



Plasma and Lung Tissue Pharmacokinetics of Ceftaroline Fosamil in Patients Undergoing Cardiac Surgery with Cardiopulmonary Bypass: an *In Vivo* Microdialysis Study

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ABSTRACT Ceftaroline fosamil, a fifth-generation cephalosporin antibiotic with activity against methicillin-resistant *Staphylococcus aureus* (MRSA), is currently approved for the treatment of pneumonia and complicated skin and soft tissue infections. However, pharmacokinetics data on free lung tissue concentrations in critical patient populations are lacking. The aim of this study was to evaluate the pharmacokinetics of the high-dose regimen of ceftaroline in plasma and lung tissue in cardiac surgery patients during intermittent and continuous administration. Nine patients undergoing elective cardiac surgery on cardiopulmonary bypass were included in this study and randomly assigned to intermittent or continuous administration. Eighteen hundred milligrams of ceftaroline fosamil was administered intravenously as either 600 mg over 2 h every 8 h (q8h) (intermittent group) or 600 mg over 2 h (loading dose) plus 1,200 mg over 22 h (continuous group). Interstitial lung tissue concentrations were measured by *in vivo* microdialysis. Relevant pharmacokinetics parameters were calculated for each group. Plasma exposure levels during intermittent and continuous administration were comparable to those of previously published studies and did not differ significantly between the two groups. *In vivo* microdialysis demonstrated reliable and adequate penetration of ceftaroline into lung tissue during intermittent and continuous administration. The steady-state area under the concentration-time curve from 0 to 8 h ($AUC_{ss\ 0-8}$) and the ratio of $AUC_{ss\ 0-8}$ in lung tissue and AUC in plasma ($AUC_{lung/plasma}$) were descriptively higher in the continuous group. Continuous administration of ceftaroline fosamil achieved a significantly higher proportion of time for which the free drug concentration remained above 4 times the minimal inhibitory concentration (MIC) during the dosing interval (% $fT_{>4 \times MIC}$) than intermittent administration for pathogens with a MIC of 1 mg/liter. Ceftaroline showed adequate penetration into interstitial lung tissue of critically ill patients undergoing major cardiothoracic surgery, supporting its use for pneumonia caused by susceptible pathogens.

KEYWORDS cardiac surgery, ceftaroline, microdialysis, pharmacokinetics, pneumonia

Ceftaroline fosamil (CTF) is a fifth-generation cephalosporin antibiotic approved for the treatment of community-acquired pneumonia (CAP) and complicated soft tissue infections in adults and children of >2 months (1–6). In plasma, the prodrug CTF is dephosphorylated into active ceftaroline (CT). CT inhibits peptidoglycan synthesis via binding to penicillin-binding proteins and exhibits broad-spectrum antimicrobial activity against Gram-positive and -negative organisms. Susceptible pathogens include

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methicillin-sensitive and -resistant strains of *Staphylococcus aureus* (MSSA, MRSA), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, and *Haemophilus influenzae* (7, 8). The clinical efficacy of CTF in CAP caused by MSSA or MRSA has been demonstrated in clinical trials (2, 3, 6, 9–17).

Patients undergoing cardiac surgery often need prolonged mechanical ventilation and are at high risk for ventilator-associated pneumonia (18). Pneumonia is the most common infectious complication after cardiac surgery, with an incidence of up to 13% (19–22), and is associated with increased mortality, length of stay, duration of ventilatory support, and health care costs (19, 23, 24).

Adequate tissue concentrations are the prerequisite for successful antibiotic therapy. For pneumonia, target site concentrations correlate with clinical outcomes (25). *In vivo* microdialysis (μ D) in lung tissue allows continuous measurement of free drug concentrations at the target site (26). In cardiothoracic surgery, microdialysis probes may be inserted into lung tissue under direct vision, which enables accurate placement and ensures patient safety.

There is a paucity of data on the tissue pharmacokinetics (PK) of CT (12, 27–29). Matzneller et al. showed good penetration of CT into subcutaneous and muscle tissue of healthy, young volunteers (27). Riccobene et al. published data on CT penetration into epithelial lining fluid (ELF) of healthy adult subjects (12), demonstrating adequate concentrations in ELF in this low-risk patient cohort. Cardiac surgery patients present with multiple comorbidities, such as chronic obstructive pulmonary disease, coronary artery disease, heart failure, diabetes mellitus, and peripheral artery disease. Thus, these patients represent a critical population that requires optimal antibiotic treatment in order to improve clinical outcomes. Additionally, the pharmacokinetics of antimicrobial drugs in these patients might differ significantly from those in healthy volunteers and exhibit large interindividual variability (30–33). The tissue pharmacokinetics and particularly the lung tissue concentrations of CT have never been formally investigated in these critically ill patients. Pathophysiologic effects of major cardiothoracic surgery, systemic inflammatory response syndrome after cardiopulmonary bypass (CPB), and intra- and postoperative fluid resuscitation all affect the pharmacokinetics of antimicrobial drugs (34, 35). Employing standardized dosing regimens inferred from studies in healthy volunteers might cause inappropriate pharmacokinetics in the critically ill, leading to treatment failure, toxicity, or development of antibiotic resistance (36, 37). Therefore, pharmacokinetics data for CT in lung tissue of critically ill patients are needed.

The aim of this study was to investigate the pulmonary pharmacokinetics of CT by means of *in vivo* microdialysis in patients undergoing major cardiothoracic surgery. Intermittent (600 mg in a 2-h bolus every 8 h [q8h]) and continuous (600 mg in a 2-h bolus plus 1,200 mg over 22 h) administrations of CT were compared in patients undergoing cardiac surgery on CPB.

RESULTS

Of 15 patients that were screened, 9 patients were included and 6 patients were excluded (due to known allergy to penicillin [$n = 1$], left ventricular ejection fraction of $<30\%$ [$n = 1$], insulin-dependent diabetes mellitus [$n = 1$], withdrawn consent [$n = 1$], and cancelled surgery [$n = 2$]). Six patients underwent coronary artery bypass grafting (CABG), 2 patients had CABG and aortic valve replacement (AVR), and 1 patient received CABG, AVR, and replacement of the ascending aorta. All operations were performed with cardiopulmonary bypass (CPB). All 9 patients completed the study. Microdialysis (μ D) catheters were placed and removed without intraoperative or postoperative complications. There were no significant differences between groups in terms of demographics and clinical features. A summary of patient demographics and intra- and postoperative data is shown in Table 1.

Concentration-time profiles of unbound (free, non-protein-bound) CT in plasma and lung tissue for both groups are shown in Fig. 1. Data are reported as the median (interquartile range). Pharmacokinetics data are summarized in Table 2.

TABLE 1 Demographic and intraoperative data^a

Parameter	Value for:	
	Intermittent group (n = 5)	Continuous group (n = 4)
Age (yrs)	71 ± 10	72 ± 5
Sex (male/female)	(5/0)	(4/0)
Ht (cm)	172 ± 2	174 ± 8
Body wt (kg)	82 ± 13	87 ± 18
BMI (kg/m ²)	27 ± 4	29 ± 4
CPB time (min)	161 ± 70	149 ± 40
ACC time (min)	97 ± 28	93 ± 29
Serum creatinine (mg/dl)	1.0 ± 0.3	1.1 ± 0.2
CL _{CR} (MDRD) (ml/min/1.73 m ²)	76.5 ± 26.1	67.3 ± 13.8

^aData are represented as the mean ± SD. ACC, aortic cross clamp; BMI, body mass index; CPB, cardiopulmonary bypass; MDRD, modification of diet in renal disease; CL_{CR}, creatinine clearance. There were no significant differences between groups in terms of demographics and clinical features (Mann-Whitney test).

CTF was well tolerated by all study subjects without any adverse events. Plasma protein binding (PPB) levels were 22.2% (18.2 to 27.3%) in the intermittent bolus group (IG) and 29.5% (21.7 to 35.0%) in the continuous administration group (CG).

In the IG, CT unbound peak plasma concentrations (C_{max}) were 13.7 (10.8 to 19.1) mg/liter 90 min after the start of the infusion. The steady-state area under the concentration-time curve from 0 to 24 h ($AUC_{ss\ 0-24}$) was 116.9 (102.9 to 191.8) (mg · h)/liter. The apparent volume of distribution (V) was 41.1 (31.2 to 58.1) liters after the first bolus and 192.4 (89.5 to 253.9) liters under steady-state conditions.

In the CG, CT unbound peak plasma concentrations were 11.6 (10.3 to 13.6) mg/liter 90 min after the start of the infusion. The $AUC_{ss\ 0-24}$ was 100.1 (79.95 to 131.3) (mg · h)/liter. The differences in C_{max} , $AUC_{ss\ 0-24}$, and PPB were not statistically significant. Assuming a MIC of 1 mg/liter, the proportion of time for which the free drug concentration remained above 4 times the MIC during the dosing interval (% $fT_{>4 \times MIC}$) was 52.5% (43.2 to 95.7%) in the IG and 50% (0 to 100%) in the CG. For unbound plasma concentrations, differences in unbound plasma % $fT_{>4 \times MIC}$ were not statistically different.

Lung microdialysis was feasible in all 9 patients. Mean probe recovery was 50% ± 28% (mean ± standard deviation [SD]). In the IG, CT peak lung concentrations were 13.7 (3.4 to 14.3) mg/liter during the 2- to 4-h interval after the start of the infusion. The $AUC_{ss\ 0-8}$ was 36.4 (26.4 to 45.1) (mg · h)/liter with an $AUC_{lung/plasma}$ of 0.9 (0.4 to 1.3). In the CG, CT peak lung concentrations were 17.1 (11.2 to 18.8) mg/liter during the 2- to 4-h interval after the start of the infusion. The $AUC_{ss\ 0-8}$ was 77.3 (45.1 to 87.1) (mg · h)/liter with an $AUC_{lung/plasma}$ of 2.3 (1.1 to 3.2). Differences in the $AUC_{lung/plasma}$ between the IG and CG were not statistically significant. Assuming a MIC of 1 mg/liter, the % $fT_{>4 \times MIC}$ was 58.5% (27.5 to 75.9%) in the IG and 100% (100 to 100%) in the CG. The % $fT_{>4 \times MIC}$ was significantly higher in the CG ($P = 0.0357$).

DISCUSSION

This prospective pharmacokinetics study investigated plasma and interstitial lung concentrations in 9 patients undergoing elective cardiac surgery on CPB. Patients received a total intravenous dose of 1,800 mg CTF either by intermittent bolus or continuous administration. In both groups, plasma exposure was adequate and comparable to published data (13, 38, 39). *In vivo* microdialysis demonstrated sufficient penetration of CT into interstitial lung tissue. Continuous administration of CTF led to significantly higher % $fT_{>4 \times MIC}$ in lung tissue, whereas all other pharmacokinetics parameters were not statistically different between the intermittent and continuous administration groups.

Currently approved dosing regimens are 600 mg q12h and 600 mg q8h. In a recently published population pharmacokinetics model, target attainment of >90% (against *S. aureus* isolates with MICs of ≤2 mg/liter) was achieved by both regimens in patients with complicated skin and soft tissue infections (40, 41). Matzneller et al. compared 600 mg CTF q8h to 600 mg CTF q12h in healthy volunteers and observed higher plasma AUC_{0-24} , higher % $fT_{>MIC}$

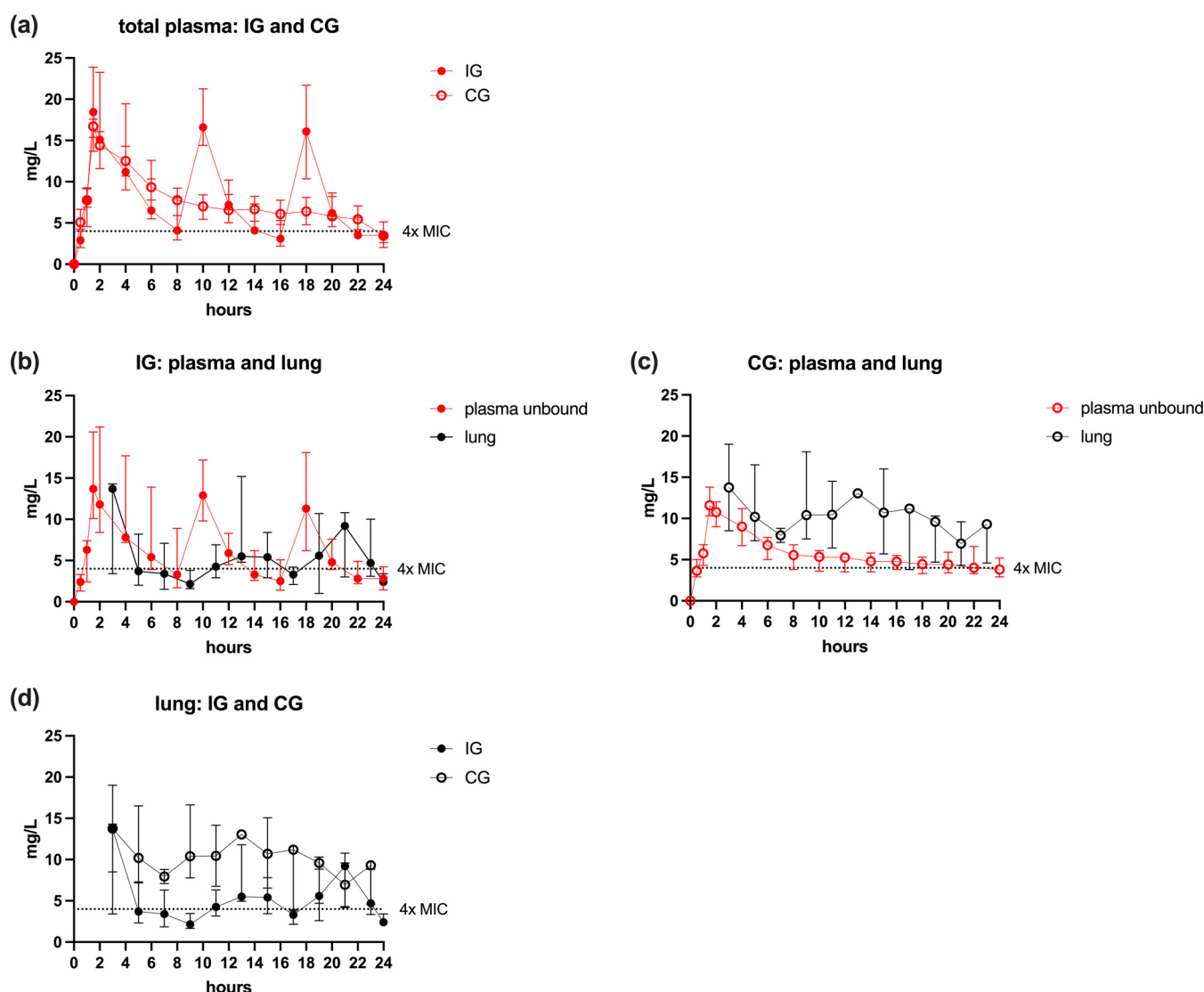


FIG 1 Concentration-time profiles for CT in plasma and lung in the IG and CG. (a) Total plasma CT concentrations in the IG (filled red circles) and CG (open red circles). (b) Unbound plasma (filled red circles) and lung (filled black circles) CT concentrations in the IG. (c) Unbound plasma (open red circles) and lung (open black circles) CT concentrations in the CG. (d) Unbound lung CT concentration in the IG (filled black circles) and CG (open black circles). Data points represent the median $\pm$ interquartile range. IG, intermittent administration group; CG, continuous administration group; CT, ceftaroline.

for bacteria with an MIC of 1 mg/liter, and better tissue penetration in the 600 mg CTF q8h group (27). Previously published *in vivo* microdialysis studies in cardiac surgery demonstrated subtherapeutic plasma and tissue concentrations of cefazolin 3 h after the initial bolus in some patients, despite administration of a high dose of 6 g cefazolin (42, 43). Subtherapeutic antibiotic concentrations were even more problematic when standard dose regimens were used (44, 45). Based on these observations, the high-dose regimen of 600 mg CTF q8h was employed in this study.

This is the first study measuring free CT concentrations in interstitial lung tissue by means of microdialysis. Riccobene et al. studied penetration of CT into human epithelial lining fluid (ELF) of healthy adult subjects (12). Concentrations in ELF were 23% of plasma concentrations for CTF 600 mg q8h. Pharmacokinetics/pharmacodynamics (PK/PD) simulations showed that 58% of subjects reached a $fT_{>MIC}$ target of 70% for MICs of 2 mg/liter. Penetration into ELF and $fT_{>MIC}$ (79% and 100% for intermittent and continuous, respectively) were both considerably lower than penetration into lung parenchyma measured by *in vivo* microdialysis in our study. Other cephalosporins exhibited higher ELF penetration, reaching 50 to 100% of plasma concentrations (46). This may

TABLE 2 Pharmacokinetics parameters for CT in plasma and lung tissue for intermittent and continuous administration of CTF^a

Parameter	Value for:	
	IG (n = 5)	CG (n = 4)
Plasma unbound		
$fC_{\max}$ (mg/liter)	13.7 (10.8–19.1)	11.6 (10.3–13.6)
$fAUC_{ss\ 0-24}$ [(mg · h)/liter]	116.9 (102.9–191.8)	100.1 (79.95–131.3)
$fAUC_{ss\ 0-8}$ [(mg · h)/liter]	39.0 (34.0–63.9)	34.35 (27.58–44.28)
$t_{1/2}$ (h)	3.0 (2.6–3.6)	NA
fCL_{ss} (liters/h)	11.7 (6.8–12.9)	18.25 (13.8–22.6)
fV (liters)	41.1 (31.2–58.1)	NA
fV_{ss} (liters)	192.4 (89.5–253.9)	NA
PPB (%)	22.2 (18.2–27.25)	29.5 (21.7–35.0)
$fT_{>4 \times MIC}$ (%) ^c	52.5 (43.2–95.7)	50 (0–100)
Lung microdialysis		
$C_{\max}$ (mg/liter)	13.7 (3.4–14.3)	17.1 (11.2–18.8)
C_{ss} (mg/liter)	NA	8.7 (5.3–9.6)
$AUC_{ss\ 0-8}$ [(mg · h)/liter]	36.4 (26.4–45.1)	77.3 (45.1–87.1)
$fT_{>4 \times MIC}$ (%) ^c	58.5 (27.5–75.9)	100 (100–100) ^b
$AUC_{ss\ 0-8}$ lung/plasma	0.9 (0.4–1.3)	2.3 (1.1–3.2)

^aData are presented as the median (interquartile range). IG, intermittent administration group; CG, continuous administration group; NA, not available; $C_{\max}$, peak lung concentration; $fC_{\max}$, unbound peak plasma concentration; AUC_{0-8} , AUC from 0 to 8 h after the third dose; $AUC_{ss\ 0-24}$, steady-state area under the concentration-time curve from 0 to 24 h; $t_{1/2}$, half-life; CL_{ss} , clearance at steady state; V , volume of distribution; V_{ss} , volume of distribution at steady state; $fT_{>4 \times MIC}$, proportion of time for which the free drug concentration remained above 4 times the MIC during the dosing interval; C_{ss} , maximum concentration at steady state. All values are for the free, unbound fraction of the drug (f).

^bSignificant difference between IG and CG (Mann-Whitney U test, $P = 0.0357$).

^cAssuming an MIC of 1 mg/liter.

be explained by the inherent technical difficulties and associated variations concerning ELF sampling and calculation of concentrations in ELF.

We administered a high dose total of 1,800 mg CTF per 24 h either by intermittent bolus or as a continuous infusion. Similar to that of other beta-lactams, the clinical efficacy of CTF correlates with the proportion of time for which free drug concentrations remain above the MIC during the dosing interval (% $fT_{>MIC}$) (47). For cephalosporins, 40% and 70% $fT_{>MIC}$ are cited thresholds for bacteriostatic and bactericidal effects, respectively (47, 48). However, a target of 100% $fT_{>4 \times MIC}$ might be appropriate for neutropenic patients, immunocompromised patients, patients on cardiocirculatory support, and critically ill patients (33, 49–54). Extended or continuous infusion of beta-lactams increase $fT_{>MIC}$ and may therefore enhance antimicrobial efficacy (55–58). In critically ill patients with respiratory infections, continuous infusion of beta-lactams was associated with a higher clinical cure rate and a lower 30-day mortality (52, 59). In addition to increased clinical efficacy, higher % $fT_{>MIC}$ targets may reduce the emergence of antibiotic resistance during treatment, a common problem encountered in critical care (60). In general, concentrations required for prevention of emergence of resistance are higher than concentrations for optimal clinical efficacy. For beta-lactams, a minimum concentration ($C_{\min}$)/MIC ratio of 1 to 8 has been suggested to reduce emergence of resistance (60). In our study, the $C_{\min}$ /MIC for lung tissue was 3.8 to 10.2 in the CG and 1.5 to 3.4 in the IG.

In our cohort of patients undergoing major cardiac surgery on CPB with mechanical ventilation, perioperative fluid shifts, and CPB-induced inflammation, the target of 100% $fT_{>4 \times MIC}$ was chosen at an MIC of 1 mg/liter. This MIC would include pathogens such as *Enterobacteriaceae* (e.g., *Klebsiella pneumoniae* [MIC, 0.5 mg/liter], *E. coli* [MIC, 0.5 mg/liter], and *Enterobacter cloacae* [MIC, 1 mg/liter]), *Streptococcus pneumoniae* (MIC, 0.25 mg/liter), and MSSA and MRSA (MIC, up to 1 mg/liter) (40, 61, 62).

In the present study, the % $fT_{>4 \times MIC}$ in plasma was 52.5% for intermittent administration and 50% during continuous infusion of CTF. In lung tissue, the % $fT_{>4 \times MIC}$ was

higher, 58.5% in the bolus group and 100% in the continuous group. The target of 100% $fT_{>4 \times MIC}$ was achieved in lung tissue during continuous infusion only, and the % $fT_{>4 \times MIC}$ was significantly higher during continuous administration than during intermittent administration. Thus, continuous administration of CTF after an initial bolus might be the preferred mode of administration for critically ill patients in order to achieve superior PK/PD targets.

Pneumonia after cardiac surgery is the most common postoperative infection and is associated with increased mortality, length of stay, duration of mechanical ventilation, and costs (19–24). Responsible pathogens in this patient group are *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Klebsiella oxytoca*, *Serratia marcescens*, *E. coli*, *H. influenzae*, and *S. aureus* (19, 22). This microbial pattern is different from that of community-acquired pneumonia (63), and therefore, CTF is probably most useful for targeted therapy of postoperative pneumonia after isolation of the responsible pathogens. Additionally, CTF may be used for MRSA coverage in patients with risk factors for MRSA or documented colonization (64).

There were some limitations of our study. The small sample size of 9 patients and the variability of patient demographics may limit the generalizability of our results. Microdialysis probes were always implanted in the left upper lobe under direct vision by the cardiothoracic surgeon, and thus, the effects of regional variations in drug distribution could not be addressed in this study. Patients in this study had no evidence of pneumonia, and thus, the impact of inflammation on pulmonary penetration of CT could not be investigated. A higher standard deviation was observed for interstitial lung concentrations in the CG. Higher standard deviations may be observed in these critically ill patients given their exceptionally dynamic perioperative course after weaning from CPB, ongoing fluid resuscitation, weaning from mechanical ventilation and extubation, and early mobilization on the intensive care unit. For these reasons, some patients may not have been at steady state. Furthermore, accumulation of CT within lung tissue in some patients may occur during continuous exposure. The CPB may influence the pulmonary pharmacokinetics of CT due to the effect on lung perfusion (contribution of pulmonary artery versus bronchial arteries).

In conclusion, this pharmacokinetics study demonstrated the feasibility and safety of *in vivo* microdialysis of CTF in interstitial lung tissue in critically ill patients. The approved high-dose regimen of CTF achieved sufficient plasma concentrations of CT in cardiac surgery patients during intermittent bolus and continuous administration. Furthermore, CT showed adequate penetration into the interstitial lung parenchyma, supporting the use of CT for treatment of pneumonia caused by susceptible pathogens in this critical patient population. Continuous administration of CTF led to greater % $fT_{>4 \times MIC}$ in interstitial lung tissue for pathogens with an MIC of ≤ 1 mg/liter.

MATERIALS AND METHODS

Ethics. This prospective pharmacokinetics study was conducted at the Department of Cardiothoracic and Vascular Anesthesia and Intensive Care Medicine at the Medical University of Vienna, Vienna, Austria, in accordance with current International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guidelines, the Declaration of Helsinki, and national and institutional standards. The study was registered under EudraCT number 2017-002508-29, approved by the Ethics Committee of the Medical University of Vienna (reference number 1752/2017), and authorized by the Austrian Agency for Health and Food Safety. Signed informed consent to study participation was obtained from all patients before inclusion.

Patients. Prior to inclusion, written informed consent was obtained preoperatively after detailed instructions about the conduct of the study. Inclusion criteria were written informed consent, planned coronary bypass grafting (CABG) with left internal mammary artery bypass, planned use of cardiopulmonary bypass, age between 18 and 90 years, and left ventricular ejection fraction of $>40\%$. Exclusion criteria were known allergy to penicillin/cephalosporins or ceftazidime, preoperative antibiotic therapy, signs of infection preoperatively, reoperation or emergency procedure, planned use of bilateral internal mammary artery bypass, preoperative renal failure, chronic severe renal insufficiency including hemodialysis, chronic severe liver disease, body mass index (BMI) of >35 , and long-standing diabetes mellitus of >7 years or insulin-dependent diabetes mellitus. Nine patients were included and randomly assigned to the intermittent bolus group (IG) or continuous administration group (CG) using a sealed envelope system.

Materials and substances. Ceftaroline fosamil was used as perioperative antibiotic prophylaxis for surgical site infections in this study. Ceftaroline fosamil (Zinforo) was purchased from Pfizer (Pfizer Corporation Austria GmbH), ceftaroline hydrochloride was purchased from AstraZeneca (AstraZeneca Österreich, Vienna, Austria), and physiological 0.9% saline solution was purchased from Medica Medicare, Kufstein, Austria. Microdialysis catheters were purchased from M Dialysis, Stockholm, Sweden.

Anesthesia and cardiopulmonary bypass. After establishment of routine monitoring (electrocardiogram, pulse oximetry, arterial blood pressure monitoring), anesthesia was induced with 0.05 to 0.1 mg/kg midazolam, 2 to 3 μ g/kg fentanyl, 1 to 3 mg/kg propofol, and 0.2 mg/kg cisatracurium. During induction of anesthesia, 5 to 10 ml/kg of Ringer's lactate solution was administered intravenously. Surgery was conducted via a full median sternotomy on cardiopulmonary bypass (CPB). Full heparinization for CPB was initiated with heparin sodium (400 IU/kg), and activated clotting time was kept above 400 s (Hemochrom 400; International Technidyne, Edison, NJ) during CPB. The CPB priming solution contained Ringer's lactate solution (1,000 ml), hydroxyethyl starch 6% (500 ml), and 10,000 IU heparin sodium. Body core temperature was maintained at 36°C. After termination of CPB, heparin was antagonized with protamine.

In vivo microdialysis. Microdialysis (μ D) is an established technique for the measurement of free, unbound drug concentrations in various tissues. The technique of *in vivo* μ D has been described previously (65, 66). μ D catheters are constantly perfused with perfusion solution. Perfusion solution reaches the semipermeable μ D membrane via the inlet tube. At the μ D membrane, analytes diffuse across the membrane depending on their concentration gradient. The dialysate leaves the catheter via the outlet tube and may be collected for further analysis.

Due to constant perfusion, diffusion across the semipermeable membrane is never in equilibrium, and thus, measured concentrations in the dialysate represent only a fraction of tissue concentration. This fraction is termed recovery and is probe specific. Calibration of individual μ D probes was performed by means of retrodialysis (65). Retrodialysis relies on the assumption that diffusion across the μ D membrane is equal in both directions. Therefore, recovery of analytes from the extracellular fluid (ECF) should be equal to loss of the same analyte into the ECF, provided that ECF analyte concentrations are negligible.

Relative recovery (RR) was calculated as follows:

$$RR (\%) = 100 - 100 \times \left(\frac{[\text{analyte}]_{\text{dialysate}}}{[\text{analyte}]_{\text{perfusate}}} \right)$$

where $[\text{analyte}]_{\text{dialysate}}$ is the concentration in the collected retrodialysis sample and $[\text{analyte}]_{\text{perfusate}}$ is the concentration used in the perfusion solution. "True" ECF analyte concentrations are calculated as follows:

$$[\text{ECF}] = 100 \times ([\mu\text{D sample}] / \text{RR}\%)$$

μ D study protocol. Each group received a total intravenous dose of 1,800 mg CTF. In the IG, 600 mg was administered every 8 h as a 120-min infusion. The CG received an initial 600-mg bolus as a 120-min infusion. Thereafter, 1,200 mg was administered over 22 h.

The first dose of CTF was administered immediately after induction of anesthesia and endotracheal intubation.

After 24 h, μ D probes were calibrated by retrodialysis using ceftaroline hydrochloride. The total study duration was 26 h.

Sampling intervals. Blood and μ D samples were collected at defined time points after the start of the first CTF dose and were identical in both groups. Plasma samples were obtained at 0.5, 1, 1.5, and 2 h after the start of the initial bolus administration and every 2 h thereafter until 24 h. μ D samples were collected in 2-h intervals as soon as μ D probes were inserted into lung tissue after a 30-min run-in period. Plasma and microdialysate were sampled for 24 h after the start of the initial bolus. For each patient, 16 plasma samples and 13 μ D samples (including 2 retrodialysis samples) were obtained for pharmacokinetics analysis.

Microdialysis sampling in lung tissue. Free, non-protein-bound CT concentrations in lung tissue were determined by means of *in vivo* μ D. A 62 gastrointestinal microdialysis catheter (M Dialysis AB, Stockholm, Sweden) with a membrane length of 30 mm and a molecular mass cutoff of 20,000 Da, a polyurethane tubing, and a polyarylethersulfone membrane was used.

After preparation of the left internal mammary artery, the left lung was exposed, and the catheter was inserted into the left upper lobe under direct vision by the cardiac surgeon. Thereafter, the probe was perfused with 0.9% saline solution at a flow rate of 2 μ l/min using a microinfusion pump. Prior to removal, probes were individually calibrated by retrodialysis. The perfusion solution for retrodialysis contained ceftaroline hydrochloride at a concentration of 30 μ g/ml. After a 30-min run-in period, the mean recovery of two consecutive 30-min retrodialysis samples was calculated.

Sample handling and analysis. For plasma samples, 4 ml of arterial blood was collected at each time point. After collection, blood samples were immediately placed on ice and centrifuged for 15 min at 3,500 rpm (4°C) within 15 min. Immediately thereafter, plasma aliquots of 2 ml each were transferred into cryovials and stored at approximately -80°C .

Microdialysate samples were immediately placed on ice and stored at approximately -80°C within 15 min from sampling until analysis.

Sample analysis. The concentration of CT in plasma and microdialysate was determined by high-performance liquid chromatography (HPLC) using a Dionex UltiMate 3000 system (Thermo Fisher Scientific, Inc., Waltham, MA) with UV detection at 243 nm. Frozen plasma samples were thawed at room temperature. After the addition of 200 μ l ice-cold acetonitrile to 100 μ l plasma, the samples were centrifuged ($13,000 \times g$ for 5 min at 4°C), and 80 μ l of the supernatant was injected onto a Hypersil BDS C₁₈ column (5 μ m, 250 by 4.6 mm inside diameter [i.d.]; Thermo Fisher Scientific, Waltham, MA) preceded by a Hypersil BDS C₁₈ guard column (5 μ m, 10 by 4.6 mm i.d.) at a flow rate of 1 ml/min. Microdialysate samples (50 μ l) were injected onto the column without any previous precipitation procedure. The column oven was set at 35°C. The mobile phase consisted of a continuous gradient mixed from ammonium acetate buffer (10 mM, pH 5.0) (mobile phase A) and acetonitrile (mobile phase B). Mobile phase B linearly increased from 5% (0 min) to 25% at 15 min, further increased to 80% at 16 min, and was kept constant at 80% until 20 min. The percentage of acetonitrile was then decreased to 25% within 1 min to equilibrate the column for 9 min before injection of the next sample. Quantification of CT was based on external calibration curves of spiked drug-free human plasma and microdialysate (pooled patient samples at time zero) with CT at concentrations ranging from 0.01 to 30 μ g/ml (average correlation coefficients > 0.998). The limit of quantification of CT in plasma and microdialysate was 0.02 μ g/ml and 0.01 μ g/ml, respectively (coefficients of accuracy and precision were < 9%).

Determination of CT protein binding. Aliquots (500 μ l) of plasma from each patient (collected 1 h after CT application) were transferred to Centriscart I ultrafiltration devices (Sartorius Stedim Biotech S.A., Aubagne, France) and centrifuged at $13,000 \times g$ for 30 min at room temperature. Subsequently, the recovered ultrafiltrate was analyzed by HPLC as described above to determine the concentration of free (unbound) drug. Samples that did not undergo ultrafiltration were assayed to determine the total (bound and unbound) drug concentration. Protein binding of CT was then calculated according to the following equation: % protein binding = $100 \times (\text{total} - \text{unbound}) / (\text{total})$.

PK/PD analysis and statistical analysis. Pharmacokinetics data were calculated by noncompartmental analysis using a commercially available software program (Phoenix WinNonlin Build 8.0; Certara USA, Inc., Princeton, NJ).

Based on published pharmacokinetics data with a reported half-life ($t_{1/2}$) of 2.1 to 2.5 h in plasma, we assumed 96.875% steady-state conditions to be present after five half-lives (27, 38, 67). During cardiopulmonary bypass, pulmonary perfusion is reduced and ventilation is halted, leading to bilateral atelectasis, which might affect pulmonary pharmacokinetics during this period. The duration of CPB was 161 ± 70 min in the IG and 149 ± 40 min in the CG and fell within the first 4 h of the study. Therefore, steady-state conditions were assumed to be present starting at 16 h after the first dose for both dosing regimens.

The $AUC_{ss, 0-24}$ for the IG was calculated by multiplying the AUC from 0 to 8 h after the third dose (referred to as $AUC_{ss, 0-8}$) by 3. Since the study drug was administered every 8 h, the third dose represents the first dose under steady-state conditions.

The $AUC_{ss, 0-24}$ for the CG was calculated by multiplying the mean steady-state concentration ($C_{ss, \text{average}}$) by 24. The $C_{ss, \text{average}}$ was calculated as the mean plasma concentration at 16 to 24 h (assumed steady state).

For calculations of the time the concentration exceeded the MIC ($\% T_{>MIC}$), an MIC of 1 mg/liter was used for both dosing regimens (40, 61, 62). For calculations of $fT_{>MIC}$, we chose an MIC of 1 mg/liter. This cutoff includes most clinical isolates (96.1% have an MIC of ≤ 1 mg/liter) of target bacterial species according to MIC distribution data from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (61).

To evaluate the clinical efficacy of CTF for treatment of pneumonia in critically ill patients, a target of 100% $fT_{>4 \times MIC}$ was chosen. Conventional targets for bacteriostatic and bactericidal effects of cephalosporins are 40% or 70% $fT_{>MIC}$, respectively (47, 48). The aggressive target of 100% $fT_{>4 \times MIC}$ might be more appropriate for neutropenic patients, immunocompromised patients, patients on cardiocirculatory support, and critically ill patients (33, 49–54). Continuous infusion of beta-lactams has been shown to increase the clinical cure rate and lower the 30-day mortality (52, 59). Furthermore, higher $\% fT_{>MIC}$ targets may reduce the emergence of antibiotic resistance during treatment (60). Therefore, 100% $fT_{>4 \times MIC}$ was deemed appropriate for our study population.

Statistical analysis was performed using a commercially available statistical program (GraphPad Prism 8; GraphPad Software, San Diego, CA). Mann-Whitney U tests were used to compare pharmacokinetics of intermittent and continuous administration. The following PK parameters were compared: for plasma, fC_{max} , $fAUC_{ss, 0-24}$, $fAUC_{ss, 0-8}$, PPB (%), and $\% fT_{>4 \times MIC}$; for lung parenchyma, C_{max} , C_{ss} , $AUC_{ss, 0-8}$, $\% fT_{>4 \times MIC}$, and the ratio of $AUC_{\text{lung/plasma}}$.

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statistical analysis; V.A.J., pharmacokinetics analysis, interpretation of data, revision of the manuscript; W.J. and M.B., chemical analysis of plasma and microdialysate samples, interpretation of data, revision of the manuscript; M.A., placement of lung microdialysis probes, revision of the manuscript; M.Z., study design, supervision of the study, interpretation of data, revision of the manuscript, final approval to publish; D.H., study design, performance of microdialysis and blood sampling for pharmacokinetics, supervision of the study, interpretation of data, revision of the manuscript, final approval to publish.

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