Human Pharmacokinetics of BL-P1654 Compared with Ampicillin

JOHN T. CLARKE, ROBERT D. LIBKE, EDWARD D. RALPH, RUEDI P. LUTHY, and WILLIAM M. M. KIRBY

Department of Medicine, University of Washington School of Medicine, Seattle, Washington 98195

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BL-P1654 is a new ureido-penicilllin which has significant activity against both pseudomonas and klebsiella. Its pharmacokinetics were evaluated in five studies in four healthy adult male volunteers after 1-g doses given as: 5- and 30-min intravenous infusions, a 30-min infusion 1 h after the oral administration of 1 g of probenecid, and an intramuscular injection. For comparison, volunteers also received a 30-min infusion of 1 g of ampicillin. Serum levels of the antibiotic were found to fit a two-compartment open model using a Burroughs-5500 computer. After a 30-min infusion, peak serum levels of BL-P1654 (72.8 µg/ml [standard deviation] ± 5.9) were 50% greater than those of ampicillin (53.6 ± 8.9). Six hours later, the relative difference was even greater (4.58 ± 0.25 versus 0.35 ± 0.09). At 75 min after the 1-g intramuscular injection of BL-P1654, peak serum levels averaged 28.4 ± 10.3 µg/ml. The half-life of BL-P1654 (2.04 h) was significantly longer than for ampicillin (1.15 h), and the renal clearances of BL-P1654 and ampicillin were 79 versus 244 ml/min per 1.73 m², respectively. Probenecid produced no significant change in blood levels, volume of distribution, half-life, or renal clearance, indicating that there is no net tubular secretion of this antibiotic.

BL-P1654 is a new ureido-penicilllin which, like carbenicillin and ticarcillin, has significant in vitro activity against Pseudomonas aeruginosa at achievable blood levels (2). In addition, BL-P1654 is also effective against klebsiella, enterobacter, and indole-positive proteus species (7).

These studies were designed to compare the pharmacokinetic parameters of BL-P1654 with ampicillin and to determine the effect of probenecid on BL-P1654. In addition, intravenous (i.v.) and intramuscular (i.m.) routes of administration were compared.

MATERIALS AND METHODS

Comparison of BL-P1654 with ampicillin. Four healthy men (group I) received a 30-min infusion of 1 g of ampicillin. Later the same volunteers received 1 g of BL-P1654 given in an identical fashion. Blood and urine were sampled frequently as described below. All studies were separated by an interval of at least 1 week.

Effect of probenecid on pharmacokinetic parameters of BL-P1654. Four male volunteers (group II) received a 1-g infusion over a 30-min period. The same men subsequently received an identical infusion 1 h after the oral administration of 1 g of probenecid (Benemid; Merck, Sharp and Dohme).

Comparison of intramuscular and intravenous administration. The same four volunteers (group II) received a rapid 5-min infusion of 1 g of BL-P1654 and subsequently the same dose was given by i.m. injection into the upper outer quadrant of the buttck.

In all the above 5- or 30-min infusion studies, blood was drawn at the end of the infusion, then at three 6-min intervals, 30, 45, 60, 90, and 120 min after stopping the infusion, and then six more times at hourly intervals. In the i.m. study, blood was drawn at 15-min intervals for the first 2 h, then at 2.5 h, then hourly on six subsequent occasions.

Administration, collection of specimens, and antibiotic assay. Four healthy adult male volunteers participated in each of the above studies, including three men who participated in all of them. They were admitted to the University Hospital Clinical Research Center after an overnight fast and were given a clear liquid diet during the first 4 h of the study. Pediatric scalp vein needles (Butterfly-21, Abbott Laboratories) were inserted into a forearm vein in each arm for the administration of antibiotic through one and the collection of blood for assay from the other.

Antibiotics were diluted in 0.9% sodium chloride and infused at a constant rate by means of an infusion pump (Multi-Speed Transmission, Harvard Apparatus Co.). To minimize errors from not injecting the exact volume intended, antibiotics were diluted to at
least 0.025 g/ml and the infusion rate always exceeded 40 ml/h.

Once blood samples had clotted, they were placed in an ice bath, then centrifuged at 4,000 rpm for 20 min. The serum was pipetted and stored at -20 C and assayed within a few days along with serum standards prepared on the day of the study.

The agar well diffusion method of Bennett et al. (1) was employed using Bacillus subtilis as the indicator strain, and assaying each sample in quintuplicate. At least 37 separate values were obtained for all serum standards between 2 and 64 μg/ml in the course of measuring the clinical samples. The variance (s^2) was calculated for each serum standard (y) in this range. When ln (1/s^2) was plotted against ln (concentration, e.g., 2, 4, 8, etc.), a straight line resulted (r = 0.999) with a slope of -2.39 and an intercept of 7.66. Hence, to calculate the weight (w) as a function of the reciprocal of variance (3) of ln (y), the following equation was used:

\[ w = \frac{1}{s^2} = \ln y (-2.39) + 7.66 \]  

Each serum sample (y) was weighted with the function \( e^{(\ln (-2.39) + 7.66)} \). This procedure placed an appropriately greater emphasis on the more reliable assay values at lower concentrations.

When vials for injection of BL-P1654 and ampicillin were assayed, they were found to contain amounts that varied considerably from the labeled dose. To determine the exact administered dose, a portion of the antibiotic infusion solution was diluted in pooled human serum and assayed along with the serum samples. The exact measured potency of 250-mg ampicillin vials (lot no. F3U40) was 289 mg (116%), the potency of 500-mg BL-P1654 vials (lot no. 74L54) was 674 mg (135%), and the potency of 1-g vials for i.m. injection was 0.684 g (68.4%). These antibiotics were all supplied by Bristol Laboratories. To evaluate renal clearance and excretion, all urine voided during the first 48 h after drug administration was collected at appropriate intervals. Urine samples were diluted with 0.15 M phosphate buffer (pH 7.35) to an approximate concentration of 10 μg/ml and assayed in the same manner as the serum samples. Creatinine determinations were performed by the clinical chemistry laboratory of University Hospital.

**Pharmacokinetic calculations.** The standard equation (9) for the relation of serum concentration (Cp) to time (t) for a two-compartment model was used.

\[ C_p = A \cdot e^{-at} + B \cdot e^{-bt} \]  

Analysis of serum antibiotic concentration-time plots was performed by the ALGOL program MEXFIT5, which utilizes a Marquardt nonlinear, least squares regression analysis (6). By chi square analysis, all i.v. studies were found to fit a two-compartment open model better than a one-compartment model. MEXFIT5 provided simultaneous estimates of A, B, α, and β, which were then corrected by the method of Loo and Reigelman (5) to simulate a rapid bolus injection.

The rate constants (K12, K13) determine the distribution of drug between the central and tissue compartment and drug elimination (Ks); Ks was the rate of drug administration.

The rate constants were derived from the above two-compartment model equation (8) as follows.

\[ K_{13} = \frac{(A + B) \alpha \beta}{(A + B) \beta + B \alpha} \]  

\[ K_{13} = \frac{\alpha \beta}{K_s} \]  

\[ K_{13} = \alpha + \beta - K_{13} - K_s \]  

The serum half-life, \( t_{1/2} \), was \( \ln 2/K_s \), and the biologic half-life was \( \ln 2/\beta \). Calculation of the area under the time-serum concentration curve (4)

\[ \text{Area} = \frac{A}{\alpha} + \frac{B}{\beta} \]  

permitted evaluation of renal (RC) and serum (SC) clearance rates.

\[ \text{RC} = \frac{\text{Total renal excretion of drug}}{\text{Area}} \]  

\[ \text{SC} = \frac{\text{Dose}}{\text{Area}} \]  

**RESULTS**

**Comparative study with ampicillin.** Average serum concentrations of BL-P1654 and ampicillin after 5- and 30-min i.v. infusions in four volunteers are shown in Fig. 1. Peak serum levels (72.8 versus 53.6 μg/ml) were greater for BL-P1654 as were levels at all other intervals. By 5 h, BL-P1654 had fallen to 6.41 μg/ml and ampicillin was less than 1. The semi-log plots of serum concentration versus time both became linear after about 3 h (Fig. 2), but were not
parallel since the rate of decline of ampicillin was twice that of BL-P1654. ($\beta = 0.600$ versus 0.340 per h).

Of interest is the fact that administering the 1-g i.v. dose in 5 rather than 30 min gave only slightly higher peak blood levels (82 versus 73 $\mu g/ml$) of BL-P1654, but subsequently levels from 0.5 to 2 h were appreciably higher with the slower infusion.

The pharmacokinetic parameters calculated during these studies are shown in Table 1 and 2. The biologic half-life of BL-P1654 (2.04 h) was nearly twice that of ampicillin (1.15 h). The volumes of distribution of BL-P1654 and ampicillin were almost identical, 16.3 and 16.9 liters per 1.73 m$^3$, respectively. However, the central compartment was larger for ampicillin (12.7 versus 7.84 liters), whereas the tissue compartment of BL-P1654 was larger (8.43 versus 4.19 liters).

The rate of plasma clearance for ampicillin, 273 ml/min, was nearly three times the value of 108 ml/min determined for BL-P1654.

The rate of renal excretion of ampicillin was greater than BL-P1654; excretion was also more complete: 99.4% of ampicillin was recovered in 48 h versus 72.6% of BL-P1654 (Fig. 3).

**Effect of probenecid on BL-P1654.** Average blood levels obtained in four volunteers after a 30-min infusion of BL-P1654 with and without oral administration 1 h previously of 1 g of probenecid were not appreciably different. At the end of the 30-min infusion, average serum concentrations were higher (77.0 versus 70.8 $\mu g/ml$), but not significantly so ($P > 0.3$) when the volunteers had not taken probenecid, and remained higher for the first hour. During the elimination phase, the differences remained insignificant. There was also no significant effect from the administration of probenecid on the average half-life (2.14 h with probenecid versus 2.37 without), volumes of distribution (16.4 versus 14.8 liters), plasma clearance (100 versus 105 ml/min), renal clearance (73 versus 76 ml/min), or total renal excretion (73.4 versus 72.6%).

**Comparison of intramuscular and intravenous administration.** An average peak serum concentration of 28.4 $\mu g/ml$ occurred 1 h and 15 min after the i.m. injection of 1 g of BL-P1654. Blood levels thereafter were slightly higher but closely resembled those following the 30-min i.v. infusion. The terminal slope of the time serum concentration line was not affected by i.m. administration and the average serum half-lives were the same (2.37 i.v. versus 2.15 i.m.).

**DISCUSSION**

BL-P1654 is a new penicillin with unique properties both in its antibacterial activity and...
Table 1. Pharmacokinetic constants for ampicillin and BL-P1654 from the 5- and 30-min studies

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Group</th>
<th>Time of infusion (min)</th>
<th>Serum concn (µg/ml)</th>
<th>Rate constants (h⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>I</td>
<td>30</td>
<td>37.2</td>
<td>12.2</td>
</tr>
<tr>
<td>BL-P1654</td>
<td>I</td>
<td>30</td>
<td>37.8</td>
<td>36.0</td>
</tr>
<tr>
<td>BL-P1654 without probenecid</td>
<td>II</td>
<td>30</td>
<td>37.9</td>
<td>39.2</td>
</tr>
<tr>
<td>BL-P1654 + probenecid</td>
<td>II</td>
<td>30</td>
<td>33.1</td>
<td>38.4</td>
</tr>
<tr>
<td>BL-P1654</td>
<td>II</td>
<td>5</td>
<td>51.8</td>
<td>28.7</td>
</tr>
</tbody>
</table>

* All values were derived from the average serum levels of four volunteers and were corrected to an administered dose of 1 g.

* Corrected by the method of Loo and Riegelman (5).

Table 2. Pharmacokinetic data for ampicillin and BL-P1654 derived from the 5- and 30-min infusion studies

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Group</th>
<th>Time of infusion (min)</th>
<th>Body surface area (m²)</th>
<th>Biologic half-lives (h)</th>
<th>Volumes of distribution (liters per 1.73 m²)</th>
<th>Clearance rates (ml/min per 1.73 m²)</th>
<th>Renal excretion (%)</th>
</tr>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>I</td>
<td>30</td>
<td>1.93</td>
<td>1.15</td>
<td>12.70</td>
<td>4.19</td>
<td>16.9 273 244 119</td>
</tr>
<tr>
<td>BL-P1654</td>
<td>I</td>
<td>30</td>
<td>1.93</td>
<td>2.04</td>
<td>7.84</td>
<td>8.43</td>
<td>16.3 108 79 110</td>
</tr>
<tr>
<td>BL-P1654 without probenecid</td>
<td>II</td>
<td>30</td>
<td>1.95</td>
<td>1.91</td>
<td>7.21</td>
<td>7.60</td>
<td>14.8 105 76 97</td>
</tr>
<tr>
<td>BL-P1654 + probenecid</td>
<td>II</td>
<td>30</td>
<td>1.95</td>
<td>2.15</td>
<td>7.54</td>
<td>8.83</td>
<td>16.4 100 73 126</td>
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<tr>
<td>BL-P1654</td>
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<td>5</td>
<td>1.95</td>
<td>2.14</td>
<td>6.82</td>
<td>9.45</td>
<td>16.3 114 86 121</td>
</tr>
</tbody>
</table>

Fig. 3. Rate of renal excretion of ampicillin and BL-P1654 with 1-g infusions in 30 min.

its pharmacology. Structurally, it is similar to ampicillin, with specific additions to the side chain where the amino group is introduced into the penicillin G nucleus (7). In addition to being active against bacteria susceptible to ampicillin, BL-P1654 is active against pseudomonas, klebsiella, enterobacter, and indole-positive proteus strains (7).

In the present study, both with rapid and slow i.v. infusions, BL-P1654 has been found by pharmacokinetic analysis to fit a two-compartment open model better than a one-compartment model. Serum concentrations are much higher and more prolonged than with ampicillin, with a serum half-life almost twice as long (2.04 versus 1.15 h). Protein binding, measured during these studies by ultrafiltration but not reported in detail, was about 20%, very similar to that of ampicillin.

The much lower renal clearance of BL-P1654 (79 versus 273 ml/min for ampicillin) seems chiefly responsible for its higher and prolonged blood levels. In addition, BL-P1654 seems unique among the penicillins so far studied in humans in that its renal excretion seems to be entirely by glomerular filtration, with no tubular component. The renal clearance is about 70% of the creatinine clearance, and is not altered by the administration of probenecid. Serum concentrations, plasma clearance, and volume of distribution are also unaffected by the administration of probenecid.

The clinical efficacy of BL-P1654 remains to be determined. However, it is apparent from the present study that the relatively high and prolonged serum concentrations that will probably be needed for certain severe gram-negative
infections can be readily attained. No signs of toxicity, or adverse reactions of any sort, have been noted during the present study.

LITERATURE CITED