Pharmacodynamics of cefepime in patients with Gram-negative infections

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We conducted a prospective, open-label study to delineate a relationship between exposure and outcomes in 36 patients treated with cefepime. Twenty patients had documented Gram-negative infections. Timed blood and urine samples were obtained at steady state to determine pharmacokinetic and pharmacodynamic parameters. Microbiological success was significantly correlated with the proportion of the dosing interval that cefepime concentrations exceeded $4.3 \times \text{MIC}$. Our results support in vitro data that suggest bactericidal activity of $\beta$-lactams is optimized at concentrations $\sim 4 \times \text{MIC}$. These results should be validated by large prospective clinical trials.

Introduction

Cefepime is a broad-spectrum cephalosporin active against many Gram-positive and -negative bacteria. Data suggest that time above the MIC ($T > \text{MIC}$) is the most important pharmacodynamic parameter predicting outcome. However, others have shown that bactericidal activity of $\beta$-lactams reaches a maximal value at $4–6.6 \times \text{MIC}$. The objective of the study was to delineate a relationship between exposure and outcomes in patients treated with cefepime.

Patients and methods

Patient selection

All patients admitted to Detroit Receiving Hospital and University Health Center between October 1999 and June 2000, and prescribed cefepime for documented or suspected infection, were identified from the Pharmacy Department and prospectively evaluated for enrolment. Relevant clinical background and laboratory data were retrieved and cross-referenced with the inclusion/exclusion criteria. For inclusion, patients had to be $\geq 18$ years of age and receiving renally adjusted doses of cefepime. Exclusion criteria were: pregnancy, severe burns (>20% body surface area), spinal cord injury, cystic fibrosis, severely under- or overweight (±40% ideal body weight). Patients with fluctuating renal function (serum creatinine ±20% since the start of therapy), severely impaired renal function [creatinine clearance (CLCR) <1.1 mL/min or on dialysis] and neutropenic fever (absolute neutrophil count <1000 cells/µL) were also excluded. This study was approved by the Wayne State University Human Investigations Committee. Informed consent was obtained from all patients or their legal representatives prior to study participation. Any adverse events related to treatment or its administration were recorded.

Antimicrobial agent administration

Cefepime was reconstituted according to the manufacturer’s guidelines, and administered as an intravenous infusion over 30 min via a syringe pump. Dosing of cefepime was based on manufacturer’s recommendations.
**Assessment of renal function**

Initial dosing was based on estimated CL\textsubscript{CR}.\textsuperscript{6} Subsequently, urine collection over 8 h during a dosing interval and concurrent serum creatinine were used to estimate creatinine clearance.\textsuperscript{7}

**Blood sampling**

Three blood samples were obtained from each subject during one dosing interval after the third or later dose of cefepime. All samples were timed in relation to the last dose given. The samples were centrifuged within 30 min of collection and the plasma frozen at –70°C until analysis.

**Analytical methods**

Serum cefepime concentrations were determined by microbiological assay utilizing *Klebsiella pneumoniae* ATCC 10031 as the reference organism. Concurrent antibiotics with activity against the reference organism were deactivated prior to performing the microbioassays (e.g. phosphate for aminoglycosides).

**Pharmacokinetic/pharmacodynamic analysis**

Pharmacokinetic parameter values were estimated using a Bayesian estimation procedure.\textsuperscript{8} Prior parameter estimates were derived from a population pharmacokinetic analysis of cefepime, displayed as functions of demographic variables.\textsuperscript{9} We obtained a point estimate for each patient in our population, using the relationships reported and that patient’s demographic variables.\textsuperscript{9} A one- or two-compartment open model was fitted to the data. Models were discriminated using Akaike’s information criterion.\textsuperscript{10} Parameter values were estimated for each patient, and the pharmacokinetic/pharmacodynamic parameters calculated. Pathogens’ MICs were determined by Etest, following manufacturer’s instructions.

**Outcomes assessment**

Patients must have received cefepime therapy for 3 days or longer to be evaluated. Clinical outcomes were classified as either cure, improvement, failure or indeterminate,\textsuperscript{11} and assessed at the discontinuation of therapy or at discharge, whichever was earlier. Patients receiving any antimicrobial agent within 3 days before cefepime therapy were not evaluated. Patients with positive culture(s) were also evaluated for microbiological outcome. Microbiological outcomes were classified as eradication, presumed eradication, presumed persistence or indeterminate.\textsuperscript{11}

**Statistical analysis**

Analysis of outcomes was performed by exact logistic regression. Classification and regression tree (CART) analysis was used to determine breakpoints, and their statistical significance was validated by two-tailed Fisher’s exact test. An α value of 0.05 was employed.

**Results**

**Patient demographics/pharmacokinetic parameters**

Thirty-six patients were enrolled, their demographics are as shown in Table 1. Positive cultures were obtained in 20 patients. All were Gram-negative bacteria except one blood culture of *Staphylococcus aureus* isolated in conjunction with *Pseudomonas aeruginosa*. All patients with a positive culture received concurrent aminoglycoside therapy. Dosing of aminoglycoside was based on our institution protocol to achieve the target $C_{\text{max}}$/MIC ratio ≥10 whenever possible. The pharmacokinetics and dosing regimens of all patients are also shown in Table 1.

**Microbiological outcomes**

Microbiological success (eradication or presumed eradication) was found to be associated with $T >$ MIC (89% when $T >$ MIC is 100% versus 0% when $T >$ MIC is <100%, $P = 0.032$). The positive and negative predictive values for total drug time above MIC for 100% of the dosing interval were 89% and 100%, respectively.

**Classification and regression analysis (CART)**

Of the independent variables tested, microbiological success was found to be associated with $C_{\text{min}}$/MIC < 1.5 mg/L (100% when MIC < 1.5 mg/L versus 44% when MIC ≥ 1.5 mg/L, $P = 0.026$), and with $C_{\text{min}}$/MIC > 5.8 (100% versus 50%, $P = 0.014$). Statistical significance did not change when the $C_{\text{min}}$/MIC breakpoint was between 4.3 and 5.8.

**Univariate logistic regression analysis**

When the variables (baseline APACHE II scores, MIC, $C_{\text{min}}$/MIC, $T >$ MIC and $T > 4.3 \times$ MIC) were tested individually, microbiological success was significantly correlated to MIC [odds ratio (OR) = 0.625, 95% confidence interval (CI): 0.391–0.934, $P = 0.016$] and $T > 4.3 \times$ MIC (OR = 645, 95% CI: 1 640 000–5.6, $P = 0.006$). Both factors were highly correlated, but $T > 4.3 \times$ MIC had the better log-likelihood. Because of the limited sample size, the analysis would only support one independent variable. Nonetheless, other factors did not significantly improve the log-likelihood.

**Probability of microbiological success**

The probability of microbiological success was graphed as a function of $T > 4.3 \times$ MIC, as shown in Figure 1. In order to achieve a probability of 80% and 90% in microbiological suc-
Pharmacodynamics of cefepime

Table 1. Patient demographics, pharmacokinetics and cefepime dosing regimens

<table>
<thead>
<tr>
<th></th>
<th>All patients enrolled</th>
<th>Patients with positive culture</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>36</td>
<td>20</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55.2 ± 18.5</td>
<td>58.0 ± 17.3</td>
</tr>
<tr>
<td>Race (AA/C/O)</td>
<td>24/11/1</td>
<td>13/7/0</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>25/11</td>
<td>14/6</td>
</tr>
<tr>
<td>APACHE II</td>
<td>12 (0–32)</td>
<td>11.5 (5–32)</td>
</tr>
<tr>
<td>CLCR (mL/min)</td>
<td>78.8 ± 38.3</td>
<td>76.1 ± 40.4</td>
</tr>
<tr>
<td>Concurrent aminoglycoside</td>
<td>31/36</td>
<td>20/20</td>
</tr>
<tr>
<td>Site of infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>respiratory tract</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>blood</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>soft tissue/wound</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>urinary tract</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>bone</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>C max (mg/L)</td>
<td>211.12 ± 243.93</td>
<td>207.24 ± 246.02</td>
</tr>
<tr>
<td>C min (mg/L)</td>
<td>12.24 ± 15.42</td>
<td>8.57 ± 9.35</td>
</tr>
<tr>
<td>Terminal t1/2 (h)</td>
<td>7.56 ± 6.11</td>
<td>7.25 ± 6.35</td>
</tr>
<tr>
<td>Dosing regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 g every 12 h</td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>2 g every 24 h</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>1 g every 24 h</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

AA, African American; C, Caucasian; O, others; CLCR, creatinine clearance; C max, maximum concentration; C min, minimum concentration.

aMean ± S.D.

bMedian (range).

cAPACHE II score at the start of cefepime therapy.

cess, it would be necessary for serum cefepime concentrations to be above 4.3 × MIC for 83% and 95% of the dosing interval, respectively.

Clinical outcomes

Twenty-eight patients were evaluable. Clinical success (cure or improvement) and failure were found in 22 patients and one patient, respectively. The clinical outcome for the remaining five patients was deemed indeterminate. Two of these five patients had a positive culture, and their therapy was switched to an alternative agent upon the identification of the pathogen (without susceptibility data) for ‘better coverage’. The renal function of the remaining three patients was unstable after the blood sampling and required dosage adjustment. We were unable to ascertain the drug exposure in these patients and they were not included in the analysis as a result.

Safety and tolerance of study drug

No adverse effects related to the drug or route of administration were observed in any patient during the study period.

Discussion

Although the pharmacodynamics of the β-lactams are well documented, most data are derived from in vitro and animal studies, where \( T > \text{MIC} \) has been shown to be the most important pharmacodynamic parameter governing bacterial killing.\(^2\)

However, there are also convincing data available to suggest that β-lactams’ bactericidal activity can be further enhanced by maintaining free drug concentrations four- to six-fold above the MIC,\(^3,4\) this concentration range enhancing maximal kill rates.

There are limited data published on the correlation of pharmacodynamics of β-lactams and outcomes in clinical settings. The in vitro and animal data cited above present a clear and convincing case that \( T > \text{MIC} \) is the pharmacodynamically linked variable for β-lactams. However, little has been done to examine whether multiples of the MIC as seen in in vitro studies are important for optimizing patient outcomes.

In our prospective study, although we found that microbiological success was associated with \( T > \text{MIC} \), the strongest statistical relationship was observed when \( T > 4.3 \times \text{MIC} \) was used as the independent variable, in line with data from time-kill studies.\(^3\) Further increases in drug concentration beyond \( 4 \times \text{MIC} \) only resulted in a marginal increase in bacterial killing.

In another study by Manduru et al.,\(^4\) using various concentrations of ceftazidime against different strains of \( P. \) aeruginosa, and fitting a sigmoid \( E_{\text{max}} \) model to their respective bactericidal activities, the optimal killing rate was reported to
be when the concentration to MIC ratio was 6.6. These studies support our observation that whereas $T > MIC$ is predictive of bactericidal activity, bacterial killing and microbiological outcome can be further enhanced by achieving a concentration $4-6 \times MIC$ throughout the dosing interval. This finding, if validated, has considerable importance for the optimal therapy of patients.

We were unable to find any variable to predict clinical success, most likely due to the small sample size we had. Two of four patients with microbiological failure had clinical success at the end of therapy. Clinical outcomes are dependent on many factors in addition to the appropriateness and adequacy of antimicrobial therapy, whereas microbiological outcomes are more closely linked to the activity of the antimicrobial agent. Although early microbiological eradication is not necessary for clinical success, it often predicts clinical success and reduces the likelihood of resistance emergence. Despite our relatively small sample size, we were still able to find a reasonably robust model to explain our positive findings. We wish to point out that all 20 evaluable patients received concurrent aminoglycosides. It is reasonable to believe that aminoglycosides contributed to bacterial killing in conjunction with cefepime. Consequently, our conclusions may not be relevant to other cohorts and will need to be validated by a large prospective randomized clinical trial.

In summary, our results support in vitro data which indicate that the bactericidal activity of $\beta$-lactams against Gram-negative bacteria is associated with $T > MIC$. In adult patients with Gram-negative infections on concurrent aminoglycosides, the probability of microbiological success was most strongly associated with the proportion of the dosing interval for which cefepime concentration exceeded $4.3 \times MIC$. If validated, this suggests dosing regimens can be further optimized to increase the probability of microbiological eradication.

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**References**


