Amoxicillin, a New Penicillin Antibiotic

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Amoxicillin (α-amino-p-hydroxybenzyl penicillin, BRL 2333) is a new semisynthetic penicillin which is structurally similar to ampicillin, differing only in the hydroxylation of the phenyl side chain (Fig. 1). Results of previous studies indicated that amoxicillin has an antibacterial spectrum comparable to that of ampicillin (6, 10), but that it is better absorbed after oral administration and thus provides higher concentrations in serum (4, 7). In addition, the excretion of amoxicillin in the urine has been correspondingly greater than that of ampicillin (7). The present report describes further the in vitro activity of amoxicillin and also its effect in the treatment of 38 patients with infections of the urinary tract.

MATERIALS AND METHODS

Laboratory studies. The minimal inhibitory concentration (MIC) of amoxicillin and ampicillin was determined for 145 isolates of Enterobacteriaceae and 30 isolates of Pseudomonas aeruginosa in Mueller-Hinton agar by use of a Steers replicator device (9). Each isolate was tested with both 10^-4 and 10^-5 dilutions of an overnight broth culture of bacterial cells, containing approximately 10^8 and 10^9 organisms ml, respectively. The MIC for each strain was defined as the lowest concentration of antibiotic in which three or fewer colonies grew in the inoculated area of the agar plates. In addition, inhibitory zones around discs containing 10 μg of amoxicillin were measured for 151 isolates and were compared with the results of agar dilution studies (3).

Clinical studies. There were adequate clinical and bacteriological data for analysis for 38 patients with infections of the urinary tract treated with amoxicillin. Twenty-two patients were treated for an isolated episode of acute uncomplicated symptomatic infection, whereas 16 had previously received antimicrobial therapy with various agents, but infection had persisted or recurred. Prior to therapy with amoxicillin, 36 of the 38 patients had organisms which were susceptible in vitro to 10 μg or less of amoxicillin per ml. All of the patients were women; their ages ranged from 18 to 73 years. Only six of the total group of patients had azotemia or structural abnormalities of the urinary tract. The patients were treated with 250 mg of amoxicillin three or four times a day for 10 days. The criteria employed for selection of patients with urinary tract infections, collection and quantitation of bacteriological specimens, and performance of serological typing have been described in previous publications (5, 8).

A survey for possible hematological, renal, and hepatic toxicity was made by determination of the hematocrit, total and differential white blood cell counts, urinalysis, blood urea nitrogen, alkaline phosphatase, and serum glutamic oxalacetic transaminase at the onset, during, and after treatment with amoxicillin in most patients.

RESULTS

In vitro susceptibility of gram-negative pathogens to amoxicillin and ampicillin. The antibacterial activity of amoxicillin and ampicillin against approximately 30 isolates each of Escherichia coli, Proteus mirabilis, Klebsiella, Enterobacter, and indole-positive Proteus species is depicted in Fig. 2–4, which also show the effect of inoculum size on determination of the MIC. At a concentration of 10 μg or less/ml, amoxicillin
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positive *Proteus* species. In addition, although not shown in the figures, amoxicillin or ampicillin exerted negligible activity against 30 isolates of *Pseudomonas aeruginosa*, regardless of the size of the inoculum. Variation in inoculum size also

or ampicillin inhibited 89% of the strains of *E. coli*. Similarly, all 30 isolates of *P. mirabilis* were inhibited by 5 μg or less of either drug per ml. On the other hand (Fig. 3 and 4), high degrees of resistance to both drugs were encountered among strains of *Klebsiella*, *Enterobacter*, and indole-

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**FIG. 1. Structural relationship of amoxicillin and ampicillin.**

**FIG. 2. Cumulative percentage of 29 isolates of *Escherichia coli* and 30 isolates of *Proteus mirabilis* inhibited by increasing concentrations of amoxicillin or ampicillin tested in agar medium with bacterial inocula of two different sizes.**

**FIG. 3. Cumulative percentage of 28 isolates of *Klebsiella* and 29 isolates of *Enterobacter* inhibited by increasing concentrations of amoxicillin or ampicillin tested in agar medium with bacterial inocula of two different sizes.**

**FIG. 4. Cumulative percentage of 29 isolates of indole-positive *Proteus* species inhibited by increasing concentrations of amoxicillin or ampicillin tested in agar medium with bacterial inocula of two different sizes.**
HANSDFIELD ET AL. had little effect on the susceptibility to amoxicillin and ampicillin in vitro of most strains of Enterobacteriaceae. However, an effect was observed with some isolates of indole-positive Proteus and Enterobacter when a higher concentration of antibiotic was used. For example, with the inoculum of 10⁶ bacterial cells, 79% of the indole-positive Proteus strains and 52% of the Enterobacter isolates were inhibited by ampicillin at 100 μg/ml (feasible urine level), whereas with the higher inoculum only 48 and 28% of these species, respectively, were inhibited. In general, the effect of the inoculum size was more apparent with ampicillin than with amoxicillin.

Comparison of data from disc diffusion and agar dilution tests. The zones of growth inhibition around discs containing 10 μg of amoxicillin were measured with 151 gram-negative isolates, including strains of Enterobacteriaceae recovered from patients in this study; these results were compared with those obtained in agar dilution studies (Fig. 5). In general, separation into susceptible and resistant populations was obtained by use of the 10-μg disc, and strains inhibited by 7.5 μg or less of amoxicillin per ml had zones of inhibition 14 mm or more in diameter. These results are similar to those reported previously with ampicillin (2). Overall, there was agreement between the results of the two types of tests in 147 of 151 determinations (97%).

Effect of amoxicillin on bacteriuria. The effect of treatment with amoxicillin on bacteriuria is summarized in Table 1. Among 32 patients

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**Table 1. Effect of amoxicillin on bacteriuria**

<table>
<thead>
<tr>
<th>Organism</th>
<th>No. of patients</th>
<th>No. sterile during treatment</th>
<th>No. eradicated on follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>32</td>
<td>29</td>
<td>22</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>10</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><em>Klebsiella</em></td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td>38</td>
<td>32</td>
<td>24</td>
</tr>
</tbody>
</table>
treated for *E. coli* infections, the urine became sterile during treatment in 29 (90%). Of these 29 patients, 22 (69%) were free from bacteriuria on follow-up examination 1 to 6 weeks after cessation of therapy. Included among the 10 patients with persistent or recurrent *E. coli* bacteriuria were 6 who relapsed with the same serological strain, 3 who became reinfected with new serogroups, and 1 woman with persistent infection during and after therapy of a strain of *E. coli* that was resistant initially to amoxicillin. Seven of the 10 patients with persistent or recurrent *E. coli* infection had previously been treated for documented urinary tract infection. Four patients were treated for *P. mirabilis* infection; only one was cured, and in two *Proteus* bacteriuria persisted during therapy despite apparent susceptibility of the initial isolates in vitro. One of the patients with persistent bacteriuria during therapy had a renal calculus. One patient with *Klebsiella* bacteriuria had an initially resistant organism and, as expected, infection persisted during treatment with amoxicillin. Finally, the urine of one patient with well-documented *Staphylococcus epidermidis* bacteriuria was rendered free from infection during and after amoxicillin therapy.

**Tolerance and toxicity.** Amoxicillin was well tolerated, and in no instance was it necessary to discontinue treatment because of adverse effects. Two patients developed *Candida* vulvovaginitis, and mild diarrhea was noted by two others. One patient complained of nausea during the course of treatment. There was one episode each of eosinophilia (500 cells/mm³) and serum glutamic oxalacetic transaminase elevation (103 units/ml) 1 week after completion of therapy, both of which returned to normal levels within the next week.

**DISCUSSION**

It is apparent that amoxicillin has an antibacterial spectrum identical to that of ampicillin. The sole advantage of amoxicillin is that it produces consistently higher levels of antibiotic in blood and urine than do comparable doses of ampicillin, a result probably related to better gastrointestinal absorption. Although in the present study amoxicillin was effective in eradicating bacteriuria due to susceptible organisms and was very well tolerated, the outcome of infection was most clearly related to the diagnostic category of urinary tract infection. For example, persistence or recurrence of bacteriuria after cessation of treatment was more common in patients with a previous history of infection or with associated structural and functional abnormalities of the urinary tract. For practical purposes, amoxicillin performed no better than a host of other drugs presently available for the treatment of acute, uncomplicated bacteriuria. Although amoxicillin has been demonstrated to be better than ampicillin in the treatment of experimental infections in animals (1), whether or not amoxicillin will be any more effective clinically remains to be seen. A possible role for amoxicillin will be in the treatment of gonococcal urethritis. Preliminary results from our laboratory have demonstrated that a single dose of 3.0 g of amoxicillin may have activity superior to that of other agents which can be administered by mouth.

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**LITERATURE CITED**