Comparison of Cyclacillin and Amoxicillin for Therapy of Acute Maxillary Sinusitis

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Cyclacillin, a new aminoalicyclic semisynthetic penicillin, was compared with amoxicillin for the therapy of acute bacterial maxillary sinusitis in 80 patients (ages, 12 to 70 years) in a prospective, double-blind, randomized clinical trial. Direct sinus aspirations for quantitative culture were done for all patients before and after 10 days of therapy. Both drugs were administered at a dosage of 500 mg orally three times daily. Among culture-positive patients, clinical cure was achieved in 23 of 26 patients and 25 of 27 patients treated with cyclacillin and amoxicillin, respectively, for an overall cure rate of 91%. Bacteriologic failure occurred in 9% (4 of 44 patients); 3 of the 4 failures were in the cyclacillin group. There was no correlation between clinical or bacteriologic cure and the results of sinus transillumination (clear, dark) at follow-up. Initial direct sinus aspirates were positive in 57 of 80 cases (70%); 25 (44%) of these were the result of *Streptococcus pneumoniae* and 23 (40%) were the result of *Haemophilus influenzae*. All of these isolates were susceptible (MIC, ≤ 0.5 $\mu\text{g/ml}$) to both study drugs; no ampicillin-resistant *H. influenzae* was recovered. On day 10 of therapy, mean concentrations of both drugs in serum were 2.5 to 2.7 $\mu\text{g/ml}$, but no antibiotic was detectable in 20 of 21 simultaneous sinus aspirates. Adverse effects (rash, diarrhea) were infrequent and similar in both groups. Cyclacillin appears equivalent to amoxicillin in the therapy of acute maxillary sinusitis.

Acute bacterial sinusitis complicates approximately 1 in every 200 common colds (3). Because children and adults develop approximately eight and three common colds per year (3), respectively, acute sinusitis is commonly encountered in office practice. However, the symptoms and signs of this entity are nonspecific and do not correlate well with the presence of pathogenic microorganisms in the maxillary antra. Roentgenograms of the sinuses are helpful diagnostically and correlate with the results of sinus aspiration (4, 8) but are expensive to obtain.

Direct puncture with aspiration of the sinus cavities has been useful in defining the etiology of acute maxillary sinusitis (1, 2, 4, 5, 7-10, 14, 15). At least 50% of aspirates from adults with acute maxillary sinusitis yield *Streptococcus pneumoniae* or *Haemophilus influenzae*, although other aerobic and anaerobic organisms are also encountered.

Antibiotic therapy of acute bacterial maxillary sinusitis should be directed against the major pathogens involved in this disorder, *S. pneumoniae* and *H. influenzae*. Ampicillin is often used for this purpose, with proven efficacy in studies with sinus aspirate cultures (1, 6, 8) if the duration of therapy exceeds 7 days. Amoxicillin has in vitro activity similar to that of ampicillin but produces peak concentrations in serum two- to threefold higher and is associated with a lower incidence of adverse effects, chiefly diarrhea and rash. Trimethoprim-sulfamethoxazole is also effective in the therapy of acute maxillary sinusitis (7).

Cyclacillin is a new aminoalicyclic semisynthetic penicillin with an in vitro spectrum comparable to that of ampicillin (6, 13). The drug is rapidly absorbed after oral administration and may produce fewer adverse effects than those noted with ampicillin. For example, diarrhea and loose stools occurred in 5% of cyclacillin-treated patients compared with 12.5% of patients receiving ampicillin in one large study of

2,581 patients (6). Similarly, rash was nearly twice as common in the ampicillin group (3.1 compared with 1.7% of cyclacillin-treated patients). Both of these differences are highly statistically significant (6).

The purpose of this study was to compare the efficacy and safety of cyclacillin and amoxicillin in the therapy of acute maxillary sinusitis in a randomized double-blind clinical trial.

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MATERIALS AND METHODS

Eighty outpatients between 12 and 70 years of age were enrolled in the trial. All had symptoms and signs compatible with acute maxillary sinusitis, including facial pain and purulent nasal discharge for no more than 2 weeks, often accompanied by fever, headache, malaise, and other constitutional symptoms. Underlying conditions (e.g., allergic disorder, recent viral illness, dental infection) were evenly distributed between the two treatment groups. The various reasons for patient exclusion included malignancy or immunosuppressive therapy; hypersensitivity to penicillin; chronic sinusitis (e.g., symptoms of longer than 3 weeks duration); previous surgery of congenital anomaly of the head and neck; antibiotic ingestion within 72 h of entry into the study; cerebrospinal fluid rhinorrhea; the presence of significant cardiac, hepatic, or renal disease; chronic vomiting; diarrhea or gastrointestinal disease; chronic granulomatous disease of childhood; and severe illness requiring intravenous antibiotics or hospitalization or both. Written informed consent, approved by the investigation review

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TABLE 1. Correlation of clinical outcome with sinus transillumination at follow-up

Clinical outcome	Sinus transillumination in culture-positive patients (n)	
	Clear	Dark
Cure	30	18
Not evaluable	0	2
Failure	0	5

board at the University of Virginia, was obtained from all patients.

The clinical diagnosis of acute maxillary sinusitis was made by an experienced otolaryngologist and confirmed by quantitative culture of an aspirate obtained by puncture of the maxillary sinus cavity via the inferior meatus after appropriate local anesthesia and preparation with betadine. One or both antra were dark by transillumination at the start of the study. A culture was considered positive if $\geq 10^4$ CFU of bacteria were present. As expected (1, 7–10), some sinus aspirates were negative on culture; the patients from whom these were taken were not included in the analysis of bacteriologic or clinical efficacy.

After performance of sinus aspirations for quantitative bacterial culture and MIC and MBC susceptibility testing, the patients were randomized by a computer-generated number table to receive either cyclacillin or amoxicillin at a dosage of 500 mg three times a day for 10 to 14 days. The same program of adjunctive therapy (e.g., vasoconstrictor agents were Neo-Synephrin, analgesics) was offered to all patients. Any patient with persistent symptoms or adverse reactions was seen during this interval. Otherwise, the patients were reevaluated clinically after 10 days of therapy; the presence or absence and the severity of the symptoms and signs of acute sinusitis, including repeat transillumination, were evaluated and recorded. A repeat sinus aspiration was performed for repeat quantitative culture, susceptibility tests, and determination of antimicrobial concentration (with a simultaneous serum sample with time for ingestion of drug recorded). Information concerning side effects was recorded. Clinical cure was defined as the elimination of all signs and symptoms of acute maxillary sinusitis, regardless of the findings upon repeat transillumination. Bacteriologic cure was defined as eradication or a ≥ 4 log reduction in the titer of bacterial pathogens isolated from the second aspirate. These criteria for clinical and bacteriologic success or failure were rigidly standardized and identical to those of previous studies of acute maxillary sinusitis performed at this institution (4, 5, 7, 8).

All sinus aspirate specimens were quantitatively cultured after 10-fold dilutions in phosphate-buffered saline aerobically and anaerobically on chocolate and blood agar plates (Difco Laboratories, Detroit, Mich.). All isolates were identified to the species level by standard microbiologic techniques. The MICs and MBCs of cyclacillin and amoxicillin were determined for all isolates (except anaerobes) in Mueller-Hinton broth (Difco) by standard microtiter techniques with a Dynatech Autodiluter II (Dynatech Industries, Inc., Alexandria, Va.). Lysed horse blood was added to the broth for susceptibility testing of *H. influenzae*. All inocula were 5×10^5 CFU. The MIC was defined as the lowest concentration inhibiting growth, and the MBC was defined as the lowest concentration killing $\geq 99.9\%$ of the initial inoculum. Cyclacillin and amoxicillin concentrations were determined on fresh simultaneous serum and sinus aspirate

specimens after ≥ 10 days of therapy by standard agar well diffusion techniques. A 0.9-ml sample of *Bacillus subtilis* spore suspension in 100 ml of antibiotic medium no. 1 (Difco) was used as the indicator. All standards were diluted in fresh human serum and phosphate-buffered saline for serum and sinus aspirate samples, respectively, on the day of use. Reproducibility was $\pm 10\%$, and the lower limit of detectability was 0.3 $\mu\text{g/ml}$ for each bioassay procedure.

RESULTS

Only 5 of the initial 80 patients (3 in the amoxicillin group, 2 in the cyclacillin group) failed to return for follow-up; all others completed the protocol. In most cases, puncture of the sinus cavity and aspiration for culture of the contents was performed on two occasions. For culture-positive patients, clinical cure, designated as complete resolution of all the symptoms of the initial disease, was achieved in 23 of 26 patients and 25 of 27 patients treated with cyclacillin and amoxicillin, respectively. This difference is not statistically significant. Thus, 91% (48 of 53) of the culture-positive patients were clinically cured with the two regimens. In addition, clinical cure was achieved in all 18 patients in whom the initial sinus aspirate failed to reveal a conventional pathogen and had bacterial concentrations $\leq 10^4$ CFU/ml. There was no correlation between a dark sinus by transillumination at follow-up after ≥ 10 days of therapy and clinical cure, as shown in Table 1. As can be seen, no clinical failures were noted in 30 patients with a clear sinus by transillumination at follow-up. All five failures had a dark antrum at follow-up by this procedure. However, 18 patients whose symptoms had cleared still had a dark antrum at follow-up. The second sinus aspirate cultures of these 18 patients were negative. This likely reflects persistent mucosal thickening despite a clinical and bacteriologic response to therapy.

As stated above, all sinuses were punctured for quantitative culture at the start of the study. The results are shown in Table 2; 57 of the 80 aspirates were positive, for an overall positive bacteriologic result in 70% of the patients, in excellent agreement with results of previous studies of sinusitis using sinus puncture techniques (4, 5, 7–10, 14, 15). It is possible that a viral etiology was responsible for some of these cases yielding no growth (7). Among culture-positive cases, the distribution of isolates was as follows: 44% were the result of *S. pneumoniae*, 40% were the result of *H. influenzae*, 7% grew *Staphylococcus aureus* in pure culture, and 7% were the result of anaerobes (*Peptostreptococcus* sp., *Bacteroides melaninogenicus*) or a mixed population of anaerobic and aerobic organisms (*Streptococcus anginosus* and *H. influenzae*, *B. melaninogenicus* and *Branhamella catarrhalis*, two *Peptostreptococcus* spp.) (all $\geq 10^4$ CFU). Thus, pneumococci and *H. influenzae* caused more than 80% of the culture-positive acute maxillary sinusitis in this study, in agreement with results published previously (7, 8, 15). In addition, the MICs and MBCs of both cyclacillin and

TABLE 2. Microbiologic results of sinus aspiration at the start of the study

Organism(s)	No. (%) ^a of aspirates
<i>S. pneumoniae</i>	25 (44)
<i>H. influenzae</i>	23 (40)
<i>S. aureus</i>	4 (7)
Anaerobic, mixed	5 (7)

^a The overall percent was 70% ($\geq \log_{10}$ 4.0 CFU/ml).

amoxicillin were all ≤ 0.5 $\mu\text{g/ml}$ against all pneumococci and *H. influenzae* strains; there were no β -lactamase-positive (or ampicillin-resistant) isolates among the 23 *H. influenzae* strains recovered in this trial.

Among 44 follow-up sinus aspirates (13 patients completed therapy and follow-up but refused a second sinus aspiration), there were four bacteriologic failures, for an overall incidence of 9%. Of the four bacteriologic failures, three occurred in the cyclacillin group (although two were judged as clinical cures), compared with only one in the amoxicillin group; this difference is not statistically significant.

Serum and sinus aspirate samples for the analysis of cyclacillin and amoxicillin concentrations were obtained from 21 consecutive patients returning for follow-up on day 10 of therapy. The mean concentrations in serum 2 to 6 h after drug administration were comparable and were 2.7 and 2.5 $\mu\text{g/ml}$ for patients treated with cyclacillin and amoxicillin, respectively. Despite these concentrations, only 1 of 21 simultaneous sinus aspirates contained detectable drug (0.9 $\mu\text{g/ml}$) by our bioassay method, with a lower limit of detectability of ≤ 0.3 $\mu\text{g/ml}$. Based on these preliminary criteria, bacteriologic and clinical cure correlated poorly with sinus aspirate antibiotic concentrations at follow-up, because most were undetectable.

Adverse effects were relatively infrequent in this study. A skin rash appeared in 5 of 80 patients treated; four of the rashes occurred in the amoxicillin group. All rashes were self-limited without mucosal membrane involvement. Nevertheless, this difference was not statistically significant. Diarrhea occurred in one patient in each group and required discontinuation of therapy. The cyclacillin-treated patient with diarrhea also developed a skin rash.

DISCUSSION

This study compared cyclacillin, a new aminoalicyclic penicillin, with amoxicillin for the therapy of acute bacterial maxillary sinusitis in 80 patients between 12 and 70 years of age. The study was prospective, double-blind, and randomized and included 80 consecutive patients seen in practice by an experienced otolaryngologist. Direct puncture of the maxillary antrum for sinus aspirates was performed before and after therapy for quantitative bacteriologic culture (and antibiotic concentration testing in some patients). On the basis of this study, cyclacillin appears equivalent to amoxicillin in the therapy of acute maxillary sinusitis in humans, as judged by (i) clinical and bacteriologic response or cure, (ii) drug concentrations in serum, and (iii) adverse reactions.

In this study, both amoxicillin and cyclacillin therapy demonstrated clinical and bacteriologic efficacy in 91% of patients with acute maxillary sinusitis at a dosage of 500 mg three times daily. These results are comparable to those achieved in previous studies (success rates, 90 to 100%) with the following drugs at the given dosages: ampicillin, 500 mg orally every 6 h; bacampicillin, 800 mg orally twice daily; trimethoprim-sulfamethoxazole, 80 and 200 mg in two tablets orally twice daily; and cefaclor, 500 mg orally every 6 h in adults (1, 4, 5, 7, 8, 11). All regimens should be administered for at least 10 days to obtain optimal results.

In this study, there was no correlation between the result of sinus transillumination at follow-up and the clinical response of the patient (Table 1). This may reflect persistent mucosal thickening despite a successful response to antimicrobial therapy. Persistent mucosal thickening was noted previously with sinus radiographs obtained days to weeks after the cure of acute maxillary sinusitis with antibiotics (7).

All sinuses were punctured and aspirated for quantitative bacterial culture at the start of the study; 57 of the 80 initial aspirates were positive (70%); some of the remaining cases may have been viral in origin, or the bacterial strains isolated in low titer ($\leq 10^2$ CFU) may also have been responsible (7). In agreement with results of previous studies using direct sinus aspirates (1, 4, 5, 7, 8, 15), $\approx 80\%$ of the cases were caused by *S. pneumoniae* or *H. influenzae*. All of these isolates were susceptible to cyclacillin and amoxicillin (MIC, ≤ 0.5 $\mu\text{g/ml}$), and no β -lactamase-positive *H. influenzae* strains were recovered. Because ampicillin-resistant strains of *H. influenzae* may cause sinusitis, alternative agents (i.e., Augmentin, a fixed combination of amoxicillin and clavulanic acid) may represent a better choice in these cases or in areas where β -lactamase-positive isolates predominate (12; E. R. Wald, B. J. S. Reilly, M. C. Casselbrant, and D. M. Chiponis, Postgrad. Med. J., in press). Augmentin is, however, more expensive and may produce more diarrhea than that encountered with amoxicillin alone.

For the last 21 patients treated in this study, serum and sinus aspirates were obtained for the simultaneous analysis of antibiotic concentrations. The concentrations in serum were low (2.5 to 2.7 $\mu\text{g/ml}$), reflecting the long interval (mean, 4.5 h) between drug ingestion and procurement of serum samples. In addition, compliance may have been poor in several patients because samples were obtained on day 10 when all had been clinically cured and asymptomatic for 3 to 5 days. Despite these concentrations in serum, only 1 of 21 simultaneous sinus aspirates contained detectable antibiotic (≥ 0.3 $\mu\text{g/ml}$). However, these sinus aspirates were clear and generally required a saline wash for the recovery of sufficient material for bioassay. Thus, little or no inflammation was present to enhance drug entry into the sinus. Finally, concentrations in the aspirate may not reflect antibiotic concentrations in the mucosal lining of the sinus, of potential (but unproven) importance in the response to therapy.

The results of this trial indicate that cyclacillin, like several other antibiotics, is of efficacy in the treatment of acute maxillary sinusitis. The advantages of cyclacillin when compared with ampicillin or amoxicillin may include a lower incidence of adverse effects (6), but such differences could not be demonstrated with the small number of patients ($n = 80$) enrolled in this trial. A typical patient with acute sinusitis may be treated with cyclacillin, ampicillin, amoxicillin, bacampicillin, trimethoprim-sulfamethoxazole, cefaclor, or Augmentin, in appropriate doses, with adjunctive nasal decongestants, analgesics, and antipyretics as necessary. Augmentin may be preferred when ampicillin-resistant *H. influenzae* or *S. aureus* (7% of the aspirates in this study) are the prevalent pathogens, but this requires further investigation, especially in adults, for whom data are scant.

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