Pharmacokinetics and Tissue Penetration of Ampicillin and Brobactam Following Oral Administration of 2085P

R. Wise,* N. O'Sullivan, J. Johnson, and J. M. Andrews

Department of Microbiology, Dudley Road Hospital, Birmingham B18 7QH, England

Received 19 August 1991/Accepted 20 February 1992

Eight healthy volunteers received a 1,000-mg single oral dose of 2085P which consisted of 800 mg of pivampicillin and 200 mg of brobactam. Concentrations of ampicillin and brobactam in plasma, inflammatory fluid, and urine were measured over the subsequent 24 h. Pivampicillin and brobactam were moderately rapidly absorbed. The mean (standard deviation) maximum concentration in plasma (Cmax) of ampicillin was 8.2 (1.9) μg/ml, and that of brobactam was 2.1 (2.0) μg/ml at mean times of 1.9 (0.5) and 2.3 (0.8) h, respectively. The elimination half-lives in plasma were 1.8 (0.5) and 1.6 (2.0) h, respectively. Both agents penetrated the experimentally induced inflammatory fluid, reaching a mean maximum at 3 h. The Cmax of ampicillin was 6.8 (2.3) μg/ml, and that of brobactam was 1.0 (0.4) μg/ml. The penetration (derived by comparing the area under the concentration-time curve from 0 h to infinity for inflammatory fluid with that for plasma) was 97.3% (26.0%) for ampicillin and 81% (22.3%) for brobactam. The 24-h urinary recovery was 54.2% (14.6%) of the administered dose for ampicillin and 40.2% (11.4%) for brobactam. These data suggest that this combination of β-lactam and inhibitor should be efficacious in treating infections caused by ampicillin-resistant pathogens.

Brobactam, or 6-β-bromopenicillanic acid, is a β-lactamase inhibitor similar to clavulanic acid (3). Pivampicillin is an oral prodrug of ampicillin (7) and is an organic base capable of reacting with an equimolar amount of an organic acid, such as brobactam, to form an addition salt, pivampicillin 6-β-bromopenicillinate. 2085P is a combined preparation of pivampicillin 6-β-bromopenicillinate and additional pivampicillin that contains pivampicillin and brobactam in a fixed 4:1 (wt/wt) ratio.

In this study, we have investigated the pharmacokinetic properties of ampicillin and brobactam after oral administration of a single dose of 2085P and determined their penetration into a chemically induced inflammatory exudate (9).

MATERIALS AND METHODS

Eight healthy adult male volunteers participated after Ethical Committee approval and written informed consent had been obtained. The volunteers were aged 22 to 39 years (mean age, 27 years), weighed between 62 and 89 kg (mean weight, 73.0 kg), and had a mean height of 1.8 m (range, 1.7 to 1.8 m). Medical history indicated no significant episodes, allergies, or intolerance of antibiotics. Hematological and biochemical profiles, including tests of renal and hepatic function, were normal. One week prior to the study, all volunteers underwent detailed physical examinations and were considered normal. In order to raise blisters, two 0.2% cantharides-impregnated plasters (1 by 1 cm) were applied to the anterior surface of one forearm and taped in place on the night before the study. After overnight fasting, the subjects were given a single 1,000-mg oral dose of 2085P (equivalent to 800 mg of pivampicillin [which itself was equivalent to 603 mg of ampicillin] and 200 mg of brobactam; Leo Pharmaceutical Products, Ballerup, Denmark) with 100 ml of water. Thereafter, fluid was taken ad libitum. Solid food was taken after 4 h. Blood was drawn through an intravenous cannula (kept patent with 2-ml doses of heparinized saline [100 IU/ml]) at 0, 15, 30, 45, 60, and 90 min and 2, 3, 4, 6, 8, and 12 h after dosing. Urine samples were collected from 0 to 4, 4 to 8, 8 to 12, and 12 to 24 h. Inflammatory exudate from the blisters was sampled with a micropipette at 3.5, 4, 5, 6, 7, 8, and 12 h. The integrity of the blisters was maintained by spraying them with a fast-drying plastic dressing, Nobecutane (Astra Pharmaceuticals Ltd., Kings Langley, United Kingdom). Antibiotic assays were performed within 1 h of sample collection by using a plate diffusion method. The brobactam was assayed with antibiotic medium no. 2 (Oxoid, Basingstoke, United Kingdom) incorporating 100 mg of piperacillin per liter and Klebsiella pneumoniae ATCC 29665. The lower limit of sensitivity of the assay was 0.04 μg/ml, and the coefficient of variation between assays was 7.7% at 0.8 μg/ml and 6.5% at 6 μg/ml; the within-assay coefficients of variation were 6 and 7.2%, respectively. Ampicillin was assayed with antibiotic medium no. 2 (Oxoid) and Micrococcus lutea as indicator organism. The lower limit of sensitivity was 0.03 μg/ml, and the coefficients of variation between assays were 9.5% at 0.4 μg/ml and 10.7% at 3 μg/ml; the within-assay coefficients of variation were 11.6 and 11.8%, respectively. The assay of ampicillin was not affected by at least 5 μg of brobactam per ml, and the assay of brobactam was not affected by a least 20 μg of ampicillin per ml. Both assays displayed linearity of response (r = 0.98) between the upper and lower standards (4 and 0.25 μg of ampicillin per ml, respectively; 2.5 and 0.15 μg of brobactam per ml, respectively).

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. Urine samples were diluted and prepared in phosphate buffer (pH 7). Results were calculated by using the correction of Bennett et al. (1).

Pharmacokinetic calculations were performed by graphical methods (2). The half-lives as determined by linear regression analysis of the concentration time, maximum concentration in serum (Cmax), and time to Cmax (Tmax) were

* Corresponding author.
observed data for individual volunteers which were not adjusted for body weight. The area under the concentration-time curve (AUC) was calculated by the trapezoidal method from 0 to 12 h, with the addition of the concentration at 12 h/elimination constant to give the AUC from 0 h to infinity (AUC\textsubscript{0-\infty}).

**RESULTS**

Table 1 shows the derived pharmacokinetic parameters for both ampicillin and brobactam, and Fig. 1 shows the levels achieved in plasma and inflammatory fluid. Both drugs were quickly absorbed. Maximum concentration occurred at 1.9 h for ampicillin and at 2.3 h for brobactam. The maximum concentration of ampicillin in plasma was 8.2 \(\mu\)g/ml, and that of brobactam was 2.1 \(\mu\)g/ml. The plasma elimination half-lives of the two agents were very similar, but the range was greater for brobactam because of one volunteer who had an elimination half-life in plasma of 6.6 h and the lowest \(C_{\text{max}}\) (1.2 \(\mu\)g/ml). However, the pharmacokinetics of ampicillin in this volunteer were similar to those in the other seven volunteers studied. At 6 h postdose, the mean concentrations in plasma were 0.82 \(\mu\)g/ml for ampicillin and 0.18 \(\mu\)g/ml for brobactam. At 8 h, the mean level of ampicillin in plasma was 0.22 \(\mu\)g/ml, but the brobactam level was below the lower limit of sensitivity of the assay in five of eight volunteers.

![Ampicillin concentrations in plasma (●) and inflammatory fluid (△) and brobactam concentrations in plasma (■) and inflammatory fluid (□) after a 1,000-\(\mu\)g oral dose of 2085P.](http://aac.asm.org/)

**TABLE 1. Pharmacokinetics of ampicillin and brobactam following the administration of 1,000 mg of 2085P**

<table>
<thead>
<tr>
<th>Parameter\textsuperscript{b}</th>
<th>Mean (SD) and range for:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ampicillin</td>
</tr>
<tr>
<td>Plasma</td>
<td></td>
</tr>
<tr>
<td>(T_{\text{max}}) (h)</td>
<td>1.9 (0.5), 1.5-3.0</td>
</tr>
<tr>
<td>(C_{\text{max}}) ((\mu)g/ml)</td>
<td>8.2 (1.9), 5.1-12.0</td>
</tr>
<tr>
<td>(t_{1/2}) (h)</td>
<td>1.8 (0.5), 1.4-2.8</td>
</tr>
<tr>
<td>AUC\textsubscript{0-\infty} ((\mu)g/ml)</td>
<td>24.6 (5.0), 15.9-32.9</td>
</tr>
<tr>
<td>Inflammatory fluid</td>
<td></td>
</tr>
<tr>
<td>(T_{\text{max}}) (h)</td>
<td>3 (0.9), 2-4</td>
</tr>
<tr>
<td>(C_{\text{max}}) ((\mu)g/ml)</td>
<td>6.8 (2.5), 3.7-11.9</td>
</tr>
<tr>
<td>(t_{1/2}) (h)</td>
<td>2.4 (0.8), 1.3-3.5</td>
</tr>
<tr>
<td>AUC\textsubscript{0-\infty} ((\mu)g/ml)</td>
<td>23.9 (5.6), 17.5-34.5</td>
</tr>
<tr>
<td>% Penetration</td>
<td>97.3 (26.0), 77.0-146.1</td>
</tr>
<tr>
<td>Urine recovery</td>
<td>(% of dose)</td>
</tr>
<tr>
<td>0-24 h</td>
<td>54.2 (16.6), 26.7-73.7</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Equivalent to 200 mg of brobactam and 800 mg of pivampicillin.

\textsuperscript{b} \(t_{1/2}\), half-life at beta phase.

Penetration of drugs into the inflammatory fluid was moderately rapid, the maximum concentration occurring at a mean time of 4 h for both agents. The maximum concentration of ampicillin in inflammatory fluid (6.8 \(\mu\)g/ml) was about sevenfold greater than that of brobactam (1.0 \(\mu\)g/ml). The elimination half-lives of the two agents were similar, i.e., 2.4 h for ampicillin and 2.2 h for brobactam. The mean percentages of penetration into inflammatory fluid (calculated from individual ratios of AUC\textsubscript{0-\infty} for inflammatory fluid and AUC\textsubscript{0-\infty} for plasma) were 97.3% for ampicillin and 81.0% for brobactam.

The ratio of the administered drugs was 1 part brobactam to 4 parts pivampicillin, which corresponds to a brobactam/ampicillin ratio of 1:3. In Table 2, the ratios of these two agents in plasma and inflammatory fluid are shown. The ratios of the two agents in plasma were remarkably consistent. In inflammatory fluid, the ratio of the two agents was lower than the administered ratio until 3 h. Thereafter, the ratio of brobactam/ampicillin was greater than the administered ratio.

The mean recovery of ampicillin from urine over 8 h was 49.4%; 54.2% was excreted by 24 h. The mean 8-h recovery of brobactam was 39.5%; 40.2% was excreted by 24 h. The volunteer noted to have the lowest \(C_{\text{max}}\) for brobactam excreted only 29.5% of the administered dose.

No adverse effects of 2085P were noted by the volunteers, and no alterations to the biochemical or hematological parameters were noted.

**DISCUSSION**

The pivampicillin component of 1 g of 2085P consists of 332 mg as the addition salt of brobactam and an additional 468 mg as pivampicillin to give a total of 800 mg, which is equivalent to 603 mg of ampicillin. Earlier studies with 700 mg of pivampicillin (equivalent to 500 mg of ampicillin) gave mean maximum concentrations in plasma of 10 to 10.7 \(\mu\)g/ml (3, 6), and Verbist (6) obtained a 78.5% recovery of ampicillin during h 0 to 9. It therefore appears that we obtained an approximately 33% lower \(C_{\text{max}}\) and 31% lower urinary recovery of ampicillin. A possible explanation for these findings is that brobactam interferes with the absorption of pivampicillin or that the pivampicillin component of the addition salt of pivampicillin 6-B-bromopenicillanate is poorly absorbed.

However, a study (4a) of the pharmacokinetics of pivampicillin with and without brobactam does not suggest such interference, and the results obtained approximate our findings, suggesting that the formulation of pivampicillin has altered since that previously reported (6).

Both ampicillin and brobactam rapidly penetrated the inflammatory exudate, the \(T_{\text{max}}\) being about 1 h after the
time of the maximum concentration in plasma. The ratio of the $C_{\text{max}}$ in inflammatory fluid was approximately 6:1 ampicillin/brobactam compared with 3:1 as administered. This suggests either a somewhat lesser penetration of the latter (shown in the penetration rate) or a smaller transfer rate constant for brobactam (81% compared with 97.3% for ampicillin). It is of interest that the differences in the AUC ratios for the drug are less than those for the $C_{\text{max}}$ ratios, providing some evidence that the differences may be more readily explained by a smaller transfer rate constant.

In general, brobactam inhibits the same range of $\beta$-lactamases as clavulanic acid and has a similar (or somewhat less) potency in $\beta$-lactamase inhibition (4, 8). The levels of ampicillin and brobactam achieved in serum are generally similar to those found for amoxicillin and clavulanic acid following a dose of 250 mg/125 mg (5), a commonly employed regimen. Clinical trials of pivampicillin-brobactam should be performed to study the efficacy of the brobactam-pivampicillin combination.

ACKNOWLEDGMENTS

We thank P. Menday of Leo Laboratories, England, for his advice and financial support and C. Bay of the Mathematical-Statistical Department, Leo Pharmaceutical Products, Denmark.

REFERENCES