Pharmacokinetics and Tissue Penetration of Ceftibuten


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The pharmacokinetics of the cephalosporin ceftibuten were determined after the fifth and final dose of 200 mg given every 12 h. Concentrations in plasma and cantharidin-induced inflammatory fluid were determined by a microbiological assay. Samples for three volunteers were assayed by a high-performance liquid chromatographic procedure to determine levels for both cis and trans ceftibuten. The mean peak level of ceftibuten in serum was 10.9 ug/ml at a mean time of 1.8 h after administration, and the mean elimination half-life from plasma was 2.5 h. Penetration into the inflammatory fluid was good, the mean peak level being 9.2 ug/ml at a mean time of 3.7 h. The mean percent penetration into the inflammatory fluid was 113.4%. High-performance liquid chromatography analysis showed that the mean peak level of the trans isomer was 5.7% that of the cis isomer. This study suggests that twice-daily doses of ceftibuten should be sufficient to treat urinary or systemic infections caused by susceptible pathogens.

Ceftibuten (Sch 39720; 7432-S) is a new oral cephalosporin having the chemical formula (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylaminol]-8-oxo-5-thia-1-aza-bicyclo-2-ene-carboxylic acid. Preliminary data (5) on the in vitro activity of this compound suggest that it is very active against members of the family Enterobacteriaceae, being somewhat more active than cefixime. It displays high activity against Haemophilus influenzae, Branhamella catarrhalis, and Neisseria sp. but has less activity against Streptococcus pneumoniae and poor activity against Staphylococcus aureus. Its stability to hydrolysis by β-lactamases is similar to that of cefixime and superior to that of cefaclor (5). Preliminary human pharmacokinetic studies (M. Nakashima, M. Iida, T. Toshiba, T. Kitagawa, T. Oguma, and H. Ishii, Program Abstr. 26th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 591, 1986) show that the drug is well absorbed and that the serum half-life is 1.5 to 2.1 h. Unlike cefuroxime axetil and cefpodoxime proxetil, which are prodrug esters, ceftibuten shares with cefixime and BMY 28100 the ability to be absorbed without esterification.

In this study we investigated the pharmacokinetics of ceftibuten after a single oral dose and determined its penetration into chemically induced blister fluid, which resembles a mild inflammatory exudate (8) of groups III, IV, and V.

MATERIALS AND METHODS

Six healthy male volunteers, 23 to 38 years of age (mean age, 29.8 years), participated after ethical committee approval and signed informed consent had been obtained. Their weights ranged from 68.5 to 87.0 kg (mean, 76.85 kg), and their heights ranged from 174 to 179 cm (mean, 176.5 cm). Their medical histories indicated no significant past illness and, in particular, no β-lactam allergies or atopic predispositions. Hematological and biochemical profiles and detailed physical examinations 1 week prior to the study were all normal.

Each volunteer received 200 mg of ceftibuten every 12 h (8:00 a.m. and 8:00 p.m.) for 2 days. At 10 p.m. on the evening of day 2, two 0.2% cantharidin-impregnated plasters (1 by 1 cm) were placed on the anterior surface of the forearm and taped in place. After overnight fasting, the subjects received the fifth and final dose of 200 mg of ceftibuten at 8:00 a.m. with 120 ml of water. Thereafter, fluid was taken ad libitum. Solid food was taken after 4 h. Blood samples were taken at time zero and 2 h after the 8:00 a.m. dose on days 1 and 2. On day 3, blood was drawn through an intravenous cannula (kept patent with 2-ml doses of heparinized saline [100 IU/ml]) at 0, 30, 60, and 90 min and 2, 3, 4, 6, 8, 12, 26, and 30 h after dosing. Inflammatory exudate from the blisters was sampled with a micropipette on day 3 at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, and 12 h. The integrity of the blisters was maintained by spraying with a fast-drying plastic dressing, Nobecucine (Astra Pharmaceuticals Ltd., Kings Langley, United Kingdom). Antibiotic assays were performed in triplicate within 1 h of sample collection by using a plate diffusion method. Samples were also assayed by high-performance liquid chromatography. For the plate diffusion assay, the indicator organism was Providencia stuartii (DRH K166). The medium was Oxoid antibiotic medium no. 1 (Oxoid, Basingstoke, United Kingdom), which had been incubated aerobically overnight at 30°C. Standards were prepared by using human serum for serum samples (pooled human serum; Flow Laboratories, Irvine, United Kingdom) and 70% human serum in phosphate buffer (pH 7) for blister inflammatory exudates (to correlate with the serum content of the exudates [8]). Results were calculated by using the correction of Bennett et al. (1). The lower limit of sensitivity was 0.05 μg/ml. The between-day coefficient of variation of the assay was 7.6%.

Three volunteers had assays performed by high-performance liquid chromatography to determine the amounts of cis and trans ceftibuten. A Spherisorb 5 ODS2 column (Phase Separations Ltd., Deeside, England) with a mobile phase of 25% methanol-10% acetic acid or 5 mM heptane sulfonic acid was used at a flow rate of 1.7 ml/min. The column eluent was maintained by a UV detector at 264 nm (model 735 LC; Kontron Analytic Ltd., London, England). The lower limit of sensitivity of the cis and trans isomers was 0.25 μg/ml. The coefficient of variation of the assay was 7.5%.

Pharmacokinetic calculations on the serum data were performed by assuming an open two-compartment linear model where elimination occurs from the central compartment, and they were undertaken by a GPHARM program.
TABLE 1. Predose and 2-h concentrations of ceftibuten in plasma

<table>
<thead>
<tr>
<th>Day</th>
<th>Time of determination</th>
<th>Concen (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>1</td>
<td>Predose</td>
<td>NDL*</td>
</tr>
<tr>
<td></td>
<td>2 h</td>
<td>7.3</td>
</tr>
<tr>
<td>2</td>
<td>Predose</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>2 h</td>
<td>8.3</td>
</tr>
<tr>
<td>3</td>
<td>Predose</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>2 h</td>
<td>10.0</td>
</tr>
</tbody>
</table>

* NDL, No detectable level.

The structural model assumed no lag time and was fitted to the data by using a least-squares algorithm with the weighting factor 1/y²(calculated). The blister fluid data were analyzed by routine graphical methods (2), the area under the concentration-time curve being calculated by a log-linear trapezoidal procedure.

RESULTS

The predose and 2-h postdose levels of ceftibuten following the administration of 200 mg of ceftibuten twice daily are shown in Table 1. The predose level in the 8:00 a.m. sample increased from 1.1 µg/ml on day 2 to 1.7 µg/ml on day 3. This was accompanied by an increase in the 2-h level from 7.3 µg/ml following the first dose to 10.0 µg/ml following the final dose. The individual variations were considerable; they were influenced by one outlet (volunteer 2) and were possibly related to the more stringent conditions of fasting and timing of samples on the study day (1).

Following the final dose, ceftibuten appears to have been rapidly absorbed, with a mean time to maximum concentration of drug in serum (Tmax) of 1.8 h (range, 1.5 to 2.5 h) (Table 2; Fig. 1). The peak levels in plasma ranged from 9.4 to 12.4 µg/ml, with a mean maximum concentration of drug in serum (Cmax) of 10.9 µg/ml. Thereafter the levels of ceftibuten declined to means of 4.1 µg/ml (standard deviation [SD], 0.9 µg/ml) at 6 h and 0.7 µg/ml (SD, 0.3 µg/ml) at 12 h.

At time zero (i.e., predose), the mean inflammatory fluid level of ceftibuten was 1.6 µg/ml (SD, 0.34 µg/ml). The penetration into the inflammatory fluid was moderately rapid, the Tmax being reached at 3.7 h, although there was considerable intersubject variation, the range being 2 to 7 h. The mean inflammatory fluid level at 2 h was 8.4 µg/ml and was 70% of the plasma level at this time. The mean percent penetration into inflammatory fluid (calculated from individual ratios of area under the concentration-time curve from 0 h to infinity for inflammatory fluid and area under the concentration-time curve from 0 h to infinity for plasma) was 113.4%, with a range of 85 to 131%. After 4 h the inflammatory fluid levels tended to be greater than those in plasma, with mean values of 3.8 and 2.4 µg/ml, respectively, at 8 h and 1.7 and 0.74 µg/ml at 12 h. The elimination half-life of ceftibuten from the inflammatory fluid was 3.2 h.

The microbiological assay when compared with high-performance liquid chromatography showed a high degree of correlation (correlation coefficient, 0.991) with the cis isomer of ceftibuten, indicating that the microbiological activity was substantially derived from the cis component. In the three volunteers assayed for both isomers, the peak trans-isomer levels were 0.83, 0.57, and 0.68 µg/ml at 1.5 to 2 h. The peak trans-isomer levels were 7.0, 4.8, and 5.4%, respectively, of the peak cis-isomer levels (mean, 5.7%). The elimination half-lives of the trans isomers were 5.1, 2.4, and 4.6 h.

No adverse effects of ceftibuten were noted by the volunteers, and no significant changes were found in the hematological and biochemical parameters.

DISCUSSION

The pharmacokinetic data presented here are generally in agreement with preliminary reports on ceftibuten (Nakashima et al., 26th ICAAC). Previous workers found that the Cmax following a single dose of 200 mg was 11.6 µg/ml and the half-lives were 1.5 to 2.1 h. We have found that the Cmax is a little lower at 10.9 µg/ml after multiple dosing but the elimination half-life is somewhat greater at 2.5 h. This is in comparison with cefuroxime axetil, for which the elimination half-life is 1.1 h (7), and cefixime, for which it is 3.8 h (6). Food appears to significantly reduce the Cmax and prolong the Tmax (K. Shiba, J. Shimada, A. Saito, and T. Miyahara, Proc. 16th Int. Congr. Chemother., p. 273, 1989), but the overall bioavailability was not affected.

TABLE 2. Pharmacokinetic parameters of ceftibuten following 200 mg twice daily for five doses

<table>
<thead>
<tr>
<th>Source of sample</th>
<th>Cmax (µg/ml)</th>
<th>Tmax (h)</th>
<th>t1/2* (h)</th>
<th>AUC0,∞ (µg·h/ml)*</th>
<th>Penetration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Range</td>
<td>Mean (SD)</td>
<td>Range</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Plasma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10.9 (1.2)</td>
<td>9.4-12.4</td>
<td>1.8 (0.4)</td>
<td>1.5-2.5</td>
<td>2.5 (0.32)</td>
</tr>
<tr>
<td>Inflammatory fluid</td>
<td>9.2 (2.2)</td>
<td>8.1-13.6</td>
<td>3.7 (1.9)</td>
<td>2-7</td>
<td>3.2 (1.1)</td>
</tr>
</tbody>
</table>

* t1/2, Elimination half-life.

* AUC0,∞, Area under the concentration-time curve from 0 h to infinity.
The penetration of ceftibuten into the inflammatory exudate was high (113.4%), being intermediate between those of cefuroxime axetil (92%) (7) and cefixime (132.6%) (6), but the speed of penetration of ceftibuten (T\text{max}, 3.7 h) was more rapid than that of cefixime (T\text{max}, 6.7 h) and similar to that of cefuroxime axetil (T\text{max}, 3.3 h). The protein binding of ceftibuten is moderately high, 77% (unpublished observation), and is greater than those of cefixime and cefuroxime (48% and 34%), but this does not appear to compromise its inflammatory fluid penetration. It is possible that the longer half-life is a more important determinant in this case.

Studies have shown that the main metabolite of ceftibuten is the trans isomer, which is said to be eightfold less active than the parent (or cis isomer) (K. Shiba, 28th ICAAC, abstr. no. 452, 1988). This worker noted 4.3 to 4.5% trans isomer in plasma and 7.2 to 9.2% in urine (of the total amount of ceftibuten). In this study we found that the peak levels of the trans isomer in plasma were 4.8 to 7% the peak cis-isomer levels and can confirm that most of the microbiological activity is due to the cis component. The half-lives of the metabolite were longer than those of the parent cis isomer, as one would expect, and confirm other preliminary studies (C. C. Lin, personal communication). This may be related to slower renal excretion of the trans isomer or to the formation of the trans metabolite. To investigate these points, it would be necessary to study the pharmacokinetics of both isomers independently in volunteers. However, we have studied the rate of in vitro transformation of the cis compound into the trans compound in serum at 37°C, and the interconversion half-life is 2.8 h (unpublished observations). The rate of the reverse process (trans into cis compound) is 3.8 h. It is doubtful whether these differences have any significant impact upon the pharmacokinetics of ceftibuten. One would not expect the trans levels to be greater than we have observed in patients with normal renal function, since this study was performed at steady state. It might, however, be advisable to investigate the levels of both isomers in renal failure, since the relative amount of trans isomer may well increase.

Studies of the in vitro activity of ceftibuten (5) show that this agent has high activity against members of the family Enterobacteriaceae, with the exception of those harboring a possible chromosomal cephalosporinase. In the former strains, the MIC for 90% of strains tested was ≥1 μg/ml. S. aureus, for which the MIC for 90% of strains tested was 32 μg/ml, must be considered resistant to ceftibuten. Against the important respiratory pathogens H. influenzae and B. catarrhalis (Moraxella catarrhalis), the MICs for 90% of strains tested were 0.06 and 2 mg/liter, respectively (4), and levels in both serum and inflammatory fluid exceeded 2 mg/liter for at least 6 h in all subjects. The MIC for 90% of strains of S. pneumoniae was 4 mg/liter (4), which was exceeded in serum for 4 h but was exceeded in the inflammatory fluid for 6 h. For the therapy of systemic infections caused by the more susceptible pathogens, a twice-daily dosing schedule is suggested. Infections caused by S. pneumoniae might respond to such a regimen, or a higher dose (or more frequent dosing) might be more appropriate. Careful clinical trials on this point are warranted.

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LITERATURE CITED