Evaluation of Ceforanide as Treatment for Staphylococcal and Streptococcal Endocarditis

RONALD H. COOPER, CARY B. SAVITCH, W. PATRICK JOSEPH, AND JOHN MILLS*

Infectious Disease Unit of the Medical Service, San Francisco General Hospital Medical Center, and the Department of Medicine, University of California, San Francisco, California 94110

Ceforanide administered parenterally twice daily was used as the sole agent to treat 17 patients with right-sided endocarditis due to Staphylococcus aureus or nonenterococcal streptococci. Fifteen patients were cured of their original infection. Two patients were withdrawn from the study. One patient was transferred to another hospital 4 days after ceforanide therapy was initiated, and the other was changed to a different antibiotic regimen when his viridans streptococcus proved tolerant to ceforanide. The intramuscular form of ceforanide was well tolerated. It was stopped in two patients after week 3 of therapy because of adverse effects, possibly related to the study drug. These findings resolved with discontinuation of the ceforanide, and no additional antimicrobial therapy was necessary. Two patients who continued to abuse drugs intravenously during the study developed bacteremia with new organisms and required additional antimicrobial therapy. Ceforanide proved to be a useful agent in the treatment of right-sided endocarditis due to susceptible S. aureus and nonenterococcal streptococci.

Ceforanide (BL-S786) is an investigational semisynthetic cephalosporin drug that achieves high serum levels after intramuscular administration (7; R. D. Smyth, F. H. Lee, M. Pfeffer, D. R. Van Harken, and G. H. Hottendorf, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 19th, Boston, Mass., abstr. no. 517, 1979). In addition, it has a serum half-life of 2.7 h, allowing administration every 12 h. These properties should make ceforanide a useful agent in the long-term treatment of infections due to susceptible organisms. To test this question, we used ceforanide alone to treat 17 patients with endocarditis due to Staphylococcus aureus and nonenterococcal streptococci (5).

MATERIALS AND METHODS

Patients and treatment. Patients admitted to San Francisco General Hospital Medical Center with signs and symptoms of right-sided endocarditis were eligible for the study. Patients were excluded if they had a serum creatinine level greater than 1.5 mg/dl, were pregnant, or had a history of allergy to penicillins or cephalosporins. After informed consent was obtained, 1 to 2 g of ceforanide was administered intramuscularly or intravenously every 12 h. Ten patients also received 1 g of probenecid orally with each injection. If an organism susceptible to ceforanide was isolated from blood cultures, the patient was continued on the regimen. No other antimicrobials were administered. All S. aureus and nonenterococcal streptococcal isolates were sensitive to ceforanide. The dosage was adjusted on the basis of serial blood cultures, serum bactericidal titers, and the clinical response of the patient. Treatment was continued for 4 weeks whenever possible. Follow-up blood cultures were performed at least 2 days after discontinuation of antibiotic therapy, and usually 3 to 4 weeks later. Tests for possible toxicity were performed on each patient, including a daily interview and examination, a complete blood count and differential, a platelet count, Coombs test, urinalysis, and tests of liver and renal function performed before and after therapy and weekly during therapy.

Susceptibility tests. Initially, susceptibility of the infecting organisms was determined by a modified Bauer-Kirby-Sherris method, using a 30-μg ceforanide disk (4). Subsequently, the minimum inhibitory and bactericidal concentrations of the isolates to ceforanide were determined in broth by the method of Barry and Sabath (1). Briefly, antibiotic concentrations (in log increments) were prepared in tryptic soy broth, and an inoculum of 10{sup 8} to 10{sup 10} colony-forming units of an overnight culture was added to give a final volume of 2 ml. After an overnight incubation, 0.1 ml was subcultured from tubes without visible turbidity. The minimum bactericidal concentration was that concentration producing a ≥99.9% drop in colony-forming units compared with the inoculum (i.e., ≤10 colony-forming units per 0.1 ml). Peak bactericidal titers were determined on serum obtained 1 h after ceforanide administration, also by the method of Barry and Sabath (1). Other laboratory tests were performed at least weekly to monitor for adverse reactions to the drug.

RESULTS

Seventeen patients with an average age of 32 years were treated with ceforanide for 10 to 43 days (average, 24 days). All were intravenous drug abusers, and seven had a history of prior endocarditis (8). Fifteen patients sought medical attention during the first week of symptoms. In three patients, the course was complicated by
septic arthritis. Three patients each had an empyema requiring placement of a chest tube for drainage. One patient had an infected prosthetic tricuspid valve, and one patient had osteomyelitis of the second and third lumbar vertebrae. Cultures of blood obtained on admission yielded mixed infections in 7 of the 17 patients (Table 1). In some instances (no. 12, 13, and 17), the mixed infection was due to two colony phenotypes of the same organism. The minimum inhibitory concentration of ceforanide for these organisms ranged from 0.20 to 8 \( \mu g/ml \) (sensitive \( \leq 8 \mu g/ml \)). Of these original isolates, one \( S. aureus \) and seven streptococci proved tolerant to ceforanide (defined as minimum inhibitory concentration, \( \leq 8 \mu g/ml \); minimum bactericidal concentration, \( >8 \mu g/ml \); and the ratio of minimum bactericidal concentration/minimum inhibitory concentration, \( \geq 8 \)) (2). These tolerant organisms were responsible for endocarditis in six patients (no. 4 to 6 and 8 to 10). In four of these six patients, adequate serum bactericidal titers were obtained, and the tolerant organisms were eradicated despite in vitro tolerance. One patient (no. 6) was withdrawn from the study because his serum was inhibitory against his isolate at a 1:16 dilution but not bactericidal at a 1:2 dilution. Although the patient became afebrile and blood cultures became sterile during ceforanide therapy, treatment was changed to

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Organism</th>
<th>Ceforanide(^a)</th>
<th>Ceforanide (2 to 4 g per day)</th>
<th>Duration of therapy (days)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MIC (( \mu g/ml ))</td>
<td>MBC (( \mu g/ml ))</td>
<td>Peak serum inhibitory titer</td>
<td>Peak serum cidal titer</td>
</tr>
<tr>
<td>1</td>
<td>( S. aureus )</td>
<td>4.0</td>
<td>16.0</td>
<td>1:16</td>
<td>1:8</td>
</tr>
<tr>
<td>2</td>
<td>( S. aureus )</td>
<td>4.0</td>
<td>32.0</td>
<td>1:4</td>
<td>1:4</td>
</tr>
<tr>
<td>3</td>
<td>( S. aureus )</td>
<td>4.0</td>
<td>32.0</td>
<td>1:4</td>
<td>1:4</td>
</tr>
<tr>
<td>4</td>
<td>( S. aureus )</td>
<td>2.0</td>
<td>32.0</td>
<td>1:8</td>
<td>1:8</td>
</tr>
<tr>
<td>5</td>
<td>Viridans streptococcus</td>
<td>0.5</td>
<td>&gt;128</td>
<td>1:64</td>
<td>1:4</td>
</tr>
<tr>
<td>6</td>
<td>Viridans streptococcus</td>
<td>2.0</td>
<td>&gt;100</td>
<td>1:16</td>
<td>&lt;1:2</td>
</tr>
<tr>
<td>7</td>
<td>( S. sanguis I ) ( S. constelatus^b )</td>
<td>2.0</td>
<td>4.0</td>
<td>1:8</td>
<td>1:8</td>
</tr>
<tr>
<td>8</td>
<td>( S. aureus )</td>
<td>4.0</td>
<td>32.0</td>
<td>1:4</td>
<td>1:2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.25</td>
<td>&gt;128</td>
<td>1:128</td>
<td>1:64</td>
</tr>
<tr>
<td>9</td>
<td>( S. aureus )</td>
<td>4.0</td>
<td>32.0</td>
<td>1:8</td>
<td>1:8</td>
</tr>
<tr>
<td></td>
<td>( S. sanguis II )</td>
<td>0.5</td>
<td>&gt;64</td>
<td>1:64</td>
<td>1:64</td>
</tr>
<tr>
<td></td>
<td>( S. sanguis I^b ) ( E. corrodens^c )</td>
<td>1.0</td>
<td>&gt;128</td>
<td>Susceptible by disk</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Viridans streptococcus 1</td>
<td>0.5</td>
<td>128</td>
<td>1:64</td>
<td>1:32</td>
</tr>
<tr>
<td></td>
<td>Viridans streptococcus 2</td>
<td>0.2</td>
<td>64.0</td>
<td>1:16</td>
<td>1:8</td>
</tr>
<tr>
<td></td>
<td>Viridans streptococcus 3</td>
<td>0.2</td>
<td>&gt;128</td>
<td>1:64</td>
<td>1:32</td>
</tr>
<tr>
<td>11</td>
<td>( S. aureus )</td>
<td>8.0</td>
<td>32.0</td>
<td>1:32</td>
<td>1:16</td>
</tr>
<tr>
<td>12</td>
<td>( S. aureus )</td>
<td>4.0</td>
<td>32.0</td>
<td>1:16</td>
<td>1:8</td>
</tr>
<tr>
<td>13</td>
<td>( S. aureus )</td>
<td>4.0</td>
<td>32.0</td>
<td>1:8</td>
<td>1:4</td>
</tr>
<tr>
<td>14</td>
<td>( S. aureus )</td>
<td>4.0</td>
<td>16.0</td>
<td>1:8</td>
<td>1:8</td>
</tr>
<tr>
<td>15</td>
<td>( S. aureus )</td>
<td>4.0</td>
<td>8.0</td>
<td>1:8</td>
<td>1:8</td>
</tr>
<tr>
<td>16</td>
<td>( S. aureus )</td>
<td>8.0</td>
<td>32.0</td>
<td>1:16</td>
<td>1:16</td>
</tr>
<tr>
<td>17</td>
<td>( S. aureus )</td>
<td>16.0</td>
<td>32.0</td>
<td>1:4</td>
<td>1:4</td>
</tr>
</tbody>
</table>

\(^a\) MIC, Minimum inhibitory concentration; MBC, minimum bactericidal concentration.

\(^b\) Superinfection with this organism.
penicillin and streptomycin (which was bacteri
cidal in vitro), and the recovery of the patient
continued without complication.

A second patient (no. 10) infected with a toler-
ant organism was withdrawn from the study after
4 days of therapy because of transfer to
another hospital. His response to ceforanide was
difficult to assess. He originally was infected
with three strains of viridans streptococci. Ade-
quate serum bactericidal levels were obtained
against two of these isolates, but the third grew
too poorly for testing. At the time of transfer the
patient was still febrile, but despite this, cultures
of blood obtained on admission at the second
hospital were sterile. Two days later, however,
a viridans streptococcus was isolated again from
the blood. Unfortunately, it was not determined
whether this organism was one of the original
isolates or a new acquisition. Reinfection was a
distinct possibility with this patient because he
continued to abuse drugs intravaneously while in
the hospital. At various times later in his hospi-
tal course, blood cultures were positive for
Eikenella corrodens and Bacteroides fragilis,
in addition to the viridans streptococci.

All 15 of the patients who were continued on
the study were cured of their original infection.
Bacteremia due to other organisms developed in
two patients (no. 7 and 9) while they were taking
ceforanide, and so another antibiotic regimen
was substituted. The superinfecting organisms
were Streptococcus constellatus (no. 7) and
Streptococcus sanguis I and E. corrodens (no.
9). Both of these patients were abusing drugs
intravaneously while in the hospital, and this,
most likely, was the cause of superinfection.

The intramuscular injections were very well
tolerated by all patients. Discomfort was mini-
mal (i.e., no complaints were made sponta-
neously or after questioning), and objective com-
lications (e.g., sterile abscesses) did not occur.
Ceforanide was discontinued in two patients
after 3 weeks of therapy because of adverse
effects, possibly related to the study drug. One
patient developed eosinophilia (25%) and
asymptomatic hepatitis with a rise in hepatocel-
lar enzymes to seven times the normal level by
week 3 of therapy. Upon admission his liver
function assays were elevated, but they de-
creased to near-normal levels during the first 10
hospital days before they increased again. The
second patient developed eosinophilia (19%),
mild neutropenia, erythema multiforme, and ar-
thritis during week 3 of therapy. These findings
resolved with discontinuation of the ceforanide
and probenecid. Neither of these patients re-
quired additional antimicrobial therapy. Two
other patients developed elevated eosinophil
counts (5 and 14%), but were otherwise asym-
ptomatic and continued on the regimen.

DISCUSSION

Based on this experience with 17 patients, we
conclude that ceforanide may be a useful agent
in the treatment of right-sided endocarditis due
to susceptible S. aureus and viridans strepto-
cocci. Fifteen patients who completed therapy
with ceforanide were cured of their original in-
fection. Some of these patients had septic ar-
thritis and osteomyelitis, which also resolved
with ceforanide therapy. Two patients were
withdrawn from the study; one was transferred
to another hospital and a second patient was
infected with a tolerant organism against which
adequate serum bactericidal activity could not
be achieved. The intramuscular route of admin-
istration was very well tolerated and proved
especially valuable in those patients with limited
intravenous access sites. Adverse reactions pos-
sibly related to the ceforanide were noted in two
patients, but they resolved promptly with dis-
continuation of the medication. A similar rate of
untoward drug reactions was reported recently
in a series of patients with S. aureus endocarditis
treated with conventional antibiotics (M. A.
Sande, O. M. Korzeniowski, and Endocarditis
Collaborative Group, Program Abstract. Intersci.
Conf. Antimicrob. Agents Chemother., 19th,

Tolerance to ceforanide was observed fre-
cently in this series, especially among the
streptococcal isolates. Many of the streptococcal
isolates were also tolerant to penicillin (C. B.
Savitch, L. Pulliam, R. Cooper, and J. Mills,
Agents Chemother., 20th, New Orleans, La.,
abstr. no. 355, 1980). The experimental con-
ditions under which tolerance is found must be
defined carefully, because this phenomenon can
vary with several factors (6). However, Weaver
et al. reported a similar high incidence of cefor-
andide tolerance among S. aureus and Strepto-
coccus pyogenes in their series (10). The clinical
significance of tolerance is still being debated,
but it may be more important in patients with
endocarditis for whom bactericidal therapy is
considered essential (2, 3, 9). Our experience
in this series suggests that adequate serum bacte-
ricidal titers and microbiological cure can be
achieved with many tolerant organisms, without
the addition of a second antimicrobial agent. If,
however, serum bactericidal activity is not ob-
tained against a tolerant organism with a single
agent, we would modify the therapy until a
bactericidal regimen is achieved.

Extrapolation of the results of this study to
endocarditis in general should be done with caution. Left-sided endocarditis tends to be a more severe illness, especially when complicated by septic emboli. In this regard, two characteristics of ceforanide deserve emphasis. First, the minimum bactericidal concentration of ceforanide for most of the \textit{S. aureus} isolates in this series was relatively high (32 \mu g/ml). Even with serum ceforanide levels of 100 to 200 \mu g/ml, the calculated peak serum bactericidal titer with this drug is not of the same magnitude as that achieved with the older cephalosporins or the penicillinase-resistant penicillins (Table 2). Second, antibiotic distribution to the central nervous system may be important in patients with left-sided endocarditis complicated by septic emboli. Cerebrospinal fluid levels of ceforanide are not yet known, but cephalosporins currently available do not reliably cross the blood-brain barrier well. To determine whether or not these characteristics of ceforanide will prove to be clinically important, further trials of the drug must be performed.

**LITERATURE CITED**