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Evaluation of Ceforanide as Treatment for Staphylococcal and Streptococcal Endocarditis

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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 Two patients were withdrawn from the study.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 $\log_2$ increments) were prepared in tryptic soy broth, and an inoculum of 10^5 to 10^6 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 $\geq$99.9% drop in colony-forming units compared with the inoculum (i.e., $\leq$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 μg/ml (sensitive ≤8 μg/ml). Of these original isolates, one *S. aureus* and seven streptococci proved tolerant to ceforanide (defined as minimum inhibitory concentration, ≤8 μg/ml; minimum bactericidal concentration, >8 μg/ml; and the ratio of minimum bactericidal concentration/minimum inhibitory concentration, ≥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 1. *Ceforanide therapy of endocarditis: clinical and in vitro data*

Patient no.	Organism	Ceforanide[a]		Ceforanide (2 to 4 g per day)		Duration of therapy (days)	Outcome
		MIC (μg/ml)	MBC (μg/ml)	Peak serum inhibitory titer	Peak serum cidal titer		
1	*S. aureus*	4.0	16.0	1:16	1:8	23	Cure
2	*S. aureus*	4.0	32.0	1:4	1:4	25	Cure
3	*S. aureus*	4.0	32.0	1:4	1:4	27	Cure, septic arthritis
4	*S. aureus*	2.0	32.0	1:8	1:8	27	Cure, septic arthritis
5	Viridans streptococcus	0.5	>128	1:64	1:4	29	Cure, prosthetic valve
6	Viridans streptococcus	2.0	>100	1:16	<1:2	14	Withdrawn
7	*S. sanguis I*	2.0	4.0	1:8	1:8	28	Cure
	S. constelatus[b]					28	Cure with penicillin and streptomycin
8	*S. aureus*	4.0	32.0	1:4	1:2	28	Septic arthritis, empyema, cure
	Group A streptococcus	0.25	>128	1:128	1:64	28	Cure
9	*S. aureus*	4.0	32.0	1:8	1:8	13	Cure
	S. sanguis II	0.5	>64	1:64	1:64	13	Cure
	S. sanguis I[b]	1.0	>128				Remained bacteremic
	E. corrodens[b]		susceptible by disk				Remained bacteremic
10	Viridans streptococcus 1	0.5	128	1:64	1:32	4	Withdrawn
	Viridans streptococcus 2	0.2	64.0	1:16	1:8	4	Withdrawn
	Viridans streptococcus 3	0.2	>128			4	Withdrawn
11	*S. aureus*	8.0	32.0	1:32	1:16	9	Cure
12	*S. aureus* 1	4.0	32.0	1:16	1:8	22	Cure
	S. aureus 2	4.0	32.0	1:8	1:4	22	Cure
13	*S. aureus* 1	4.0	16.0	1:8	1:8	18	Cure
	S. aureus 2	4.0	16.0	1:8	1:8	18	Cure
14	*S. aureus* 1	4.0	16.0	1:16	1:4	29	Empyema, cure
	S. aureus 2	4.0	8.0	1:8	1:8	29	Empyema, cure
15	*S. aureus*	8.0	32.0	1:16	1:16	29	Empyema, cure
16	*S. aureus*	4.0	16.0	1:8	1:8	43	Vertebral osteomyelitis, cure
17	*S. aureus* 1	16.0	32.0	1:4	1:4	28	Cure
	S. aureus 2	16.0	32.0	1:2	<1:2	28	Cure

[a] MIC, Minimum inhibitory concentration; MBC, minimum bactericidal concentration.
[b] Superinfection with this organism.

penicillin and streptomycin (which was bactericidal in vitro), and the recovery of the patient continued without complication.

A second patient (no. 10) infected with a tolerant 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. Adequate 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 intravenously while in the hospital. At various times later in his hospital course, blood cultures were positive for *Eikenella corrodens* and *Bacteriodes 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 constelatus* (no. 7) and *Streptococcus sanguis* I and *E. corrodens* (no. 9). Both of these patients were abusing drugs intravenously 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 minimal (i.e., no complaints were made spontaneously or after questioning), and objective complications (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 hepatocellular enzymes to seven times the normal level by week 3 of therapy. Upon admission his liver function assays were elevated, but they decreased 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 arthritis during week 3 of therapy. These findings resolved with discontinuation of the ceforanide and probenecid. Neither of these patients required additional antimicrobial therapy. Two other patients developed elevated eosinophil counts (5 and 14%), but were otherwise asymptomatic 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 streptococci. Fifteen patients who completed therapy with ceforanide were cured of their original infection. Some of these patients had septic arthritis 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 administration was very well tolerated and proved especially valuable in those patients with limited intravenous access sites. Adverse reactions possibly related to the ceforanide were noted in two patients, but they resolved promptly with discontinuation 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 Abstr. Intersci. Conf. Antimicrob. Agents Chemother., 19th, Boston, Mass., abstr. no. 362, 1979).

Tolerance to ceforanide was observed frequently 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, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother., 20th, New Orleans, La., abstr. no. 355, 1980). The experimental conditions 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 ceforanide tolerance among *S. aureus* and *Streptococcus 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 bactericidal 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 obtained 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

TABLE 2. *Comparison of theoretical serum bactericidal titers of three antistaphylococcal agents*

Drug	Dose and route[a] of administration	Peak serum concn (μg/ml)	*S. aureus* MBC[b] (μg/ml)	Calculated serum cidal titer
Nafcillin	1.0 g, i.v.	30	0.4[c]	1:75
Cephalothin	1.0 g, i.v.	50	0.2[d]	1:250
Ceforanide	1.0 g, i.m.	74[e]	32	1:2 to 1:4
Ceforanide	2.0 g, i.m.	130[e]	32	1:4 to 1:8

[a] i.v., Intravenously, i.m., intramuscularly.
[b] MBC, minimal bactericidal concentration.
[c] See reference 11.
[d] See reference 5.
[e] See reference 10. Ceforanide concentrations just before the next dose were 7 to 14 μg/ml.

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 *S. aureus* isolates in this series was relatively high (32 μg/ml). Even with serum ceforanide levels of 100 to 200 μg/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.

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