Twice-Daily Intramuscular Ceforanide Therapy of *Staphylococcus aureus* Endocarditis in Parenteral Drug Abusers

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Twice-daily intramuscular ceforanide therapy of *Staphylococcus aureus* endocarditis in parenteral drug abusers was compared in a randomized prospective trial with intravenous cephapirin therapy. Dosage regimens were ceforanide, 1 g every 12 h, and cephapirin, 2 g every 4 h. Mean minimal inhibitory and bactericidal concentrations of ceforanide for *S. aureus* treated with ceforanide were 0.78 and 1.56 μg/ml compared to cephapirin for patient isolates of 0.08 and 0.14 μg/ml, respectively. Serum killing levels with ceforanide were 1:5.7 and 1:1.5 at peak and trough levels, compared to 1:134 (peak) and 1:4.2 (trough) with cephapirin. Despite this apparent in vitro advantage of cephapirin, patients treated with ceforanide did as well as those with cephapirin. Of 16 ceforanide-treated patients, all responded initially to therapy, and 15 were cured with 28 days of therapy. One patient relapsed at the end of therapy. Of 16 cephapirin-treated patients, 1 was a clinical and microbiological failure, and 3 others relapsed at the end of therapy. In addition, one ceforanide-treated patient and two cephapirin-treated patients developed central nervous system abscesses. These were cured with drainage and continuation of antibiotic therapy. Ceforanide was well tolerated by the intramuscular route. Cost analysis suggests that therapy with intramuscular ceforanide would result in an approximate 70% decrease in drug therapy cost when compared to intravenous cephapirin. Ceforanide appears to be a safe, efficacious, convenient, and relatively inexpensive drug for treating staphylococcal endocarditis in parenteral drug abusers.

Bacterial endocarditis is a common complication of intravenous drug abuse. Endocarditis in intravenous drug abusers is most frequently caused by *Staphylococcus aureus* and usually involves the right side of the heart (1, 2, 7, 9, 11, 15, 16). Mortality from this disease, when appropriately treated, has been low in most reported series from the last decade (1, 7, 9, 15, 16). Recently, single-drug intravenous β-lactam antibiotic therapy has been shown to be as efficacious in effecting a cure as combination therapy, including an aminoglycoside antibiotic (1, 7). Such intravenous therapy requires continuous intravenous access for 4 weeks in patients with already traumatized veins. This has presented a problem in completing therapy and has frequently led to the necessity of placement of central catheters or surgically placed peripheral catheters. Prolonged intravenous therapy thus has an inherent risk of nosocomial, catheter-related bacteremia. In addition, a small proportion of patients refuse such invasive therapeutic access and have left the hospital prematurely, against medical advice.

Ceforanide (BL-S786R) is an investigational cephalosporin antibiotic that is usually well tolerated intramuscularly in doses up to 2 g (12). The pharmacokinetics of the agent demonstrate a mean serum half-life of 2.2 to 3.0 h (4, 5, 12). Mean peak and trough serum levels have been reported to be approximately 70 and 5 μg/ml, respectively, after 1 g administered intramuscularly every 12 h (12). Mean minimal inhibitory concentrations (MIC) of ceforanide for *S. aureus* have been shown to be approximately 1 μg/ml with all methicillin-susceptible strains susceptible to 4 μg of ceforanide per ml (13, 14). The minimal bactericidal concentrations

(MBC) of ceforanide have uniformly been within fourfold higher than the corresponding MIC. Serum protein binding of ceforanide has been reported to be approximately 80% (10).

Because of the potential therapeutic and economic advantages of a twice-daily intramuscular regimen for treating staphylococcal endocarditis in drug abusers, we undertook a study to compare the efficacy of ceforanide therapy with that of a standard intravenous regimen; in this study 2 g of cephapirin was administered intravenously every 4 h. We felt justified in treating with a cephalosporin alone pending culture results, since, at our institution over the previous 4 years, 93 of 95 episodes of endocarditis in addicts have been caused by *S. aureus* or other cephalosporin-susceptible agents.

MATERIALS AND METHODS

From May 1980 to December 1982, intravenous drug abusers admitted to Jackson Memorial Hospital or Miami Veterans Administration Medical Center and suspected of having bacterial endocarditis on clinical grounds were evaluated by a member of the Infectious Diseases Division. If, after consultation, the primary physician elected to begin antimicrobial therapy, informed consent was obtained and patients were prospectively randomized to receive either ceforanide, 1 g every 12 h, or cephapirin, 2 g every 4 h, according to a table of random numbers. Ceforanide was given intramuscularly unless an intravenous line was in place for other reasons, in which case it was given intravenously until the line was removed.

Endocarditis was diagnosed by criteria that we have previously employed (1, 15). In addition to three or more blood cultures positive for *S. aureus*, a patient had to have one or more of the following findings for the diagnosis of endocarditis: (i) multinodular infiltrates on chest roentgenogram or other radiographic evidence of septic pulmonary

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emboli in the absence of any obvious extracardiac source; (ii) auscultatory evidence of a new cardiac murmur; or (iii) echocardiographic evidence of vegetations on a cardiac valve. Cardiac involvement was considered to be right sided if auscultatory or echocardiographic findings demonstrated involvement of the tricuspid or pulmonic valve or if roent-genographic findings were compatible with septic pulmonary emboli. Cardiac involvement was considered to be left sided if there were auscultatory or echocardiographic findings showing involvement of the aortic or mitral valve.

Patients were evaluated daily by a member of the Infectious Diseases Division for such features as fever, congestive heart failure, or evidence of metastatic infectious foci. Complete blood count, sedimentation rate, urinalysis, and hepatic and renal function tests were obtained on a weekly basis unless the patient's clinical status dictated more frequent testing. Roentgenographic examinations and echocardiograms were obtained when appropriate.

Repeat blood cultures were obtained on days 3 and 7 and then weekly for the course of therapy. MIC and MBC of the treatment drug (cephapirin or ceforanide) for infecting organisms were determined by broth dilution studies by the method of Barry and Sabath (3). Serum bactericidal titers were determined on serum obtained at times corresponding to peak (30 min after either drug) and trough (11.5 h after ceforanide and 3.5 h after cephapirin) serum antibiotic concentrations on day 5. Serum antibiotic concentrations were determined on these samples by high-pressure liquid chromatography, courtesy of Bristol Laboratories.

All patients were seen as outpatients 2 to 6 weeks (mean, 3.5 weeks) after completion of therapy, and physical examinations and repeat blood cultures were performed. Cure was defined as being clinically well and having negative blood cultures at this follow-up visit.

RESULTS

Therapy was begun for 54 suspected episodes of endocarditis. Fourteen patients subsequently did not fulfill the criteria for continuation in the study. Eight patients had

TABLE 1. Comparison of demographic and clinical features of patients with *S. aureus* endocarditis

| Characteristic	No. of patients	
	Ceforanide	Cephapirin
Demographic		
Total no. of patients	16	16
Sex		
Male	8	9
Female	8	7
Race		
Black	15	10
White	1	6
Age (mean), yr	31.4	28.4
Clinical		
Cardiac involvement		
Right-sided involvement alone	13	13
Left-sided involvement alone	1	1
Both right and left sided..........	2	2
Extracardiac		
Septic pulmonary emboli	14	14
Cerebrospinal fluid pleocytosis	3	4
Brain abscess	0	2
Spinal epidural abscess.............	1	0
Septic arthritis	2	2
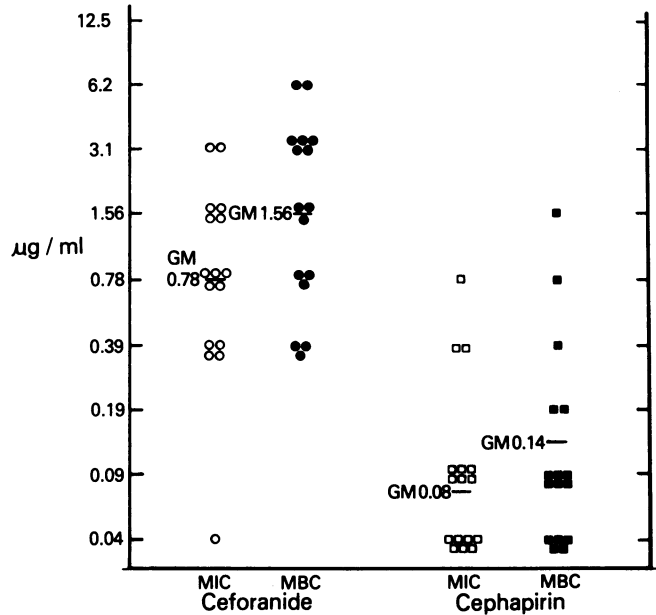
FIG. 1. MICs (open symbols) and MBCs (closed symbols) of ceforanide (○,●) and cephapirin (□,■) for blood isolates of *S. aureus* from patients treated with the respective drugs. GM, Geometric mean.

sterile blood cultures, three had alpha-streptococcal endocarditis, and one each had group A streptococcal bacteremia, staphylococcal pneumonia with negative blood culture, and bacteremic *Escherichia coli* pyelonephritis. No patient was excluded from entrance to the study because of clinical severity of disease or the bias of his primary physician toward one form of therapy.

We thus began treatment of 40 patients with *S. aureus* endocarditis. Of these, eight were eventually not evaluable. Four were withdrawn early in the course of therapy by their primary physician to change to a standard oxacillin regimen. Three of these four were on the ceforanide regimen early in the course of the study. They did well on continued oxacillin therapy and were cured. Three patients left the hospital against medical advice after less than 2 weeks of therapy, and one ceforanide patient was switched to oxacillin because of a protocol exclusion of pregnancy. The 32 patients treated for 4 weeks form the basis of this report.

Demographic and clinical characteristics of the patients are shown in Table 1. All patients admitted using intravenous drugs, and most had injected a drug intravenously within 1 week of hospitalization. The clinical features of the two groups were comparable. Cerebrospinal fluid pleocytosis was evident in 7 of 12 lumbar punctures, 3 in ceforanide patients and 4 in patients treated with cephapirin. Three patients had central nervous system abscesses which became apparent several weeks into the course of therapy. One ceforanide patient developed a spinal epidural abscess, and two cephapirin patients developed brain abscesses. These three patients were subsequently cured with drainage of their abscesses and continued protocol antibiotic. Septic arthritis, culture positive for *S. aureus*, occurred in two patients in each group. Most patients in each group were febrile for less than 10 days before admission. Mean peak temperatures during the initial 24 h of hospitalization was similar in both groups (103.6°F for ceforanide and 103.8°F for cephapirin). Initial laboratory data including hematocrit, leukocyte count, serum glutamic-oxalacetic transaminase,
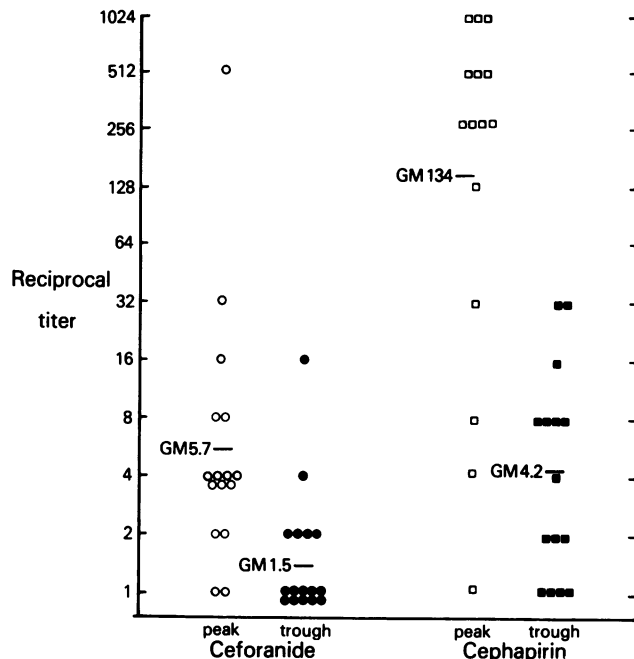
FIG. 2. Serum killing level, peak (O) and trough (●), with ceforanide and peak (□) and trough (■) with cephapirin against infecting *S. aureus*. Serum was obtained after 1 week of therapy. The peak serum level was obtained 30 min after dose, and trough levels were obtained 11.5 h after dose with ceforanide and 3.5 h after dose with cephapirin. GM, Geometric mean.

and blood urea nitrogen were comparable in both groups.

The time to defervescence of the two groups was not significantly different: ceforanide patients became afebrile (temperature <38°C for 24 h) in a mean of 7.5 days (standard error of the mean, 1.21) compared to 6.6 days (standard error of the mean, 1.64) for patients treated with cephapirin. Of 16 ceforanide-treated patients, 12 received a mean of 4.2 days of ceforanide by the intravenous route. Five patients had positive blood cultures on day 3: two treated with ceforanide and three with cephapirin. Only one patient had positive blood cultures through day 7. This was a cephapirin-treated patient who remained bacteremic for 14 days and was deemed a treatment failure. No extracardiac focus was identified. His organism demonstrated MIC and MBC of cephapirin of 0.09 and 0.19 μg/ml, respectively. The patient was switched to a three-drug regimen including vancomycin, gentamicin, and rifampin. Blood cultures became sterile within 3 days, and he was subsequently cured after 4 weeks of the three-drug regimen.

Four patients, one treated with ceforanide and three with cephapirin, relapsed after completion of 28 days of therapy, all within 48 h of discontinuing therapy. In all four instances the phage type of the *S. aureus* was the same as the initial isolate. Three of these patients were subsequently cured with further therapy with oxacillin. In one instance the patient failed a second course of antibiotic therapy with 4 weeks of oxacillin. She was subsequently cured with 4 weeks with a three-drug regimen of vancomycin, gentamicin, and rifampin.

No patients developed congestive heart failure or required valve replacement. No mortality occurred in either group.

No patients required discontinuation of drug due to drug toxicity. Four cephapirin patients developed significant phlebitis at the injection site. One patient each had mild

neutropenia or transminase elevation, seemingly related to cephapirin. Two ceforanide patients complained of pain at the injection site; one requested that his therapy be switched back to intravenous ceforanide. No other drug-related adverse reactions were noted in ceforanide patients.

Results of MIC and MBC testing for the infecting organisms are shown in Fig. 1. Mean MIC and MBC of ceforanide were 0.78 ± 0.42 and 1.56 ± 1.23 μg/ml, respectively. Mean MIC and MBC of cephapirin were 0.08 ± 0.10 and 0.14 ± 0.17 μg/ml, respectively.

Peak and trough serum bactericidal levels are shown in Fig. 2. The geometric mean peak serum bactericidal level with ceforanide was 1:5.7, and the trough serum bactericidal level was 1:1.5. With cephapirin, corresponding peak and trough values were 1:134 and 1:4.2, respectively.

Mean peak (30 min post) and trough (11 h 30 min post) ceforanide serum levels were 27.8 ± 7.2 and 2.9 ± 1.1 μg/ml, respectively. Cephapirin serum levels were not determined.

DISCUSSION

Ceforanide appears to be a well tolerated and efficacious antibiotic in the treatment of staphylococcal endocarditis in intravenous drug abusers. Even though the MIC and MBC values of ceforanide were approximately 10-fold higher than those of cephapirin and the serum killing levels at peak concentration were only 1:5.7 with ceforanide compared to 1:134 with cephapirin, the clinical outcome with ceforanide therapy was excellent. Although there was no statistically significant difference between the two therapeutic modalities and overall mortality was zero in both groups, there was a trend toward more failures, relapses, and central nervous system abscesses in the cephapirin-treated group.

Previous studies at our institution (1, 15) have included 71 patients treated with oxacillin alone or in combination with an aminoglycoside drug. In these patients there were no primary drug failures and no relapses noted, although follow-up as rigorous as in this study was obtained in only 25 of these 71 patients. Also, no central nervous system abscesses were noted in the previous patients, although such complications have been well described by others (6, 8, 17). Two unanswered questions can be posed by this study. First, do cephalosporins lead to a higher rate of failure or relapse than semisynthetic penicillinase-resistant penicillins? Second, might cephalosporin therapy lead to a higher incidence of clinically apparent central nervous system abscesses?

Economically, intramuscular therapy is traditionally less expensive than intravenous therapy. A cost analysis of the

TABLE 2. Cost comparison of intramuscular ceforanide with intravenous cephapirin

Regimen	Cost/day
1 (Ceforanide, 1 g i.m. every 12 h)	
Drug cost (estimate, $8.00/g) × 2	$16.00
Administration cost (intramuscular injection, $5.00 each) × 2	10.00
Total	$26.00
2 (Cephapirin, 2 g i.v. every 4 h)	
Drug cost ($3.00/g) × 12	$36.00
Administration costs	
Minibag and piggyback set ($5.00/dose) × 6	30.00
Intravenous tubing, catheter, and "keep open" intravenous bottle	15.00
Total	$81.00

two modes of therapy confirms this (Table 2). Two 1-g intramuscular injections of ceforanide, with drug cost estimated at $8.00/g, results in a total daily cost of approximately $26.00. Intravenous administration of cephapirin at a drug cost of $3.00/g results in an estimated daily cost of $81.00, not including the extra pharmacy and nursing time necessary to administer six intravenous dosages. Thus, at least a 68% savings can be realized in addition to increased convenience to the patient, the nursing staff, and the pharmacy.

In conclusion, intramuscular ceforanide appears to be a convenient, inexpensive, and efficacious therapy for staphylococcal endocarditis in intravenous drug abusers. It appears that it will be a valuable cephalosporin for treating this entity when it becomes clinically available. Further studies are necessary to prove that ceforanide is equally as efficacious as oxacillin or naficillin.

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