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Biliary pharmacokinetic/pharmacodynamic analysis of continuous infusion ceftazidime–avibactam in a case series of orthotopic liver transplant recipients

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Objectives: To assess the biliary pharmacokinetic/pharmacodynamic (PK/PD) of continuous infusion (CI) ceftazidime–avibactam in a series of critical orthotopic liver transplant (OLT) recipients having pre-emptive therapy during OLT because of carbapenemase-producing *Enterobacterales* (CPE) rectal colonization or targeted therapy of CPE intra-abdominal (IAIs) and/or biliary tract infections (BTIs).

Methods: We performed an exploratory, hypothesis-generating prospective case series including critical OLT recipients carrying a Kehr's tube and undergoing therapeutic drug monitoring of ceftazidime and avibactam in both bile and plasma simultaneously while receiving CI ceftazidime–avibactam pre-emptive or targeted therapy. Biliary aggressive joint PK/PD target attainment [defined as a free ceftazidime steady-state concentrations fC_{ss}/MIC ratio >4 coupled with an avibactam fC_{ss}/target concentration (C_T = 4 mg/L) ratio >1] was selected as optimal threshold of ceftazidime–avibactam efficacy, given this was previously shown to be independently associated with lower rates of microbiological failure and resistance development. Bile-to-plasma fC_{ss} ratios were calculated.

Results: Overall, four critical OLT recipients were included. Aggressive biliary ceftazidime–avibactam joint PK/PD target during treatment with CI 2 g/0.5 g q8 h over 8 h was attained in 2/4 cases (quasi-optimal and suboptimal in one case each). Median (range) fC_{ss} bile-to-plasma ratios were 0.28 (0.22–0.38) for ceftazidime and 0.24 (0.11–0.52) for avibactam.

Conclusions: Our limited cases series suggested that both ceftazidime and avibactam showed a moderate and broadly similar biliary penetration. Administration by CI may be helpful in attaining an aggressive biliary joint PK/PD target of ceftazidime–avibactam against pathogens with an MIC up to 8 mg/L.

Introduction

Rectal colonization by carbapenemase-producing *Enterobacterales* (CPE) may occur in ∼10% of patients undergoing orthotopic liver transplant (OLT).[1] In high-risk patients undergoing OLT CPE rectal colonization may cause life-threatening infections,[2] thus an anti-CPE pre-emptive therapy should be considered in the peri-operative period.[3] In addition, intra-abdominal infections (IAIs) and biliary tract infections (BTIs) caused by CPE may also represent common complications in the early post-OLT period.[4,5]

Ceftazidime–avibactam is a beta-lactam/beta-lactamase inhibitor combination (BL/BLIc) approved for treating complicated IAIs and BTIs caused by KPC- or OXA-48-producing *Enterobacterales*.[6] Preclinical models showed that the minimum conservative joint

pharmacokinetic/pharmacodynamic (PK/PD) target needed for granting ceftazidime–avibactam efficacy should be a free (f) ceftazidime concentration persisting for at least 50% of the dosing interval above the MIC of the pathogen (50%$fT_{>MIC}$) coupled with a f avibactam concentration persisting for at least 50% of the dosing interval above the target concentration of 1 mg/L (50%$fT>C_T$).[7] Recent clinical evidence suggested that an aggressive joint PK/PD target, namely 100%$fT_{>4xMIC}$ of ceftazidime coupled with 100% $fT>C_T$ of 4 mg/L of avibactam, was associated with better microbiological eradication rate and lower resistance occurrence among critically ill patients receiving ceftazidime–avibactam by continuous infusion (CI).[8–10] In case of BTIs, it would be of interest to assess whether or not this aggressive PK/PD target may be attained even at the infection site.[11]

The aim of this study was to perform a biliary PK/PD analysis of ceftazidime–avibactam in a series of critical OLT recipients receiving CI ceftazidime–avibactam as pre-emptive or targeted therapy.

Methods

An exploratory, hypothesis-generating prospective case series was carried out in the period 1 June 2024–30 November 2024 at the post-transplant-ICU of the IRCCS Azienda Ospedaliero-Universitaria of Bologna, Italy. It included critically ill OLT recipients carrying a Kehr's tube and having simultaneous therapeutic drug monitoring of ceftazidime and avibactam in bile and plasma while receiving CI ceftazidime–avibactam as pre-emptive treatment of a KPC- or OXA-48-producing *Enterobacterales* rectal colonization in the peri-OLT period or as targeted treatment of KPC- or OXA-48-producing *Enterobacterales* related IAIs-BTIs. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the local ethical committee (CE AVEC: 272/2024/Sper/AOUBo on 16 May 2024). Signed informed consent was collected from each included patient.

Rectal colonization was defined as the isolation of the index pathogen from a rectal swab in absence of any clinical sign and symptom of infections.[12] IAI or BTI were defined as the isolation of the index pathogen in at least one occasion from the abdominal fluid or the bile, respectively, collected from an abdominal drainage or from a Kehr's tube, or during surgery.[13]

Broth microdilution method (panel provided by Merlin Diagnostika GmbH, Bornheim-Hersel, Germany) was used for testing *in vitro* ceftazidime–avibactam susceptibility within a MIC range of 0.25–64 mg/L in the presence of a fixed target avibactam concentration (C_T) of 4 mg/L. Values were interpreted according to the EUCAST guidelines.[14] Multiplex immunochromatographic assay NG-Test CARBA 5 (NG Biotech, Guipry-Messac, France) was used for detecting the specific type of carbapenemase.

Ceftazidime–avibactam treatment was started with a loading dose of 2 g/0.5 g over 2 h followed by a maintenance dose of 2 g/0.5 g q8 h over 8 h (namely by CI). Reconstitution and delivery times were in agreement with stability data of aqueous solutions at room temperature.[15] A single pair of blood and bile samples was simultaneously collected after at least 24 h from starting therapy for measuring total plasma and biliary steady-state concentrations (C_{ss}) of ceftazidime and avibactam.[16] Details concerning bile samples collection and analysis are reported in the Supplementary Material. Free (f) plasma and biliary C_{ss} were calculated by multiplying the total C_{ss} by the known fraction unbound (namely 0.90 for ceftazidime and 0.93 for avibactam) based on a plasma protein binding of 10% and 7%, respectively.[17] Aggressive joint PK/PD target was selected in both plasma and bile as the best predictor of ceftazidime–avibactam efficacy for all cases given this target was previously shown to be independently associated with lower rates of both microbiological failure and resistance development.[8,10] It was defined as optimal if both the ceftazidime fC_{ss}/MIC ratio was >4 and the avibactam fC_{ss}/C_T ratio was >1, and quasi-optimal or suboptimal if only one or none of the two thresholds were attained, respectively.[18] The avibactam C_T was the fixed target concentration of 4 mg/L used by the EUCAST for testing the *in vitro* the susceptibility to ceftazidime–avibactam.[14] In cases having documented IAI and/or BTI, microbiological outcome was assessed and defined as eradication or failure depending on the elimination or not of the index pathogen from the abdominal and/or the biliary cultures collected at end of treatment.[8]

Results

Overall, four critically ill OLT recipients were retrieved (Table 1). Patient 1 received a 24-h peri-OLT pre-emptive therapy with CI ceftazidime–avibactam because of a rectal colonization by an OXA-48-producing *Klebsiella pneumoniae* (MIC = 2 mg/L). Aggressive joint PK/PD target attainment in the bile was quasi-optimal (ceftazidime fC_{ss}/MIC ratio = 12.56 and avibactam fC_{ss}/C_T ratio = 0.58).

Patient 2 received a 12 days of therapy with CI ceftazidime–avibactam because of an IAI plus BTI caused by a KPC-producing *Klebsiella pneumoniae* (MIC = 8 mg/L) at day 28 post-transplant. Aggressive joint PK/PD target in the bile was optimal (ceftazidime fC_{ss}/MIC ratio = 5.50 and avibactam fC_{ss}/C_T ratio = 2.44), and microbiological eradication was documented at end of treatment from both the bile and the peritoneal fluid.

Patient 3 (73 years; 80 kg; CL_{CR} 89 mL/min/1.73 m^2) received a 24-h peri-OLT pre-emptive therapy with CI ceftazidime–avibactam because of rectal colonization by a KPC-producing *Klebsiella pneumoniae* (MIC = 2 mg/L). Aggressive joint PK/PD target attainment in the bile was suboptimal (ceftazidime fC_{ss}/MIC ratio = 3.33 and avibactam fC_{ss}/C_T ratio = 0.35).

Patient 4 received a 15-day therapy with CI ceftazidime–avibactam because of a bacteraemic IAI caused by KPC-producing *Klebsiella pneumoniae* (MIC = 1 mg/L) at day 37 post-OLT. Aggressive joint PK/PD target attainment in the bile was optimal (ceftazidime fC_{ss}/MIC ratio = 14.58 and avibactam fC_{ss}/C_T ratio = 1.77). Eradication of the index pathogen was documented from follow-up blood cultures, whereas no follow-up blood culture was performed in the peritoneal fluid.

No clinically relevant toxicity was attributable to ceftazidime–avibactam in these patients.

Discussion

To the best of our knowledge, our exploratory, hypothesis-generating case series was the first to assess the biliary PK/PD profile of ceftazidime–avibactam during CI administration in critically ill OLT recipients receiving pre-emptive or targeted therapy. Interestingly, both ceftazidime and avibactam showed a moderate and broadly similar bile/plasma ratios during CI administration [median (min–max) bile-to-plasma ratio of 0.28 (0.22–0.38) and 0.24 (0.11–0.52), respectively].

The only previous study assessing bile-to-plasma ratio of ceftazidime–avibactam in 10 patients undergoing elective hepatobiliary surgery receiving a single dose of 2 g/0.5 g over 2 h did not allow any direct comparison with our findings in terms of penetration rates.[19] Unfortunately, the sampling times differed among

Table 1. Bile and plasma steady-state concentrations, biliary penetration rate and PK/PD target attainment of CAZ/AVI administered by CI in four OLT recipients as prophylaxis or targeted therapy against KPC- or OXA-48-producing Enterobacterales

ID case	Age/ gender	Weight (kg)	Isolate and CAZ/ AVI MIC	Rationale for CAZ/AVI treatment	CAZ/AVI initial MD	Renal function	Plasma CAZ *f*Css (mg/L)	Plasma AVI *f*Css (mg/L)	Bile CAZ *f*Css (mg/L)	Bile AVI *f*Css (mg/L)	CAZ bile/ plasma ratio	AVI bile/ plasma ratio	Bile CAZ *f*Css/MIC	Bile AVI fC_{ss}/C_T	Aggressive joint PK/PD target in the bile
#1	48/F	89	OXA-48-producing Kp 2 mg/L	Pre-emptive therapy due to rectal colonization	2 g/0.5 g q8 h CI	Oliguria (urine output 500 mL/day) +CVVDHF (Q_{ef} 3170 mL/h—Q_b 150 mL/min)	65.70	20.65	25.11	2.33	0.38	0.11	12.56	0.58	Quasi-optimal
#2	51/M	75	KPC-producing Kp 8 mg/L	IAI plus BTI	2 g/0.5 g q8 h CI	Anuria + CVVHDF (Q_{ef} 2800 mL/h—Q_b 150 mL/min) +CytoSorb	140.49	38.32	44.01	9.77	0.31	0.25	5.50	2.44	Optimal
#3	73/M	80	KPC-producing Kp 2 mg/L	Pre-emptive therapy due to rectal colonization	2 g/0.5 g q8 h CI	CL_{CR} 89 mL/min	30.06	6.23	6.66	1.40	0.22	0.22	3.33	0.35	Suboptimal
#4	47/M	102	KPC-producing Kp 1 mg/L	IAI plus BSI	2 g/0.5 g q8 h CI	Anuria + CVVHDF (Q_{ef} 3330 mL/h—Q_b 150 mL/min)	59.31	13.49	14.58	7.07	0.25	0.52	14.58	1.77	Optimal

AVI, avibactam; BSI, bloodstream infection; CAZ, ceftazidime; CAZ/AVI, ceftazidime/avibactam; CI, continuous infusion; CL_{CR}, creatinine clearance; C_{ss}, steady-state concentrations; C_T, target concentration; CVVHDF, continuous veno-venous hemodiafiltration; KPC-producing Kp, KPC-producing *Klebsiella pneumoniae*; MD, maintenance dose; Q_b, blood flow rate; Q_{ef}, total effluent flow rate.

patients (1.65 up to 5.71 h after drug administration), so that extremely changeable bile-to-plasma ratios were observed due to the hysteresis phenomenon.[19] Noteworthy, the authors found highly variable bile concentrations for both ceftazidime and avibactam after intermittent administration. Furthermore, the pooling of single individual bile concentrations indicated that just 3.9 h after dosing both ceftazidime and avibactam concentrations fell below the conservative joint PK/PD target against *Enterobacterales* having an MIC of 8 mg/L (namely 50%$T_{>MIC}$ of 8 mg/L for ceftazidime and 50%$fT > C_T$ of 1 mg/L for avibactam), which is at slightly below 50% when administered at 8 h intervals.[19] This may allow us to speculate that standard dosing regimens by intermittent infusion might fail even in attaining the conservative PK/PD target in the bile against pathogens having borderline susceptibility. Conversely, administering the standard ceftazidime–avibactam dose by CI may be a valuable strategy not only for preventing biliary fluctuations of ceftazidime and avibactam concentrations but also for increasing the likelihood of attaining an aggressive biliary PK/PD target or the entire dosing interval. Interestingly, among our case series, aggressive joint PK/PD target attainment was optimal in two cases and quasi-optimal in another one. It may be speculated that optimal biliary aggressive joint PK/PD target attainment allowed biliary microbiological eradication of the KPC-producing *Klebsiella pneumoniae* strain with an MIC of 8 mg/L causing a BTI plus IAI in Patient 2. We preferred administering the full dosage by CI even in the three cases undergoing CVVHDF to avoid the potential risk of underexposure associated with the high flow rates adopted (~3 L/h).[20]

Limitations of the study must be recognized. The very limited sample size and the peculiar setting of critical OLT recipients mainly undergoing CRRT may limit the generalizability of our findings. Only total plasma and biliary ceftazidime and avibactam concentrations were measured, and the free fractions were calculated based on the plasma protein binding reported in the literature. This could affect proper estimation of real free biliary concentrations. Although the bile/plasma ratios were based on a single pair of concentrations from each patient, this should not affect reliability being measured at steady-state.

In conclusion, PK/PD findings from our limited cases series suggested that both ceftazidime and avibactam showed a moderate penetration and a broadly similar pharmacokinetic behaviour in the bile. CI administration may help in attaining an aggressive biliary joint ceftazidime–avibactam PK/PD target against pathogens with an MIC up to 8 mg/L.

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Transparency declarations

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Author contributions

Matteo Rinaldi (Data curation, Formal analysis)Cristiana Laici (Data curation, Formal analysis)Simone Ambretti (Data curation, Formal analysis)Antonio Siniscalchi (Writing - Review &Editing)Pierluigi Viale (Writing - Review & Editing)Federico Pea (Conceptualization, Writing - Review & Editing)

Ethical approval

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the local ethical committee (CE AVEC: 272/2024/Sper/AOUBo on 16 May 2024). Signed informed consent was collected from each included patient.

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