Plasma, urine and skin pharmacokinetics of cefepime in burns patients

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We studied the pharmacokinetics of cefepime (2 g bd) in six burns patients. Blood, urine and skin samples were collected to measure cefepime concentrations. A two-compartment model was fitted to the data. At day 1, \( t_{1/2} \) was 2.45 ± 0.56 h, \( V_{ss} \) 0.36 ± 0.1 L/kg, total clearance 152 ± 25.2 mL/min, and AUC 217 ± 34 mg·h/L. There was no statistical difference between day 1 and day 3 for any of the pharmacokinetic parameters. We demonstrated good penetration of cefepime in skin. These results show that it is not necessary to change the standard dosage of cefepime in burns patients.

Introduction

Cefepime is a broad-spectrum cephalosporin. It acts against members of the Enterobacteriaceae and \textit{Pseudomonas aeruginosa} but maintains activity against Gram-positive isolates that is similar to that of first- or second-generation cephalosporins. Pharmacokinetic studies have indicated that cefepime exhibits linear pharmacokinetic behaviour. Cefepime is cleared primarily by urinary excretion (85%). Elimination is prolonged in patients with compromised renal function.\textsuperscript{1} In normal male subjects, cefepime has a mean elimination half-life of about 2.2 h and a volume of distribution (\( V_{ss} \)) of 19.3 L. The pharmacokinetics of cefepime in burns patients is not well documented. For many drugs in these patients, \( V_{ss} \), \( t_{1/2} \) and clearance are often modified. For instance, \( V_{ss} \) of ceftazidime and ticarcillin is increased in burns patients. The same results are observed for \( t_{1/2} \) of ceftazidime, and clearance of vancomycin.\textsuperscript{2–4}

The purpose of this study was therefore to characterize the pharmacokinetics of cefepime in burns patients after administration of 2 g bd iv doses.

Materials and methods

Patients

Six burns patients (five males and one female) were studied. Their mean age was 39.8 ± 11.3 years (range 30–62), height 169.5 ± 8.2 cm (range 155–178), weight 72.1 ± 11 kg (range 54–82), creatinine clearance 123 ± 26 mL/min (range 88–152), abbreviated burn severity index (ABSI) score 8.5 ± 1.97 (range 6–10) and the body surface area deep burn was 31.5 ± 23.6 (range 8–60). Patients participated in the study after informed consent. This protocol was approved by the Committee for the Protection of the Rights of Human Subjects according to French law. Patient inclusion criteria included: absence of drug allergies or intolerance to \( \beta \)-lactams, absence of pregnancy, a minimum of 18 years of age, burns at least 48 h old with ABSI score 6–10 and bacterial infection susceptible, or likely to be susceptible, to cefepime. All the patients were haemodynamically stable.

Drug administration and sample collection

Cefepime (2 g bd) was given as a constant rate iv infusion over 30 min. Eight heparinized blood samples were drawn from each subject after infusion at day 1 and day 3. Blood sampling times relative to the start of infusion were as follows: start of the infusion, 30 min and 1, 2, 4, 6, 8 and 12 h after the beginning of infusion. Four urine samples were collected: (0–2 h), (2–4 h), (4–8 h) and (8–12 h) after the beginning of the first infusion. Urine output was recorded for each period. At day 3, a burned skin biopsy was obtained 3–5 h after the start of infusion and stored at −80°C. For a given sampling time, the ratio between skin and plasma concentrations was determined.
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Cefepime analysis

Cefepime was a gift from Bristol-Myers Squibb (Paris, La Defense, France). Plasma and urine samples were analysed for intact cefepime according to a validated HPLC–UV method. Skin samples were pulverized following freezing with liquid nitrogen and incubated for 2 h in NaCl 0.9% at 4°C to allow diffusion. After centrifugation, the supernatant was recovered and processed as for plasma samples. The inter-day precision was 7.7–12.5% for cefepime concentrations ranging from 2 to 40 mg/L.

Pharmacokinetic analysis

The Siphar computer program was used to obtain pharmacokinetic parameter estimates. Weighted least squares regression was used to fit the data. Determination of the optimal compartment model was based on visual inspection of the concentration–time curves. Two compartment models were used to fit the observed concentration–time data for all patients. $V_s$, $t_{1/2}$ and the area under the serum concentration–time curve (AUC) were estimated. Cefepime total clearance ($Cl_T$), renal clearance ($Cl_R$), non renal clearance ($Cl_{NR}$) and the percentage of cefepime excreted in urine were calculated using standard formulae.

Statistical analysis

A paired Student’s $t$ test was used to compare the pharmacokinetic parameter estimates obtained after the initial cefepime dose and after multiple dosing. A $P$ value of <0.05 was considered significant.

Results

Individual, mean plasma cefepime concentrations obtained in burn patients are shown in the Figure. The maximum cefepime concentrations obtained in plasma after infusion ranged from 89 to 146 mg/L at day 1 and from 71.5 to 243 mg/L at day 3. The average cefepime concentrations remaining 12 h after the beginning of infusion were, respectively, 2.1 ± 1.1 mg/mL and 2.4 ± 0.95 mg/mL at day 1 and day 3.

The pharmacokinetic parameters estimated from plasma data obtained at day 1 and day 3 are shown in the Table. No statistically significant difference was noted between day 1 and day 3 for estimated pharmacokinetic parameters.

The individual urinary pharmacokinetic parameters from five of the six patients at day 1 after the first dose of cefepime are 122 ± 24 mL/min (range 96–163) for $Cl_R$, 45 ± 36 mL/min (range 11–86) for $Cl_{NR}$. In five patients, 76% of the total dose was excreted within 12 h. The cefepime concentrations measured in burned skin are 33 ± 41.6 μg/g (range 9–115). The ratio skin/plasma measured was 1.52 ± 1.82 (range 0.42 –5.06).

Discussion

The pharmacokinetics of drugs when used in burns patients may be greatly altered (e.g. aztreonam and ceftazidime). However, few pharmacokinetic studies are available in burns patients. The pharmacokinetic profile of cefepime is altered in patients with various degrees of renal dysfunction. For practical reasons we did not match burns patients with healthy volunteers. We, therefore, compared our results with data from previous studies.

In our study, the peak at day 1 (122 ± 23 mg/L) was consistent with that observed by Van der Auwera et al. in healthy volunteers (126 ± 21.7 mg/L). There was no statistical difference between day 1 and day 3. For AUC, $t_{1/2}$, $Cl_T$ and $V_s$, the individual data of the burns patients did not show wide inter-individual variability, although Kvaric et al. did observe a wide variability of this parameter in patients with respiratory tract infections.

The mean $t_{1/2}$ of 2.5 h was similar to the value of approximately 2.2 h reported in healthy volunteers. Generally, there is a tendency for a decrease in $t_{1/2}$ in burns patients (e.g. for aminoglycosides). $V_s$ and $Cl_T$ of cefepime as determined in our study were similar to those in normal subjects (19.3 ± 3.4 L and 138 ± 22 mL/min, respectively) with only
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To our knowledge, there have been no studies on cefepime penetration of the skin. We demonstrated that cefepime has good penetration in burned skin and this phenomenon may be important in successful treatment of burn-associated infections. However, the interpretation of the skin/plasma ratio and skin concentration is difficult because of vascularization of the sample site, which exhibits wide variability between individuals.

The pharmacokinetic parameter estimates for cefepime (2 g bd) in six burns patients were similar to estimates in normal volunteers. These results demonstrate that it is not necessary to change the standard dosage of cefepime in burns patients.

Acknowledgement

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References


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Table. Cefepime plasma pharmacokinetic parameters for the different patients

<table>
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<tr>
<th></th>
<th>day 1</th>
<th>day 3</th>
<th>ClT (mL/min)</th>
<th>day 1</th>
<th>day 3</th>
<th>AUC (mg·h/L)</th>
<th>day 1</th>
<th>day 3</th>
<th>Vss (L/kg)</th>
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<td>Mean</td>
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<td><strong>152</strong></td>
<td><strong>133</strong></td>
<td><strong>217</strong></td>
<td><strong>262</strong></td>
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<td>(-8.9; 70.2)</td>
<td>(-16.7; 122)</td>
<td>(-0.05; 0.15)</td>
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<sup>a</sup>S.D., standard deviation

<sup>b</sup>Confidence interval of differences between pharmacokinetics parameters on day 1 and day 3.