Double-Blind Clinical Trials of Oral Cyclacillin and Ampicillin

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A double-blind study was performed to compare the clinical response and the incidence of side effects in 2,581 patients administered ampicillin or cyclacillin for infections of the genitourinary or respiratory tract, infections of the skin and soft tissues, or for otitis media. There was no significant difference in clinical response and bacterial eradication. All side effects, including diarrhea and skin rash, were approximately twice as frequent in patients treated with ampicillin.

Cyclacillin, 6-(1-aminocyclohexanecarboxamido)penicillanic acid, belongs to a new group of semisynthetic penicillins designated as aminocyclic penicillins. It is acid stable, has a low serum binding capacity of less than 25%, distributes well into tissues, and is more resistant to staphylococcal penicillinase than ampicillin (12). The in vitro activity of cyclacillin against gram-positive and gram-negative microorganisms is 25 to 50% below that of ampicillin (17). However, tests of in vitro susceptibility have been shown to be poor indicators of the therapeutic activity of this drug. Cyclacillin is as effective as ampicillin in mice infected with penicillin-susceptible Staphylococcus aureus, Streptococcus pyogenes, S. pneumoniae, and Haemophilus influenzae, less effective against Proteus mirabilis, and slightly more effective against Escherichia coli (17).

Peak serum concentrations of cyclacillin occur earlier and are three to four times greater in magnitude (6, 17) than equal doses of ampicillin.

Clinical trials also have indicated that cyclacillin and ampicillin are equally safe and effective for a variety of infections caused by susceptible gram-positive and gram-negative microorganisms (8, 13). However, these studies have suggested that patients treated with cyclacillin develop fewer gastrointestinal disorders and cutaneous rashes than patients treated with ampicillin (5, 13). Consequently, a large double-blind study was performed involving more than 2,500 patients to compare the efficacy and safety of both antibiotics.

MATERIALS AND METHODS

A total of 2,581 patients were treated with cyclacillin or ampicillin. A culture for the identification of the etiological agent was made from the source of infection before treatment was started. Quantitative clean midstream urine cultures were made from the urine of patients with urinary tract infections, and a count of at least 1 × 10⁵ organisms per ml was considered indicative of infection.

Cyclacillin and ampicillin were prepared as identical tablets or oral suspensions. Medications were allocated at random so that both physician and patient were unaware of which drug was given. No concomitant antibiotics or anti-infective agents were administered. Approximately 75% of the patients treated with cyclacillin and ampicillin were adults. Of the adult patients, 39% were males, 61% were females, and the mean age was 44.7 years. Children treated with the cyclacillin suspension had a mean age of 2.8 years, and children treated with the ampicillin suspension had a mean age of 3.6 years. Adults were treated for genitourinary, lower respiratory, or skin and soft-tissue infections and they received the antibiotic in tablet form. The dosage most often given was 500 mg every 6 h; 75% of the adults were treated for 1 to 2 weeks. Children were treated primarily for otitis media. They received 50 to 100 mg/kg per day of cyclacillin or ampicillin in oral suspension, and 75% of them were treated for 9 to 12 days.

Thirty patients in the cyclacillin group and 38 in the ampicillin group had received other antibiotics, with unsatisfactory results, within 10 days of entering the study. Patients were monitored throughout the course of therapy, and clinical effectiveness was judged by the disappearance of presenting symptoms and signs. Culture and susceptibility tests were repeated during therapy and at its conclusion. In addition, the progress of patients with urinary tract infections was also followed up to 2 to 4 weeks later. Bacteriological efficacy was judged by the eradication of the bacteria causing the original infection as well as its actions against other bacteria which occasionally emerged during treatment.

A total of 959 of 1,370 patients (70%) administered cyclacillin and 860 of 1,211 patients (71%) treated with ampicillin were eligible for an evaluation of efficacy. The remaining patients were excluded because no etiological agent was identified or they had infections caused by resistant organisms, or it had become necessary to discontinue therapy due to side effects. The course of therapy was completed, or sufficient improvement was made, to evaluate 847 patients (88%) accepted for efficacy from the cyclacillin group and 725 patients (84%) from the ampicillin group.

All side effects related to the medications were recorded. In particular, the presence or absence of a
rash was noted and the type of rash categorized. Diarrhea was defined as the change in normal stool patterns to the presence of watery or semiliquid stools. The severity and number of patients developing this side effect was also determined.

Drug-related side effects were evaluated in 1,286 patients treated with cyclacillin (94%) and 1,129 patients administered ampicillin (93%).

RESULTS

Table 1 lists the 1,819 patients for which the two antibiotics were evaluated for efficacy, according to site of infection. Half the patients treated with cyclacillin and ampicillin were treated for genitourinary tract infections, and equal numbers were treated for infections of the respiratory tract or skin and soft tissues, or for otitis media.

Table 2 shows the primary site of infection, the etiological agent, and the clinical and bacteriological responses to therapy.

A favorable clinical response was obtained in approximately 90% of patients treated with cyclacillin and ampicillin for genitourinary tract infections caused by *E. coli* and *P. mirabilis*, with both antibiotics being equivalent in eradicating these bacteria. In respiratory tract infections, namely bronchitis and pneumonia, both antibiotics resulted in an excellent clinical response as well as the eradication of *S. pneumoniae*, *H. influenzae*, and other streptococcal species. Equal numbers of patients from each treatment group comprised the 300 cases treated for skin and soft-tissue infections such as impetigo, cellulitis, carbuncle, furuncle, skin ulcers, or abscesses. Almost identical clinical and bacteriological responses were documented for cyclacillin and ampicillin.

Children in this study were most often treated for otitis media. All patients included in the efficacy analysis had diagnostic myringotomy before initiating therapy. Effectiveness was determined in approximately 20% of the patients with post-therapy myringotomy, whereas the remainder had clinically normal tympanic membranes after treatment. Both antibiotics gave clinical responses and bacteriological eradica-

tions greater than 95% for pneumococcal otitis media and 85% for those infected with *H. influenzae*.

Side effects. The total number of patients who developed side effects, particularly gastrointestinal and integumentary ones, are given in Table 3. Drug-related side effects were reported in 128 of 1,286 (10%) patients taking cyclacillin and 202 of 1,129 (18%) patients taking ampicillin. This difference was statistically significant (*P* < 0.001).

Diarrhea and skin rash were the side effects most often reported during the study. Diarrhea

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<th>TABLE 1. Primary sites of infection of treated patients</th>
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<tr>
<td>Genitourinary tract</td>
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<td>Respiratory tract</td>
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<td>Skin and soft tissue</td>
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<td>Otitis media</td>
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<tr>
<th>TABLE 2. Efficacy of cyclacillin and ampicillin</th>
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<td>Infection site*</td>
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<tr>
<td>Genitourinary tract</td>
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<td>Lower respiratory tract (bronchitis, pneumonia)</td>
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*No significant differences were obtained (using the chi-square method) between therapies.
was reported in 5.1% of cyclacillin-treated patients and 12.5% of ampicillin-treated patients, the difference being statistically significant ($P < 0.001$).

Approximately one-half of the patients taking either antibiotic developed this side effect within the first 72 h of therapy. Among patients reporting diarrhea as a side effect, therapy was discontinued in 14% of those taking cyclacillin and 28% of those receiving ampicillin. This was statistically significant. Although the diarrhea in the ampicillin-treated patients tended to be more severe, the difference was not significant.

Children treated with cyclacillin suspension experienced a 9.1% diarrhea rate, whereas diarrhea was recorded in 19.2% of children treated with the ampicillin suspension ($P < 0.001$). No cases of pseudomembranous colitis were reported with either drug.

The incidence of rash observed with cyclacillin (1.7%) was significantly less than that observed with ampicillin (3.1%). The incidence of rash in children 12 years of age or less treated with cyclacillin suspension was 2.1%, and it was 5.8% for children treated with ampicillin suspension ($P < 0.03$) (Table 3). No cases of Stevens-Johnson syndrome or mononucleosis associated rashes were noted.

### DISCUSSION

Cyclacillin and ampicillin are broad-spectrum penicillins, equally effective in the treatment of infections due to susceptible gram-positive and gram-negative microorganisms. When all infections in this study caused by gram-positive microorganisms were combined, clinical efficacy was 95% for cyclacillin and 98% for ampicillin; eradication of gram-positive bacteria was 90% for cyclacillin and 87% for ampicillin. The antibacterial effectiveness against isolated gram-negative bacteria was 90% for each group; bacteriological eradication was 83% for cyclacillin and 85% for ampicillin.

When patients who received cyclacillin or ampicillin were compared to each other, significant differences were found in the numbers experiencing drug-related side effects. Diarrhea was the most prevalent side effect observed; 12.5% of the patients receiving ampicillin, as opposed to 5.1% of cyclacillin patients, developed this symptom.

The incidence of ampicillin-associated diarrhea obtained in this study is in agreement with previously reported data. Bass et al. treated 400 children, 2 months to 6 years of age, with 50, 100, 150, or 200 mg of ampicillin per kg per day in four equally divided doses for 7 days. The incidence of diarrhea in these study groups ranged from 18 to 30% (1). Other studies involving ampicillin recorded a diarrhea incidence of 8% (6) and 11% (7).

The rapid and efficient absorption of cyclacillin from the upper gastrointestinal tract, with consequent decreased alteration of the microbial flora of the lower intestine, is the most likely explanation for the low incidence of diarrhea in cyclacillin-treated patients (12; R. W. Schaeder, unpublished data).

An erythematous macular or maculopapular rash was observed in 1.7% (22/1,286) of the cyclacillin-treated patients and 3.1% (35/1,129) of the patients on ampicillin. A statistically significant difference in the incidence of rash was noted in children age 12 or less treated with cyclacillin suspension (2.1%) when compared to the ampicillin suspension control group (5.8%).

Ampicillin rash has been reported to occur in 5% (1), 7.3% (4), and 9.5% (14) of treated patients. Nearly all patients with infectious mononucleosis given 1.5 g or more of ampicillin will develop a rash (10), and an increased incidence of rash is known to occur with ampicillin therapy in patients with salmonella infections (15, 16), cytomegalovirus infection (9), and chronic lymphatic leukemia (3).

In summary, cyclacillin and ampicillin are equally satisfactory in the treatment of susceptible gram-positive and gram-negative infec-
tions. However, this double-blind study indicates that cyclacillin is better tolerated than ampicillin and results in a lesser incidence of diarrhea and rash.

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LITERATURE CITED