Ceftolozane Pharmacokinetics in a Septic Critically Ill Patient under Different Extracorporeal Replacement Therapies

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Ceftolozane-tazobactam (C/T), a novel fifth-generation cephalosporin/ β -lactamase inhibitor combination active against multidrug-resistant (MDR) *Pseudomonas aeruginosa*, is currently approved by the U.S. Food and Drug Administration (FDA) to treat complicated intra-abdominal and urinary tract infections at the label dosage (1 g/0.5 g/8 h intravenously), as well as nosocomial and ventilator-associated pneumonia at a high dose (2 g/1 g/8 h). In the era of MDR and with critical patients underrepresented in pivotal studies, off-label use of antimicrobials offers good clinical responses (1). Ceftolozane pharmacokinetics (C-PK) have been assessed under renal support with continuous venovenous hemodiafiltration (CVVHDF) (2–4), but the effect of molecular-adsorbent-recirculating-system (MARS; Baxter, Deerfield, IL) since liver support on C-PK has yet to be documented. This circuit removes both protein-bound and water-soluble molecules through a large-pore hemodialyzer, and little is known about the impact of potentially enhanced antibiotic clearance under this device on patient outcome.

A 37-year-old woman diagnosed with acute lymphoblastic leukemia was admitted to the medical intensive care unit with septic shock secondary to *P. aeruginosa* permanent catheter-related bacteremia. After initial improvement, the patient experienced hemodynamic and renal deterioration. Abdominal computed tomographic imaging revealed typhilitis. Empiric antimicrobials were changed to high-dose 3-h-infusion C/T, metronidazole, linezolid, and anidulafungin. CVVHDF was initiated using an oXiris filter (Baxter, Meyzieu, France), a polyethylenimine and unfractionated heparin-coated AN69 membrane with a 1.5-m² surface area, and blood flow, replacement, and dialysate fluid rates of 180 ml/min, 1600 ml/h, and 500 ml/h, respectively. Shortly afterward, the liver function declined, with refractory encephalopathy and hyperbilirubinemia. An 8-h MARS session was added, and high-dose 3 h-infusion C/T was maintained without any related adverse effects. Anidulafungin-resistant *Candida tropicalis* fungemia was documented. Unfortunately, the patient remained refractory to treatment and died after life support withdrawal.

Serum ceftolozane concentrations (SCC) were measured by high-performance liquid chromatography after drug infusion and immediately before the next scheduled dose under three scenarios (Fig. 1). The following pharmacokinetic (PK) parameters were determined by noncompartmental analysis during MARS and

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FIG 1 Simulation of ceftolozane plasma concentrations over time under three scenarios: (i) CVVHDF, (ii) 8-h MARS+CVVHDF session, and (iii) after withdrawal of both. Circles represent experimental plasma concentrations. MIC, the ceftolozane minimum inhibitory concentration for *P. aeruginosa* according to the European Committee on Antimicrobial Susceptibility Testing breakpoint.

CVVHDF: clearance, 3.39 liters/h; volume of distribution, 24.0 liters; elimination half-life, 5.3 h; AUC_{0-8h} , 589 mg/h/liter (calculated by log-linear trapezoidal rule); and extraction ratio, $15.3 \pm 6.9\%$. SCC are shown in Table 1. Our findings are similar to results obtained in a previous study evaluating elimination under MARS of extended infusion of piperacillin-tazobactam, with a comparable 20 to 30% protein binding profile as C/T: similar concentrations under a 7-h session, with $>50\%$ existing drug in the access line present in the return one, and surpassing the desired MIC for Gram-negative infection treatment (5). Concerning renal support, the ceftolozane C_{min} was slightly higher than that reported by Oliver et al. (51 versus 31 mg/liter) (4), both with similar filtration flow (2 liters/h) and extended infusion, but with higher C/T dosage (2 g/1 g/8 h). However, SCC were comparable to previous reports with the same high dose and lower time 1 h-infusion ($C_{min} = 50$ to 56 mg/liter) despite a higher flow rate of 3 liters/h (2, 3). The SCC far exceeded the recommended concentration of four times the *P. aeruginosa* susceptibility breakpoint (4 $\mu\text{g/ml}$) throughout the dosing interval in all three scenarios (Fig. 1), suggesting that high-dose extended infusion of C/T is unnecessary for susceptible strains. The limitations of the present study include omitted tazobactam concentration measurement and different flow rates used with extracorporeal devices.

In conclusion, we confirm already-known results on C-PK under renal replacement therapy, but to our knowledge this is the first published report on C-PK in a critically ill patient during MARS therapy, with high-dosage 3-h-infusion C/T maintaining safe SCC even for MDR *P. aeruginosa*. Additional PK studies are required to validate these findings.

TABLE 1 Serum ceftolozane concentrations in pre- and postcombination systems (i.e., MARS and CVVHDF)^a

Sampling time	SCC plasma sample (mg/liter)	
	Before MARS+CVVHDF	After MARS+CVVHDF
Predose	55.0	—
Postdose		
3.2 h	112.7	—
5.0 h	90.5	67.3
6.0 h	66.5	57.9
7.0 h	59.0	51.8
8.0 h	51.44	47.1

^aPlasma samples were obtained after the fourth C/T dose of 2 g/1 g administered as an intravenous 3-h infusion. —, not calculated because the combined systems were initiated 3.5 h after the fourth dose.

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