Comparative Clinical Pharmacology of Amoxicillin and Ampicillin Administered Orally

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Ampicillin and amoxicillin (α-amino-p-hydroxybenzyl penicillin) were administered orally in 500-mg doses to eight fasting volunteers in a comparative study in which pharmacokinetic techniques were used. The absorption of amoxicillin was significantly better, as demonstrated by a higher mean peak serum concentration of 7.6 μg/ml as compared to 3.2 μg/ml for ampicillin, an average “area under the curve” that was approximately double that of ampicillin, and an 8-hr urinary recovery for amoxicillin of 60% as compared to 34% for ampicillin. Serum half-lives were the same for the two antibiotics, with values of 60.3 (+3.3) min for ampicillin and 61.3 (+5.6) min for amoxicillin. The latter drug gave measurable concentrations in the blood at 8 hr in all of eight volunteers, as compared to only three of eight with ampicillin.

Amoxicillin (BRL-2333, α-amino-p-hydroxybenzyl penicillin) is a semisynthetic penicillin that is comparable to ampicillin in antibacterial spectrum and in vitro activity but yields higher concentrations in the blood after equivalent oral doses (3, 16–18). Neu and Winshell reported an average peak concentration in serum of 7.6 μg/ml after oral administration of 500 mg of amoxicillin to volunteers, as compared to 3.8 μg/ml for ampicillin (17). Considerably higher peak blood concentrations, 10.8 μg/ml for amoxicillin and 6.3 μg/ml for ampicillin, were found with the same doses in another study (3). Further, only a 20% difference in the urinary recovery of the two agents was noted in one of the studies, as compared with 37% in the other (3, 17). Peak serum concentrations of ampicillin attained after 500 mg orally as reported in the literature have ranged from 1.5 to 6.3 μg/ml (2, 3, 8, 13–15, 17). Because of these inconsistencies and the desire to get more complete information regarding the precise pharmacokinetics of these two ampicillins, including the comparative half-lives, the present study was carried out.

MATERIALS AND METHODS

Eight healthy adult male volunteers received two 250-mg capsules of amoxicillin and of commercially available ampicillin (Beecham Pharmaceuticals) in crossover fashion, with an interval of 7 days or more between the two parts of the study. The volunteers reported to the laboratory after an overnight fast and were instructed to empty their bladders. They were then given the antibiotic capsules with 100 ml of water, and were allowed no food during the first 3 hr of the experiment. Blood samples taken at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hr, and samples of urine collected between 0 to 4 and 4 to 8 hr, were assayed for antibiotic content by use of a previously described agar-well diffusion technique, with Bacillus subtilis as the test organism (1). Appropriate standards were prepared in pooled human serum and urine on the morning of each study, with the use of antibiotic powders provided by Beecham Research Laboratories. Specimens and standards were frozen at −20°C, and all assays were carried out within a few days of collection of the samples.

The serum levels of ampicillin and amoxicillin as determined by assay in the eight volunteers were plotted against time on separate sheets of squared, lined paper to allow a comparison of the “area under the curve” for the two drugs in each individual (7, 19). The individual curves were then cut out with scissors and weighed on an electronic balance, a procedure which has been found to be as satisfactory for comparing the “area under the curve” as complex mathematical calculations (6). The relative “area under the curve” for ampicillin was expressed as a percentage of the “area” for amoxicillin for each volunteer, and the percentages for the eight volunteers were also averaged.

To calculate the half-lives of the two ampicillins, the serum levels obtained for each volunteer between 3 and 8 hr were plotted against time on semilogarithmic paper, and yielded an essentially straight line. The best estimate for this straight line, and also the slope of the line which represents the rate constant of drug elimination in per cent per hour, Ke, were calculated by the method of least squares (9). The half-life was then determined by the formula

\[
\text{Half-life (hr)} = \frac{\ln 2}{Ke}
\]
Table 1. Concentrations of ampicillin and amoxicillin in the serum of fasting volunteers after the oral administration of 500 mg

<table>
<thead>
<tr>
<th>Drug</th>
<th>Subject no.</th>
<th>0.5 hr</th>
<th>1 hr</th>
<th>1.5 hr</th>
<th>2 hr</th>
<th>3 hr</th>
<th>4 hr</th>
<th>5 hr</th>
<th>6 hr</th>
<th>7 hr</th>
<th>8 hr</th>
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<tr>
<td>Amoxicillin</td>
<td>1</td>
<td>3.20</td>
<td>7.50</td>
<td>5.50</td>
<td>4.92</td>
<td>4.05</td>
<td>2.04</td>
<td>0.70</td>
<td>0.29</td>
<td>0.18</td>
<td>0.15</td>
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<td></td>
<td>2</td>
<td>1.10</td>
<td>6.00</td>
<td>5.17</td>
<td>5.15</td>
<td>2.55</td>
<td>1.10</td>
<td>0.53</td>
<td>0.41</td>
<td>0.23</td>
<td>0.16</td>
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<tr>
<td></td>
<td>3</td>
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<td>7.60</td>
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<td>4.15</td>
<td>1.63</td>
<td>0.84</td>
<td>0.29</td>
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<td>4</td>
<td>3.58</td>
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<td>8.00</td>
<td>8.15</td>
<td>5.37</td>
<td>2.21</td>
<td>1.15</td>
<td>0.68</td>
<td>0.38</td>
<td>0.24</td>
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<tr>
<td></td>
<td>5</td>
<td>5.60</td>
<td>10.20</td>
<td>10.10</td>
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<td>12.20</td>
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<tr>
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<td>7</td>
<td>3.70</td>
<td>7.50</td>
<td>6.55</td>
<td>6.60</td>
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<td>0.72</td>
<td>0.34</td>
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<td>8</td>
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<td>7.10</td>
<td>5.78</td>
<td>5.80</td>
<td>3.78</td>
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<td>0.92</td>
<td>0.45</td>
<td>0.26</td>
<td>0.18</td>
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<tr>
<td>Mean</td>
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<td>7.48</td>
<td>7.61</td>
<td>7.02</td>
<td>4.29</td>
<td>1.95</td>
<td>0.89</td>
<td>0.50</td>
<td>0.28</td>
<td>0.19</td>
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</table>

RESULTS

Serum concentrations of ampicillin and amoxicillin as determined on 10 occasions during a period of 8 hr after single 500-mg oral doses in the fasting state are shown in Table 1. Mean serum concentrations of the two ampicillins are also presented in Table 1 and are compared graphically in Fig. 1. Mean peak amoxicillin concentrations were approximately 2.5 times those of ampicillin, and the maximum occurred at 1.5 hr with amoxicillin, as compared to 2 hr with ampicillin. At 8 hr, all of the volunteers had measurable levels of amoxicillin (>0.1 μg/ml), whereas detectable levels were present in only three of the eight volunteers with ampicillin (Table 1).

Individual comparisons of the “area under the curve” for the two ampicillins as determined by dividing the weight of each ampicillin graph by that of the amoxicillin graph and multiplying by 100 are listed in Table 2. Areas under the ampicillin curves as expressed in this manner ranged from 28.9 to 76.0% of those for amoxicillin. When these figures were averaged, the area under the curve for ampicillin was 50.3% of that for amoxicillin.

In four of the eight volunteers (no. 3, 4, 5, and 8), semilogarithmic plots of serum concentrations yielded five or more points on a straight line from 3 to 8 hr after ingestion of the antibiotics. A representative plot is illustrated in Fig. 2 (subject 8). The half-lives derived from these regression lines averaged 60.3 (± 3.3) min for ampicillin and 61.3 (± 5.6) min for amoxicillin.

Urinary excretion of the two drugs is presented in Table 3. Most of the ampicillin or amoxicillin recovered during the 8-hr collection period was found in the 0- to 4-hr sample (27.9 and 53.4% of the administered dose, respectively); only 5.9 and 6.9%, respectively, was present in the 4- to 8-hr collections. The average 8-hr urinary excretion of amoxicillin was 60.2% of the dose administered, whereas only 33.8% of the dose of ampicillin was recovered. Recovery in the urine of approximately twice as much amoxicillin as ampicillin is consistent with the “area under the curve” for amoxicillin, which was two times that of ampicillin.

DISCUSSION

Two previous studies comparing the clinical pharmacology of amoxicillin and ampicillin have both demonstrated significantly higher peak serum concentrations of amoxicillin after a 500-mg oral dose (3, 17). These studies did not agree, however, in regard to the peak serum concentrations attained with either antibiotic. Indeed, the peak for ampicillin of 6.3 μg/ml in one study was not much lower than that for amoxicillin in the other (7.6 μg/ml). This high
ampicillin concentration widens the range reported in the literature for the peak blood concentration observed after an oral dose of 500 mg to 1.5 to 6.3 μg/ml (2, 3, 8, 13-15, 17). These differences, plus an interest in elucidating the pharmacokinetics of the two drugs, prompted us to undertake the present study.

In comparing the two antibiotics in the same volunteers, we found the mean peak serum concentration of amoxicillin after a 500-mg oral dose to be more than twice as high as that of ampicillin. The peak values of 7.6 μg/ml for amoxicillin and 3.2 μg/ml for ampicillin noted in the present study correlate well with the 7.6 μg/ml and 3.8 μg/ml reported by Neu and Winshell (17), but are considerably lower than the 10.8 μg/ml and 6.3 μg/ml obtained by Croydon and Sutherland (3). Peak concentrations of ampicillin have been reported to be as low as 1.5 μg/ml by Kunin and Finkelberg and as high as 6.3 μg/ml in the study by Croydon and Sutherland (3, 15).

The present study, in which there was a close correlation of all parameters measured, i.e., serum concentration, "area under the curve," and urinary excretion, yielded a peak of 3.2 μg/ml, which is midway in the more usually reported range of 2.7 to 3.8 μg/ml (2, 8, 13, 14).

Few previous studies of the half-life of ampicillin have been reported in the literature. Dittert and associates found values of 1.0 hr after the administration of 250 mg intravenously and 1.1 hr with a 500-mg intramuscular dose (4, 5). Kunin and Finkelberg reported a longer half-life of 1.8 hr between 3 and 4 hr after a 500-mg oral dose in alcoholic patients in a state hospital (15). Their half-life determinations are open to question, however, because only two points were present on the regression line and the serum concentrations found were the lowest that have been reported in the literature. In the present study...
only regression lines with five or more points falling on an essentially straight line were utilized in the calculation of half-lives. This occurred in four of the eight volunteers, and the coefficient of correlation with a straight line always exceeded 0.992. The half-life was found to be 60.3 (± 3.3) min for ampicillin and 61.3 (± 5.6) min for amoxicillin, figures that agree closely with the data for ampicillin cited above with parenteral studies. This demonstrates that half-lives can be determined after oral administration provided sufficient time is allowed for absorption and that an adequate number of points are present on the regression lines.

Published studies comparing the urinary excretion of amoxicillin and ampicillin have not agreed with regard to the percentage of the administered dose that is recovered. Neu and Winshell recovered 42% of the 500-mg dose of ampicillin in a 6-hr urine collection and 79% of the dose of amoxicillin (17). Croydon and Sutherland recovered 40% of the ampicillin dose and 60% of the amoxicillin (3). In the present study, the recovery of 60% of the amoxicillin was almost double that of ampicillin (34%) and correlated well with the “area under the curve” for amoxicillin, which was twice that of ampicillin.

The finding of higher peak serum concentrations, larger “area under the curve,” and greater urinary excretion of amoxicillin, with identical half-lives for the two antibiotics, all reflect much better absorption of this ampicillin analogue. In this regard, ampicillin is known to be less well absorbed orally than some other antibiotics; for example, peak serum concentrations of cephalaxin and dicloxacin are about six times as high, approximately 18 µg/ml with a 500-mg dose (10, 11). A 500-mg oral dose of amoxicillin, however, gives a peak serum concentration approaching that obtained with the same dose of ampicillin given intramuscularly (12). Thus, it may be possible with amoxicillin to treat orally infections that have heretofore required parenteral therapy with ampicillin.

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LITERATURE CITED


