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CASE REPORT

Pharmacokinetic Changes of Ceftazidime–Avibactam with Veno-Arterial Extracorporeal Membrane Oxygenation in a Critically Ill Patient with Severe Renal Impairment: A Case Report

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Abstract: Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is an advanced life support therapy, but evidence regarding its impact on the pharmacokinetic (PK) characteristics of ceftazidime–avibactam (CAZ-AVI) is still limited. This study reports a 47-year-old man who developed severe renal impairment during VA-ECMO support following cardiac arrest and was treated with CAZ-AVI for pneumonia caused by carbapenem-resistant *Klebsiella pneumoniae* (CRKP). Therapeutic drug monitoring (TDM) was performed before and after VA-ECMO weaning. PK analysis showed that, compared to the period with VA-ECMO support, the clearances (CLs) of CAZ and AVI increased after VA-ECMO weaning, resulting in 31.1% and 34.5% decreases in systemic exposure to CAZ and AVI, respectively. Despite these reductions, trough concentrations remained above the PK/PD targets of 100% fT > 20.0 mg/L for CAZ and 100% fT > 4.0 mg/L for AVI, respectively. Unfortunately, the patient's renal function progressively worsened, complicated by hyperkalemia, and he experienced a second cardiac arrest on day 5 after ECMO weaning, resulting in death. These findings suggest that in patients undergoing prolonged VA-ECMO support, the exposure of CAZ-AVI may decline after ECMO weaning, underscoring the need for reassessment of dosing strategies.

Keywords: Ceftazidime, Avibactam, Pharmacokinetics, VA-ECMO

Introduction

Ceftazidime-avibactam (CAZ-AVI) is a novel beta-lactam/beta-lactamase inhibitor combination with valuable activity against carbapenemase-resistant (CR) Enterobacterales and/or multidrug-resistant (MDR) *Pseudomonas aeruginosa*.[1,2] Nowadays, CAZ-AVI has been approved for the treatment of complicated intra-abdominal infections (cIAI), complicated urinary tract infections (cUTI), hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) in many countries.[1,2] Multiple Phase III non-inferiority trials using carbapenems as comparators have demonstrated the clinical efficacy of CAZ-AVI in treating cIAI, cUTI, HAP and VAP in adults, establishing it as a novel therapeutic option for these serious infections.[1,2]

The pharmacokinetic/pharmacodynamic (PK/PD) targets for CAZ and AVI are the percentage of the dosing interval during which free drug concentration remains above the minimum inhibitory concentration (%fT>MIC) and above a certain threshold concentration (%fT>CT), respectively.[3–7] In critically ill patients, the recommended PK/PD targets are 100%fT>4–5×MIC for CAZ and 100%fT>CT for AVI.[3–7] Failure to achieve PK/PD targets may lead to treatment failure and the development of bacterial resistance, although the reported likelihood of resistance emergence is currently low. In addition, excessively high free drug concentrations may increase the risk of adverse events, such as central nervous

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system toxicity and renal impairment.[1] To optimize clinical outcomes and prevent further resistance development, the use of CAZ-AVI should be strictly guided by susceptibility testing and antimicrobial stewardship principles. In clinic, the standard adult dosage is 2 g CAZ/0.5 g AVI administered via 2-hour intravenous infusion every 8 hours (q8h), with dose reductions required in patients with renal impairment.[8,9]

Extracorporeal membrane oxygenation (ECMO) is an advanced life support therapy that temporarily replaces the function of the heart and lungs in critically ill patients with cardiopulmonary failure, providing continuous oxygenation and hemodynamic support through an external circuit.[10] Clinically, two primary modes are utilized in clinical practice: veno-venous (VV) ECMO, which primarily supports respiratory function, and veno-arterial (VA) ECMO, which provides both respiratory and hemodynamic support.[10] Despite its life-saving role, ECMO is associated with a high burden of complications and organ dysfunction. Potentially life-threatening bleeding events are the most frequent complication during ECMO,[11] while infections related to prolonged intensive care unit stay and vascular cannulation are also common.[12] Importantly, ECMO influences drug pharmacokinetics through multiple mechanisms, including increased apparent volume of distribution (Vd), sequestration of drugs within the extracorporeal circuit, and altered apparent clearance (CL) secondary to impaired organ function.[13] Although some studies have found no significant differences in pharmacokinetics of certain β-lactam/β-lactamase inhibitors between ECMO and non-ECMO patients,[14,15] some studies reported that ECMO increased the Vd of Cefepime, potentially leading to suboptimal PK/PD target attainment and treatment failure.[16–18]

Like most β-lactam/β-lactamase inhibitors, both CAZ and AVI are highly hydrophilic molecules with LogP values below zero, reflecting limited Vd that may be affected by ECMO.[17–19] However, few studies have reported the effect of ECMO on the pharmacokinetics of CAZ-AVI, especially the PK changes occurring before and after ECMO weaning. A recent report of the impact of ECMO on CAZ-AVI only examined whether patients using CAZ-AVI achieved the target drug concentrations, lacking a control group of patients who did not use ECMO.[20] Additionally, only a single blood sample was collected from each patient, making it impossible to reflect detailed PK parameters.[20] Here, this study characterizes the PK changes of intravenous CAZ-AVI before and after VA-ECMO weaning in a patient who underwent 12 days of VA-ECMO support following cardiac arrest.

Case Presentation

A 47-year-old man was admitted to the emergency department following cardiac arrest. After 10 minutes of cardiopulmonary resuscitation (CPR) without restoration of spontaneous circulation, VA-ECMO life support was initiated, resulting in restoration of spontaneous cardiac activity. The patient had a history of hypertension. Coronary angiography revealed acute coronary syndrome, and he was simultaneously diagnosed with acute kidney injury, aspiration pneumonia, and hepatic dysfunction. The patient was managed with intensive care, analgesia and sedation, and endotracheal intubation. A drug-eluting coronary stent was implanted, and empirical antimicrobial therapy was initiated, along with other necessary supportive treatments.

Approximately one week later, the patient showed elevated infection markers (white blood cell count 16.3 × 10^9/L, C-reactive protein 126.1 mg/L, and procalcitonin 7.6 ng/mL), developed fever, and sputum culture revealed infection with carbapenem-resistant *Klebsiella pneumoniae* (CRKP). Given the markedly reduced renal function (serum creatinine: 499.9 μmol/L; estimated glomerular filtration rate (eGFR): 11.06 mL/min/1.73m^2), a renal-adjusted dose of 1 g CAZ/0.25 g AVI was administered every 8 hours via a peripherally inserted central catheter (PICC) using a micro-infusion pump over 2 hours for anti-infective therapy. After 12 days of VA-ECMO support (including 5 days of CAZ-AVI therapy), the patient's cardiac function improved, and hemodynamics gradually stabilized, prompting consideration of VA-ECMO weaning. At the time of weaning, the VA-ECMO rotational speed was 2400 rpm. Pre-weaning laboratory results showed serum creatinine of 352.3 μmol/L, eGFR of 16.88 mL/min/1.73m^2, and serum albumin of 36.6 g/L. Post-weaning values were comparable, with serum creatinine of 365.2 μmol/L, eGFR of 16.16 mL/min/1.73m^2, and serum albumin of 36.7 g/L. The CAZ-AVI dosing regimen remained unchanged before and after VA-ECMO weaning. A comprehensive timeline of events including pre- and post-weaning laboratory results were shown in Table 1. Blood samples for therapeutic drug monitoring (TDM) were obtained at pre-infusion and 1, 2, 4, 6, and 8 h post-infusion within a single dosing interval, specifically during the third-to-last dosing interval prior to VA-ECMO weaning and the first dosing interval following weaning, respectively. The schedule of treatment and sampling is shown in Figure 1.

Table 1 A Comprehensive Timeline of Events Including Pre- and Post-Weaning Laboratory Results

Inspection Items	Day 0	Day 7	Day 12	Day 13	Day 18	Reference Values
White blood cell count (×10^9/L)	16.65	16.3	15.24	17.44	33.75	3.50–9.50
C-reactive protein (mg/L)	10.7	126.1	100.7	113.9	98.4	0.0–10.0
Procalcitonin (ng/mL)	-	7.6	6.8	9.2	10	0.00–0.25
Serum creatinine (μmol/L)	173.6	499.9	352.3	365.2	517.7	57.0–97.0
eGFR (mL/min/1.73 m^2)	39.72	11.06	16.88	16.16	10.60	-
Serum albumin (g/L)	35.3	39.0	36.6	36.7	30.1	40.0–55.0
Body temperature (°C)	35.7–37.8	35.7–37.8	36.4–37.2	36.5–37.3	37.1–37.2	36.0–37.5
Alanine transaminase (IU/L)	328	29	25	37	196	9-50
Aspartate aminotransferase (IU/L)	1065	57	-	-	543	15-40
Total bilirubin (umol/L)	13.6	15.0	15.4	16.4	22.0	3.0–22.0
Fluid balance (mL/day)	1237	1696	−2051	−79	3157	-
VA-ECMO rotational speed (rpm)	3400	3700	2400	2400-0	-	-
Clinical events	Cardiac arrest, VA-ECMO initiated	CAZ/AVI (1 g/0.25 g) initiated	Blood sampling	VA-ECMO weaning, Blood sampling	Death	-

Abbreviations: VA-ECMO, veno-arterial extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; CAZ-AVI, ceftazidime–avibactam.

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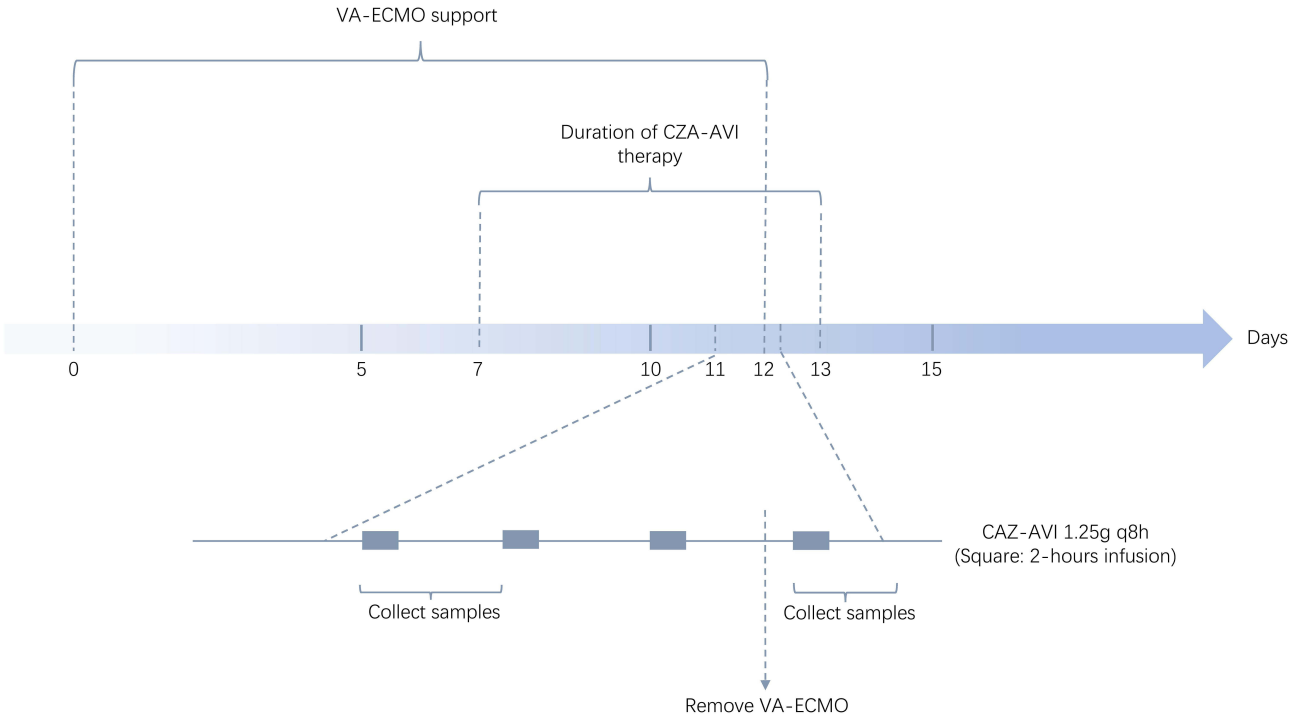

Figure 1 Schematic diagram of the timing of treatment and sampling.

Plasma concentrations of CAZ and AVI were simultaneously quantified by a validated high performance liquid chromatography and tandem mass spectrometry method (HPLC-MS/MS) on AB4500MD (AB Sciex, USA). 100 μL plasma was spiked with internal standard (IS, cefepime for CAZ, sulbactam for AVI), and methanol was added to precipitate proteins. Chromatography was reverse phase with a Supelco Discovery HS-C18 (50 mm × 4.6 mm, 3 μm) column (Merck Drugs & Biotechnology, Germany). For gradient elution, the mobile phase was composed of (A) 0.1% formic acid in water and (B) 0.1% formic acid in methanol. Ion-ization was by positive and negative mode electrospray. Mass spectrometric detection was performed using electrospray ionization in both positive and negative modes: CAZ and its IS were monitored in positive ion mode with mass transitions m/z 546.9→468.0 and 481.3→223.1, respectively, while AVI and its IS were detected in negative ion mode with mass transitions m/z 264.1→96.0 and 232.7→141.0, respectively. The method was linear from 0.2–80 μg/mL for both analytes. The validation results demonstrated that the method exhibited satisfactory precision and accuracy across four concentration levels, with a coefficient of variation below 12.0% and accuracy ranging from 87.7% to 109.8%. Test samples were assayed in batches alongside matrix-matched calibrators and quality controls, and results were subject to batch acceptance criteria. PK parameters were estimated by non-compartmental analysis using R software (v4.4.1).

Unfortunately, the patient's renal function progressively worsened, complicated by hyperkalemia, and he experienced a second cardiac arrest on day 5 after ECMO weaning, resulting in death.

Results

The plasma concentration–time curves of CAZ and AVI were shown in Figure 2. The PK parameters listed in Table 2 indicate that, compared to the period with VA-ECMO support, the area under the plasma concentration–time curve extrapolated to infinity ($AUC_{0-\infty}$) of CAZ and AVI decreased by 31.1% and 34.5%, respectively, after VA-ECMO weaning. Similarly, the maximum concentration (C_{max}), the Vd and the terminal elimination half-life ($t_{1/2}$) of CAZ and AVI also decreased after weaning. In contrast, the CL of CAZ and AVI showed an 23.5% and 27.3% increase after weaning respectively.

As reported, CAZ-AVI is a time-dependent antimicrobial agent.[3] For critically ill patients, the recommended PK/PD targets are 100%fT > 4–5×MIC for CAZ and 100%fT > target concentration (C_T) for AVI, as failure to reach this threshold may result in treatment failure and bacterial resistance.[3–7] The patient was infected with CRKP. The

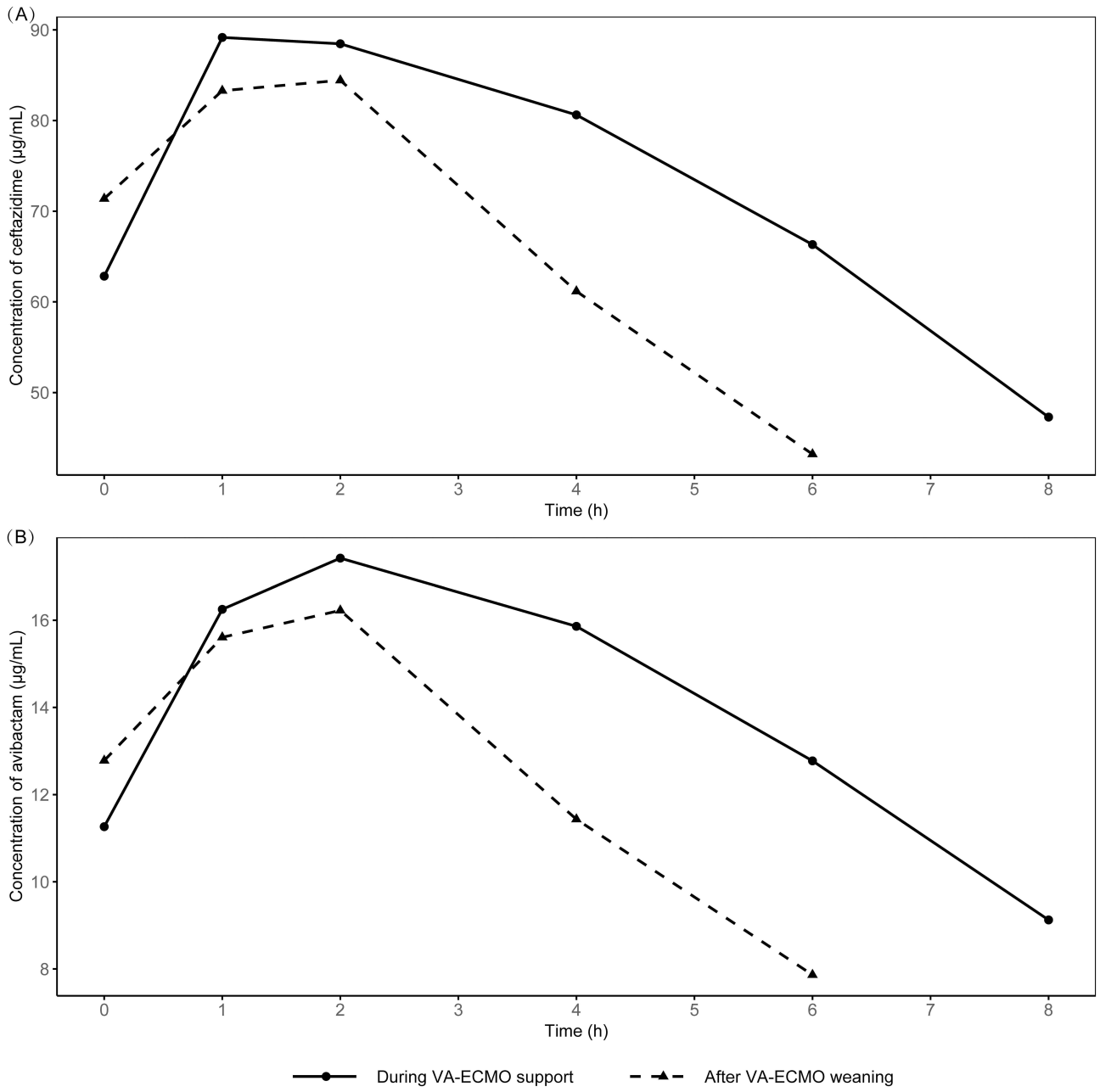

Figure 2 Plasma concentrations of (**A**) ceftazidime and (**B**) avibactam over an 8-h dosing interval in a patient during venous-arterial extracorporeal membrane oxygenation (VA-ECMO) support and after VA-ECMO weaning.

antimicrobial susceptibility of CAZ/AVI was tested by the broth microdilution method. The MIC of CAZ was approximately 4.0 mg/L with a C_T of 4.0 mg/L for AVI. Due to impaired renal function, with an eGFR of 11.06 mL/min/1.73 m^2 at the initiation of therapy, the patient was administered 1 g CAZ/0.25 g AVI via 2 h intravenous infusion q8h. Given the low plasma protein binding rates of CAZ and AVI (<10%), the free concentrations of CAZ (42.6 mg/L) and AVI (9.1 mg/L) consistently met the PK/PD target of 100% fT > 20.0 mg/L (5×MIC) for CAZ and 100% fT > 4.0 mg/L for AVI prior to VA-ECMO weaning. After VA-ECMO weaning, TDM showed that free concentrations of CAZ remained above 20.0 mg/L (5×MIC), and those of AVI remained above 4.0 mg/L during the first 6 h post-dose. Due to the lack of TDM data at 8 h post-dose, concentrations were estimated using a first-order elimination model (Equations (1) and (2)). The predicted concentrations at 8 h were 27.3 mg/L for CAZ and 5.4 mg/L for AVI, representing declines of approximately 36% and 41%, respectively, from their pre-weaning values.

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Table 2 Pharmacokinetic Characteristics of Ceftazidime and Avibactam During Venous-Arterial Extracorporeal Membrane Oxygenation Support and After Weaning, with Selected Parameters Derived by Extrapolation

Pharmacokinetic Parameter	During VA-ECMO Support		After VA-ECMO Weaning	
	Ceftazidime	Avibactam	Ceftazidime	Avibactam
C_{max} (mg/L)	89.2	17.4	84.4	16.2
$AUC_{0-\infty}$ (mg·h/L)	957.7	181.8	659.7	119.1
CL (L/h)	1.7	2.2	2.1	2.8
Vd (L)	12.6	15.8	11.9	14.8
$t_{1/2}$ (h)	5.2	5.0	4.0	3.7

Abbreviations: C_{max}, observed maximum concentration; $AUC_{0-\infty}$, area under the plasma concentration–time curve extrapolated to infinity; CL, apparent clearance; Vd, apparent volume of distribution; $t_{1/2}$, terminal elimination half-life.

$$k = CL/Vd \tag{1}$$

where k is the elimination rate constant, CL is the clearance, and V_d is the volume of distribution.

$$C = C_0 * e^{-kt} \tag{2}$$

where *C* is the concentration at time *t, C_0* is the initial concentration, and *k* is the elimination rate constant as defined in Equation (1).

Discussion

PK analysis showed that, compared to the period with VA-ECMO support, the CLs of CAZ and AVI increased after VA-ECMO weaning, resulting in 31.1% and 34.5% decreases in systemic exposure to CAZ and AVI, respectively. However, despite the decreases in systemic exposure of CAZ and AVI after VA-ECMO weaning, the trough concentration levels remained above their PK/PD targets of 100% fT > 20.0 mg/L for CAZ and 100% fT > 4.0 mg/L for AVI, respectively. This case indicates that, for pathogens with MIC of 4.0 mg/L for CAZ and C_T of 4.0 mg/L for AVI, and in a patient with an eGFR of approximately 16 mL/min/1.73 m^2, administration of 1 g CAZ/0.25 g AVI as a 2-h intravenous infusion every 8 h was appropriate both before and after VA-ECMO weaning. However, this conclusion was based on trough concentrations obtained by extrapolation, which has inherent limitations, such as assuming first-order drug elimination and stable physiological conditions (eg, renal function) during the period. In addition, the substantial reduction in CAZ and AVI exposure observed after VA-ECMO weaning warrants careful attention. In patients with different degrees of renal function, particularly those with improved renal clearance after VA-ECMO weaning, or when higher PK/PD targets are required, regimen optimization may be necessary after VA-ECMO weaning to ensure adequate antimicrobial exposure. TDM is recommended to help guide individualized dosing strategies, aiming to achieve adequate drug efficacy while reducing the potential risk of adverse effects.

VA-ECMO support may induce PK changes via multiple pathways. First, it is known that components of the ECMO circuit, such as the oxygenator and tubing, can adsorb drugs to varying degrees, particularly those with lipophilic properties or high protein-binding capacity.[21] Although both CAZ and AVI exhibit low protein binding, adsorption to the ECMO circuit cannot be ruled out. An ex vivo study demonstrated significant loss of CAZ in the ECMO circuit, confirming its adsorption.[22] Adsorption by the ECMO circuit may lead to reduced drug concentrations during the initial phase of administration. However, once the adsorption sites become saturated, the slow release of the drug from the circuit may subsequently increase overall drug exposure. As a result, prolonged ECMO support may further contribute to elevated drug exposure.

In this case, the patient underwent 13 days of VA-ECMO support and received CAZ–AVI for 6 days before VA-ECMO weaning. Blood remaining in the VA-ECMO circuit was returned to the patient depending on his volume status, but the volume of discarded blood and removal of saturated adsorption sites may contribute to a decrease in plasma drug concentrations, thereby resulting in an apparent increase in CLs of CAZ and AVI. In addition, although the blood volume lost during VA-ECMO weaning was relatively small, the patient's net fluid output between the two sampling periods increased markedly (~1.2 L), primarily due to increased urine output, which may contribute to the slight decrease in Vds of CAZ and AVI.

Existing studies have only investigated whether patients receiving ECMO can achieve PK/PD target without adjustments to the standard CAZ-AVI dosing regimen. However, to our knowledge, no study has compared the pharmacokinetics of CAZ-AVI in the same patients before and after ECMO weaning. One clinical study found that none of the patients receiving ECMO had CAZ concentrations below 32.0 mg/L, suggesting that CAZ can be safely administered without dose modification in this population.[23] But another clinical study investigating the impact of veno-venous ECMO (VV-ECMO) on CAZ-AVI found that while CAZ consistently achieved its PK/PD target, AVI did not.[20] Notably, most patients who failed to reach the PK/PD target were also undergoing continuous renal replacement therapy (CRRT), and increased renal clearance (creatinine clearance >130 mL/min) may be a more significant factor influencing the pharmacokinetics of CAZ-AVI.[20] In addition, due to the lack of a control group, the study was unable to definitively attribute the observed PK changes of CAZ and AVI to ECMO support.[20] In contrast, this present case provides additional descriptive evidence by examining the pharmacokinetics of CAZ-AVI in the same patient before and after VA-ECMO weaning. Although limited to a single case, the within-patient comparison reduces interindividual variability and helps to partially mitigate the influence of confounding factors such as infection characteristics, dosing regimen, and baseline organ function. This approach allows for a more focused evaluation of PK changes temporally associated with VA-ECMO weaning and may contribute to a better understanding of CAZ-AVI exposure during ECMO transitions in critically ill patients.

This study also has several limitations. First, it is based on a single patient, which limits the generalizability of the findings and precludes assessment of interindividual variability. Second, due to the adsorptive properties of the ECMO circuit, its impacts on the concentrations of CAZ and AVI may differ between the initial dosing phase and the steady-state phase. Further studies involving larger cohorts and population pharmacokinetic approaches are therefore warranted to better characterize CAZ-AVI pharmacokinetics during and after VA-ECMO support and to inform dosing optimization across varying degrees of renal function.

Conclusion

In summary, this case study demonstrated that weaning from prolonged VA-ECMO support was associated with PK changes of CAZ-AVI, characterized by increased CL and reduced systemic exposure after VA-ECMO weaning. Although free drug concentrations remained above the established PK/PD targets, the substantial reduction in CAZ and AVI exposure observed after weaning warrants careful attention. These findings highlight the dynamic impact of VA-ECMO weaning on CAZ–AVI pharmacokinetics and underscore the importance of reassessing drug exposure and optimizing dosing through TDM during and after VA-ECMO support.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Ethical approval to report this case was obtained from the Ethics Committee of Zhejiang Provincial People's Hospital (Approval no. 2025-143). Informed consent for sampling and publication was obtained from the patient's next of kin since the patient was under sedation.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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