Efficacy and Pharmacodynamic Target Attainment for Ceftazidime–Avibactam Off-Label Dose Regimens in Patients with Continuous or Intermittent Venovenous Hemodialysis: Two Case Reports

Xiao-Shan Zhang · Yu-Zhen Wang · Da-Wei Shi · Fang-Min Xu · Jun-Hui Yu · Jie Chen · Guan-Yang Lin · Chun-Hong Zhang · Xu-Ben Yu · Cong-Rong Tang

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ABSTRACT

Limited data are available for ceftazidime–avibactam (CZA) dosing in patients receiving renal replacement therapy, especially the data on the dosing in patients receiving intermittent hemodialysis (IHD). In this report, we firstly described a case in which CZA was administered as 2.5 g after each time of IHD, and a dose of 1.25 g was added on the 48th-hour for the 72-h interdialytic interval. Plasma concentrations of CZA measured at different time indicated that > 50% of administered ceftazidime and avibactam were removed during the 4-h hemodialysis. In addition, we described another case on continuous venovenous hemodialysis (CVVHD), in which CZA was administered as 2.5 g q12h in 2-h infusions. The dose regimen for these two cases could achieve trough concentration of ceftazidime higher than fourfold of the MIC and trough concentration of avibactam higher than the threshold of 1 μg/mL during the treatment, and exert efficient antimicrobial effect.

Keywords: Ceftazidime–avibactam; Dosing regimen; Intermittent hemodialysis; Continuous venovenous hemodialysis; Plasma concentration
**Key Summary Points**

The dose recommendation and validation of ceftazidime–avibactam (CZA) is limited in patients receiving renal replacement therapy, especially there is no data in intermittent hemodialysis (IHD) patients. This is the first case report on exposure of CZA in IHD patient, in which CZA was administered as 2.5 g (2 g ceftazidime and 0.5 g avibactam) after each time of IHD, and a dose of 1.25 g was added on the 48th-hour for 72-h interdialytic interval. The dose regimen in this case could achieve the joint pharmacokinetic/pharmacodynamic (PK/PD) targets for CZA and alleviate the peritoneal dialysis-associated peritonitis caused by *Klebsiella pneumoniae*.

We reported another case that CZA administered as 2.5 g q12h in 2-h infusions could adequately achieve the joint PK/PD targets in the patient on continuous venovenous hemodialysis (CVVHD), and alleviated the pneumonia caused by carbapenem-resistant *Klebsiella pneumoniae*.

**INTRODUCTION**

Ceftazidime–avibactam (CZA) is a novel β-lactam/β-lactamase inhibitor combination (ceftazidime: avibactam = 4:1) for the treatment of serious infections caused by resistant Gram-negative pathogens [1, 2]. In patients with renal insufficiency, dosage adjustments based on renal function are needed according to the label approved by FDA [2]. However, the dose regimen for patients with renal replacement therapy is absent in the label inserts.

Research data for CZA dosing in patients undergoing renal replacement therapy are limited to two cases, and both are focused on continuous renal replacement therapy (CRRT) [3, 4]. One of the cases reported by Wenzler et al. [3] who used the dose regimen of 1.25 g q8h for a patient with continuous venovenous hemofiltration (CVVHF), while another case reported by Soukup et al. [4] who used a more aggressive dose regimen of 2.5 g q8h for a patient with continuous venovenous hemodialfiltration (CVVHDF). Both two cases could achieve the joint pharmacokinetic/pharmacodynamic (PK/PD) target of CZA throughout the treatment. However, the case reported by Wenzler et al. [3] had persistent bacteremia 5 days after CZA initiation and was eventually succumbed to the infection. Another case reported by Soukup et al. [4] had the trough concentration of ceftazidime as high as 70 μg/mL. In addition, although the label of CZA recommend the dose of 940 mg (ceftazidime 750 mg and avibactam 190 mg) every 48 h given post-hemodialysis for patients with end-stage renal disease (ESRD) on intermittent hemodialysis (IHD) [2], the validation of the recommended dosage by the label inserts has not been reported.

Despite the growing use of RRT in critically ill patient, the lack of PK/PD data during RRT nowadays limits evidence-based dosing recommendations for novel antibiotics. It has been reported that CRRT was an independent risk factor for ceftazidime–avibactam treatment failures and development of resistance with carbapenem-resistant Enterobacteriaceae infections [5]. In general, real-world data are needed to guide appropriate dosing in patients with renal replacement therapy. Here, we reported two clinical cases receiving CZA treatment, (1) a patient with peritoneal dialysis-associated peritonitis on IHD and (2) a patient with pulmonary infection on continuous venovenous hemodialysis (CVVHHD).

**METHODS**

Serial blood samples were collected from peripheral vein into a red-top collection tube which containing no preservatives or anticoagulants, and were immediately sent for analysis after sampling. In case one, trough concentration was collected 30 min before the initiation of CZA dosing, while peak concentration was collected 30 min after finishing CZA infusion.
Meanwhile, the concentrations 30 min before and after IHD were collected. In case two, serial blood samples were collected before the CZA infusion and 3, 5, 12 h after starting 2-h CZA infusion. The quantification of concentration of ceftazidime and avibactam was performed using a validated high performance liquid chromatography–tandem mass spectrometry (LC–MS/MS) assay [6]. The calibration ranges for ceftazidime and avibactam were 0.1–200 µg/mL and 0.1–100 µg/mL respectively. The method validations including calibration curve, selectivity, accuracy, precision, matrix effect, recovery, and stability met the requirement of FDA principles. The pharmacokinetics parameters for both ceftazidime and avibactam were estimated using a noncompartmental analysis (WinNonlin Version 7.0). This study was conducted following the legal requirements and the Declaration of Helsinki and its subsequent amendments. The informed consent for publication of the clinical data were obtained. The basic characteristics of cases were listed in Table 1.

CASE ONE

A 75-year-old female patient was diagnosed with ESRD and started on continuous ambulatory peritoneal dialysis (CAPD, 2 L dialysate × 4 cycles with 10–12 h dwell time at night) since 6 years ago. She was presented with 2 days of intermittent abdominal pain accompanied by fever and diarrhea, while the peritoneal dialysis (PD) fluid was cloudy when performing CAPD at home. Peritoneal dialysis-associated peritonitis was then diagnosed. The patient was initially treated with cefazoline (0.5 g added into 2 L dialysate i.p. qid) contaminant with amikacin (0.02 g added into 2 L dialysate i.p. qid).

On day 3, the PD fluid culture reported Klebsiella pneumoniae with positive extended-spectrum β-lactamase (Table 2), the antimicrobial treatment was then changed to imipenem and cilastatin sodium (0.5 g added into 2 L dialysate i.p. qid) and levofloxacin (0.5 g po qod). Although the fever and diarrhea were alleviated, the patient was still suffering abdominal pain. On day 7, the blood culture collected at onset of infections reported negative inbacteria growth. On day 14, considering the infection might be derived from the PD catheter, the PD catheter was then removed, and the patient was started on IHD therapy. The schedule of the patient receiving 4-h IHD was on Monday, Wednesday, and Friday per week. Imipenem and cilastatin sodium was

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case one</th>
<th>Case two</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>75</td>
<td>82</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Dose regimen</td>
<td>2.5 g administered after each time of IHD, while an additional dose of 1.25 g was added on the 48th-hour for the 72-h interdialytic interval</td>
<td>2.5 g q12h</td>
</tr>
<tr>
<td>ceftazidime</td>
<td></td>
<td></td>
</tr>
<tr>
<td>avibactam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR (mL/min)</td>
<td>12.1</td>
<td>18.3</td>
</tr>
<tr>
<td>Isolated pathogen</td>
<td>Klebsiella pneumoniae</td>
<td>Klebsiella pneumoniae</td>
</tr>
<tr>
<td>MIC (µg/mL)</td>
<td>2.0</td>
<td>4.0</td>
</tr>
<tr>
<td>for CZA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection type</td>
<td>Abdominal infection</td>
<td>Pulmonary infection</td>
</tr>
<tr>
<td>RRT mode</td>
<td>Intermittent hemodialysis</td>
<td>Continuous venovenous hemodialysis</td>
</tr>
<tr>
<td>Blood flow rate:</td>
<td>260 mL/min; dialysate flow rate: 500 mL/min</td>
<td>Blood flow rate: 200 mL/min; dialysate flow: 2000 mL/h</td>
</tr>
<tr>
<td>Antimicrobial combination</td>
<td>Metronidazole</td>
<td>Linezolid</td>
</tr>
</tbody>
</table>
administered intravenously of 1 g every 12 h. On day 16, the patient developed a high fever with a temperature higher than 39 °C, and the abdominal pain was not alleviated. Laboratory tests showed a serum procalcitonin (PCT) of 1.26 ng/mL and a C-reactive protein (CRP) of 90 mg/L. In addition, the culture of PD fluid collected before removing the catheter still reported the Klebsiella pneumoniae, and the reported results were same as before. While the cultures of blood samples collected on day 10 reported no bacteria growth. On day 18 (Friday), the antimicrobial treatment was changed to CZA contaminant with metronidazole. The dose regimen of CZA was 2.5 g administered after each time of IHD (Gambro AK 96, blood flow of 260 mL/min, and dialysate flow of 500 mL/min), while a second dose of 1.25 g was added on Sunday per week. The concentration of ceftazidime and avibactam was monitored between day 27 (Sunday) and day 30 (Wednesday) (Fig. 1). After being treated with CZA for 5 days, the patient’s abdominal pain and fever were gradually alleviated. No adverse events of CZA were observed during the CZA treatment.

**CASE TWO**

An 82-year-old male patient with a history of resection of malignant thyroid tumor was diagnosed with neck metastasis and laryngeal stenosis. The total laryngectomy was performed, and the patient was then discharged with normal body temperature. However, a few

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Case one</th>
<th>Interpretation</th>
<th>Case two</th>
<th>Interpretation</th>
<th>Thresholds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>≤ 2.0</td>
<td>S</td>
<td>≥ 64.0</td>
<td>R</td>
<td>≤ 16, ≥ 64</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>≥ 32</td>
<td>R</td>
<td>≥ 32</td>
<td>R</td>
<td>≤ 8, ≥ 32</td>
</tr>
<tr>
<td>Ampicillin–sulbactam</td>
<td>≥ 32</td>
<td>R</td>
<td>≥ 32.0</td>
<td>R</td>
<td>≤ 8, ≥ 32</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>≥ 64</td>
<td>R</td>
<td>≥ 64.0</td>
<td>R</td>
<td>≤ 2, ≥ 8</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>≥ 64</td>
<td>R</td>
<td>≥ 64.0</td>
<td>R</td>
<td>≤ 2, ≥ 8</td>
</tr>
<tr>
<td>Cefotetan</td>
<td>≤ 4</td>
<td>S</td>
<td>≥ 64.0</td>
<td>R</td>
<td>≤ 16, ≥ 64</td>
</tr>
<tr>
<td>Cefepime</td>
<td>2.0</td>
<td>S</td>
<td>≥ 64.0</td>
<td>R</td>
<td>≤ 2, ≥ 16</td>
</tr>
<tr>
<td>Cefazidime–avibactam</td>
<td>2.0</td>
<td>S</td>
<td>4</td>
<td>S</td>
<td>≤ 8, ≥ 16</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>≥ 4.0</td>
<td>R</td>
<td>≥ 4.0</td>
<td>R</td>
<td>≤ 0.25, ≥ 4</td>
</tr>
<tr>
<td>Colistin</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>S</td>
<td>≤ 0, ≥ 4</td>
</tr>
<tr>
<td><strong>ESBL detection</strong></td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ertapenem</td>
<td>≤ 0.5</td>
<td>S</td>
<td>≥ 8.0</td>
<td>R</td>
<td>≤ 0.5, ≥ 2</td>
</tr>
<tr>
<td>Imipenem</td>
<td>≤ 1.0</td>
<td>S</td>
<td>≥ 16.0</td>
<td>R</td>
<td>≤ 1, ≥ 4</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>1.0</td>
<td>I</td>
<td>≥ 8.0</td>
<td>R</td>
<td>≤ 0.5, ≥ 2</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>≤ 4</td>
<td>S</td>
<td>≥ 128.0</td>
<td>R</td>
<td>≤ 16, ≥ 128</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>8</td>
<td>I</td>
<td>≥ 16.0</td>
<td>R</td>
<td>≤ 4, ≥ 16</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>S</td>
<td>≤ 2, ≥ 8</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>≥ 320</td>
<td>R</td>
<td>≥ 320</td>
<td>R</td>
<td>≤ 40, ≥ = 80</td>
</tr>
</tbody>
</table>

MIC minimum inhibitory concentration, ESBL extended-spectrum β-lactamase
weeks later, the patient developed a high fever with temperature higher than 39 °C, accompanied with cough and dyspnea and readmitted to the local hospital. The chest computed tomography (CT) suggested pulmonary infection. Imipenem and cilastatin sodium, and vancomycin were given for initially antimicrobial therapy, but the patient was still presented of 1.25 g was added on the 48th-hour for the 72-h interdialytic interval. Solid line: Ceftazidime serum levels (µg/mL). Dashed line: Avibactam serum levels (µg/mL).
with a repeated low fever. After treating for 16 days in the local hospital, he was then transferred to our hospital for further treatment. After admission, the chest CT showed scattered inflammatory lesions and pleural effusion on both sides of the lungs. The laboratory test showed white blood cell counts (WBC) of 63.34 \times 10^9/L, CRP of 67.10 mg/L, PCT of 9.750 ng/mL. Thus, intrathoracic drainage catheter insertion was performed, imipenem and cilastatin sodium (1 g ivgtt q8h) was initially used. On the third day since his admission to our hospital, the patient developed irritability, which was considered to be caused by imipenem and cilastatin sodium, as it was the only drug in use which meets the probable grade of the Naranjo criteria for adverse drug reactions. Meanwhile, the oxygen saturation and blood pressure were decreased, the drainage of pleural fluid was cloudy, and the WBC, CRP, PCT levels were further increased. On day 4, the pleural fluid cultures and sputum cultures reported the same carbapenem-resistant Klebsiella pneumoniae (CRKP) (Table 2), the blood sample culture reported negative in bacteria growth. In the meantime, the patient developed anuric renal failure, necessitating the initiation of CRRT. The patient was started on CZA 2.5 g every 12 h in 2-h infusions while on CRRT via a Gambro AK 200 hemodialysis machine (Baxter Healthcare) with a 1.5 m² polyethersulfone membrane filter. After three doses of CZA, the plasma concentration of CZA during CVVHD throughout the entire 12-h dosing interval was continuously detected (Fig. 2), which indicated the current dose of CZA could achieve the joint PK/PD target of CZA. The pharmacokinetics parameters of ceftazidime and avibactam were presented in Table 3. On the day when plasma samples were collected, the CVVHD parameters were set as following that the blood flow was 200 mL/min, the dialysate flow was 2000 mL/h. Besides, his daily urine volume was 30 mL, indicating that the patient had little residual renal function to remove CZA. There were no interruptions in CVVHD during the 4th dose of CZA. After being treated with CZA for 5 days, the body temperature decreased to around 37 ºC, and the WBC, CRP and PCT levels were also decreased, indicating the infection was alleviated. The blood cultures collected at different timepoints during the therapy reported negative in bacteria growth. However, the patient developed coagulation disorder due to the advanced thyroid tumor, leading to disseminated intravascular coagulation and eventually died.

**DISCUSSION**

A recent report described that RRT was independently associated with CZA clinical failure [5]. However, there are no data on CZA dosing in patients on IHD, and only two recent studies reported CZA concentrations in patients on CRRT [3, 4]. To our knowledge, this was the first report on efficacy and pharmacodynamic target attainment of CZA in patients on IHD or CRRT. A joint PK/PD target for CZA is defined as simultaneous achievement of 50% time during each dosing interval that free plasma concentrations exceed CZA minimal inhibitory concentration for ceftazidime (50% fT > MIC), and 50% fT above a threshold concentration (CT) of 1 \mu g/mL for avibactam (50% fT > 1 \mu g/mL) [7]. 50% fT > MIC is an established PK/PD target for ceftazidime and other cephalosporins, and a target of 8 \mu g/mL was chosen based on global surveillance studies where a CZA MIC of < 8 \mu g/mL was observed to include ≥ 90% of clinical isolates of Enterobacteriaceae and P. aeruginosa.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ceftazidime</th>
<th>Avibactam</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (h·\mu g/mL)</td>
<td>985.15</td>
<td>496.76</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>4.99</td>
<td>9.93</td>
</tr>
<tr>
<td>Cmax (\mu g/mL)</td>
<td>147.35</td>
<td>58.23</td>
</tr>
<tr>
<td>Cmin (\mu g/mL)</td>
<td>38.46</td>
<td>29.32</td>
</tr>
<tr>
<td>CL (L/h)</td>
<td>2.03</td>
<td>1.01</td>
</tr>
<tr>
<td>Vdss (L)</td>
<td>15.25</td>
<td>14.82</td>
</tr>
</tbody>
</table>

\(AUC\) area under the concentration–time curve, \(Cmax\) maximum serum concentration, \(Cmin\) minimum serum concentration, \(CL\) clearance, \(Vdss\) volume of distribution at steady state.
Moreover, some experts supported a target of 100% fT > fourfold MIC for cef-
tazidime to maximize efficacy and minimize the potential of drug resistance in critically ill
patients [13].

In case one, considering the severity of illness of the patient, the dose of CZA used was
extrapolated from the dosing recommendations by label inserts. CZA was administered as 2.5 g
after each time of IHD, and a dose of 1.25 g was added on the day with 72-h interdialytic inter-
val. As shown in Fig. 1, > 50% of administered ceftazidime and avibactam were removed dur-
during the 4-h hemodialysis, which was in accordance with the study reported by Merdjan et al.,
who found that > 50% of the administered avibactam was removed during a 4-h hemodialysis session [14]. As shown in Fig. 1, the 48-h interval without hemodialysis
decreased nearly 50% of plasma concentration of CZA. Besides, the estimated glomerular fil-
tration rate (eGFR) was 12.1 mL/min on the day before hemodialysis, demonstrating that her
intrinsic renal function could remove part of CZA. What’s more, except for the short session
at the end of 4-h IHD, the current dose regimen could achieve the trough concentration of cef-
tazidime higher than fourfold of the MIC threshold (8 \mu g/mL) of CZA and the trough
concentration of avibactam higher than the 1 \mu g/mL threshold during the treatment. Taken
together, the dose regimen used in case one could achieve the joint PK/PD target for CZA. It
was noted that the peak concentration of CZA at third dose was much lower than that of the
fourth dose. As the blood samples collected for case one were not continuous, the peak con-
centration was defined as the concentration of blood sample collected 30 min after finishing
CZA infusion. However, the timepoint of collect-
ning peak concentration might not reach to the
timepoint of the max concentration
because of the incomplete drug distribution,
which led to lower value of peak concentration
at third dose. Thus, the possible reason for these
two different peak concentrations might be the
inter-individual difference in the time needed
for completing drug distribution. Another lim-
itation caused by the discontinuous sample
collection scheme is that it leads to incapable to
calculate PK parameters.

Limited data are available for CZA dosing
during CRRT. To our knowledge, clearance of
CZA in patients receiving CRRT has not been
evaluated in a large, prospective fashion, and
CRRT may impact antibiotic dosing through a
range of variables including volume of distrib-
ution dynamics, flow of dialysis fluid, replac-
ment fluid infusion site, and type and surface of the used membrane. Only two cases
reported the pharmacokinetics of CZA during
CRRT [3, 4]. Wenzler et al. [3] found that the
CVVHF accounted for 57.1% of total clearance
of ceftazidime and 54.3% of the total clearance
of avibactam. Both cases could achieve con-
centrations with 100% T > fourfold MIC over
the dosing interval for ceftazidime and 100%
fT > 1 \mu g/mL for avibactam in the patients on
CRRT. In our case two patient, using a non-
compartmental analysis, the pharmacokinetic
parameters of ceftazidime and avibactam were
shown in Table 3. In addition, the concentra-
tion data showed that dose regimen of 2.5 g
q12h could achieve the same PK/PD target
throughout the 12-h dosing interval. Given that
antibiotic therapy cannot be guided by a clini-
cal endpoint (measurable marker of effective-
ness) in a timely manner, achievement of PK/
PD target provides the clinician with an appro-
priate target to guide antibiotic dosing.

Despite achieving target plasma PK/PD end-
point with current dose regimens in these two
cases, the concentrations of CZA in dialysate
and post-filtration were not collected in these
two cases. Thereby, the estimations of removal
of ceftazidime and avibactam by RRT, such as
extraction ratio, clearance by RRT were not
calculated. Based on these two case reports
and the available evidence, the off-label dose regi-
mens for patient on IHD received CZA of 2.5 g
administered after each time of IHD, while a
second dose of 1.25 g was added on the 48th-
hour for the 72-h interdialytic interval, while
patient on CVVHD received CZA of 2.5 g q12h
could achieve the PK/PD target and exert effi-
cient antimicrobial effect. Additional studies are
still required to evaluate CZA PK alteration in
distinct dialysis modalities in multiple patients
to verify the optimal dosing strategy of CZA.
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Author contributions. X.B.Y., and C.H.Z. conceptualized and planned the work that led to the manuscript. Y.Z.W., F.M.X., J.H.Y. and J.C. collected and analyzed the data, X.S.Z., D.W.S. and G.Y.L. drafted the manuscript. C.R.T. drafted the revised manuscript and replenished the data. The final submitted version of manuscript was reviewed and approved by all the authors.

Disclosures. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Xiao-Shan Zhang, Yu-Zhen Wang, Da-Wei Shi, Fang-Min Xu, Jun-Hui Yu, Jie Chen, Guan-Yang Lin, Chun-Hong Zhang, Cong-Rong Tang and Xuben Yu all have nothing to disclose.

Compliance with ethics guidelines. This study was conducted following the legal requirements and the Declaration of Helsinki and its subsequent amendments. The informed consent for publication of the clinical data was obtained.

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

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