Comparison of Ceftazidime and Cefamandole Pharmacokinetics and Blister Fluid Concentrations

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Eight healthy male volunteers received 1 g of either ceftazidime or cefamandole as an intravenous injection. Serial blood samples were taken over the next 8 h. Urine samples were collected over 24 h. Levels of these antibiotics were measured in the fluid of blisters resulting from application of cantharides. The concentration of ceftazidime in serum at 0.25 h after intravenous injection was 83.3 μg/ml. The serum half-lives for the respective drugs were 1.8 and 0.8 h. The mean apparent volume of distribution of ceftazidime (13.6 liters) was greater than that of cefamandole (9.8 liters). Plasma clearance was 111 ml/min for ceftazidime and 216 ml/min for cefamandole. The maximum blister fluid concentration of ceftazidime was 45.9 μg/ml, and that of cefamandole was 22.1 μg/ml. The relative availability of each drug in blister fluid compared with serum was similar.

Ceftazidime (GR 20263) is a new broad-spectrum cephalosporin at present undergoing clinical evaluation (4, 6). When administered parenterally to humans, it attains high levels in serum with no evidence of metabolic breakdown and has a somewhat longer half-life than do certain other clinically available cephalosporins (4). This study provides a comparison of the pharmacokinetics of ceftazidime and cefamandole in healthy male volunteers and a comparison of the penetration of blister tissue fluid by these drugs.

MATERIALS AND METHODS

Eight healthy males, ages 24 to 38 years, with a mean weight of 73.8 kg (standard deviation [SD], 7.5 kg), volunteered for this study. All eight volunteers received both drugs separated by an interval of 5 weeks, allowing the cantharides blisters to heal. Medical history and physical examination conducted on each volunteer revealed no abnormal findings. In particular, there was no evidence of renal or liver disease and no history of atopy or allergy to drugs. None was on any other medication. Each received a written protocol, and written informed consent was obtained.

Analyses of blood for biochemistry and a full blood count and midstream urine samples were normal in the week before the study.

All volunteers abstained from strenuous exercise, alcohol, and excessive fluid intake for 12 h before dosing and for 24 h afterwards. On the evening before the study, two 0.2% cantharides plasters (1 by 1 cm) were lightly taped to the anterior surface of the forearm. The next morning, the volunteers took a light breakfast at least 1 h before dosing. An intravenous cannula was inserted in a suitable forearm vein and kept patent with heparinized saline (100 IU/ml) after each sample. The urinary bladder was emptied immediately before dosing. A 1-g dose of the antibiotic dissolved in 10 ml of sterile water was injected intravenously into the contralateral arm over a period of 3 to 5 min. Blood samples were taken via the intravenous cannula (after discarding the first 2 to 3 ml) at 0, 15, 20, 30, 45, 60, and 90 min and at 2, 3, 4, 5, 6, 7, and 8 h. The samples were allowed to clot for 1 h and then centrifuged at 3,000 rpm. The serum was decanted and assayed on the same day. Urine was collected from 0 to 2, 2 to 4, 4 to 8, 8 to 12, and 12 to 24 h. Volumes passed were measured before aliquots were used for assay.

Duplicate samples of blister fluid (24-μl volume) were withdrawn into a pipette at 30 min after dosing and hourly thereafter to 8 h. Samples were placed on sterile, preweighed, 6-mm filter paper disks which were reweighed immediately to ascertain the weight of fluid to be assayed. No bleeding resulted from these samplings. Fluid loss from the blisters was prevented by use of plastic spray dressings.

Assays were performed by a routine agar plate diffusion technique against standards prepared in human serum for serum samples and in 70% human serum for blister fluid. Previous studies (7) showed that the protein content of blister fluid is 70% of that of serum. The standards for the blister fluid were applied to identical disks in the same volume as that calculated, by weighing, to be on the test disk. A separate set of standards was therefore used for each blister fluid sample.

The urine samples were assayed against standards prepared in phosphate-buffered saline (pH 6.6).

The indicator organism for bioassay of ceftazidime was Escherichia coli NCTC 10418, and for bioassay of cefamandole, Bacillus subtilis NCTC 8236 was used. The 95% confidence limits for triplicate assays of serum and urine were more than ±13%. The area under the curve (AUC) for blister fluid was measured by trapezoidal methods.
Pharmacokinetic analysis was performed by using a computer program for a nonlinear curve-fitting procedure.

Plasma and renal clearances were calculated as follows. Plasma clearance (milliliters per minute) = dose/AUC_{inf}. Renal clearance (milliliters per minute) = amount excreted in urine in 24 h/AUC_{inf}, where AUC_{inf} is the area under the concentration/time curve from time zero to infinity (computer derived). The total apparent volume of distribution (V_d) was the sum of the central volume of distribution and peripheral volume of distribution and was calculated as described by Greenblatt and Koch-Weser (3).

RESULTS

The concentrations of each antibiotic in serum at various times after dosage are shown in Table 1. The results of the pharmacokinetic analysis, fitting a two-compartment open model, are summarized in Table 2. The level of ceftazidime in serum at 15 min after dosing was 83.3 μg/ml, similar to that of cefamandole, which was 77.7 μg/ml. Both compounds exhibited a rapid distribution phase followed by a slower elimination phase. The half-life of ceftazidime was 1.8 h; that of cefamandole was 0.8 h. β describes the slope of the terminal log-linear phase of drug distribution. Whereas the concentration of cefamandole in serum was at a barely detectable level by 6 h, the concentration of ceftazidime was 4.7 μg/ml. The apparent total volume of distribution of ceftazidime was approximately 40% greater than that of cefamandole.

Recovery of ceftazidime in urine was greater than that of cefamandole, thus giving a difference between total and renal clearance for ceftazidime that was smaller than that for cefamandole.

Both agents readily penetrated blister fluid. The standard deviation of the assays on blister fluid was greater than that of serum assays. The highest concentration of ceftazidime, 45.9 μg/ml (SD, 3.5 μg/ml), was reached at 1 h; that for cefamandole, 22.1 μg/ml (SD, 4.8 μg/ml) was reached at 0.5 h. It is possible that the 0.5-h sample of blister fluid might have missed the peak level of cefamandole. The terminal blister fluid half-lives were slightly longer than the serum half-lives. The relative availability of each drug in blister fluid compared with serum was calculated from blister AUC_{0-8 h} × 100/serum AUC_{0-8 h}. Blister fluid AUC_{0-8 h} was 128.4 (SD, 6.5) and 62.5 (SD, 8.6) for ceftazidime and cefamandole, respectively; serum AUC_{0-8 h} was 148 (SD, 7.7) and 78.4 (SD, 3.5) for the two compounds. The relative availability was similar, being 89.2 for ceftazidime and 81.0 for cefamandole.

DISCUSSION

The serum half-life of cefamandole has been reported to be 0.6 h after intravenous infusion and 1.0 h after intramuscular injection (2), whereas in this study, the half-life was found to be 0.8 h. The difference is possibly due to differences in the technique of deriving the half-life, since these workers used a single-compartment model. The urinary recovery of cefamandole was similar to that found in an earlier study (2).

The serum half-life of ceftazidime, very close to that reported previously (4) was somewhat longer than that of cefamandole. Protein binding of cefamandole (74%) (2) was greater than that of ceftazidime (17%) (4). As measured by relative availability, both penetrated tissue fluid equally well. Previous studies with other β-lactams (7) could be compared with the present results.

### Table 1. Mean concentrations of cefamandole and ceftazidime in serum and blister fluid

<table>
<thead>
<tr>
<th>Time (h) after intravenous injection</th>
<th>Drug concn (μg/ml)*</th>
<th>Ceftazidime</th>
<th>Cefamandole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum</td>
<td>Blister fluid</td>
<td>Serum</td>
</tr>
<tr>
<td>0.25</td>
<td>83.3 (10.6)</td>
<td>77.7 (11.3)</td>
<td>60.9 (6.8)</td>
</tr>
<tr>
<td>0.50</td>
<td>48.7 (5.4)</td>
<td>29.5 (4.3)</td>
<td>40.9 (4.4)</td>
</tr>
<tr>
<td>1.0</td>
<td>30.0 (4.0)</td>
<td>12.0 (2.5)</td>
<td>22.9 (3.8)</td>
</tr>
<tr>
<td>1.5</td>
<td>14.3 (2.4)</td>
<td>2.7 (0.8)</td>
<td>19.7 (4.7)</td>
</tr>
<tr>
<td>2</td>
<td>6.3 (1.1)</td>
<td>0.5 (0.3)</td>
<td>9.7 (1.7)</td>
</tr>
<tr>
<td>3</td>
<td>4.7 (1.2)</td>
<td>0.1 (0.1)</td>
<td>6.3 (1.1)</td>
</tr>
<tr>
<td>4</td>
<td>3.4 (0.9)</td>
<td>ND*</td>
<td>4.7 (2.3)</td>
</tr>
<tr>
<td>7</td>
<td>2.3 (0.6)</td>
<td>3.6 (1.7)</td>
<td>ND</td>
</tr>
</tbody>
</table>

* Standard deviations are given within parentheses.

* ND, Not detectable.

### Table 2. Pharmacokinetics of cefamandole and ceftazidime*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Serum half-life (h)</th>
<th>β (h⁻¹)</th>
<th>V_d (liters)</th>
<th>AUC_{inf}</th>
<th>% of dose recovered in urine</th>
<th>Mean clearance (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Plasma (m_l_/min)</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>1.8 (0.1)</td>
<td>0.394 (0.04)</td>
<td>13.6 (1.9)</td>
<td>153.5 (23.1)</td>
<td>88.7 (12.8)</td>
<td>111 (17)</td>
</tr>
<tr>
<td>Cefamandole</td>
<td>0.8 (0.2)</td>
<td>0.896 (0.08)</td>
<td>9.8 (1.0)</td>
<td>78.4 (9.9)</td>
<td>74.9 (6.1)</td>
<td>216 (30)</td>
</tr>
</tbody>
</table>

* Numbers within parentheses are standard deviations. V_d, volume of distribution.
have indicated that less penetration might be expected in the case of the more highly bound drug. This suggests that protein binding is not the only factor influencing tissue penetration. In the case of cefamandole, other physicochemical factors (1) may be of greater importance.

Since serum and tissue fluid levels of ceftazidime exceeded the minimum inhibitory concentration for 90% of the strains of Enterobacteriaceae (6) for 8 h or longer, this agent could possibly be administered twice daily, whereas cefamandole is usually administered three or four times daily, or even more frequently. Even though ceftazidime is relatively less active against Staphylococcus aureus (minimum inhibitory concentration for 90% of strains, 16 µg/ml) (6), the serum and tissue fluid levels were in excess of 16 µg/ml for about 3 h, suggesting that therapy directed against this pathogen may be possible if the drug is administered more frequently or in a higher dose.

Previous studies (7) have shown that cantharides blister fluid is similar in composition to superficial burn fluid (5). The minimum inhibitory concentration of ceftazidime against 90% of strains of Pseudomonas aeruginosa, 2.0 µg/ml (6), suggests that this agent may be useful in the treatment of burns and tissue infections caused by this pathogen.

ACKNOWLEDGMENTS

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LITERATURE CITED