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The effect of direct hemoperfusion with polymyxin B immobilized cartridge on meropenem in critically ill patients requiring renal support

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ABSTRACT

Purpose: To evaluate the effect of direct hemoperfusion with polymyxin B immobilized cartridge (DHP-PMX) on meropenem pharmacokinetics in critically ill patients with sepsis requiring continuous venovenous hemofiltration (CVVH).

Material and methods: After intravenous infusion of 1 g meropenem over 3 h repeated every 8 h for at least 3 doses, 2 serial blood and ultrafiltration fluid samples were collected: one over a dose interval of meropenem with DHP-PMX therapy; and the other on the following day over a dose interval of meropenem with no DHP-PMX therapy. Meropenem concentrations were measured by high performance liquid chromatography. Pharmacokinetic parameters of meropenem and extraction ratio of DHP-PMX were calculated.

Results: Mean AUC_{0-8} of meropenem on DHP-PMX day was comparable to that of the DHP-PMX free day (285.2 ± 138.2 vs 297.8 ± 130.2 mg ∗ h/L; paired *t*-test, $p = .618$). No statistical significance of peak and trough concentrations, volume of distribution, sieving coefficient, or half-life were found. Extraction ratio of DHP-PMX on meropenem was 0 [0–0.03] and clearance by DHP-PMX was 0.04 [0–0.2] L/h which was not considered clinically significant.

Conclusions: No significant effect of DHP-PMX on meropenem pharmacokinetics was observed among severe sepsis/septic shock patients during CVVH treatment.

Trial registration: Clinical Trial Registry detail: NCT registry: 02413541 (First registered March 3, 2015, last update October 16, 2017).

1. Introduction

Severe sepsis and septic shock are recognized as unpredictable, life-threatening syndromes associated with high mortality rates. Among such patients, despite receiving standard medical treatment and appropriate antibiotics [1], 37% do not survive [2]. Furthermore, approximately 54% of critically ill patients develop acute kidney injury (AKI), and if renal replacement therapy (RRT) is needed, their prognosis worsens [3].

Bacterial endotoxin is the key factor that triggers sepsis [4]; thus any strategies that remove endotoxin in the early phase of sepsis may increase survival. The 2-hour direct hemoperfusion with polymyxin B immobilized cartridge (DHP-PMX) is one of the most commonly used techniques for removal endotoxin in the bloodstream. DHP-PMX has been approved for clinically use in Japan since 1994. [5] Although recent meta-analyses and a large randomized control trial showed conflicting

Abbreviations: AKI, acute kidney injury; APACHE, acute physiology and chronic health evaluation II; AUC, area under the concentration-time curve; BFR, blood flow rate; CL_{CVVH}, clearance contributed by CVVH; CL_{PMX}, drug adsorption contributed by DHP-PMX; CL_R, renal clearance; CL_{TOT}, total clearance; C_{max}, highest concentration; C_{min}, lowest concentration; CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; DHP-PMX, direct hemoperfusion with polymyxin b-immobilized cartridge; ER, extraction ratio; HPLC, high pressure liquid chromatography; ICU, intensive care unit; K_e, constant of elimination; LPS, lipopolysaccharide; MIC, mean inhibitory concentration; Sc, sieving coefficient; SOFA, sequential organ failure assessment; $t_{1/2}$, half-life of elimination; T>MIC, the time that the concentration remained above MIC; UF, ultrafiltration fluid; UFR, ultrafiltration fluid rate; Vd, volume of distribution.

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results [6-10], this specific technique has been clinically used in many countries in Asia and some countries in Europe.

The adsorptive cartridge used in the DHP-PMX circuit is comprised of 2 main parts: a *co*-polymer of polystyrene and polypropylene as the basement fiber; and immobilized polymyxin B which is coated on the surface.

Data from in-vitro study showed that polymyxin B immobilized cartridge might adsorb some antibiotics. [11,12] The interaction of this cartridge on each antibiotic is still unknown and unable to predict. If this interaction really happens in clinical setting, it can cause suboptimal drug plasma concentration. Therefore, an appropriate antibiotic dose during DHP-PMX treatment is essential and may be an important factor for successful treatment in such patients.

Meropenem is one of the most widely used antibiotics for sepsis patients in the intensive care unit (ICU) [13]. Pharmacokinetic data of meropenem in critically ill patients who received continuous venovenous hemofiltration (CVVH) is insufficient, especially when meropenem was administered via prolonged intravenous infusion. Furthermore, there is no data on patients receiving CVVH with DHP-PMX. Therefore, the aim of this study is to evaluate meropenem pharmacokinetics in critically ill patients receiving CVVH, and to determine the effect of DHP-PMX on meropenem pharmacokinetics in these patients.

2. Material and methods

2.1. Study design

This prospective pharmacokinetic study was a substudy of a randomized controlled study [14] and was conducted at a tertiary hospital (King Chulalongkorn Memorial Hospital, Bangkok, Thailand) from September 2016 to October 2017. The study protocol was approved by The Institutional Review Board committee, Faculty of Medicine, Chulalongkorn University (COA No. 259/2016). Study information was provided to the patients and/or their surrogates before obtaining written informed consent. For the current prospective pharmacokinetic study, inclusion criteria consisted of critically ill patients aged ≥18 years with severe sepsis or septic shock, who had anuric or oliguric AKI, and who received CVVH with DHP-PMX and 1 g of intravenous meropenem infusion over 3 h repeated every 8 h for at least 3 doses. Exclusion criteria consisted of a history of allergy to meropenem, polymyxin B or colistin, white blood cell counts <3000/μL, platelet counts <30,000/μL, or having received probenecid. Eligible patients were given two treatment regimens during the 2-day study period: (1) on the first day of the study (the day after enrollment), the second session of DHP-PMX was initiated 3 h after starting meropenem infusion (DHP-PMX day); (2) on the next day, meropenem without DHP-PMX (DHP-PMX free day) was initiated. Study population selection and sample collection can be seen in Fig. 1.

2.2. Drug dosage regimen

Upon hospital admission, one gram of meropenem was diluted with 100 mL of normal saline and administered over 3 h as an intravenous infusion. The process was repeated every 8 h using an infusion pump, and a total of 3 g/day was administered.

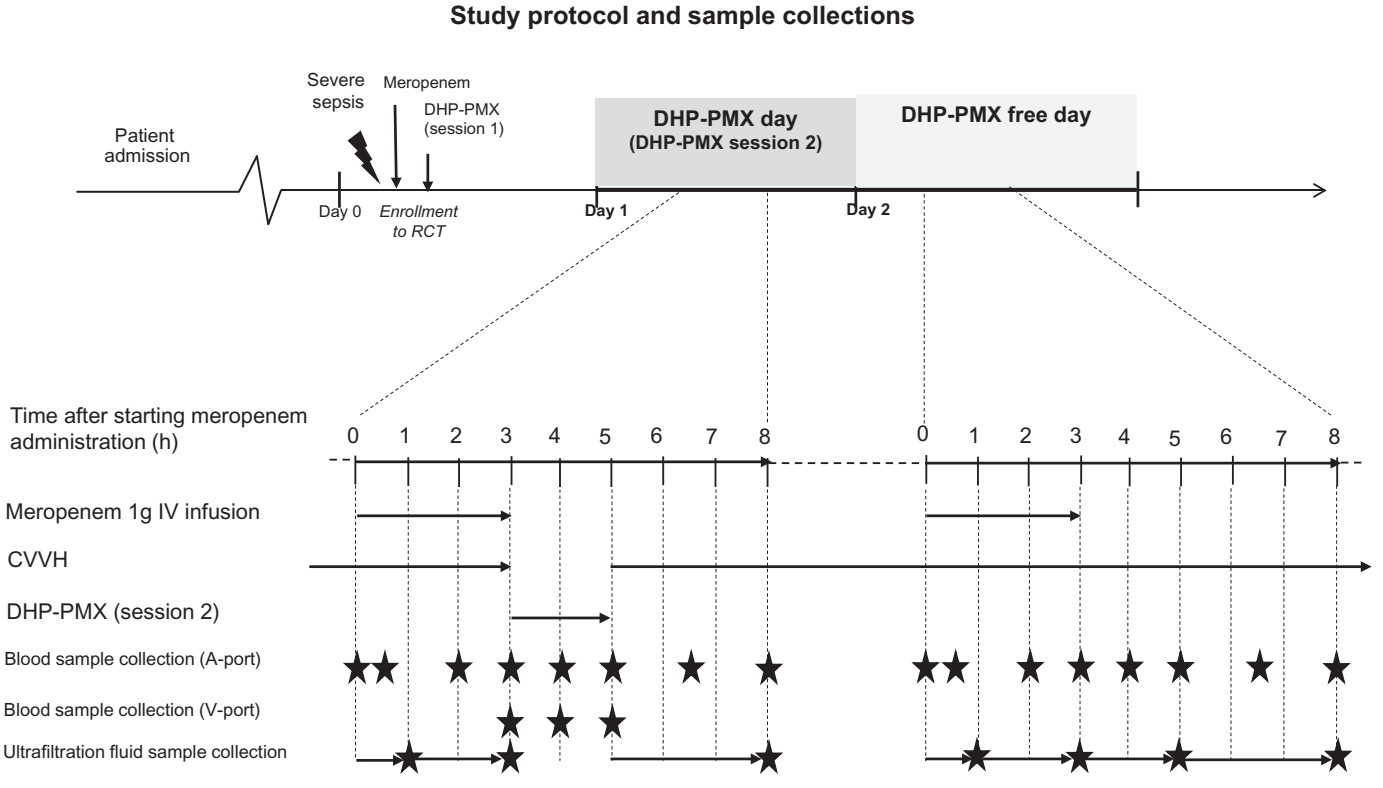

Fig. 1. The study protocol and sample collections. - One gram meropenem was administered via 3-hour intravenous infusion repeated every 8 h. - On Day 0, which was an enrollment day, the first session of DHP-PMX was performed. - On the first day of the study (day 1, DHP-PMX day): the second session of DHP-PMX was initiated 3 h after starting meropenem infusion. CVVH was temporarily stopped during treatment with DHP-PMX. In total, 11 blood samples were drawn: five 2-mL blood samples from the arterial port of CVVH circuit at 0, 0.5, 2, 6.5 and 8 h, and 3 blood samples each from the arterial and venous ports of the DHP-PMX circuit at 3, 4 and 5 h after the initiation of meropenem infusion. Three 10-mL ultrafiltration fluid (UF) samples were collected from the effluent bags during the intervals of 0–1, 1–3 and 5–8 h after the initiation of meropenem infusion. - On the second day of the study (day 2, DHP-PMX free day). Meropenem was administered with the same dose and method as the previous day. Eight blood samples were drawn from the arterial port of the CVVH circuit at 0, 0.5, 2, 3, 4, 5, 6.5 and 8 h after starting the meropenem dose and 4 UF samples were collected from the effluent bags during the intervals of 0–1, 1–3, 3–5 and 5–8 h after the initiation of meropenem infusion.

2.3. Direct hemoperfusion with polymyxin B immobilized cartridge procedure and continuous venovenous hemofiltration procedure

A 2-hour DHP-PMX technique was used for 2 sessions on consecutive days. The first session was performed on the enrollment day and the second on the subsequent day. On the second day of DHP-PMX (DHP-PMX day), DHP-PMX was initiated 3 h after the initiation of meropenem infusion to give time for the medication to get distributed from the blood to the tissue. The CVVH circuit was temporarily disconnected and a new connection to the DHP-PMX circuit was established. Blood was delivered from the femoral vein through the DHP-PMX circuit and returned to the patient. Toraymyxin® PMX-20R (Toray Industries, Inc., Japan) was used as an adsorptive cartridge for DHP-PMX. The blood flow rate (BFR) was set as 7.2 L/h for each patient. After each DHP-PMX session, the circuit was disconnected and disposed of. Then, the CVVH circuit was reconnected without further interruption for the remainder of the study.

CVVH was initiated before enrollment and performed continuously except during the 2-hour sessions of DHP-PMX. Polyacrylonitrile hollow-fiber high-flux dialyzer (M100®, Gambro, France) was used in the CVVH circuit. A double-lumen catheter was used for vascular access to the femoral vein or the internal jugular vein. BFR and ultrafiltration fluid rate (UFR) were determined to be 9–12 L/h and 1.5–1.8 L/h, respectively. Depending on the UFR, the replacement fluid with combined prefilter and postfilter infusion was about 1.5–1.8 L/h. Low-dose heparin was used as an anticoagulant unless there were contraindications.

2.4. Blood sample and ultrafiltration fluid sample collection

On the DHP-PMX day, in total, 11 blood samples were drawn: five 2-mL blood samples from the arterial port of CVVH circuit at 0, 0.5, 2, 6.5 and 8 h; and 3 blood samples each from the arterial and venous ports of the DHP-PMX circuit at 3, 4 and 5 h after the initiation of meropenem infusion. Three 10-mL ultrafiltration fluid (UF) samples were collected from the effluent bags during the intervals of 0–1, 1–3 and 5–8 h after the initiation of meropenem infusion.

On the DHP-PMX free day, 8 blood samples were drawn from the arterial port of the CVVH circuit at 0, 0.5, 2, 3, 4, 5, 6.5 and 8 h after starting the meropenem dose and 4 UF samples were collected from the effluent bags during the intervals of 0–1, 1–3, 3–5 and 5–8 h after the initiation of meropenem infusion (Fig. 1).

All samples were immediately centrifuged at 3000*g*, 25 °C for 10 min and mixed with 2-morpholinoethanesulfonic acid, a stabilizer (1:1 ratio), before storing them at −80 °C until analysis.

2.5. Analytical methods

Meropenem concentrations in plasma and UF samples were analyzed using the high-performance liquid chromatography (HPLC) technique with ultraviolet detection at 295 nm which was adapted from Dailly et al. [15] The stationary phase was a Kinetex® Pentafluorophenyl core-shell LC column (2.6 μm, 100 × 4.6 mm ID). The mobile phase was a mixture of methanol and sodium phosphate buffer with a gradient method and was delivered at a rate of 0.7 mL/min. Ceftazidime was used as an internal standard. The validation tests showed a lower limit of quantification of 0.4 mg/L. The assay was linear from 0.4 to 100 mg/L for both plasma and UF samples. Bias and precision were within 10% and 5%, respectively.

2.6. Pharmacokinetic analysis

C_{min} and C_{max} were the lowest and highest plasma meropenem concentrations observed. The area under the concentration-time curve during the 8-h interval of meropenem dosing (AUC_{0-8}) was calculated using a linear trapezoidal rule [16].

The elimination half-life ($t_{1/2}$) of meropenem was calculated as: $t_{1/2} = 0.693/K_e$, where K_e was a constant of elimination and calculated as: $K_e = (\ln C_{A3} - \ln C_{A8})/5$, where C_{A3} and C_{A8} were the arterial plasma meropenem concentrations at 3 and 8 h after the initiation of meropenem infusion, respectively.

Total clearance (CL_{TOT}) was calculated as: $CL_{TOT} = 1000/AUC_{0-8}$ and volume of distribution (Vd) was calculated as: $Vd = CL_{TOT}/K_e$ [16].

Sieving coefficient (Sc) was calculated by the meropenem concentration in UF divided by the meropenem concentration in plasma. Clearance by CVVH (CL_{CVVH}) was calculated as: $CL_{CVVH} = UFR/Sc \times [BFR/(BFR + RFR_{PRE})]$, where BFR was blood flow rate of the CVVH circuit and RFR_{PRE} was the prefilter replacement fluid flow rate of the CVVH circuit [17].

Drug adsorption by DHP-PMX (CL_{PMX}) was calculated as: $CL_{PMX} = BFR \times ER$, where BFR was the blood flow rate in the DHP-PMX circuit and ER was the extraction ratio which was calculated as: $ER = (C_A - C_V)/C_A$, where C_A and C_V were meropenem concentrations from pre-cartridge blood samples and post-cartridge blood samples in the DHP-PMX circuit [18].

The time that meropenem concentrations remained above MIC (2 mg/L) during dosing intervals (T > MIC) was calculated as: T > MIC = $(t_{C>2}/\tau) \times 100$ (%), where $t_{C>2}$ was the time that plasma concentrations remained above 2 mg/L and τ was the dosing interval (8 h) [19].

2.7. Statistical analysis

Statistical analyses were performed using SPSS software version 17.0 (SPSS Inc., USA) with statistical significance set as P value <.05. Categorical variables were summarized as n (percentage), and continuous variables were summarized as mean ± standard deviation (SD) if normally distributed and as using the median (interquartile range, IQR) if skewed. The Shapiro-Wilks test was used to detect departures from normality. Because data were collected on the same patients at different times, comparisons between the DHP-PMX day measures and the DHP-PMX free day measures were performed using either the paired t-test or Wilcoxon rank-sum test. CL_{PMX} was considered clinically significant if it contributed >25% of CL_{TOT}.

3. Results

3.1. Patient characteristics

There were 15 critically ill patients who received DHP-PMX during the PMX study period. We excluded 1 patient who refused to participate, 3 died before enrollment, 2 died before all the samples were collected and 1 patient did not undergo CVVH. In the end, there were 8 critically ill patients eligible for the study. Baseline patient characteristics are shown in Table 1. Briefly, all patients were male, with the mean age being 68.9 ± 14.2 years. The mean actual body weight on DHP-PMX day was 74.6 ± 19.7 kg and on the DHP-PMX free day was 75.1 ± 18.0 kg. The mean APACHE II score was 21.4 ± 5.6 and the mean SOFA score was 11.8 ± 3.2. The median BFR and UFR for CVVH settings were 9.0 [9.0–12.0] L/h and 1.5 [1.5–1.8] L/h, respectively. By day 28 after the DHP-PMX day, 3 patients had died.

3.2. Meropenem pharmacokinetics

3.2.1. Meropenem adsorption by DHP-PMX

The median extraction ratio was 0 [0–0.03]. The median CL_{PMX} was 0.04 [0–0.2] L/h, which contributed approximately 1% of CL_{TOT}.

3.2.2. Meropenem pharmacokinetics in patients receiving CVVH with DHP-PMX

Table 2 summarizes the meropenem pharmacokinetics on the DHP-PMX day. The mean ± SD for: plasma meropenem AUC_{0-8} was 285.2 ± 138.2 mg ∗ h/L; C_{min} 20.1 ± 10.3 mg/L; C_{max} 50.5 ± 22.8 mg/L; and K_e

Table 1
Patient characteristics and outcome.

Characteristic	Patient								Mean ± SD or median [IQR]
	1	2	3	4	5	6	7	8	
Gender	Male	Male	Male	Male	Male	Male	Male	Male	–
Age (years)	83	82	82	58	67	76	45	58	68.88 ± 14.17
Weight (kg)	96.0	60.0	69.8	90.0	40.1	75.2	68.6	98.1	74.65 ± 19.74
Height (cm)	170	160	165	170	160	165	n/a[a]	170	165.71 ± 4.50
Body temperature (°c)	38.8	36.4	36.0	36.1	37.4	35.0	37.0	36.0	36.0 [36.0–37.0]
MAP (mmHg)	69.3	80.3	79.0	102.7	78.0	75.3	69.0	74.7	76.67 [70.67–80.00]
APACHE II score	13	19	31	19	25	17	25	22	21.38 ± 5.60
SOFA score	7	7	11	14	12	14	15	14	11.75 ± 3.20
Serum albumin (g/dL)	2.8	4.0	4.5	2.6	2.8	2.7	3.1	2.3	3.10 ± 0.76
BFR (L/h)	12.0	9.0	9.0	9.0	9.0	12.0	12.0	9.0	9.00 [9.00–12.00]
UFR (L/h)	1.8	1.5	1.8	1.5	1.2	1.8	1.8	1.8	1.80 [1.50–1.80]
Outcome[b]	Died	Survived	Survived	Survived	Survived	Died	Survived	Died	–

APACHE II, acute physiology and chronic health evaluation II; BFR, blood flow rate; DHP-PMX, direct hemoperfusion with polymyxin b-immobilized cartridge; MAP, mean arterial pressure; SOFA, sequential organ failure assessment; UFR, ultrafiltration fluid flow rate.
[a] Data not available.
[b] Outcome at Day 28 after the patient received the second session of DHP-PMX.

$0.16 \pm 0.12\ h^{-1}$. The median [IQR] for: Vd was 31.5 [20.5–43.4] L; $t_{1/2}$ 5.6 [3.0–9.8] h; Sc 0.92 [0.72–1.2]; CL_{TOT} 3.7 [2.6–5.2] L/h; and CL_{CVVH} 1.3 [1.1–2.0] L/h.

3.2.3. Meropenem pharmacokinetics in patients receiving CVVH without DHP-PMX

Table 3 summarizes the meropenem pharmacokinetics on the DHP-PMX free day. The mean ± SD for: plasma meropenem AUC_{0-8} was 297.8 ± 130.2 mg ∗ h/L; C_{min} 23.3 ± 14.1 mg/L; C_{max} 54.7 ± 20.2 mg/L; and K_e $0.16 \pm 0.07\ h^{-1}$. The median [IQR] for: Vd was 26.0 [18.9–33.2] L; $t_{1/2}$ 4.8 [3.2–5.6] h; Sc 0.94 [0.8–1.2]; CL_{TOT} 3.6 [2.4–4.7] L/h and CL_{CVVH} 1.3 [1.0–1.7] L/h.

3.3. Comparison of pharmacokinetics and effect of DHP-PMX on meropenem concentrations

None of the pharmacokinetic parameters were statistically significant between the DHP-PMX day and the DHP-PMX free day (Table 4).

4. Discussion

In our prospective study of patients receiving CVVH we found that plasma meropenem AUC_{0-8} and other pharmacokinetic parameters were not different between the DHP-PMX day and the DHP-PMX free day.

Our findings are concordant with the findings of a previous in-vitro study by Shimokawa et al. [11] They reported an adsorption rate of polymyxin B immobilized fiber on various antibiotics in bovine plasma as being only 1.4% for meropenem. The exact mechanisms of the adsorption of DHP-PMX on each antibiotic was still unknown. Protein binding is one of many factors that can be used to predict drug removal via continuous renal replacement therapy (CRRT) but it seems to not work with DHP-PMX. [20] In our study, the clearance of meropenem by 2-h DHP-PMX was very low, only 0.04 L/h.

In the current study, one gram of meropenem was diluted with 100 mL of normal saline and intravenously administered over 3 h. The mean AUC_{0-8} was 297.8 mg ∗ h/L, which is slightly higher than that reported by Jamal et al. [16] In their study of 8 critically ill patients with AKI undergoing CVVH, they evaluated the pharmacokinetics of an intravenous bolus of meropenem given every 8 h and reported a median AUC_{0-8} of 250.8 mg ∗ h/L. Conversely, in this study the median UFR and observed CL_{CVVH} were lower than those reported by Jamal et al.: 1.8 vs 2.0 L/h; and 1.3 vs 2.1 L/h, respectively. In our study, the mean AUC_{0-8} was approximately 3 times higher than that of patients without renal impairment [19,21] and 4 times higher than that of healthy subjects [22]. The mean C_{min} in our study (23.3 mg/L) was much higher than the C_{min} of patients without renal impairment [19] and was also higher than previously reported in critically ill patients treated with meropenem 3 g/day where the C_{min} was between 6.6 and 17.0 mg/L. [16,18,23] However, the mean C_{max} in our study (54.7 mg/L) was similar

Table 2
Meropenem pharmacokinetics in critically ill patients receiving CVVH with DHP-PMX.

Parameter	Patient								Mean ± SD/median [IQR]
	1	2	3	4	5	6	7	8	
AUC_{0-8} (mg ∗ h/L)	66.62	266.09	402.64	275.74	215.50	354.46	513.86	187.04	285.24 ± 138.15
C_{min} (mg/L)	2.75	21.26	34.18	19.11	11.99	28.37	28.86	14.53	20.13 ± 10.31
C_{max} (mg/L)	22.01	40.96	80.31	44.33	44.18	57.77	85.90	28.81	50.53 ± 22.82
K_e (h^{-1})	0.42	0.13	0.17	0.11	0.26	0.04	0.06	0.12	0.16 ± 0.12
Vd (L)	36.08	28.65	14.54	32.13	17.79	62.90	30.88	45.89	33.61 ± 15.41
$t_{1/2}$ (h)	1.67	5.28	4.06	6.14	2.66	15.45	11.00	5.95	5.62 [3.01–9.78]
Sc	2.08	1.21	0.72	1.03	0.82	1.17	0.72	0.72	0.92 [0.72–1.20]
Extraction ratio	0.07	0	0.03	0	0	0.01	0.02	0	0 [0–0.03]
CL_{TOT} (L/h)	15.01	3.76	2.48	3.63	4.64	2.82	1.95	5.35	3.70 [2.56–5.17]
CL_{CVVH} (L/h)	3.33	1.56	1.08	1.37	0.87	2.09	1.16	1.08	1.26 [1.08–1.96]
CL_{NR} (L/h)	11.69	2.20	1.40	2.26	3.77	0.74	0.79	4.27	2.23 [0.94–4.14]
CL_{PMX} (L/h)	0.48	0.02	0.03	0	0	0	0.06	0.04	0.04 [0–0.18]
T>MIC (%)	100	100	100	100	100	100	100	100	100 [100−100]

AUC_{0-8}, area under the concentration-time curve of meropenem from 0 to 8 h; DHP-PMX, direct hemoperfusion with polymyxin b-immobilized cartridge; C_{max}, highest plasma meropenem concentration; C_{min}, lowest plasma meropenem concentration; CL_{CVVH}, clearance distributed by CVVH; CL_{NR}, non-renal clearance; CL_{PMX}, clearance contributed by DHP-PMX; CL_{TOT}, total clearance; CVVH, continuous venovenous hemofiltration; K_e, constant of elimination; Sc, sieving coefficient; $t_{1/2}$, half-life of elimination; T > MIC, the time that the concentrations remained above MIC; Vd, volume of distribution.

Table 3
Meropenem pharmacokinetics in critically ill patients receiving CVVH with no DHP-PMX.

Parameter	Patient								Mean ± SD/median [IQR]
	1	2	3	4	5	6	7	8	
AUC_{0-8} (mg ∗ h/L)	94.06	244.30	275.16	334.20	280.60	445.30	502.70	206.38	297.84 ± 130.17
C_{min} (mg/L)	6.49	20.39	16.97	29.08	11.51	42.19	45.02	15.04	23.34 ± 14.14
C_{max} (mg/L)	22.01	39.20	65.34	59.75	52.87	78.08	80.30	39.95	54.69 ± 20.25
K_e (h^{-1})	0.24	0.13	0.27	0.14	0.17	0.12	0.06	0.14	0.16 ± 0.07
Vd (L)	45.53	31.31	13.48	20.78	21.23	18.24	30.78	33.89	26.66 ± 9.89
$t_{1/2}$ (h)	2.84	5.30	2.57	4.81	4.13	5.63	10.72	4.85	4.83 [3.16–5.55]
Sc	1.78	1.29	0.91	0.94	0.95	0.94	0.59	0.77	0.94 [0.80–1.20]
CL_{TOT} (L/h)	10.63	4.09	3.63	2.99	3.56	2.25	1.99	4.85	3.60 [2.44–4.66]
CL_{CVVH} (L/h)	2.84	1.65	1.37	1.24	1.00	1.66	0.95	1.15	1.30 [1.04–1.66]
CL_{NR} (L/h)	7.79	2.44	2.26	1.75	2.56	0.58	1.04	3.69	2.35 [1.22–3.41]
T>MIC (%)	100	100	100	100	100	100	100	100	100 [100–100]

AUC_{0-8}, area under the concentration-time curve of meropenem from 0 to 8 h; DHP-PMX, direct hemoperfusion with polymyxin b-immobilized cartridge; C_{max}, highest plasma meropenem concentration; C_{min}, lowest plasma meropenem concentration; CL_{CVVH}, clearance distributed by CVVH; CL_{NR}, non-renal clearance; CL_{TOT}, total clearance; CVVH, continuous venovenous hemofiltration; K_e, constant of elimination; Sc, sieving coefficient; $t_{1/2}$, half-life of elimination; T > MIC, the time that the concentrations remained above MIC; Vd, volume of distribution.

to previous studies in which meropenem was administered as an intravenous bolus within 15–30 min [16,23,24]. Due to the small amounts of urine output in these oligo-anuric patients, renal clearance (CL_R) was insignificant [23] and no CL_R can be assumed. The mean Sc was comparable with previous studies and CL_{CVVH} contributed one-third to the CL_{TOT}. This was concordant with previous meropenem pharmacokinetic studies. [18,25,26]

In patients without renal impairment, meropenem has a short $t_{1/2}$ of 1–2 h. [19,21] In our study of critically ill patients receiving CVVH, we observed a longer $t_{1/2}$ of approximately 5 h. Following the study protocol, to lessen the effects of DHP-PMX on the pharmacokinetics of meropenem, we started DHP-PMX 3 h after the intravenous infusion with meropenem.

Due to unexpected high trough concentrations of plasma meropenem observed in these patients, we concluded that dose adjustment and therapeutic drug monitoring (TDM) are needed in patients receiving CVVH with or without DHP-PMX.

Our study has several strengths. First, to our knowledge, it is the only clinical study that has determined the effect of DHP-PMX on antibiotics.

Table 4
Comparison of meropenem pharmacokinetics in critically ill patients receiving CVVH with DHP-PMX and with no DHP-PMX.

Parameter	CVVH + DHP-PMX[a]	CVVH[a]	Difference	*P* value
AUC_{0-8} (mg ∗ h/L)	285.24 ± 138.15	297.84 ± 130.17	−12.59 ± 68.26	0.618[b]
C_{min} (mg/L)	20.13 ± 10.31	23.34 ± 14.14	−3.20 ± 10.56	0.419[b]
C_{max} (mg/L)	50.53 ± 22.82	54.69 ± 20.25	−4.15 ± 11.77	0.352[b]
K_e (h^{-1})	0.16 ± 0.12	0.16 ± 0.07	0.00 ± 0.09	0.881[b]
Vd (L)	31.50 [20.50–43.44]	26.00 [18.88–33.24]	–	0.401[c]
$t_{1/2}$ (h)	5.62 [3.01–9.78]	4.83 [3.16–5.55]	–	0.327[c]
Sc	0.92 [0.72–1.20]	0.94 [0.80–1.20]	–	0.528[c]
CL_{TOT} (L/h)	3.70 [2.56–5.17]	3.60 [2.44–4.66]	–	0.263[c]
CL_{CVVH} (L/h)	1.26 [1.08–1.96]	1.30 [1.04–1.66]	–	0.441[c]
CL_{NR} (L/h)	2.23 [0.94–4.14]	2.35 [1.22–3.41]	–	0.327[c]
T>MIC (%)	100 [100–100]	100 [100–100]	–	1.000[c]

AUC_{0-8}, area under the concentration-time curve of meropenem from 0 to 8 h; DHP-PMX, direct hemoperfusion with polymyxin b-immobilized cartridge; C_{max}, highest plasma meropenem concentration; C_{min}, lowest plasma meropenem concentration; CL_{CVVH}, clearance distributed by CVVH; CL_{NR}, non-renal clearance; CL_{TOT}, total clearance; CVVH, continuous venovenous hemofiltration; K_e, constant of elimination; Sc, sieving coefficient; $t_{1/2}$, half-life of elimination; T > MIC, the time that the concentrations remained above MIC; Vd, volume of distribution.

[a] Mean ± standard deviation or median [interquartile range].
[b] *P* value was calculated using Paired *t*-test.
[c] *P* value was calculated using Wilcoxon signed ranks test.

Second, our study provides pharmacokinetic data regarding patients receiving CVVH with DHP-PMX. As a result, our findings could lessen the concern of clinicians when administering suboptimal drug concentrations in this setting since the observed T > MIC was 100%. Even though there has been a lot of research on meropenem pharmacokinetics during AKI [16,27], there was no study on the pharmacokinetics of meropenem in oligo-anuric AKI patients undergoing CVVH after receiving 3-h intravenous infusions of meropenem. Thus, our study provides information for this missing gap.

There are some limitations to our study. First, all patients had oligo-anuric AKI, and thus, our results may not apply to patients with significant residual renal function. Second, DHP-PMX was started 3 h after the initiation of meropenem to assure that the drug was distributed from blood to tissue. In a situation where DHP-PMX could be immediately initiated after the initiation of meropenem, an effect of DHP-PMX on meropenem might be seen. However, a very low extraction ratio and CL_{PMX} suggest that the effect of DHP-PMX on meropenem is minimal. Third, the BFR and UFR of CVVH are lower than in almost all previous meropenem pharmacokinetic studies. Lastly, the sample size is small and further studies with more participants are needed to validate our findings. As a result, clinicians should consider these limitations when applying these pharmacokinetic parameters to individual patients.

5. Conclusions

In conclusion, this clinical study determined the effect of DHP-PMX on meropenem plasma concentrations and its pharmacokinetics in critically ill patients receiving CVVH. DHP-PMX did not demonstrate a clinically and statistically significant effect on meropenem. Therefore, there is no need for meropenem dosage increments during DHP-PMX treatment. In situations where patients were started on CRRT, meropenem dosing should be based only on the CRRT setting.

Furthermore, the effect of DHP-PMX on other drugs cannot be inferred from the results of this study. Further studies are needed to determine the effect of DHP-PMX on the pharmacokinetics of other drugs.

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Competing interests

None declared.

Ethics approval and consent to participate

Ethics approval was obtained from the Faculty Ethical Committee (COA No. 259/2016). Written informed consent was obtained from each patient or the patient's surrogate.

Availability of data and materials

On reasonable request, data from this study are available from the corresponding author.

Authors' contributions

WS, SV, NA, SW, WC, and NS were responsible for research design, research conduct and writing of the manuscript. WS and SV were responsible for data analysis. WS, SV, and NS had primary responsibility for the final content of the manuscript. WS, NA, and SW were responsible for drug concentration analysis. WS, SV, and WC were responsible for the pharmacokinetic parameters calculation. All authors read and approved the final manuscript.

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