Intrapulmonary penetration of ceftolozane/tazobactam and piperacillin/tazobactam in healthy adult subjects

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Objectives: Appropriate antibiotic exposure at the site of infection is important for clinically effective therapy. This study compared the epithelial lining fluid (ELF) penetration of ceftolozane/tazobactam, which has potent in vitro activity against many Gram-negative pathogens causing nosocomial pneumonia, with that of piperacillin/tazobactam in healthy adult volunteers.

Methods: In this Phase 1, open-label trial, 51 healthy adult subjects were randomized to receive three doses of either ceftolozane/tazobactam 1.5 g administered every 8 h via a 60 min infusion or piperacillin/tazobactam 4.5 g administered every 6 h via a 30 min infusion. Serial blood samples were obtained for determination of plasma drug concentrations. Bronchoscopy and bronchoalveolar lavage were performed at pre-specified time-points in five subjects per timepoint in each treatment group to determine the ELF drug concentration. The penetration of individual analytes into the ELF was determined from the ratio of the area under the plasma concentration–time curve in ELF to that in plasma (AUCELF/AUCplasma).

Results: Plasma and ELF concentrations of ceftolozane, piperacillin and tazobactam increased rapidly, reaching maximal concentrations at the end of the infusion. Mean maximum concentration and AUC from time 0 to the end of the dosing interval (AUCt) for ceftolozane in ELF were 21.8 mg/L and 75.1 mg.h/L, respectively. Corresponding values for piperacillin were 58.8 mg/L and 94.5 mg.h/L. The ELF/plasma AUC ratio for ceftolozane was 0.48 compared with 0.26 for piperacillin.

Conclusion: This study demonstrated that ceftolozane penetrated well into the ELF following parenteral administration of ceftolozane/tazobactam.

Keywords: pharmacokinetics, epithelial lining fluid, Gram-negative

Introduction

Nosocomial pneumonia is a serious infection associated with considerable morbidity and mortality.1 Gram-negative organisms, especially Pseudomonas aeruginosa, are a major cause of serious life-threatening nosocomial infections.2,3 Pseudomonal infections can be particularly difficult to treat because of both intrinsic and acquired resistance.4 Effective antibiotic therapy requires the use of an agent with reliable antimicrobial activity at adequate concentrations at the site of infection. Although there are limited clinical data correlating epithelial lining fluid (ELF) concentrations and clinical outcome in pneumonia, pulmonary penetration of antibiotics (i.e. achievement of clinically significant concentrations in the ELF) has been suggested as a possible predictor for the appropriate treatment of pneumonia.5–8

Ceftolozane/tazobactam (previously referred to as CXA-201 or CXA-101/tazobactam) is a combination of the β-lactamase inhibitor tazobactam and the novel parenteral cephalosporin ceftolozane (previously referred to as CXA-101), which has potent in vitro activity against many Gram-negative pathogens known to cause nosocomial pneumonia.9 The anti-pseudomonal activity of ceftolozane is the most potent among all currently available β-lactams, including the anti-pseudomonal penicillins, cephalosporins and carbapenems.9 The addition of tazobactam broadens coverage to include most Enterobacteriaceae harbouring extended-spectrum β-lactamases.9 Ceftolozane/tazobactam is currently under clinical investigation for the treatment of serious Gram-negative infections, including those caused by multidrug-resistant P. aeruginosa.

This study was designed to compare the ELF penetration of ceftolozane/tazobactam with that of piperacillin/tazobactam,
a well-characterized \( \beta \)-lactam/\( \beta \)-lactamase combination antibiotic commonly used for the treatment of nosocomial pneumonia. The primary objective of the study was to determine ELF-to-plasma AUC ratios of multiple doses of intravenous ceftolozane/tazobactam compared with piperacillin/tazobactam in healthy adult volunteers.

**Patients and methods**

**Study design**

This was a Phase 1, open-label, comparator-controlled, randomized study. Non-smoking, healthy adult male and female subjects aged \( \geq 18 \) years were considered for inclusion in this study. The study consisted of a screening period lasting 21 days before randomization, a 24 h treatment period and a post-treatment assessment on study day 4. Subjects were randomly assigned in a 1:1 ratio to ceftolozane/tazobactam or piperacillin/tazobactam, with randomization stratified by gender. Subjects assigned to ceftolozane/tazobactam received three 1.5 g doses (1000 mg ceftolozane plus 500 mg tazobactam) administered every 8 h via a 60 min infusion. Subjects assigned to piperacillin/tazobactam received three 4.5 g doses (4000 mg piperacillin plus 500 mg tazobactam) administered every 6 h via a 30 min infusion. Subjects were confined to the study centre during administration of all three doses of study therapy.

This study was performed in accordance with Good Clinical Practice according to the International Conference on Harmonisation, including the archiving of essential documents. The study was approved by the investigational review board of the study centre and all subjects provided written informed consent.

**Subjects**

Healthy male or female volunteers 18–50 years of age (inclusive) with a body mass index \( \geq 18.5 \) and \( \leq 30 \) kg/m\(^2\) were eligible for enrolment. Subjects were required to have a forced expiratory volume in 1 s (FEV\(_1\)) \( \geq 80\%\). Key exclusion criteria included concurrent pregnancy/lactation, a history of moderate or severe hypersensitivity to any \( \beta \)-lactam antibiotic, clinically significant systemic disease, or the existence of any surgical or medical condition that potentially interfered with the distribution, metabolism or excretion of ceftolozane/tazobactam. Subjects were also excluded if they had a history of asthma or any restrictive or obstructive lung disease, had a history of smoking or abuse of narcotics or alcohol, had tested positive for HIV, hepatitis B surface antigen or hepatitis C antibodies, had any condition or situation where bronchoscopy was not advisable, or had impaired renal function (i.e. calculated creatinine clearance \( <90 \) mL/min).

**Assessments**

Blood samples for pharmacokinetic (PK) analysis were obtained from 25 subjects at 0 (pre-third dose), 1, 2, 4, 6 and 8 h after the start of the infusion of the third dose of ceftolozane/tazobactam. Subjects (\( n=25 \)) receiving piperacillin/tazobactam had their blood samples collected at 0 (pre-third dose), 0.5, 1, 2, 4 and 6 h after the start of the infusion of the third dose of the drug.

Bronchoalveolar lavage (BAL) samples were obtained at 1, 2, 4, 6 and 8 h following the start of the infusion of the third dose of ceftolozane/tazobactam, and at 0.5, 1, 2, 4, and 6 h after the start of the infusion of the third dose of piperacillin/tazobactam. The sampling times were selected to provide concentration-time data over the dosing interval of each drug. For ethical and logistical reasons, each subject underwent only one BAL procedure at one of the scheduled timepoints. The timing of BAL in each subject was determined by the site staff based on scheduling and was assigned prior to subjects returning to the study centre for dosing. Five subjects were assessed per BAL timepoint in each treatment group.

ELF was obtained via BAL using standard bronchoscopy, performed in accordance with the procedures set forth at the study centre. Subjects were required to fast for \( \geq 4 \) h before the start of bronchoscopy and ELF procedures. Before bronchoscopy, subjects gargled and expectorated 3 mL of 4% lidocaine, after which topical lidocaine (2%) was applied to the upper airway. A fibre-optic bronchoscope (Olympus BF-P40, Olympus Corporation, Center Valley, PA, USA) was inserted and wedged into a sub-segment of the right middle lobe. Following proper positioning of the bronchoscope, four 50 mL aliquots of sterile 0.9% saline were instilled into the right middle lobe, and each specimen was immediately aspirated and placed in ice. The aspirate from the first 50 mL instillation was collected separately and discarded. The aspirates recovered from the second, third and fourth instillations were pooled and used to determine study drug and urea concentrations in the BAL.

Ceftolozane, piperacillin and tazobactam concentrations in plasma and ELF were measured by liquid chromatography–tandem mass spectrometry (LC/MS/MS) at MicroConstants, Inc. (San Diego, CA, USA). The standard curves for ceftolozane, piperacillin and tazobactam in plasma were linear \(( r^2 \geq 0.99)\) over the concentration ranges of 0.250–150, 0.500–50.0 and 0.100–50.0 mg/mL, respectively. The inter-day coefficients of variation were 4.70%–7.60% for ceftolozane, 2.63%–6.31% for piperacillin and 2.88%–6.63% for tazobactam. The accuracy of the method was determined by comparing the mean measured concentrations with the theoretical concentrations, and the deviation did not exceed \( \pm 4.93\%\), \( \pm 6.00\%\) and \( \pm 6.25\%\) for ceftolozane, piperacillin and tazobactam, respectively. The lower limits of detection for ceftolozane, piperacillin and tazobactam in plasma were 0.250, 0.500 and 0.100 mg/mL, respectively.

The standard curves for ceftolozane, piperacillin and tazobactam in ELF were linear \(( r^2 \geq 0.99)\) over the concentration ranges of 1.00–1000, 1.00–500 and 1.00–250 ng/mL, respectively. The inter-day coefficients of variation were 3.55%–7.96% for ceftolozane, 4.54%–7.58% for piperacillin and 3.49%–7.65% for tazobactam. The accuracy of the method was \( \pm 5.40\%\), \( \pm 2.60\%\) and \( \pm 4.80\%\) for ceftolozane, piperacillin and tazobactam, respectively. The lower limit of detection for all three drugs in ELF was 1.00 ng/mL.

Urea concentrations in plasma and ELF were performed at MicroConstants, Inc. (San Diego, CA, USA) using a colorimetric technique (Urea Assay Kit Z5030016, BioChain, Hayward, CA, USA). The standard curve for the plasma urea assay was linear \(( r^2 \geq 0.99)\) over a concentration range of 2.50–50 mg/dL. The inter-day coefficients of variation ranged from 6.10% to 6.49% and the accuracy was \( \pm 11.5\%\). The standard curve for the ELF urea assay was linear \(( r^2 \geq 0.99)\) over a concentration range of 0.150–2.50 mg/dL. The inter-day coefficients of variation ranged from 7.23% to 18.2% and the accuracy was \( \pm 5.00\%\). Because of low observed urea concentrations in some BAL samples, the method was modified and a second standard curve range was established to be linear \(( r^2 \geq 0.99)\) over a concentration range of 0.050–1.00 mg/dL. The inter-day coefficients of variation for this lower sensitivity were 5.53%–13.2% and accuracy was \( \pm 4.13\%\).

The ELF volume was calculated by the urea dilution method, using urea as an endogenous marker of ELF recovered by BAL. Concentrations of ceftolozane/tazobactam and piperacillin/tazobactam in ELF were estimated from the concentration of drug in BAL fluid, the volume of BAL fluid collected and the ratio of urea concentration in BAL fluid to that in plasma using the following formula:

\[
\text{ELF concentration} = \frac{[\text{Drug}]_{\text{BAL}} \times V_{\text{BAL}}}{V_{\text{ELF}}}
\]

where \([\text{Drug}]_{\text{BAL}}\) is the concentration of the drug (ceftolozane, piperacillin or tazobactam), \(V_{\text{BAL}}\) is the volume of aspirated BAL fluid (total), and \(V_{\text{ELF}}\) is
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\[ V_{BAL} \times [\text{urea}]_{BAL}/[\text{urea}]_{plasma} \times [\text{urea}]_{BAL} \] is the concentration of urea in the BAL fluid (supernatant) and [urea]_{plasma} is the concentration of urea in the plasma specimens.

Safety assessments included adverse event reporting, physical examinations, vital signs and clinical laboratory evaluations. Treatment-emergent adverse events (TEAEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA 13.1) by system organ class and preferred term overall and by severity and relationship to study medication.

Statistical methods

No formal hypothesis tests were conducted. For demographic, baseline and safety variables, descriptive statistics were used. For continuous variables, descriptive statistics included the number of observations, mean, standard deviation, median and range. For categorical variables, descriptive statistics included frequency and percentage. For continuous variables, descriptive statistics were used. For categorical variables, descriptive statistics included frequency and percentage. The PK population included all subjects \( n=50 \) who received three doses of study medication and had both BAL and plasma samples collected sufficient to construct a PK profile. The safety population included all randomized subjects \( n=51 \) who received any dose (including partial doses) of study medication.

PK parameters were determined using non-compartmental analysis (Phoenix WinNonlin v 6.1; Pharsight Corporation, Mountain View, CA, USA). Plasma PK parameters computed using individual plasma concentrations versus time data included maximum concentration \( (C_{\text{max}}) \), last observed quantifiable concentration \( (C_{\text{min}}) \), and area under the plasma concentration–time curve from time 0 to the end of the dosing interval \( (\text{AUC}_{0\rightarrow\infty}) \). PK parameters for ELF were computed using the mean concentrations from each bronchopulmonary sampling time and consisted of \( C_{\text{max}}, C_{\text{min}} \) and \( \text{AUC}_{0\rightarrow\infty} \). The last sampling time for ELF (6 or 8 h) was also used as the value at time zero for determining AUC_{0\rightarrow\infty} for ELF.

Results

Subjects

A total of 51 subjects were randomized into the study, including 25 subjects in the ceftolozane/tazobactam group and 26 in the piperacillin/tazobactam group. All 51 subjects received at least one dose of study medication (safety population) and 50 received all three doses of study drug and completed the BAL procedure (PK population). One subject in the piperacillin/tazobactam group withdrew from the study because of a type 1 hypersensitivity reaction during administration of the first dose. Table 1 summarizes the demographic and baseline characteristics of subjects in the safety population. Overall, there were no statistical differences in baseline characteristics between the two treatment groups or among patients assigned to each BAL timepoint \( (P<0.05) \).

Pharmacokinetic assessments

Mean \( (+SD) \) plasma concentration–time profiles for ceftolozane/tazobactam and piperacillin/tazobactam are displayed in Figures 1 and 2, respectively. The mean \( C_{\text{max}} \) values \( \pm SD \) for ceftolozane and tazobactam were 67.2 \( \pm \) 12.1 and 14.9 \( \pm \) 2.4 mg/L, respectively, after administration of ceftolozane/tazobactam, and the mean total exposures (expressed as \( \text{AUC}_{0\rightarrow\infty} \)) were 158.5 \( \pm \) 24.1 and 19.3 \( \pm \) 2.9 mg-h/L, respectively. The mean \( C_{\text{min}} \) values \( \pm SD \) for ceftolozane and tazobactam were 3.3 \( \pm \) 1.1 and 0.2 \( \pm \) 0.1 mg/L, respectively. For piperacillin/tazobactam, the mean plasma \( C_{\text{max}} \) values \( \pm SD \) for piperacillin and tazobactam were 314.6 \( \pm \) 62.4 and 35.0 \( \pm \) 7.5 mg/L, respectively, and \( \text{AUC}_{0\rightarrow\infty} \) values were 357.3 \( \pm \) 65.9 and 46.1 \( \pm \) 8.7 mg-h/L, respectively. The mean \( C_{\text{min}} \) values \( \pm SD \) for piperacillin and tazobactam were 2.6 \( \pm \) 1.3 and 0.5 \( \pm \) 0.3 mg/L, respectively.

The individual ELF concentrations of ceftolozane/tazobactam and piperacillin/tazobactam following the last dose of each regimen are shown in Figures 3 and 4, respectively. Notably, measurable concentrations of ceftolozane were observed in ELF.
throughout the dosing interval in all patients, with mean and median $C_{\text{min}}$ values of 4.2 and 2.7 mg/L (range 1.7–7.3 mg/L), respectively. In addition, there was rapid entry of ceftolozane into ELF, and ELF concentrations showed a time pattern similar to plasma concentrations with minimal hysteresis.

The mean (±SD) concentrations of ceftolozane, piperacillin and tazobactam in plasma and ELF at the BAL collection times are summarized in Table 2. Mean $C_{\text{max}}$ for ceftolozane in ELF was 21.8 mg/L and total exposure (AUC $0–\infty$) was 75.1 mg.h/L. Corresponding values for piperacillin were 58.8 mg/L and 94.5 mg.h/L. $C_{\text{max}}$ and AUC $0–\infty$ values for tazobactam were 4.5 mg/L and 8.5 mg.h/L, respectively, when administered as ceftolozane/tazobactam and 15.3 mg/L and 24.7 mg.h/L, respectively, when administered as piperacillin/tazobactam.

The total ELF/plasma AUC ratio for ceftolozane was 0.48 compared with 0.26 for piperacillin. The total ELF/plasma AUC ratio for tazobactam was 0.44 when given as ceftolozane/tazobactam and 0.54 when given as piperacillin/tazobactam. The plasma protein binding is 20% for ceftolozane and $\sim 30\%$ for piperacillin, yielding free fraction penetration ratios (unbound plasma concentrations) of 0.59 and 0.38, respectively.

### Safety

All 51 patients who received study medication were included in the safety population. Overall, the incidence of adverse events...
was generally similar between the two treatment groups (44% for ceftolozane/tazobactam and 54% for piperacillin/tazobactam, respectively), and the pattern was consistent with those expected for β-lactam antibiotics. Five subjects in the ceftolozane/tazobactam group (20.0%) and six patients in the piperacillin/tazobactam group (23.1%) experienced at least one TEAE. The most common adverse event, occurring in three subjects in the piperacillin/tazobactam arm and one subject in the ceftolozane/tazobactam arm, was diarrhoea. In the ceftolozane/tazobactam arm, the following TEAEs occurred in one patient each: diarrhoea, viral upper respiratory tract infection, musculoskeletal chest pain, somnolence, haematuria and cough. In the piperacillin/tazobactam arm, the following TEAEs occurred in one patient each: diarrhoea, viral upper respiratory tract infection, musculoskeletal chest pain, somnolence, haematuria and cough. No serious adverse events were of mild severity. One patient in the piperacillin/tazobactam group withdrew from the study because of a type I hypersensitivity reaction during administration of the first dose. No serious adverse events were of mild severity. One patient in the piperacillin/tazobactam group withdrew from the study because of a type I hypersensitivity reaction during administration of the first dose. No serious adverse events were of mild severity. One patient in the piperacillin/tazobactam group withdrew from the study because of a type I hypersensitivity reaction during administration of the first dose.

**Discussion**

Gram-negative nosocomial pneumonia, particularly that caused by *P. aeruginosa*, is a severe and often life-threatening infection. Appropriate antibiotic coverage of the infecting organism is critical and, when initiated early, is associated with improved clinical outcomes. Although serum concentrations are most commonly used to estimate the therapeutic activity of an administered antibiotic, such measurements may exceed concentrations at the site of infection. Clinical efficacy is dependent on the delivery of therapeutic concentrations of antibiotics at the site of infection. Thus, ELF concentrations are a rational way to estimate the distribution of antibiotics into the lower respiratory tract.

The observed plasma concentrations in our study are similar to those recently reported from single- and multiple-dose PK studies in healthy adult subjects. The mean (±SD) *C*\(_{\text{MAX}}\) and AUC values after 10 days of intravenous administration of ceftolozane 1000 mg every 8 h were 58.0 ± 6.0 mg/L and 143.3 ± 22.1 mg-h/L, respectively. The slightly greater corresponding values of 67.2 ± 12.1 mg/L and 158.5 ± 24.1 mg-h/L in this study may be explained, in part, by differences in study design, such as the limited number of sampling times (*n* = 6) in the present study versus extensive sampling times (*n* = 15) in the previously reported Phase 1 PK study. These values are within the variation expected in different populations in different settings. The current study demonstrated that the ELF concentrations of ceftolozane/tazobactam achieved in this study exceed the MICs of the majority of common Gram-negative pathogens causing nosocomial pneumonia. The ELF concentrations of ceftolozane ranged from 1.71 to 29.6 mg/L, and 100%, 96% and 80% of the values were greater than 1, 2 and 4 mg/L, respectively. Microbiological studies have reported MIC\(_{50}\) and MIC\(_{90}\) values for ceftolozane/tazobactam of 1 and 2 mg/L, respectively, for *P. aeruginosa*. For β-lactam agents, efficacy is dependent on the length of time, as a percentage of the dosing interval, that the drug concentrations remain above the MIC. As the ELF concentration of ceftolozane exceeded 8 mg/L for >60% of the 8 h dosing interval, it suggests that the dose regimen of 1.5 g every 8 h will inhibit the growth of 99% of all *P. aeruginosa*. The concentration of tazobactam needed for activity in *vivo* is unknown, but the concentration >4 mg/L in the ELF for at least 1 h used in this study is believed to allow sufficient time for tazobactam, based on its high potency, to bind irreversibly to susceptible β-lactamases. For these susceptible β-lactamases, IC\(_{50}\) values are typically <100 nM. Additionally, the majority of β-lactamase inhibition with tazobactam occurs rapidly, within 20–30 min. Thus, it is hypothesized that, if there is enough tazobactam present early in dosing, it binds to the β-lactamases present, resulting in a susceptible bacterial population that the active component, ceftolozane, can then kill.

Our observations of intrapulmonary concentrations for both piperacillin/tazobactam and ceftolozane/tazobactam in healthy subjects are likely a conservative estimate of the magnitude of drug concentrations that may be observed in patients with infections and/or inflammatory conditions. Two previously published...
studies have reported ranges of mean ELF-to-plasma ratios (based on single paired concentrations) of 0.42–0.57 for piperacillin and 0.67–1.09 for tazobactam.17,18 These studies suggest that higher piperacillin and tazobactam ELF-to-plasma penetration ratios occur in critically ill patients on mechanical ventilation with severe nosocomial pneumonia compared with the ratios observed in our healthy adult subjects. However, several other differences in study designs, drug administration, assay methodologies, BAL sampling techniques and penetration ratio calculations make direct comparison of the three studies extremely difficult.

An additional finding in the current study was that the plasma and ELF concentrations of tazobactam following piperacillin/tazobactam administration were >2-fold higher ($P<0.0001$) than when an equivalent dose of tazobactam was given as ceftolozane/tazobactam. This observed difference is most likely explained by the dissimilarity in dosing regimens (e.g. every 8 h versus every 6 h) and infusion periods (e.g. 60 versus 30 min) resulting in lower plasma tazobactam concentrations with the ceftolozane regimen because of the short elimination half-life (~0.9 h) of tazobactam.19 In addition, the higher tazobactam concentrations observed when given as piperacillin/tazobactam may also be due to the known inhibition of tazobactam renal tubular excretion by piperacillin.20 Finally, both antibiotics were well tolerated, with adverse events consistent with those expected with β-lactam antibiotics.

Conclusions

The results from this study demonstrate that the ratio of ELF to total plasma AUC for ceftolozane was 0.48 in healthy adult subjects. The observed plasma and ELF concentrations resulting from a dosage regimen of 1.5 g ceftolozane/tazobactam intravenously every 8 h suggests that this dose is likely to provide adequate antibacterial coverage in the ELF in patients. Higher doses are expected to provide an increased assurance of clinical success; however, additional studies are needed to establish the safety of higher doses of ceftolozane/tazobactam. In summary, these findings support the continued clinical development of ceftolozane/tazobactam for the treatment of nosocomial pneumonia.

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Author contributions

G. C. made substantial contributions to the conception and design, acquisition of data, analysis and interpretation of data, critically revised the article for important intellectual content, and gave final approval of the version to be published. J. A. H. made substantial contributions to the analysis and interpretation of data, critically revised the article for important intellectual content, and gave final approval of the version to be published. M. H. G. made substantial contributions to the acquisition of data, critically revised the article for important intellectual content, and gave final approval of the version to be published. K. A. R. made substantial contributions to the interpretation of data, critically revised the article for important intellectual content, and gave final approval of the version to be published. O. U. made substantial contributions to the conception and design, acquisition of data, analysis and interpretation of data, critically revised the article for important intellectual content, and gave final approval of the version to be published.

References

9 Sader HS, Rhomberg PR, Farrell DJ et al. Antimicrobial activity of CXA-101, a novel cephalosporin tested in combination with tazobactam against Enterobacteriaceae, Pseudomonas aeruginosa, and Bacteroides


18 Boselli E, Breilh D, Cannesson M et al. Steady-state plasma and intrapulmonary concentrations of piperacillin/tazobactam 4 g/0.5 g administered to critically ill patients with severe nosocomial pneumonia. Intensive Care Med 2004; 30: 976–9.
