Phase 1 study assessing the steady-state concentration of ceftazidime and avibactam in plasma and epithelial lining fluid following two dosing regimens

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Objectives: The aim of this Phase 1, open-label study (NCT01395420) was to measure and compare concentrations of ceftazidime and avibactam in bronchial epithelial lining fluid (ELF) and plasma, following administration of two different dosing regimens in healthy subjects.

Patients and methods: Healthy volunteers received 2000 mg of ceftazidime + 500 mg of avibactam (n = 22) or 3000 mg of ceftazidime + 1000 mg of avibactam (n = 21), administered intravenously every 8 h for 3 days (total of nine doses). Bronchoscopy with bronchoalveolar lavage was performed once per subject, 2, 4, 6 or 8 h after the last infusion. Pharmacokinetic parameters were estimated from individual plasma concentrations and the composite ELF concentration–time profile. Safety was assessed.

Results: Forty-three subjects received treatment (2000 mg of ceftazidime + 500 mg of avibactam, n = 22; 3000 mg of ceftazidime + 1000 mg of avibactam, n = 21). Plasma and ELF concentrations increased dose-proportionally for both drugs, with 1.5- and 2-fold increases in AUC for respective components. Ceftazidime Cmax and AUC in ELF were ≏ 23%–26% and 31%–32% of plasma exposure. Avibactam Cmax and AUC in ELF were ≏ 28%–35% and 32%–35% of plasma exposure. ELF and plasma elimination were similar for both drugs. No serious adverse events were observed.

Conclusions: Both ceftazidime and avibactam penetrated dose-proportionally into ELF, with ELF exposure to both drugs ≏ 30% of plasma exposure.

Introduction

Hospital-acquired pneumonia is one of the most common hospital infections, and ventilator-associated pneumonia is the most common infection observed in the ICU. Nosocomial pneumonia may be caused by a wide range of pathogens, including MDR Gram-negative strains such as Pseudomonas aeruginosa, Klebsiella pneumoniae and Acinetobacter spp.2,3 Traditionally, carbapenems have been used for treatment of infections caused by extended-spectrum β-lactamase-producing pathogens; however, production of carbapenemases is an increasingly important mechanism of antibiotic resistance.4–7 Avibactam is a novel non-β-lactam β-lactamase inhibitor that has been shown to restore the in vitro activity of ceftazidime against Gram-negative bacteria expressing class A, C and some class D β-lactamases.8–10

Results from a murine pneumonia model showed that humanized ceftazidime/avibactam dosing (2000 mg of ceftazidime + 500 mg of avibactam given as a 2 h infusion every 8 h) resulted in significant drug exposure in the lung.11 This resulted in efficacy against all but one of the 27 P. aeruginosa strains tested in the lung infection model with ceftazidime/avibactam MICs up to 32 mg/L, in which the epithelial lining fluid (ELF) fraction of time (fT) ≥ MIC was ≥19%.

The primary objective of the present study was to assess lung exposure to ceftazidime/avibactam by measuring and comparing the concentrations of ceftazidime and avibactam in bronchial ELF and plasma following two different dosing regimens (2000 mg of ceftazidime + 500 mg of avibactam or 3000 mg of ceftazidime + 1000 mg of avibactam) in healthy volunteers.

Patients and methods

This was a Phase 1, open-label study (ClinicalTrials.gov identifier NCT01395420; sponsor protocol number D4280C00009) conducted in healthy volunteers at a single centre in London, UK, between September 2011 and July 2012.
The study was approved by the Yorkshire Independent Ethics Committee (UK), and was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and are consistent with International Conference on Harmonization/Good Clinical Practice. All participants provided written informed consent before the start of the study.

Subjects
Healthy adult subjects, aged 18–50 years, with BMI 19–30 kg/m², and with veins suitable for cannulation or repeated venipuncture, were included. Subjects were excluded from the study if they had any clinically significant ongoing disease or disorder, including a history of chronic respiratory disease, e.g. asthma, chronic obstructive pulmonary disease, cystic fibrosis or interstitial lung disease, or significant illness, medical/surgical procedure or trauma within 4 weeks of the first administration of the study drug. Other exclusion criteria included: females of child-bearing potential; subjects with prolonged or shortened QT interval or family history of prolonged QT interval syndrome; history of drug/alcohol/nicotine abuse; history of drug hypersensitivity; use of any prescribed or non-prescribed medication other than paracetamol/acetaminophen, herbal remedies, vitamins and minerals during the 2 weeks prior to first administration of the study drug.

Study design
A total of 43 subjects were enrolled by cohort to receive either 2000 mg of ceftazidime + 500 mg of avibactam or 3000 mg of ceftazidime + 1000 mg of avibactam. Both regimens were administered as a 2 h intravenous infusion every 8 h for 3 days; ceftazidime and avibactam were combined in a single infusion (volume kept at 100 mL in all cases). Each subject received a total of nine doses of ceftazidime/avibactam and subjects remained resident at the study centre from day −1 to day 5.

In both cohorts, bronchoscopy with bronchoalveolar lavage (BAL) was performed in accordance with British Thoracic Society Guidelines, once on each subject at one of the following timepoints after the start of the final infusion: 2, 4, 6 and 8 h. Because of the time required to prepare for these procedures, subjects were not randomized for time of BAL. The aim was to have approximately five subjects per BAL timepoint. All subjects were required to fast for ≥6 h (with moderate water intake permitted up to 4 h) before the planned start of bronchoscopy. A meal was given 2 h after bronchoscopy. BAL fluid (BALF) aspirates were analysed for ceftazidime, avibactam and urea concentrations, as described in the supplementary methods (available as Supplementary data at JAC Online).

Pharmacokinetics
In all subjects, plasma samples for pharmacokinetic (PK) evaluation were collected on day 3 at pre-dose and at 1, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 h after the start of the infusion, and evaluated as described in the supplementary methods. The actual sampling times were used for calculating the individual PK parameters in plasma.

The PK parameters in ELF were derived from the composite concentration–time profile, consisting of the mean of the ELF concentrations obtained at each scheduled timepoint, using the urea dilution method. Ceftazidime and avibactam concentrations in ELF \( \left( C_{\text{ELF}} \right) \) were calculated as \( C_{\text{ELF}} = C_{\text{BAL}} \times \left( C_{\text{urea,BAL}} / C_{\text{urea,BAL}} \right) \), where \( C_{\text{BAL}} \) is concentration in BALF, and \( C_{\text{urea,BAL}} \) and \( C_{\text{urea,ELF}} \) are urea concentrations in plasma and BALF, respectively. The individual ratios of \( C_{\text{ELF}} \) relative to plasma concentration \( C_{\text{p}} \) for ceftazidime and avibactam were also calculated at each shared timepoint when applicable. For AUC calculations in ELF, the pre-dose concentrations in ELF for the last dose on the last day were estimated from the mean pre-dose concentration in plasma using the ratio of \( C_{\text{ELF}} \) to the \( C_{\text{p}} \) at 8 h post-dose.

PK variables included: \( C_{\text{max}} \) in plasma and ELF; AUC during the dosing interval (AUC\(_{12} \)) in plasma and ELF following multiple dosing (calculated by linear up/log down trapezoidal summation); terminal elimination \( t_{1/2} \) in plasma and ELF; and \( T_{\text{max}} \) in plasma and ELF obtained directly from the observed concentration versus time data. Visual assessment was used to identify the terminal linear phase of the concentration–time profile, with a minimum of three datapoints used for determination. In addition, estimated ratios of \( C_{\text{max}} \) in ELF over \( C_{\text{max}} \) in plasma (\( C_{\text{max,ELF}} / C_{\text{max,p}} \)), and AUC, in ELF over AUC, in plasma (\( \text{AUC}_{\text{ELF}} / \text{AUC}_{\text{p}} \)) were calculated. Ratios were based on total drug in plasma and ELF concentration, i.e. they were not corrected for differences in protein binding in plasma and ELF. In addition, protein-binding assessments were not undertaken in plasma; thus, all PK concentrations of avibactam and ceftazidime in plasma represent total drug. Similarly, no protein binding correction was undertaken for ELF data.

Safety
Blood samples were collected for complete laboratory safety assessments [consisting of serology (performed at the screening visit only), clinical chemistry, haematology, coagulation and urinalysis] at screening, day 1, at discharge on day 5 and on follow-up. Samples were collected for laboratory safety assessments (clinical chemistry, haemoglobin, leucocyte count and leucocyte differential count only) on days 3 and 4.

Adverse events (AEs) were assessed throughout the study until the follow-up visit, 7–10 days after last dose of study medication. Complete physical examination was performed at screening and at the follow-up visit, with a brief physical examination performed on day 1 and at discharge. Vital signs were measured at regular intervals throughout, including before BAL on day 4.

Digital ECG was performed at screening, on days 1, 2, 4 (before BAL) and 5 (at discharge) and at the follow-up visit. Additionally, paper ECG was performed 30 min before the start of first study drug infusion and at 1, 2, 3 and 6 h after the start of the first infusion. Telemetry was conducted from 1 h before to 24 h after the first infusion (0–24 h) and, if there were any safety concerns, telemetry was continued. Lung function test was performed at screening and before and after bronchoscopy.

Statistical analysis
Sample size was based on the requirement to obtain data to achieve the objectives of the study while exposing as few healthy subjects as possible to study medication and procedures. A total of five evaluable healthy subjects were required at each BAL timepoint. The PK analysis set included all healthy subjects who received nine doses of ceftazidime and avibactam and had at least one post-dose PK measurement, with no major protocol violations that would affect PK parameters. The PK variables for ceftazidime and avibactam were summarized using descriptive statistics, and shown as the geometric mean [coefﬁcient of variation (%)] for plasma, and a composite concentration – time proﬁle for ELF. As ELF sample numbers at each timepoint were small, the ELF composite proﬁle consisted of the median (area-corrected) concentration at each scheduled timepoint. Geometric mean (SD) plasma concentration–time data are presented graphically on linear and semi-logarithmic scales by study cohort; the ELF concentration–time proﬁle (area-corrected) is presented as both a composite value and individual values.

If at any timepoint ≥1 value was above the lower limit of quantification (LLOQ), but <50% of values were below the LLOQ, then all values below the LLOQ were set to the LLOQ and a mean (SD) and CV calculated. If >50% of values were below the LLOQ, only individual values were reported. If all values were below the LLOQ at any timepoint, no descriptive statistics were calculated for that timepoint.

All healthy subjects who received at least one dose of study medication and had available post-dose data were included in the safety analysis set.
Continuous safety variables (i.e. haematology, clinical chemistry, thyroid function and vital signs) were summarized using descriptive statistics for each cohort and each scheduled assessment point, both as absolute value and as change from baseline. Categorical variables (i.e. urinalysis) were summarized in frequency tables by cohort and scheduled assessment point.

**Results**

**Subjects**

Forty-three healthy adults received treatment with either 2000 mg of ceftazidime + 500 mg of avibactam (n=22) or 3000 mg of ceftazidime + 1000 mg of avibactam (n=21). One subject in the higher dose group was withdrawn due to a protocol deviation (under-dosing as a result of a leakage at the tap connection during the third infusion), and was excluded from the PK analysis set, but included in the safety analysis set. Baseline characteristics are shown in Table 1. All subjects were male, and baseline characteristics were generally similar between groups.

**Table 1. Subject baseline characteristics (safety analysis set)**

<table>
<thead>
<tr>
<th></th>
<th>2000 mg of ceftazidime + 500 mg of avibactam (n=22)</th>
<th>3000 mg of ceftazidime + 1000 mg of avibactam (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>30 (8)</td>
<td>33 (9)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>22 (100.0)</td>
<td>21 (100.0)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>white</td>
<td>17 (77.3)</td>
<td>19 (90.5)</td>
</tr>
<tr>
<td>black or African</td>
<td>3 (13.6)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>American</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>2 (9.1)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Height (cm), mean (SD)</td>
<td>178 (6.6)</td>
<td>179 (5.1)</td>
</tr>
<tr>
<td>Weight (kg), mean (SD)</td>
<td>75.4 (9.36)</td>
<td>80.8 (7.45)</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>23.9 (2.62)</td>
<td>25.2 (2.06)</td>
</tr>
</tbody>
</table>

**Pharmacokinetics**

The geometric mean (SD) plasma concentration–time profiles and composite median ELF concentration–time profiles are shown in Figure 1 for ceftazidime and Figure 2 for avibactam. No plasma or ELF samples were below the LLOQ for ceftazidime and only five of 419 plasma samples, all in the lower dose cohort at the 24 h timepoint, were below the LLOQ for avibactam, and none of the ELF samples.

Plasma and ELF concentrations increased with dose for both ceftazidime (2000–3000 mg) and avibactam (500–1000 mg), with ~1.5- and 2-fold increases in AUC, for the respective components: in plasma, the geometric mean AUC for ceftazidime increased from 295 mg·h/L with the 2000 mg dose to 454 mg·h/L with the 3000 mg dose, and for avibactam it increased from 39.2 mg·h/L with the 500 mg dose to 77.6 mg·h/L with the 1000 mg dose. In ELF, the geometric mean AUC for ceftazidime increased from 92.3 to 147 mg·h/L and for avibactam it increased from 13.7 to 24.8 mg·h/L (Table 2 and Figures 1 and 2). Peak concentrations were observed at the end of infusion (2 h) for both ceftazidime and avibactam. ELF ceftazidime and avibactam concentrations were generally proportionally lower than those of plasma. Graphical comparison indicated that the elimination patterns were broadly similar between the ELF and plasma concentration–time profiles for both ceftazidime and avibactam.

The estimated ELF/plasma ratios for AUC, were 0.313 for ceftazidime and 0.349 for avibactam for the 2000 mg of ceftazidime + 500 mg of avibactam cohort, and 0.324 for ceftazidime and 0.320 for avibactam for the 3000 mg of ceftazidime + 1000 mg of avibactam cohort. Thus, the AUC values for ceftazidime in ELF were ~31%–32% of those in plasma. Similarly, the AUC values for avibactam in ELF were ~32%–35% of those in plasma.

**Safety**

The overall incidence of AEs was similar in the two cohorts (Table 3). The most frequently reported AE in both cohorts was headache (23.3% overall). In the 2000 mg of ceftazidime + 500 mg of avibactam group, three of the seven cases of headaches were considered by the investigator to be related to study drug. Influenza-like illness was observed in four subjects (all in the 2000 mg of ceftazidime + 500 mg of avibactam cohort); none

![Figure 1. Geometric mean (SD) plasma and median ELF ceftazidime concentration–time profiles (with individual ELF concentrations) following administration of 2000 mg of ceftazidime + 500 mg of avibactam (a) or 3000 mg of ceftazidime + 1000 mg of avibactam (b) (semi-log scale) (PK analysis set). *(n=6 for ELF median concentrations at 2 and 4 h in the 2000 mg of ceftazidime + 500 mg of avibactam group.)*](https://academic.oup.com/jac/article/70/10/2862/829935/figure1)
was considered study drug-related. For 2000 mg of ceftazidime + 500 mg of avibactam, other AEs considered related to study drug were: abnormal urine odour, four subjects (18.2%); and somnolence, one subject (4.5%). For 3000 mg of ceftazidime + 1000 mg of avibactam AEs were: diarrhoea, two subjects (9.5%); abdominal discomfort, infusion site reaction, hypoesthesia, anxiety and cough (one subject each, 4.8%). All AEs were considered to be of mild intensity except for two events (headache and influenza-like illness in one subject each in the cohort receiving 2000 mg of ceftazidime + 500 mg of avibactam, which were of moderate intensity). There were no deaths, serious AEs or AEs leading to discontinuation of study drug.

There were occasional reports of haematology or clinical chemistry values above or below the laboratory reference ranges, but none was considered by the investigator to be of clinical significance. Twelve subjects had transient elevations in liver function tests, all \(2 \times \) upper limit of normal, but these were not considered to be clinically significant. There were no clinically significant findings from urinalysis. No changes in vital signs or ECG evaluations were considered to be clinically significant, and no significant trends were observed.

**Discussion**

The focus of the current study was to determine the bronchopulmonary availability of ceftazidime/avibactam using concentrations of these agents in ELF as a means to characterize lung
penetration. We showed that both ceftazidime and avibactam penetrate into human ELF, with elimination patterns broadly similar between ELF and plasma based on the ceftazidime and avibactam concentration–time profiles. Concentrations of both ceftazidime and avibactam in ELF were on average \( \approx 25\%–30\% \) of those in plasma and were dose-proportional.

For the present study, measuring the concentration of antimicrobial therapy in ELF was considered as a means to characterize the penetration of ceftazidime/avibactam concentrations into the lung tissue. Recent data have revealed that serum concentration of two cephalosporins (ceftazidime and cefepime) in excess of the MIC for \( \approx 50\% \) of the dosing interval is associated with favourable microbiological response in ventilator-associated pneumonia,\(^{15} \) and similar targets predict clinical efficacy of ceftazidime in patients with nosocomial pneumonia.\(^{16} \)

In preclinical studies, plasma targets are also associated with efficacy in lung infection models, where there is equivalent or slightly lower ELF penetration than in humans.\(^{19,20} \) In a neutropenic pneumonia model in mice, humanized ceftazidime/avibactam dosing (2000 mg of ceftazidime + 500 mg of avibactam as a 2 h infusion every 8 h) similar to that used in the present study also resulted in significant drug exposures in the lung, with no difference in exposure between infected and non-infected mice. This resulted in reductions of \( >1 \log_{10} \) cfu against 26 of 27 P. aeruginosa isolates with ceftazidime/avibactam MICs \( \leq 32 \) mg/L.\(^{11,17} \)

In another neutropenic mouse model study, the effect of avibactam was also primarily dependent on the time during which plasma levels were above the threshold %\( fT > C_T \) 1 mg/L, with a mean value of 37.7% of the dosing interval required for a static effect.\(^{18} \)

Moreover, similar plasma–ELF AUC ratios for unbound ceftazidime and avibactam of 0.27 and 0.24, respectively, have been observed in both neutropenic murine thigh and lung infection models, independently of the doses administered.\(^{17} \) Such similar penetration of the two drugs in both models suggests that the effect of ceftazidime/avibactam is independent of the infection location.\(^{17} \)

Plasma concentrations of ceftazidime and avibactam observed in the present study were similar to those observed in previous studies that have evaluated this dose regimen.\(^{19,20} \) In the current study, the AUC values of ceftazidime in ELF were \( \approx 31\%-32\% \) of plasma AUC. Similarly, the AUC values of avibactam in ELF were \( \approx 32\%-35\% \) of plasma AUC. It should be noted that, for a single subject in the 2000 mg of ceftazidime + 500 mg of avibactam group, the ELF concentration at 6 h for both ceftazidime and avibactam appeared lower than expected based on the 4 and 8 h timepoints and the other participants’ concentrations at 6 h for 2000 mg of ceftazidime + 500 mg of avibactam (Figures 1 and 2; the same subject in each figure); this was due to a low plasma/BAL urea ratio in this subject. Median ELF concentrations were as expected at the end of the dosing interval. The consistency of ceftazidime and avibactam ELF penetration in humans and mice suggests that, as in this animal model, human plasma concentrations of ceftazidime/avibactam provide a good surrogate for exposure in the lung and therefore efficacy in nosocomial pneumonia.

### Table 3. Number (%) of subjects with at least one AE and frequency of each AE (safety analysis set)

<table>
<thead>
<tr>
<th></th>
<th>2000 mg of ceftazidime + 500 mg of avibactam (n=22)</th>
<th>3000 mg of ceftazidime + 1000 mg of avibactam (n=21)</th>
<th>Total (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with any AE</td>
<td>15 (68.2)</td>
<td>12 (57.1)</td>
<td>27 (62.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (31.8)</td>
<td>3 (14.3)</td>
<td>10 (23.3)</td>
</tr>
<tr>
<td>Abnormal urine odour</td>
<td>4 (18.2)</td>
<td>0 (0.0)</td>
<td>4 (9.3)</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>4 (18.2)</td>
<td>0 (0.0)</td>
<td>4 (9.3)</td>
</tr>
<tr>
<td>Back pain</td>
<td>3 (13.6)</td>
<td>0 (0.0)</td>
<td>3 (7.0)</td>
</tr>
<tr>
<td>Cough</td>
<td>1 (4.5)</td>
<td>1 (4.8)</td>
<td>2 (4.7)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0 (0.0)</td>
<td>2 (9.5)</td>
<td>2 (4.7)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1 (4.5)</td>
<td>1 (4.8)</td>
<td>2 (4.7)</td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>2 (9.1)</td>
<td>0 (0.0)</td>
<td>2 (4.7)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>0 (0.0)</td>
<td>1 (4.8)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0 (0.0)</td>
<td>1 (4.8)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Catheter site pain</td>
<td>0 (0.0)</td>
<td>1 (4.8)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Contusion</td>
<td>1 (4.5)</td>
<td>0 (0.0)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0 (0.0)</td>
<td>1 (4.8)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Hypoaesthesia</td>
<td>0 (0.0)</td>
<td>1 (4.8)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Infusion site reaction</td>
<td>0 (0.0)</td>
<td>1 (4.8)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Local swelling</td>
<td>1 (4.5)</td>
<td>0 (0.0)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>0 (0.0)</td>
<td>1 (4.8)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Nightmare</td>
<td>0 (0.0)</td>
<td>1 (4.8)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Oedema peripheral</td>
<td>0 (0.0)</td>
<td>1 (4.8)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>1 (4.5)</td>
<td>0 (0.0)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>1 (4.5)</td>
<td>0 (0.0)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>1 (4.5)</td>
<td>0 (0.0)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1 (4.5)</td>
<td>0 (0.0)</td>
<td>1 (2.3)</td>
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Nicolau et al. 2000
A previous study by Cazzola et al. used a lung biopsy approach to assess lung penetration of ceftazidime 1000 mg given by intramuscular injection in patients with bronchitis. Drug concentrations in ELF were consistently much lower than those in bronchial mucosa and the authors concluded that ELF concentrations were a poor guide to ceftazidime pulmonary penetration. However, β-lactams exhibit poor cell penetration and the lung biopsy approach to assessing penetration has been shown to provide inconsistent results.

In a study in critically ill patients with nosocomial pneumonia, employing continuous infusion of ceftazidime, ceftazidime exhibited ~21% penetration into ELF at steady-state, although in contrast to the present study this was based on point estimate comparisons rather than a composite profile AUC calculation. Nevertheless, these results are broadly in line with results observed in the present study. Indeed, 2000 mg of ceftazidime is indicated for the treatment of nosocomial pneumonia. Interestingly, results observed in the present study in healthy volunteers are also similar to data reported in a recent study of the β-lactam antibiotic meropenem in patients with ventilator-associated pneumonia, which showed an AUC_{ELF}/AUC_{plasma} penetration ratio of 30%. This concordance may reflect relatively similar physicochemical properties between these two agents.

The joint PK/pharmacodynamic (PD) plasma target of ceftazidime 50% \(T_{\text{MS}50}\) of ceftazidime/avibactam and avibactam 50% \(fT\geq\text{MIC}\) of 1 mg/L has been shown to provide adequate probability of PK/PD target attainment at the 90th percentile of MIC of ceftazidime/avibactam against major causative pathogens for patients with nosocomial pneumonia from European ceftazidime/avibactam surveillance studies in 2012. Both 2000 mg of ceftazidime + 500 mg of avibactam and 3000 mg of ceftazidime + 1000 mg of avibactam appeared to be generally well tolerated in healthy subjects, with no apparent dose-related trends. Transient elevations of liver function tests were observed in 12 subjects in this study (six in each cohort), but were not considered clinically significant. Such transient liver function test elevations have been reported previously following acquired and ventilator-associated pneumonia [REPROVE (NCT01808092)] is ongoing.

Conclusions

This study confirms the penetration of both ceftazidime and avibactam into ELF. Plasma and ELF concentrations increased approximately proportionally with dose for both ceftazidime (2000–3000 mg) and avibactam (500–1000 mg). The ELF drug concentrations of both ceftazidime and avibactam displayed a similar PK profile to that of plasma, and appeared to be proportionally lower than those of plasma; ELF \(C_{\text{max}}\) and AUC values of both ceftazidime and avibactam were on average approximately one-quarter to one-third those of plasma.

Both regimens, 2000 mg of ceftazidime + 500 mg of avibactam and 3000 mg of ceftazidime + 1000 mg of avibactam, were generally well tolerated in the healthy volunteers included in this ELF study. Transient elevations of liver function tests were observed, but were not considered clinically significant, and do not alter the risk–benefit profile of ceftazidime/avibactam.

The level of ELF penetration observed in this study and previous animal model studies supports the investigation of the utility of ceftazidime/avibactam 2000–500 mg in nosocomial pneumonia via a Phase 3 trial.
Acknowledgements
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The design and conduct of the study, as well as the analysis of the study data and opinions, conclusions and interpretation of the data, are the responsibility of the authors.

Author contributions
D. P. N.: study design, data collection and data interpretation. L. S.: data collection and data interpretation. J. A.: study design, data interpretation and statistical analysis. J. L.: study design and data interpretation. T. E.: study design and data interpretation. M. L.: study design and data interpretation. S. D.: study design and data interpretation. All authors critically reviewed the content of the manuscript at each stage of manuscript development, and gave approval of the final version.

Supplementary data
Supplementary methods are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References


