Critical Care

CORRESPONDENCE

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Effect of therapeutic plasma exchange on antimicrobials in critically ill patients

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Dear Editor,

Therapeutic plasma exchange (TPE) is a procedure in which plasma is separated from the cellular components of whole blood by various methods. The removed plasma is replaced with albumin or fresh frozen plasma (FFP). TPE aims to eliminate disease-related pathogens [1]. Removal of significant amounts of plasma during TPE can alter the pharmacokinetic profiles of antimicrobials, resulting in inadequate therapeutic efficacy. In addition, critically ill patients may have altered pharmacokinetic profiles for many drugs. Data on antimicrobial elimination via TPE in intensive care unit (ICU) patients are scarce. Few studies have examined the effect of TPE on antimicrobials [2].

Several factors may influence antimicrobial elimination during TPE. High plasma protein-binding (> 80%) and low volume of distribution (V_d < 0.2 L/kg) are important pharmacokinetic factors indicating a high rate of removal via TPE [3]. Studies have also shown that allowing an adequate interval for drug distribution significantly decreases drug elimination via TPE [4]. It is important to note that distribution half-life values are not typically available to clinicians through drug monographs. However, because the distribution phase generally has a shorter half-life than the elimination phase, elimination half-life data can be used as a surrogate measure of drug distribution half-life [5].

We report the plasma levels of meropenem, teicoplanin, voriconazole, and amikacin immediately before and after TPE, along with the amounts of antimicrobials in plasmapheresate (removed plasma) from three critically ill ICU patients. All antimicrobials were at steady-state during TPE sessions, with none given immediately before or during TPE. TPE was performed using the Spectra Optia Apheresis System (TERUMOBCT) by continuous-flow-centrifugation. Plasma levels of these drugs are routinely monitored at our hospital using liquid chromatography with tandem mass spectrometry (LC–MS/MS). The amount of drug removed (mg) (Q_{TPE}) was calculated as follows: drug concentration in plasmapheresate (mg/L) x volume of plasma removed (L). To the best of our knowledge, this study is the first to provide data on the effect of TPE on steady-state plasma levels of meropenem, teicoplanin, and amikacin, as well as the first to report on the effect of TPE on the disposition of amikacin.

A 40-year-old male patient with hemochromatosis, chronic liver disease, type 2 diabetes, and atrial fibrillation was admitted to the medical ICU for neutropenic fever and community-acquired pneumonia (Case 1). He underwent 7 TPE sessions with FFP to treat worsening hyperbilirubinemia associated with hepatic encephalopathy. The patient's antimicrobial therapy included

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Table 1 Clinical data and pre-TPE laboratory values of the patients undergoing TPE sessions

Age	Gender	BW (kg)	BMI (kg/m^2)	APACHE II	SOFA	MRC-ICU	MV	ICU LOS (days)	Mortality	Day of the TPE session	eGFR CKD-EPI (mL/min)	Serum creatinine (mg/dL)	Albumin (g/dL)	Total protein (g/dL)	Hematocrit (%)	Total bilirubin (mg/dL)	ALT (U/L)	AST (U/L)
Case 1																		
40	Male	80	23.9	16	8	12	No	27	Yes	4	122	0.65	2.17	4.87	28.6	27.7	70	88
										5	123	0.63	2.09	4.73	29.2	28.3	82	100
										6	114	0.82	2.28	4.64	27.3	23.3	79	106
Case 2																		
76	Female	62	24.8	28	5	9	Yes	68	No	5	118	0.22	3.10	4.71	31.1	0.74	35	33
										6	107	0.33	2.81	4.31	30.0	0.68	25	24
Case 3																		
67	Male	75	25.4	24	10	8	No	27	Yes	14	72	1.12	3.35	5.64	25.7	23.8	64	88

ALT alanine transaminase; *APACHE* acute physiology, and chronic health evaluation; *AST* aspartate aminotransferase; *BMI* body mass index; *BW* body weight; *eGFR* estimated glomerular filtration rate; *ICU* intensive care unit; *LOS* length of stay; *MRC-ICU* medication regimen complexity-intensive care unit; *MV* mechanical ventilation; *SOFA* sepsis-related organic failure assessment; *TPE* therapeutic plasma exchange

Table 2 Plasma exchange parameters and drug concentration measurements in patients with TPE

Drug	F_b (%) [9]	V_d (liters/kg) [9]	$t_{1/2}$ (h) [9]	Case no	Day of drug therapy	Day of the TPE session	Removed volume (mL)	Duration (min)	Time from infusion end to TPE (h)	Pre-TPE C_{Drug} (mg/L)	Post-TPE C_{Drug} (mg/L)	Plasmapheresate C_{Drug} (mg/L)	Q_{TPE} (mg)	Q_{TPE}/ dose (%)
Meropenem	2	0.35	1	1	Day 5	4	4322	130	3.2	12.0	5.4	10.0	43.22	2.16
					Day 7	5	4293	120	5.3	5.6	6.0	10.0	42.93	2.15
					Day 8	6	4455	113	2.8	6.0	2.0	8.0	35.64	1.78
				2	Day 3	5	3382	90	2.5	12.2	5.6	n/a	n/a	n/a
					Day 5	6	3381	90	5.3	6.3	3.2	8.1	27.39	1.37
Teicoplanin	60–90	0.5–1.2	4–11	1	Day 5	4	4322	130	17.2	15.0	12.0	12.0	51.86	5.4
					Day 7	5	4293	120	19.3	4.7	6.3	5.6	24.04	2.5
					Day + 1*	6	4455	113	25.8	2.2	3.2	2.7	12.03	1.25
Voriconazole	60	4.6	12	1	Day 5	4	4322	130	0.3	22.0	12.3	10.5	45.38	14.18
					Day 7	5	4293	120	2.3	14.4	11.6	6.9	29.62	9.26
					Day 8	6	4455	113	7.8	11.8	16.9	11.6	51.68	16.15
Amikacin	5 <	0.22–0.5	2	3	Day 4	14	3315	90	21.6	7.7	0.0	7.1	23.53	2.09

C_{Drug} drug concentration; F_b plasma protein-binding affinity; Q_{TPE} amount of drug removed; *TPE* therapeutic plasma exchange; V_d volume of distribution

*The last teicoplanin dose was administered on day 7 of antimicrobial therapy (5th TPE session day). Due to its presence in plasma, teicoplanin level measurements were performed during the 6th TPE session

meropenem for neutropenic fever, teicoplanin for gram-positive pathogens due to epididymitis, and voriconazole for *Aspergillus fumigatus*. Maintenance doses were meropenem 2 g q8h as a prolonged infusion, teicoplanin 12 mg/kg q24h (after a loading dose of 12 mg/kg q12h for 3 doses), and voriconazole 4 mg/kg q12h (after a loading dose of 6 mg/kg q12h). The Q_{TPE} ranged from 35.64 to 43.22 mg for meropenem, 12.03 mg to 51.86 mg for teicoplanin, and 29.62 mg to 51.68 mg for voriconazole after the 4th, 5th and 6th TPE sessions. Antifungal therapy was changed to liposomal amphotericin B due to supratherapeutic voriconazole levels. The patient's clinical improvement was unaffected by the amount of antimicrobial eliminated, allowing the patient to complete his treatment.

A 76-year-old female patient with myasthenia gravis, metastatic carcinoma, and hypertension was admitted to the medical ICU for a myasthenic crisis (Case 2). She underwent 7 TPE sessions with albumin. The patient was treated with meropenem for hospital-acquired pneumonia caused by extended-spectrum β-lactamase-producing *Klebsiella pneumonia*. Meropenem was administered at a maintenance dose of 2 g q8h as a prolonged infusion (3-h) after the loading dose. The Q_{TPE} for meropenem was 27.39 mg after the 6th TPE session. Based on the culture results, antibacterial therapy was escalated to trimethoprim-sulfamethoxazole on day 5 of meropenem treatment.

A 67-year-old male patient with non-Hodgkin's lymphoma, pancreatic adenocarcinoma, and type 2 diabetes was admitted to the surgical ICU for neurological deterioration (Case 3). He underwent 15 TPE sessions with FFP to treat hyperbilirubinemia associated with hepatic encephalopathy. Amikacin was prescribed at a dose of 15 mg/kg q24h for the treatment of å sepsis associated with intra-abdominal infection. The Q_{TPE} for amikacin was 23.53 mg after the 14th TPE session. The patient passed away due to cardiac arrest while on amikacin therapy.

Detailed clinical data and TPE parameters for the three patients are presented in Tables 1 and 2.

In the present study, we assumed adequate time for tissue distribution of meropenem, teicoplanin and amikacin based on their elimination half-lives. For meropenem, this resulted in a Q_{TPE} range of 27.39 mg to 43.22 mg, with 1.37% to 2.16% after a single administered dose. The Q_{TPE} for meropenem in our study is lower than that reported in a previous study of patients receiving a 1 g dose of meropenem by 1-h infusion concurrent with TPE, resulting in a mean Q_{TPE} of 142.23 ± 110.31 mg [6]. These differences may be explained by differing intervals for drug distribution. Similarly, the Q_{TPE} of teicoplanin in the first patient ranged from 12.03 to 51.86 mg, with

1.25% to 5.4% of the single administered dose removed. Again, this is substantially lower compared to a previous study 12 patients who received intravenous teicoplanin at a dose of 6 mg/kg immediately prior to TPE, resulting in a mean Q_{TPE} of 74.6 ± 34.6 mg [7].

The amount of voriconazole removed in the plasmapheresate ranged from 29.62 to 51.68 mg, with 9.26% to 16.15% of the single administered dose removed. In a case study where TPE was initiated following a 1-h voriconazole infusion, the calculated Q_{TPE} was approximately 10.1 mg [8]. The voriconazole plasma level in our first patient was 18.1 mg/L on the non-TPE day between the 4th and 5th TPE sessions. There were no drug interactions with voriconazole. Plasma voriconazole levels were unexpectedly high for unknown reasons. These high levels may have affected our measurements.

The current report is also the first to report on the effect of TPE on amikacin, showing a Q_{TPE} of 23.53 mg, with 2.09% of the single administered dose removed. Low protein-binding affinity and a 21.6-h interval from the end of infusion to TPE may be related to measurements.

Ibrahim et al. [3] propose that the most reliable method to assess the effect of TPE on drug disposition is to measure the amount of drug removed in the plasmapheresate. In the presented cases, the amount of drug removed via TPE was not significant in comparison to the administered single dose, as shown in Table 2. Therefore, it can be stated that all antimicrobials in our study were minimally affected via TPE.

In conclusion, the results of this real-world study emphasize that attention should be paid to the timing of drug distribution, allowing sufficient time between drug administration and TPE to minimize antimicrobial elimination. In addition, therapeutic drug monitoring may help to improve antimicrobial management during TPE in critically ill patients.

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Author contributions
U.B. was a major contributor in conceptualization, methodology, data analysis, and writing-original draft. E.K. contributed to conceptualization, methodology, and writing-review&editing. E.K.K., O.I.O., M.A., A.T., K.Y., and K.D. contributed to resources and writing-review&editing. All authors read and approved the final manuscript.

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Declarations

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Ethical approval was not required. Informed consent was obtained from the patients.

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The authors declare no competing interests.

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