Treatment of Cellulitis with Ceforanide

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Thirty-five patients with cellulitis were treated with ceforanide, 1 g every 12 h, intramuscularly. A good clinical response was observed in 33 cases. Drug failure in the remaining two patients was thought to be due to the lack of surgical debridement. Drug concentrations well in excess of inhibitory levels for *Streptococcus pyogenes* were generally present throughout the treatment period; although this was not true of ceforanide concentrations relative to inhibitory levels for *Staphylococcus aureus*, the clinical response in patients with staphylococcal infection still appeared to be entirely satisfactory. Killing of *S. pyogenes* by 5, 50, and 500 $\times$ the minimum inhibitory concentration of ceforanide proceeded at the same rate in vitro as did killing by 5, 50, and 500 $\times$ the minimum inhibitory concentration of penicillin.

Ceforanide is a new cephalosporin which has been shown to be effective in vitro (5, 6, 9) and in vivo (3, 6, 9) against organisms which are ordinarily susceptible to first-generation cephalosporins. Previous clinical studies have shown it to provide good results in treating pneumonia (2, 11), urinary tract infection (2), and a few cases of cellulitis (2). The present study was designed to investigate the use of ceforanide in treating cellulitis or erysipelas which was of sufficient severity to warrant hospitalization.

MATERIALS AND METHODS

Patient selection. Patients were hospitalized because of cellulitis or erysipelas and were referred to the Infectious Disease Service at the time of admission. The nature of the study was explained to them, and they were asked to sign a consent form that had previously been approved by Subcommittees on Experimentation Involving Human Subjects at the Baylor College of Medicine and the Houston Veterans Administration Medical Center. Patients who were unable to give a truly informed consent, those who were receiving chemotherapy for treatment of malignancy, and those who had a life-threatening, unrelated illness were excluded.

Experimental design. Patients were initially examined by one of the investigators and begun on treatment with ceforanide, 1 g intramuscularly every 12 h. They were reexamined every day thereafter, with changes in clinical status and the response of infected tissues being noted. Purulent material, when available, was cultured at 35°C on sheep blood agar aerobically and anaerobically. In the absence of frank pus, aspiration of the most fluctuant areas and the advancing margin of the lesion was attempted, generally with a 19- to 20-gauge needle and a 10- to 20-ml syringe. Tissue fluid was cultured anaerobically in tryptic soy broth; if enough was obtained, fluid was also cultured aerobically and anaerobically on sheep blood agar. If

no fluid was obtained, 0.5 to 1 ml of water or saline was injected and reaspirated for culture in broth and on sheep blood agar. Complete blood counts and serum chemistries were studied on admission and at least once during and once at the end of the treatment period.

In vitro studies. The minimum inhibitory concentration (MIC) was determined for causative bacteria as follows. Twofold dilutions of antibiotics were made in tryptic soy broth, and the tubes were inoculated with 10⁶ colony-forming units of the organism to be tested. The MIC was defined as the lowest concentration of antibiotic that prevented obvious turbidity after incubation for 18 h at 37°C. The rate of killing of *Streptococcus pyogenes* was studied by inoculating tryptic soy broth which contained varying concentrations of ceforanide or penicillin with 10⁷ colony-forming units per ml and subculturing quantitatively 3, 7, 24, and 48 h later. The lower level of sensitivity of this method was such that <10 colony-forming units per ml could not be detected. An agar diffusion technique was used to measure ceforanide concentrations in serum obtained 1, 6, and 12 h after an intramuscular dose, usually on day 3 or 4 of treatment.

Adverse reactions. Ceforanide caused very little discomfort when given intramuscularly. One patient had a transient elevation of serum glutamate oxaloacetic transaminase to 280 U during ceforanide therapy; this returned to normal after the drug was discontinued.

RESULTS

Patients. Thirty-five male patients (mean age, 47.6 years) were included in this study. Twenty had at least one underlying systemic condition thought to contribute to decreased ability of the host to respond to pyogenic infection, such as alcoholism (with or without liver disease), diabetes mellitus, or renal insufficiency. Twenty-four had an identifiable factor which

compromised local resistance to infection, including blunt or penetrating trauma, self-injection, extremely poor hygiene, burns, or dermatological disease. In all but one patient, at least one predisposing factor, systemic or local, could be identified.

Symptoms and severity of infection. Illnesses were usually acute in onset (average duration of symptoms before admission, 4.9 days; range, 1 to 21 days). The severity of infection was graded by the following criteria: (i) mild disease represented a localized area of cellulitis with no lymphangitic streaks, systemic toxicity, or fever; (ii) moderate disease represented a more extensive area of cellulitis with or without lymphangitic streaks, leukocyte elevation, and low-grade fever, but with no systemic toxicity; (iii) severe disease represented an extensive area of cellulitis with regional lymphadenopathy, leukocyte elevation, fever, and systemic toxicity. None of the 35 patients had mild infection, reflecting the fact that all had been hospitalized with their infection as the primary diagnosis; 7 had moderate, 13 had moderate to severe, and 15 had severe infection. Twenty-one patients had fever (temperature $\geq 100.2^{\circ}\text{F}$ [ca. 37.9°C]), 5 had lymphangitis (red streaks with enlarged, tender draining lymph nodes), and 17 had a leukocyte count $>10,000$; at least one of these abnormalities was present in 26 of 35 cases. A clinical distinction between cellulitis and erysipelas was not attempted (1, 4).

Bacteriological diagnosis. A bacterial cause of infection was identified in 27 cases either by aspirating through unbroken skin (14 cases) or by swabbing obviously purulent material (13 cases). No bacteriological diagnosis was made in the remaining eight cases despite at least two attempts at aspiration from the infected tissues in every case. When direct needle aspiration yielded grossly visible fluid, cultures were usually positive. If fluid was obtained only after injection of a sterile solution, cultures were usually negative. The yield was slightly higher with aspiration from the center of lesions than from the margin, although in most instances if one was positive, both were. Causative organisms were *Streptococcus pyogenes* (14 cases), *Staphylococcus aureus* (3 cases), *S. pyogenes* and *S. aureus* (9 cases), and *Streptococcus agalactiae* (1 case). Blood cultures were obtained in all but two patients and were negative.

Response to treatment. Of the 21 febrile patients, 21 defervesced (temperature $\leq 99.6^{\circ}\text{F}$ [ca. 37.5°C]) within 48 h of onset of therapy; the one exception will be discussed below. All patients except for the one who failed to defervesce felt substantially better within 48 h after ceforanide therapy had been instituted. To observe

the response to therapy, criteria were established to determine the reduction of inflammation in involved tissues; these included the finding of decreased heat, redness, and tenderness and a crinkly appearance of the involved skin, consistent with resolving edema. The actual area involved was often less, although initially this was not essential to considering a response to have been present. An appreciable reduction of inflammation was observed within 48 h (rapid response) in 16 patients, 48 to 96 h (adequate response) in 14 patients, and 96 to 168 h (slow response) in 5 patients. Five patients required surgical intervention 1 to 5 days after antibiotic therapy had been begun, either for debridement or to drain loculated collections of pus: three of these had already shown a good clinical response; the other two are discussed below. The mean duration of ceforanide therapy was 7.4 days (range 3 to 15 days). All patients were kept in the hospital until a good clinical resolution had been achieved with ceforanide. Eighteen patients received additional oral antibiotics for up to 2 more weeks; this was generally prescribed by the primary care physician, presumably to allow for more complete recovery of infected tissues.

Two patients were not cured by medical treatment with ceforanide. In both, the lack of appropriate surgical drainage was thought to be responsible. One had severe cellulitis and fasciitis due to *S. pyogenes*; after 48 h his temperature was still 103°F (ca. 39.4°C ; down from a peak of 104.8°F [ca. 40.4°C]). Surgical drainage was refused, and penicillin (500,000 U intravenously every 4 h) was given in place of ceforanide. The patient continued to defervesce slowly during 5 additional days; inflammatory changes and serosanguinous drainage from a few necrotic areas persisted for 3 weeks. Cultures of drainage obtained immediately before the first dose of penicillin were sterile. A second patient with cellulitis due to *S. pyogenes* defervesced on ceforanide, but the area of inflammation decreased only slightly and, on day 6 of treatment, began to extend. Serum ceforanide levels were $130\text{ }\mu\text{g/ml}$ 1 h after an intramuscular dose and $14\text{ }\mu\text{g/ml}$ after 12 h. Procaine penicillin G ($1.2 \times 10^6\text{ U}$) was given intramuscularly every 12 h. Within 23 h the intensity of the cellulitis was reduced, but the area of involvement remained unchanged. Penicillin therapy was continued. Three days later, two small fluctuant areas were incised, and a small amount of dark red, cloudy material which was culture negative was removed. Thereafter, the patient rapidly improved.

MIC and rate of bactericidal killing. The median MIC of ceforanide for 23 isolates of *S. pyogenes* was $0.3\text{ }\mu\text{g/ml}$ (range, 0.15 to $0.6\text{ }\mu\text{g/ml}$).

ml). The median MIC of ceforanide for 12 isolates of *S. aureus* was 3.1 $\mu\text{g/ml}$ (range, 1.6 to 6.2 $\mu\text{g/ml}$). The rate of bacterial killing, studied for 19 isolates, was proportional to the concentration of ceforanide and paralleled that of penicillin at equivalent multiples of the MIC. Figure 1 shows that this also was true of isolates from the two therapeutic failures.

Serum levels. The mean concentration of ceforanide in serum 1 h after intramuscular injection was 65 $\mu\text{g/ml}$ (range, 21 to 104 $\mu\text{g/ml}$). Six hours after injection the serum level was 29 $\mu\text{g/ml}$ (range 6 to 60 $\mu\text{g/ml}$), and 12 h after injection, it was 10 $\mu\text{g/ml}$ (range, 2.1 to 31 $\mu\text{g/ml}$).

DISCUSSION

Ceforanide appeared to provide effective antimicrobial therapy in 33 of 35 patients who had cellulitis that was severe enough to warrant hospitalization. The median MIC of *S. pyogenes*, which was isolated as the sole pathogen in 14 cases and as one of two possible pathogens in 9 additional cases, was 0.3 $\mu\text{g/ml}$ with all isolates being inhibited by $\leq 0.6 \mu\text{g/ml}$; these results are similar to those reported for other cephalosporins (8). The concentrations of ceforanide in serum were much higher than the above levels throughout the treatment period. The MIC of ceforanide for *S. aureus* was nearly tenfold greater than that for *S. pyogenes*, confirming the observations of Laverdiere et al. (5). These results indicate that in some patients, ceforanide may not be present at effective anti-staphylococcal levels throughout the day. Even so our

patients with staphylococcal infections appeared to respond quite adequately to treatment with this antibiotic. The two patients who failed to respond to ceforanide were both in need of surgical debridement. One patient eventually recovered on penicillin without surgical intervention probably because he developed spontaneous drainage at sites of tissue breakdown. The other improved initially on penicillin, as he had on ceforanide, but cure was thought to result from surgical drainage, not from changes in antibiotic therapy.

In vitro studies showed that higher concentrations of ceforanide or penicillin killed *S. pyogenes* more rapidly and more completely than did lower concentrations. The mean peak and trough ceforanide levels in our subjects were nearly 200 and 30 times, respectively, the MIC for *S. pyogenes*. Serum levels of penicillin in patients who receive 1.2×10^6 U of aqueous procaine penicillin every 12 h are likely to exceed the median MIC of 0.006 $\mu\text{g/ml}$ (8) by a substantially greater margin (10). Whether this greater therapeutic margin of penicillin is clinically significant awaits further studies in which the therapeutic effect of these two antibiotics is compared prospectively; in one such study the response of soft-tissue infection to penicillin was similar to the response to cefazolin (7).

Our study suggests that ceforanide has a role in treating cases of severe cellulitis. This drug was well tolerated and appeared to be effective in vivo when administered intramuscularly every 12 h. The unavailability of a long-acting penicillinase-resistant penicillin which can be

FIG. 1. Rate of killing of *S. pyogenes* by varying concentrations of penicillin or ceforanide. Circles, squares, and triangles indicate 5, 50, and 500 $\times$ MIC, respectively, of penicillin (open symbols) or ceforanide (closed symbols). $\times$, Control (no antibiotic). (A) Results obtained with the isolate from the first patient and (B) those obtained with the isolates from the second patient who failed to be cured by treatment with ceforanide.

given intramuscularly, and the fact that *S. aureus* was implicated as an etiological agent in 44% of cases in which a bacteriological diagnosis could be made, support the use of a long-acting cephalosporin in the initial treatment of cellulitis. Continued use of such a drug is indicated when penicillinase-resistant *S. aureus* is isolated from the lesions or when diagnostic attempts fail to disclose the causative organism.

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