride solution (CaCl₂ flow rates were based on calcium levels measured in arterial blood).

All CRRT settings (timing, modality, intensity of dialysis, RCA) were identical for each participant at the beginning of the procedure and were subsequently adapted to the patient's clinical status in accordance with KDIGO recommendations (blood flow 120–150 mL/min; dialysate flow rate 2000–3450 mL/h; patient fluid removal [ultrafiltration], 0 in the first hour, and then 100 mL/h and higher according to clinical condition) [11]. The CRRT intensity was calculated as an effluent flow rate (dialysate rate [mL/h] + ultrafiltrate [mL/h]/weight [kg]). Regarding the CRRT settings, the median intensity at baseline was 31.4 mL/kg/h (range 25–35 mL/kg/h), and the median blood flow was 124 mL/min (range 120–150 mL/min). All CRRT settings, including dialysate rate, ultrafiltrate rate, blood flow, as well as CaCl₂ and citrate solution flow rates, were recorded for each participant.

Meropenem dosing

Meropenem was administered intravenously through a separate lumen of a central venous catheter in a prolonged infusion, according to the dosing schedule identical for all patients (2 g in 3-h infusion administered every 8 h). Each dose was reconstituted in 50 mL of 0.9% sodium chloride.

Blood sampling

Blood samples for each patient were collected at specified time points before the drug administration and then at 30, 60, 90, 120, 180, and 450 min after meropenem infusion. The first set of samples was collected around the time of the first meropenem infusion after the decision on the introduction of RCA-CVVHD was made based on the above criteria for patients with sepsis. Subsequently, on the same day, RCA-CVVHD was initiated according to local practice by the ICU personnel. The second set of samples was collected when the first meropenem infusion was given during RCA-CRRT. For each sample, 2 mL of blood was collected from an arterial catheter. Samples were centrifuged at 3500 rpm for 10 min at 4 °C and stored at –80 °C until further analysis.

The study timeline is shown in Fig. 1.

Meropenem measurements

The measurement of plasma meropenem concentrations was performed in the Department of Molecular Biology and Clinical Genetics of Jagiellonian University Medical College. The concentrations of unbound drug were measured using high-performance liquid chromatography (Prominence, Shimadzu, Tokyo, Japan) coupled with tandem mass spectrometry (Qtrap 4000, AB Sciex, Toronto, Canada). The tris buffer (0.2 mL) and chemically identical deuterated internal standard meropenem-d6 (5 µg) were added to plasma (0.2 mL). The sample was extracted with the mixture of tert-butyl methyl ether and methanol (4:1, v:v) twice. An organic layer was collected and evaporated under the stream of nitrogen. After evaporating the solvent, the residue was reconstituted in mobile phase (30 µl). Chromatography separation was performed using Zorbax Eclipse XDB C-18 column (1 × 50 mm, 3 µm) (Agilent, Santa Clara, CA, USA) and mobile phases consisting of water–formic acid (100:0.1%) and acetonitrile–methanol–formic acid (50:50:0.1%) to gradient elution. Meropenem was measured using the multiple reaction monitoring in the positive ionization mode, monitoring transition m/z 384 > 141 and m/z 384 > 68 for meropenem and m/z 390 > 147 and m/z 390 > 68 for deuterated meropenem-d6. Meropenem concentrations were determined using a calibration curve in the range of 0.05–250 µg/mL ($r^2=0.997$) [16, 17].

Statistical analysis

Dependent quantitative variables were compared using the paired Student *t* test or the Wilcoxon test for matched pairs depending on the distribution of the difference between two variables. Observed correlations were analyzed using a linear mixed model. Confidence intervals and *p* values were calculated using the likelihood ratio method. The normality assumption was examined using the Shapiro–Wilk test.

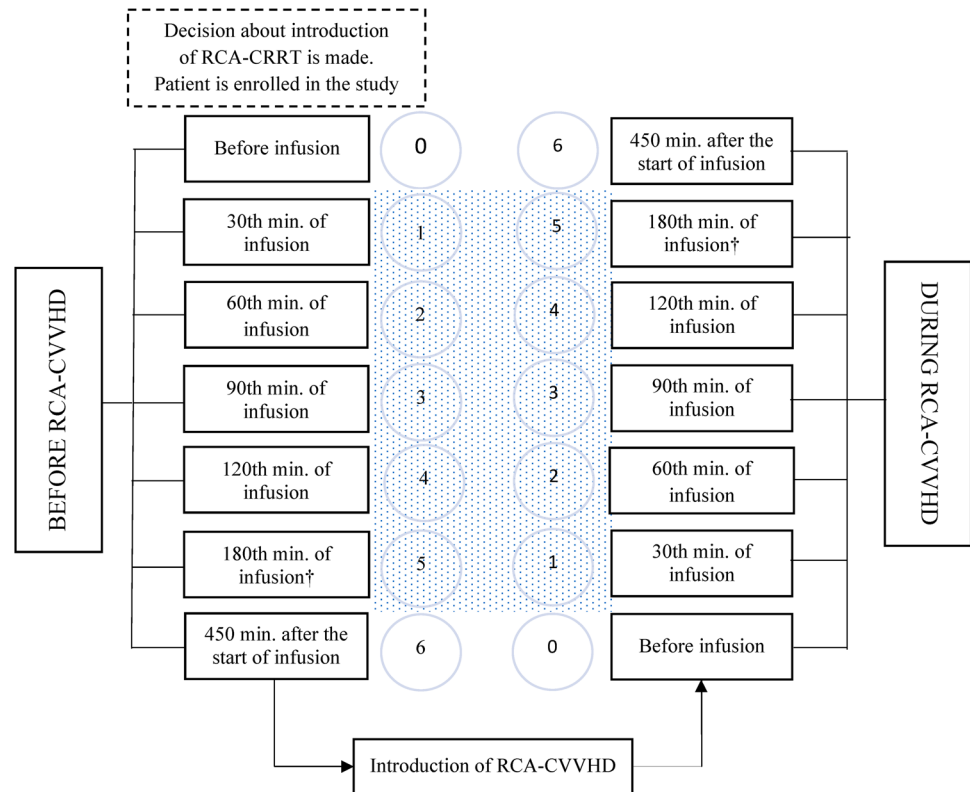
The level of 0.05 was assumed as significant. The analysis was carried out using the R software, version 3.4.1. (R Foundation for Statistical Computing, Vienna, Austria).

Results

The study included 15 eligible patients (mean age, 57.8 ± 7.5 years; five women, ten men) with sepsis or septic shock who received meropenem and RCA-CVVHD. Baseline demographic and clinical characteristics of the patients are shown in Table 1.

All patients were mechanically ventilated due to respiratory failure, and 13 patients (87%) required vasopressors. The median APACHE IV and SOFA scores were 118 points (interquartile range [IQR] 97–134 points) and 19.5 points

Fig. 1 Flow chart of the study timeline showing the time of meropenem administration and use of continuous venovenous hemodialysis with regional citrate anticoagulation (RCA-CVVHD). †End of infusion. Dotted area represents the time of meropenem infusion



(IQR 18–21 points), respectively. The mean predicted mortality rate for the APACHE IV and SOFA scores was 68.6% and > 90%, respectively.

Respiratory tract infection was the most common cause of sepsis (73%; 11 patients), followed by urinary tract infection (27%; four patients). Bloodstream infection was confirmed in four cases (27%; four patients). The pathogen for sepsis was identified in 13 cases (87%): Gram-positive bacteria in five cases (*Staphylococcus aureus*, vancomycin-resistant enterococci, coagulase-negative staphylococci) and Gram-negative bacteria in 8 cases (*Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Citrobacter freundii*, and *Escherichia coli*). Data concerning infection sites and pathogens are shown in Table 2.

Analysis of meropenem concentrations

We did not find significant differences in meropenem concentrations measured before and during CRRT at any time point after drug infusion (Table 3). The drug concentration in plasma reached its peak 2 h after the start of the infusion and then steadily declined, as shown in Fig. 2. Moreover, there were no statistically significant differences in meropenem concentrations measured before and during CRRT at any time point after drug infusion among patients with anuria (66.7%; ten patients) and those with residual diuresis (33.3%; 5/patients). Among the five patients with available

MIC for meropenem, the concentrations were 0.25 µg/mL or less in four cases (66.7%) and 0.125 µg/mL in two cases (33.3%). The number of measurements in which plasma meropenem concentrations exceeded the respective hypothetical MICs before and during RCA-CRRT is shown in Table 4.

Discussion

In this prospective observational study including 15 patients with sepsis-induced AKI, we found that prolonged infusions of meropenem resulted in similar concentrations of the drug before and after the initiation of CRRT.

Critically ill patients presenting with severe sepsis or septic shock are at higher risk of receiving insufficient doses of antimicrobials due to increased volume of distribution, hypoalbuminemia, as well as altered renal and nonrenal clearance [8]. To improve outcomes in this challenging population, it is crucial to achieve proper antibiotic concentrations. Several authors have suggested that the antibiotic concentration should be systematically measured in these patients and titrated accordingly [18]. It is particularly complicated in the context of severe sepsis or septic shock with concomitant AKI requiring CRRT. In a study by Economou et al. [19], the antibiotic dose had to be adjusted in 35% of critically ill patients undergoing CRRT in whom therapeutic

Table 1 Baseline demographic and clinical characteristics of the study group

Characteristic	Value
Age (years); mean (SD)	57.8 (7.5)
Male sex; <i>n</i> (%; 95% CI)	10 (66.7%; 38.7–87.0%)
Body weight (kg); mean (SD)	81 (8.6)
BMI (kg/m ²); mean (SD)	27.5 (3.2)
APACHE IV score; median (IQR)	118 (97–134)
Day 1 SOFA score; median (IQR)	19.5 (18–21)
Day 3 SOFA score (12/15 patients); median (IQR)	20.5 (17–23)
Day 7 SOFA score (10/15 patients); median (IQR)	18.5 (16.3–21)
Organ dysfunction, <i>n</i> (%; 95% CI)	
Respiratory (ARDS)	15 (100%; 74.7–100%)
Renal	15 (100%; 74.7–100%)
Cardiovascular	11 (73.3%; 44.8–91.1%)
Hematologic	10 (66.7%; 38.7–87.0%)
Central nervous system	2 (13.3%; 2.3–41.6%)
Liver	2 (13.3%; 2.3–41.6%)
Medication, <i>n</i> (%; 95% CI)	
Vasopressors	13 (86.7%; 58.4–97.7%)
Mechanical ventilation	15 (100%; 74.7–100%)
Laboratory results	
White blood cell ($\times 10^9/L$); mean (SD)	10.9 (4.2)
Serum albumin (g/dL); mean (SD)	25.5 (3.1)
Baseline serum creatinine ($\mu\text{mol/L}$); mean (SD)	138.5 (41.3)
Pre-CRRT serum creatinine ($\mu\text{mol/L}$); mean (SD)	235.7 (52.1)
Preserved diuresis; <i>n</i> (%; 95% CI)	5 (33.3%; 9.5–57.2%)
Volume of diuresis (mL/24 h); median (IQR)	162.5 (300–900)
ICU survivors; <i>n</i> (%; 95% CI)	8 (53.3%; 27.4–77.7%)
CRRT settings	
Blood flow rate (mL/min); mean (SD)	124 (5.8)
Dialysate flow rate (mL/h); median (IQR)	2400 (2000–2700)
Ultrafiltrate (mL/h); median (IQR)	100 (50–100)

APACHE IV Acute Physiology and Chronic Health Evaluation IV, ARDS acute respiratory distress syndrome, BMI body mass index, SOFA sequential organ failure assessment

Table 2 Infection events in the study group

Site of infection	Value
Respiratory tract; <i>n</i> (%; 95% CI)	11 (73.3%; 44.8–91.1%)
Urinary tract; <i>n</i> (%; 95% CI)	4 (27%; 8.9–55.2%)
Bloodstream <i>n</i> (%; 95%CI)	4 (27%; 8.9–55.2%)
Pathogen identified; <i>n</i>	
<i>Acinetobacter baumannii</i>	2
Coagulase-negative staphylococci	2
<i>Staphylococcus aureus</i>	2
<i>Klebsiella pneumoniae</i>	2
<i>Pseudomonas aeruginosa</i>	2
<i>Citrobacter freundii</i>	1
<i>Escherichia coli</i>	1
Vancomycin-resistant enterococci	1

drug monitoring (TDM) was performed [19]. Unfortunately, TDM is rarely available in ICUs worldwide; thus, the appropriateness of antibiotic dosing usually remains uncertain.

Previous studies evaluating meropenem concentrations during CRRT, based on pharmacokinetic models and simulations, have reported conflicting results [20, 21]. Moreover, these discrepancies were related not only to dosing but also to the administration method (continuous infusion versus intermittent bolus administration; 30 min versus 3 h) [22, 23]. The recommended dose for such patients ranges from 500 mg every 12 h to 2 g every 8 h. In this study, we decided to use the latter dose due to the high prevalence of multidrug-resistant bacteria, high ultrafiltration and dialysate flow rates, as well as the presence of the abovementioned factors inherent in patients with sepsis that reduce plasma concentrations of the antibiotic [24]. Another difficulty is associated with the largely unpredictable influence of various

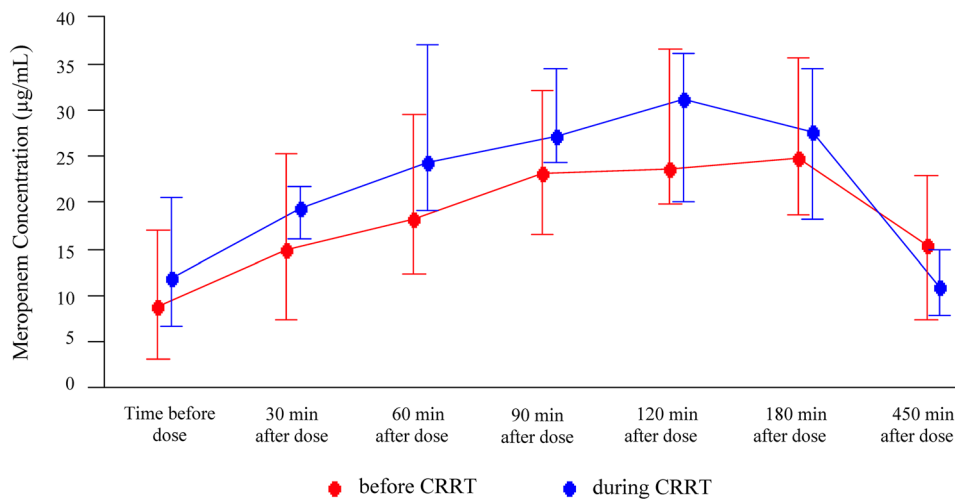
Table 3 Meropenem concentrations ($\mu\text{g/mL}$) in blood before and during continuous renal replacement therapy

Time point	CRRT	<i>N</i>	Median	Min	Max	<i>Q</i> 1	<i>Q</i> 3	<i>p</i> value*
(0)	Before	15	8.8	0.1	38.7	3.15	17.05	0.359
	During	15	11.9	2.7	32.4	6.65	20.65	
(1) 30 min	Before	15	15	4.3	48.6	7.35	25.2	0.169
	During	15	19.4	6.2	48.4	16.2	21.85	
(2) 60 min	Before	15	18.2	5.3	53	12.25	29.6	0.151
	During	15	24.4	9.3	46.8	19.25	37	
(3) 90 min	Before	15	23.2	13.2	49.3	16.45	32.2	0.389
	During	15	27.1	11.1	43.1	24.35	34.4	
(4) 120 min	Before	15	23.7	15.1	62	19.95	36.7	0.804
	During	15	31.1	12.2	41.5	20.2	36.15	
(5) 180 min	Before	15	24.9	2	60.6	18.7	35.65	0.847
	During	15	27.6	10.7	52.4	18.1	34.4	
(6) 450 min	Before	15	15.4	2.9	52.4	7.28	22.85	0.064
	During	14	10.9	1.8	30.6	7.75	14.8	

Continuous variables are expressed as median and interquartile range (*Q*1, 25th percentile and *Q*3, 75th percentile)

CRRT continuous renal replacement therapy

*Significant *p* value (<0.05); paired Student *t* test or the Wilcoxon test for matched pairs depending on the distribution of the difference between two variables

Fig. 2 Meropenem concentration before and during continuous renal replacement therapy (CRRT). Dots and whiskers represent median and interquartile range, respectively

modalities of CRRT on antibiotic concentrations. Some studies have shown that β -lactam clearance can vary at least partially depending on the CRRT modality [25]. Finally, little is known about the effect of anticoagulation used for CRRT and antibiotic concentrations.

The RCA-CVVHD is gaining popularity in the routine management of critically ill patients [13]. However, the recommendations on dosing of widely used medications among patients with severe sepsis and septic shock treated with RCA-CRRT are lacking. Therefore, we decided to determine the effect of RCA-CVVHD on meropenem concentrations in patients with AKI treated in the ICU due to severe sepsis or septic shock. Our patients had high

median APACHE IV and SOFA scores indicating critical condition, thus making them suitable candidates for RCA according to KDIGO recommendations [15]. Initial CRRT intensity was identical for all patients and was consistent with KDIGO recommendations. Moreover, administration of an identical dose of meropenem in all patients as well as fixed dosing before CRRT and in the first hours after its initiation provided a well-suited setting for the assessment of differences in drug concentrations associated with RCA-CVVHD. We did not find any differences between the plasma concentrations of meropenem before RCA-CVVHD and in the first 450 min of the procedure. Our results suggest that antibiotic dose adjustment might not be

Table 4 Achievement of hypothetical minimum inhibitory concentration (MIC) before and during renal replacement therapy with regional citrate anticoagulation (RCA-CRRT) among study participants

Number of measurements $C_{\text{Meropenem}} > \text{MIC}$	Hypothetical MIC ($\mu\text{g/mL}$)						
	0.25	0.5	1	2	4	8	16
Before RCA-CRRT							
0/7	15 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)
1/7	15 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)
2/7	15 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)	13 (86.7%)
3/7	15 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)	12 (80%)
4/7	15 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)	14 (93.3%)	9 (60%)
5/7	15 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)	11 (73.3%)	8 (53.3%)
6/7	15 (100%)	15 (100%)	15 (100%)	15 (100%)	13 (86.7%)	9 (60%)	6 (40%)
7/7	14 (93.3%)	13 (86.7%)	12 (80%)	11 (73.3%)	9 (60%)	7 (46.7%)	5 (33.3%)
During RCA-CRRT							
0/7	15 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)
1/7	15 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)	14 (93.3%)
2/7	15 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)	14 (93.3%)
3/7	15 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)	13 (86.7%)
4/7	15 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)	12 (80%)
5/7	15 (100%)	15 (100%)	15 (100%)	15 (100%)	15 (100%)	14 (93.3%)	10 (66.7%)
6/7	14 (93.3%)	14 (93.3%)	14 (93.3%)	14 (93.3%)	13 (86.7%)	10 (66.7%)	5 (33.3%)
7/7	13 (86.7%)	13 (86.7%)	13 (86.7%)	12 (80%)	11 (73.3%)	8 (53.3%)	1 (6.7%)

Data presented as number (percentage) of patients

necessary while using RCA-CVVHD, particularly shortly after its initiation, which is contradictory to an observed tendency to reduce doses recommended for CRRT in this period [18]. Our observations also cast doubt on the use of TDM in the first hours after the introduction of RCA-CVVHD and suggest that high doses of meropenem can be safely administered. To our knowledge, there have been no similar prospective studies evaluating the influence of RCA-CVVHD on meropenem concentrations in patients with severe sepsis or septic shock.

We are aware of several important limitations of our study. First, the study group was relatively small, but at the same time, it was very homogeneous as it consisted of critically ill patients with severe sepsis or septic shock with very high predicted mortality according to commonly used scoring systems for the severity of illness in critical care. Second, we did not measure meropenem concentrations in the time points exceeding the prespecified 450 min. Such a measurement would allow us to evaluate the effect of filter lifespan during the procedure. Also, we did not measure meropenem concentrations in urine, ultrafiltrate, and at the site of infection. The lack of these measurements limited our ability to calculate several significant pharmacokinetic variables. Finally, the study group was heterogenous in terms of residual diuresis, a factor that influences drug clearance.

Conclusion

Plasma concentrations of high-dose meropenem (2 g every 8 h) administered in a prolonged infusion were similar before and after the initiation of RCA-CVVHD.

Acknowledgements The manuscript was edited by a professional English proofreader, Małgorzata Wiesner-Spyrczyńska. The authors thank Maria Foks and Alicja Dudek for help in clinical data extraction and database management.

Author contributions IN-K: conceptualization, methodology, writing-original draft preparation, resources. KJP: writing-reviewing and editing, software, validation, formal analysis, data curation. JG: writing-reviewing and editing, resources. JF: writing-reviewing and editing, software, validation, formal analysis, data curation. AG: investigation, resources. BS: investigation, resources. MC: writing-reviewing and editing, validation. BK: writing-reviewing and editing, validation. WS: methodology, writing-reviewing and editing, supervision.

Funding This study was supported by a grant awarded to I. Nowak-Kozka by the National Science Centre Poland (Preludium: predoctoral Grants, No. 2014/15/N/NZ5/03646). Open access publishing of this article was funded by the Ministry of Science and Higher Education under the agreement No. 879/P-DUN/2019.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

Ethics approval and consent to participate The study protocol was approved by the Jagiellonian University Bioethics Committee (No. KBET/262/B/2013).

Consent for publication All authors have reviewed and approved the manuscript for publication.

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