High extracellular levels of cefpirome in unaffected and infected lung tissue of patients

Jörg Lindenmann†, Sylvia A. Kugler‡, Veronika Matzi¹, Christian Porubsky¹, Alfred Maier¹, Peter Dittrich³, Wolfgang Graninger⁴, Freyja M. Smolle-Jüttner¹ and Christian Joukhadar¹,²,⁵,⁶*

¹Division of Thoracic and Hyperbaric Surgery, Medical University of Graz, Graz, Austria; ²J&P MEDICAL RESEARCH Ltd, Vienna, Austria; ³Institute of Pharmaceutical Sciences, Department of Pharmacology and Toxicology, Karl-Franzens University, Graz, Austria; ⁴Department of Infectious Diseases and Tropical Medicine, Medical University of Vienna, Vienna, Austria; ⁵Beth Israel Deaconess Medical Center, Boston 02215, MA, USA; ⁶Harvard Medical School, Boston 02115, MA, USA

*Corresponding author. Tel: +43-1-8760432-10; Fax: +43-1-8760432-33; E-mail: christian.joukhadar@jp-medical-research.com or cjoukhad@bidmc.harvard.edu

†Contributed equally to this study.

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Objectives: The objective of the present investigation was to measure the extracellular concentrations of cefpirome in unaffected and infected lung tissue of septic patients.

Methods: A single intravenous dose of 30 mg/kg total body weight of cefpirome was administered to eight patients every 12 h prior to insertion of microdialysis probes into lung tissue.

Results: The median (minimum, maximum) peak concentration (C_{max}), time to C_{max} (T_{max}), area under the concentration–time curve from 0 to 4 h (AUC 0–4) and AUC0–1 of unbound cefpirome for unaffected lung were 48 (32, 107) mg/L, 0.83 (0.17, 3.17) h, 117 (60, 177) mg·h/L and 182 (80, 382) mg·h/L, respectively. The corresponding values for infected lung tissue were 45 (6, 122) mg/L, 1.17 (0.83, 2.83) h, 92 (17, 253) mg·h/L and 206 (49, 379) mg·h/L, respectively. The median apparent terminal elimination half-lives (t_{1/2z}) of cefpirome were 2.61, 3.05 and 3.39 h for plasma, unaffected lung and infected lung, respectively. The median ratios of the AUC0–1 for lung to the AUC 0–1 for plasma were 0.63 (0.19, 1.55) and 0.46 (0.32, 0.98) for unaffected and infected lung, respectively.

Conclusions: We provide strong evidence that cefpirome penetrates effectively into the extracellular space fluid of lung tissue. Under steady-state conditions, the median concentrations of cefpirome in plasma, unaffected lung and infected lung exceeded the MICs of the majority of relevant bacteria over the entire dosing interval of up to 12 h after intravenous administration of a dose of 30 mg/kg total body weight.

Keywords: penetration, human, microdialysis

Introduction

The antibiotic cefpirome, a fourth-generation intravenous cephalosporin, is widely prescribed for the empirical therapy of severe bacterial infections in critically ill patients in intensive care, oncology and transplantation units in distinct member states of the European Union and Asia. In recent years, cefpirome was utilized as a model compound to describe the tissue penetration properties of β-lactams in selected patient populations in various clinical or experimental settings. From these studies, we learned that unbound plasma levels of anti-infectives, including cefpirome, closely mimic the interstitial concentration–time profiles assessed in peripheral soft tissues, healthy lung or inflamed wounds. Thus, the excellent ability of cefpirome to penetrate into the extracellular space fluid of tissues combined with its documented safety profile and bactericidal effects make cefpirome essential in the therapy of serious infections caused by bacteria such as meticillin-susceptible Staphylococcus aureus, streptococci, Pseudomonas aeruginosa and many others. The pharmacokinetic profile of cefpirome is well characterized for peripheral soft tissues in inflamed or healthy conditions. Its pharmacokinetic profile was also determined previously in healthy lung tissue in patients undergoing elective lung surgery due to lung cancer. However, at present, no information on extracellular concentrations of cefpirome is available for inflamed and infected lung tissue in the medical literature.
This information is essential, as bacteria typically reside and proliferate in the extracellular space fluid. The present study is aimed at addressing this important clinical question.

Methods

This study was performed at the Division of Thoracic Surgery, Department of Surgery, Landeskrankenhaus Universitätsklinikum Graz (State Hospital University Clinic of Graz, Graz, Austria). The study protocol was approved by the local ethics committee. All patients were given a detailed description of the study and their written informed consent was obtained prior to the start of study-related procedures. The study was performed in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines of the European Commission.

Patients

Sepsis was diagnosed according to the criteria of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee.8 Conservative treatment options had failed in all eight patients scheduled for surgical intervention. All patients suffered from sepsis due to pneumonia and/or metapneumonic pleural empyema. In these subjects, lateral thoracotomy, debridement and sublobular resection in cases of lung abscess were considered the treatment of choice. Co-administration of antimicrobial agents or medications other than the study drug was permitted if medically indicated. Exclusion criteria were known allergy to penicillins or cephalosporins, and renal dysfunction indicated by a creatinine clearance of <40 mL/min, as estimated by the Cockcroft–Gault formula.8 Sepsis scores were not consistently evaluated in all patients during this study.

Measurement of extracellular cefpirome concentrations and chemical analysis

The principles of microdialysis are described in detail elsewhere.2,10 In brief, one microdialysis probe was implanted into infected lung tissue close to the resection margin under visual control. Similarly, the reference probe was inserted into an unaffected region of lung tissue of the same lobe. After a 20 min equilibration period, a single dose of 30 mg/kg total body weight (BW) of cefpirome (Cefrom®; Sanofi-Aventis GmbH, Vienna, Austria) was administered to each patient intravenously every 12 h over 20–30 min. After centrifugation of venous blood at 1600 g for 10 min, microdialysates and plasma aliquots were stored at approximately −70°C until analytical tests were performed.

Cefpirome concentrations in specimens were determined by using a previously published HPLC method, with modification.11 The limit of quantification for cefpirome was 1 mg/L. The intraday and interday coefficients of variation were <0.07.

Pharmacokinetic calculations

Pharmacokinetic parameters were calculated by non-compartmental analysis. The maximum observed plasma concentration (Cmax) and the time to reach Cmax (Tmax) after drug administration were determined directly from the plasma concentration–time curves. The apparent terminal elimination half-life (t1/2z) and the area under the concentration–time curves from time zero (the start of infusion) to 4 h (AUC0–4) and the AUC from zero to the last quantifiable plasma concentration of cefpirome (AUC0–last) were calculated by using the log-linear trapezoidal rule. AUC0–∞ was derived by adding Cmax/kel to AUC0–last. The terminal elimination rate constant (kel) was estimated from the slope of the terminal exponential phase of the logarithmic plasma concentration–time profile using more than three data points. The value of t1/2z was calculated as 0.693/kel. The concentrations at 12 h were calculated by mathematical extrapolation using the formula: C12 = C∞ × e−k×t12, where C∞ is the concentration at 4 h after the start of infusion and kel is the elimination rate constant. Tissue pharmacokinetic parameters, such as Cmax, Tmax, AUC0–last, AUC0–∞ and t1/2z, were calculated using the same formulae as for plasma samples.

Commercially available computer software (KinettaTM, version 3.0; Thermo Electron Corporation, Waltham, MA, USA) was employed.

The time that cefpirome concentrations remained above the MIC for selected bacteria (%T>MIC) was calculated for the mean plasma concentration profile by the formula: T>MIC = ln(C0.5/MIC)/kel + 0.5.

Results and discussion

In the present pharmacokinetic study, five male and three female patients were included. The pharmacokinetic profile of unaffected lung tissue of one subject was not eligible for further evaluation, because of microdialysis probe malfunction. Demographic and pharmacokinetic data were non-normally distributed and are shown as median (minimum, maximum), unless otherwise stated. The median age was 55 (26, 80) years. Subjects had a median total BW of 76 (45, 100) kg and a median body mass index of 25 (14, 31) kg/m2. All patients were discharged from hospital within 7–12 days without any clinical signs of relapse (median follow-up of 4 months).

Median (minimum, maximum) values of Cmax, Tmax and AUC0–∞ for unaffected lung were 48 (32, 107) mg/L, 0.83 (0.17, 3.17) h and 182 (80, 382) mg·h/L, respectively, after administration of an intravenous dose of 30 mg/kg total BW of cefpirome. The corresponding values for infected lung tissue were 45 (6, 122) mg/L, 1.17 (0.83, 2.83) h and 206 (49, 379) mg·h/L, respectively. The median values for t1/2z of cefpirome were 2.61, 3.05 and 3.39 h for plasma, unaffected lung and infected lung, respectively. The magnitude of penetration of cefpirome into extracellular lung tissue was determined by calculating the ratios of the AUC0–∞ for lung to the AUC0–∞ for plasma. These median ratios were 0.63 (0.19, 1.55) and 0.46 (0.32, 0.98) for unaffected and infected lung tissues, respectively. Cefpirome was well tolerated in all subjects. No relevant adverse events related to microdialysis probe insertion were observed or reported.

We demonstrated that cefpirome penetrates well into the extracellular space fluid of inflamed and unaffected lung tissue in septic patients. After a very short period of plasma-to-tissue equilibration, the concentration–time profiles of cefpirome in plasma, and infected and unaffected lung tissues were almost identical (Figure 1), confirming the hypothesis that cefpirome distributes predominantly into the extracellular compartment. The main pharmacokinetic parameters are summarized in Table 1. These data indicate that severe inflammation did not exert any clinically relevant effect on the ability of cefpirome to penetrate infected lung tissue. Hence, the present investigation provides strong evidence of almost complete equilibration of cefpirome between plasma and the extracellular space fluid of lung tissues in inflammatory and normal states (Figure 1). This phenomenon has already been reported in previous studies for other non- or low plasma protein-bound antibiotics, such as meropenem or fosfomycin.3–5 In contrast, the pharmacokinetic concentration profiles of highly plasma protein-bound antibiotics, such as daptomycin, teicoplanin, vancomycin, ceftriaxone or ertapenem,
were substantially lower in the interstitial space fluid of soft tissues when compared with corresponding total plasma levels.\textsuperscript{12–14} This observation relates to the fact that only the unbound fraction of the drug is able to penetrate from the vascular compartment into the extracellular space fluid of tissues and exert its antimicrobial activity. Importantly, daptomycin is explicitly not approved for the therapy of lung infections. The plasma-protein binding of cefpirome is very low, with binding rates of between 2% and 8% reported in the scientific literature. More relevant changes in plasma-protein binding are to be expected for highly protein-bound antibiotics, particularly in patients suffering from hypoalbuminaemia. Albumin is responsible for most drug–protein binding activity. Thus, highly bound antimicrobial agents have an elevated affinity for binding sites on the albumin molecule. Further, drug–drug interactions, uraemia, free fatty acids, cirrhosis, hyperbilirubinaemia, hypoalbuminaemia and other factors might exert a significant impact on the unbound drug fraction in plasma. These clinical settings are likely to be present in many critically ill subjects. Therefore, some authors advocate the use of unbound concentration data for dosage recommendations of highly bound antibiotics.\textsuperscript{14,15} In the present investigation, individual values of plasma-protein binding were not determined, as moderate changes in plasma-protein binding are not anticipated to significantly affect cefpirome’s pharmacokinetic profile in tissues and plasma in septic patients.\textsuperscript{15}

**Figure 1.** Individual concentration–time profiles of cefpirome for (a) plasma (n = 8), (b) infected lung (n = 8) and (c) unaffected lung (n = 7) after a single intravenous dosage of 30 mg/kg total BW given every 12 h. Horizontal lines indicate different MICs, ranging from 8 to 32 mg/L.

**Table 1.** Main pharmacokinetic data after administration of a single intravenous dose of 30 mg/kg total BW of cefpirome given every 12 h

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Plasma (n = 8)</th>
<th>Lung unaffected (n = 7)</th>
<th>Lung infected (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (mg/L)</td>
<td>109 (55, 264)</td>
<td>48 (32, 107)</td>
<td>45 (6, 122)</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>0.33 (0.33, 0.67)</td>
<td>0.83 (0.17, 3.17)</td>
<td>1.17 (0.83, 2.83)</td>
</tr>
<tr>
<td>$\text{AUC}_{0-4}$ (mg.h/L)</td>
<td>188 (93, 410)</td>
<td>117 (60, 177)</td>
<td>92 (17, 253)</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty}$ (mg.h/L)</td>
<td>291 (133, 713)</td>
<td>182 (80, 382)</td>
<td>206 (49, 379)</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>2.61 (1.53, 6.68)</td>
<td>3.05 (1.23, 5.36)</td>
<td>3.39 (1.97, 5.42)</td>
</tr>
</tbody>
</table>

Data are presented as median (minimum, maximum).
Table 2. Calculated values for %T$_{MIC_{90}}$ for mean plasma, unaffected lung and infected lung concentration–time profiles after administration of a single intravenous dose of 30 mg/kg total BW of cefpirome and theoretic dosing intervals of 12, 8 and 6 h

<table>
<thead>
<tr>
<th>Dosing interval (h)</th>
<th>MIC$_{90}$ (mg/L)</th>
<th>plasma lung unaffected lung infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 h</td>
<td>8</td>
<td>91 70 82</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>70 47 57</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>48 23 33</td>
</tr>
<tr>
<td>8 h</td>
<td>8</td>
<td>137 105 122</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>104 70 86</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>72 35 50</td>
</tr>
<tr>
<td>6 h</td>
<td>8</td>
<td>182 140 163</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>139 93 115</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>96 46 67</td>
</tr>
</tbody>
</table>

As plasma pharmacokinetic profiles of cefpirome show large variability in the critically ill patient population, the individual values for %T$_{MIC_{90}}$ will also change accordingly.

From previous pharmacokinetic–pharmacodynamic experiments, we may assume that effective bacterial killing for cephalosporins, such as cefpirome, may be expected when the pathogen’s MIC is exceeded for 40%–50% and 70%–80% of the dosing interval for Gram-positive and Gram-negative bacteria, respectively. With regard to the intravenous dose of ~30 mg/kg total BW of cefpirome and the pharmacokinetic–pharmacodynamic calculations provided in Table 2, it becomes clear that this criterion is met for mean concentration–time profiles of plasma, infected and unaffected lung for MICs of up to 32 mg/L. Current MIC$_{90}$ values for cefpirome range between 0.5 mg/L for S. aureus and 32 mg/L for P. aeruginosa, suggesting that an intravenous dose of ~30 mg/kg total BW given at 12 h intervals might be effective in the majority of Gram-positive infections. However, for infections related to Gram-negative bacilli, the free concentrations in plasma will not exceed the pathogen’s MIC for sufficiently long enough periods to exert optimal bacterial killing. This holds particularly true if intersubject variability in tissue and plasma pharmacokinetic profiles are taken into account. All these factors may expose distinct individuals to the potential risk of inadequate and insufficient dosing regimens, especially in the case of infections related to P. aeruginosa. Such infections may require optimization of cefpirome’s dosing strategy. Shorter dosing intervals of 8 or 6 h, or continuous infusion may be considered as potential alternatives, provided that, like in the present study, subjects have a creatinine clearance of >40 mL/min (Table 2). With this in mind, total daily doses of up to 8 g of cefpirome are approved and may be a more appropriate therapeutic approach. In the event of treating patients suffering from pronounced impaired renal function, the dose of cefpirome may be adapted with ease, as its total clearance correlates well with renal creatinine clearance.

In summary, we demonstrated that the free concentration–time profile of cefpirome in the extracellular compartment of infected lung tissue closely mimics the pharmacokinetic profiles determined in plasma and unaffected lung. This indicates that cefpirome effectively penetrates infected lung tissue. Although the present explorative pharmacokinetic–pharmacodynamic study provides strong support to the notion of good clinical efficacy of cefpirome in patients presenting with complicated pneumonia, this remains to be confirmed by separate, well-designed clinical studies that specifically test the clinical efficacy of cefpirome in this indication.

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Transparency declarations
S. A. K. is an employee of J&P MEDICAL RESEARCH Ltd, which is an international independent research institute basically operating according to the Public–Private–Partnership concept. C. J. is managing director of J&P MEDICAL RESEARCH Ltd, owns 100% options and is a consultant for pharmaceutical companies. All other authors declare having no relationship with companies that make products relevant to the manuscript and have no conflicts of interest with the present work.

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