Sultamicillin in the Treatment of Superficial Skin and Soft Tissue Infections in Children

JOHANNA GOLDFARB,1,2 STEPHEN C. ARONOFF,2,3 ARTHUR JAFFE,2,4 MICHAEL D. REED,1,2 AND JEFFREY L. BLUMER1,2*

Division of Pediatric Pharmacology and Critical Care,1 Division of Infectious Diseases,2 and General Pediatrics,4 Rainbow Babies and Children’s Hospital, and Departments of Pediatrics and Pharmacology, Reserve University School of Medicine,2 Cleveland, Ohio 44106

Received 8 September 1986/Accepted 10 January 1987

Fifty-two children with superficial skin and soft tissue infections were randomized to receive sultamicillin or cloxacillin for 7 days. Twenty-one children in each group finished the study. A total of 16 of 21 in the sultamicillin group and 13 of 21 in the cloxacillin group were cured. One child in the sultamicillin group and two in the cloxacillin group failed therapy. Four children who received sultamicillin and six who received cloxacillin had recurrences of lesions. Differences were not statistically significant.

Superficial skin and soft tissue infections are common pediatric problems treated in an ambulatory setting with oral antibiotics (4). Since Staphylococcus aureus and Streptococcus pyogenes are the major pathogens in superficial skin infections, initial outpatient therapy for most skin and soft tissue infections should be effective against both pathogens (2–4, 7). Sultamicillin is an oral beta-lactam antibiotic consisting of ampicillin esterified to sulbactam, a beta-lactamase inhibitor. This combination expands the in vitro spectrum of ampicillin to include S. aureus as well as most ampicillin-resistant strains of beta-lactamase-producing isolates of Haemophilus influenzae, Escherichia coli, and Branhamella catarrhalis (8). Pharmacokinetic studies of sultamicillin in children have shown greater ampicillin bioavailability when the sultamicillin ester is administered. Peak concentrations in serum occur about 90 min after an oral dose (5). Clinical studies of sultamicillin in children have demonstrated its efficacy in the therapy of acute otitis media (6) and pharyngitis (1), with mild diarrhea being the main side effect (1, 6). Sultamicillin may, therefore, be useful in the treatment of skin and soft tissue infections in children.

This study was designed to compare the efficacy and safety of sultamicillin with those of cloxacillin, an oral isoxazoyl penicillin, standard therapy for staphylococcal and streptococcal skin infections. Children (6 months to 12 years of age) with bacterial infections of the skin or soft tissues or both requiring antibiotic therapy were eligible for the study. Impetigo was diagnosed by the presence of superficial crusting lesions with or without the presence of vesicles or bullae. Exclusion criteria included children with a known penicillin allergy, those receiving a potentially effective antimicrobial agent within 48 h of enrollment, and those requiring concomitant therapy with other antimicrobial agents. This study was approved by the Institutional Review Board for Human Subjects Experimentation, and prior informed written consent was obtained.

Treatment was determined by a computer-generated randomized list and consisted of either sultamicillin twice daily or cloxacillin four times daily. Doses were calculated according to age and weight. Sultamicillin was given as 250 mg twice daily to children under 5 years, 500 mg twice daily to those over 5 years, and 750 mg twice daily to those over 20 kg. Cloxacillin was given as 50 mg/kg per day to children under 20 kg and 250 mg four times daily to those over 20 kg. Therapy was for 7 days, and only the pharmacy was aware of drug assignments.

Samples for bacterial cultures were obtained from lesions prior to therapy. Impetiginous lesions were cleaned with soap and water, and samples of the exudate or skin under the crusts were cultured. Abscesses were aspirated in a sterile manner, and pus was cultured directly; sterile saline was injected and cultured if no pus was obtained. Follow-up cultures were done during therapy and 5 to 9 days posttherapy for any remaining or new lesions. Organisms were identified on blood agar by routine methods, and disk susceptibilities were determined on Mueller-Hinton plates for amoxicillin, sultamicillin, and cloxacillin. Determinations of complete blood counts, serum glutamic oxaloacetic transaminase, alkaline phosphatase, total bilirubin, creatinine, and glucose and urinalyses were done before, during, and after therapy.

Side effects and compliance were monitored by a research nurse. Medication bottles of the dispensed drug were collected, and if 10% or more of the doses were missed, the patient was judged noncompliant.

A total of 52 children were enrolled in the study; 27 received sultamicillin, and 25 received cloxacillin (Table 1). A total of 18 of the 21 evaluable children in the sultamicillin group and 20 of the 21 evaluable children in the cloxacillin group had impetigo. Most children had had lesions for more than 3 days. Other diagnoses included the following: abscess (in two children), folliculitis, adenitis, and cellulitis (each in a single patient). S. aureus was the organism isolated from wound cultures most frequently: 22 of 27 initial cultures from the sultamicillin group and 20 of 25 initial cultures from the cloxacillin group. S. pyogenes was present alone in two patients from each group. This group included two children with impetigo, a child with an infected burn (cellulitis), and a child with cervical adenitis who had a negative node aspirate but a throat culture positive for group A streptococci. S. pyogenes and S. aureus together were present in five of the sultamicillin-treated impetigo patients and in four impetigo patients in the cloxacillin group.

* Corresponding author.
A successful outcome, defined as a clinical cure of the infection (no recurrence on follow-up visits, with full healing and no crusts or pus present in cases of cellulitis), was documented in 16 children in the sultamicillin group and in 13 children in the cloxacillin group. One child in the sultamicillin group and two in the cloxacillin group failed therapy. These children did not respond to the study drug and required a change in therapy. Recurrences of impetigo, defined as a recurrence of lesions in children who had initially responded completely, occurred in four children in the sultamicillin group and in six in the cloxacillin group. Differences in therapeutic responses between the groups were not statistically significant, as determined by chi-square analysis ($P < 0.05$).

Compliance was good in both groups, except for one child, who was removed from evaluation in the cloxacillin group because of a failure to take appropriate doses. Mild diarrhea occurred in three children in the sultamicillin group and in five in the cloxacillin group. None of these children had to stop the medication for medical reasons, although three of these children were removed from the study at parental request (two in the sultamicillin group and one in the cloxacillin group). One child in the cloxacillin group developed a drug rash and was removed from the study of this reason. Diaper rashes occurred in four children and were treated with local therapy. No adverse drug effects were seen in the blood and urine tests.

In this small randomized double-blind study, there was no significant difference in the efficacy of sultamicillin versus cloxacillin in the treatment of superficial skin and soft tissue infections. Cure rates, however, were low for both drugs: 76 and 61%, respectively.

The rate of recurrence of impetigo (4 of 21 children in the sultamicillin group and 6 of 21 in the cloxacillin group) was also high. The organisms isolated during recurrences showed no significant change in antibiotic susceptibilities, and the recurrences may be related to factors other than drug therapy not investigated in this study.

The high rate of $S. aureus$ isolation from our cases of impetigo was striking. Some of the lesions were old (more than 3 days), but a high rate of staphylococcal disease appeared to be truly present in our population, as the staphylococci were frequently isolated as the sole pathogens.

The major side effect of both drug therapies was diarrhea. Although judged mild medically, it did prompt removal from the study of three children. Sultamicillin did not appear more likely to cause this side effect than cloxacillin.

In this small clinical study, sultamicillin therapy appeared to be at least equivalent to standard oral therapy for the treatment of superficial skin and soft tissue infections.

The high failure and recurrence rates in our study, with both standard and sultamicillin therapies, are a cause for concern. Further studies to examine the length of therapy as well as other factors, such as the etiology of the recurrences (reexposure versus true relapse), would be useful in trying to improve cure rates.

This research was supported in part by a grant from Pfizer Central Research, Pfizer Inc., Groton, Conn.

**LITERATURE CITED**