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Results of a Clinical Trial of Cefoxitin, a New Cephamycin Antibiotic

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Cefoxitin was administered intravenously to 143 patients, 67% of whom were seriously ill. The rate of cure or improvement was 93%. The study was conducted in two phases; the first was an open, controlled clinical comparison of cefoxitin and cephalothin. In this phase, 28 patients received cefoxitin and 29 received cephalothin. In the second phase, cefoxitin alone was used for the treatment of an additional 115 patients. Twenty bacteremic patients treated with cefoxitin were cured or improved in 95% of cases. The infecting organism was eradicated in all bacteremic patients. All of 14 anaerobic or predominantly anaerobic infections were cured or improved. The infecting anaerobic organism was eliminated in 86% of the cases. Twenty-five patients infected by cephalothin-resistant, cefoxitin-susceptible gram-negative rods were cured. Three patients each with infective endocarditis and osteomyelitis were cured. The incidence of adverse experiences was: 1.4% drug eruption; 2% each asymptomatic serum transaminase elevation and leukopenia; and 2.5% asymptomatic eosinophilia. The incidence of severe thrombophlebitis was 5%. No permanent or serious adverse reactions were encountered. Although the numbers of patients in some categories were too small to permit statistical evaluation, I feel that cefoxitin may be a useful new antibiotic for treatment of infections caused by cehalothin-resistant bacteria and by anaerobic organisms.

Cefoxitin is a new semisynthetic antibiotic derived from cephamycin C, an antibacterial substance produced by *Streptomyces lactamdurans* (2, 3, 13). An important and unique property of cefoxitin is its resistance to hydrolysis by β-lactamase produced by both gram-negative (16) and gram-positive bacteria (12). Cefoxitin not only possesses the antibacterial spectrum of the cephalosporin antibiotics, but also is active against anaerobic organisms, indole-positive *Proteus* species, and other strains of gram-negative bacteria that are resistant to cephalothin (7, 9, 10, 14, 17). These preliminary results suggested that the cephamycin antibiotics, and cefoxitin in particular, represent a potentially significant therapeutic advance and deserved additional clinical trials. We report here the results of such a clinical trial.

MATERIALS AND METHODS

Patient population. All patients were adults hospitalized on the medical or surgical services of the Daroff Division, Albert Einstein Medical Center, Philadelphia, Pa. The nature of the antibiotic and the studies necessary to monitor safety and efficacy were fully explained by the investigator to the patient before his or her signed informed consent was obtained. The antibiotics were administered intravenously only. The study was performed in two phases, the first being a controlled comparison of the safety, efficacy, and tolerance of cefoxitin and cephalothin. Patients were assigned to one of these antibiotics in a random fashion by means of the last digit of their admission number. The second phase was an open treatment trial of cefoxitin. Written informed consent was obtained from all patients enrolled in the second phase. The intravenous infusions were initiated and maintained by a intravenous team consisting of three registered nurses (6). All intravenous infusions were given through 20-gauge butterfly needles. The intravenous location site was changed whenever local conditions indicated. No intravenous infusion was allowed to continue for more than 48 h without a change in location.

Studies performed. Cultures of the blood, sputum, urine, body fluids, and purulent exudates were obtained before, during, and after antibiotic therapy. Whenever possible, patients who had urinary tract infections returned for urine cultures within 14 days of the termination of treatment. All bacteria identified as etiological agents of infection were identified as to genus and species. Antibiotic susceptibility to cefoxitin and cephalothin was determined, as was the susceptibility of the etiological organisms to antibiotics in general use. Susceptibility studies were performed by the single-disk method (1). A 30-μg disk was used for cefoxitin. Zone diameter standards previously described by Moellering for inter-

preting diameters of zones of inhibition in relation to cefoxitin minimal inhibitory concentration were used to determine the percentage of strains susceptible to cefoxitin (15).

The following laboratory findings were determined before, during, and after treatment with cefoxitin: complete hemogram; prothrombin time; quantitative platelet determination; direct Coombs test; alkaline phosphatase; bilirubin, serum glutamic oxalacetic transaminase (SGOT), and serum glutamic pyruvic transaminase (SGPT); lactate dehydrogenase; serum concentrations of sodium, potassium, chloride, CO_2, and blood urea nitrogen; serum creatinine; blood glucose; and urinalysis.

Definitions. An illness was defined as severe if accompanied by bacteremia or physiological impairments which in the judgment of the investigator were life threatening. Examples of life-threatening physiological impairments that were used in this evaluation were: (i) pneumonia (arterial pO_2, <50 mm of Hg, bilateral involvement, evidence of congestive failure, arterial-alveolar oxygen gradient, metastatic suppuration, empyema); (ii) urinary tract infection (obstruction, progressive renal failure, hypotension); (iii) skin and soft-tissue infections (location in head or neck, anatomical extent, extensive lymphangitic spread); and (iv) general (fever, impaired consciousness, metabolic acidosis, severe anemia, severe wasting, carcinomatosis). These parameters were followed in each patient by the investigator personally during treatment and for at least 4 weeks after treatment. The identification of an isolated species as the causative agent of pneumonia was based on bacteremia, identification from transtracheal aspirate, or repeated isolation from nasotracheal aspirates or sputum obtained by aerosolization and vibropercussion. Infections accompanied by less severe disturbances of parenchymal function of the organ involved or limited in anatomical extent were designated as moderate. A cure was defined as complete resolution of the anatomical abnormalities and physiological impairments plus eradication of the infecting organism. Any other result was designated as improved if the organism was eradicated or suppressed. If there was no eradication or suppression of the organism, or if suprainfection by a resistant organism occurred with failure to resolve the anatomical and physiological abnormalities, this outcome was designated as not improved.

Cefoxitin was administered as 2 g of cefoxitin in 250 ml of normal saline solution over a 0.5-h period by intermittent intravenous infusion. In the first study comparing cefoxitin and cephalothin, the dose of each antibiotic was 2 g every 8 h for each patient. In the second treatment study, the dose of cefoxitin varied from 6 to 12 g daily. The dose of cephalothin and cefoxitin in this phase was 6 g daily. Cefoxitin serum concentrations are higher than cephalothin serum concentrations at this dose (72 μg/ml is the mean cefoxitin concentration 0.5 h after a 2-g infusion) (8). Administration of cephalothin at 6 g/day was felt to be a reasonable dose for treatment of most infections under close clinical supervision. No patient required a higher dose of cephalothin during the study because of an unsatisfactory response.

RESULTS

These data are derived from observations in 143 patients: 104 who received no antibiotic therapy before cefoxitin treatment, and 39 who received pre-cefoxitin antibiotic therapy subsequently proven to be ineffective against the infecting organism on the basis of disk susceptibility studies. The amounts of cefoxitin received varied from an average of 69-g total dose of cefoxitin given over 9 days of treatment (7.6 g/day) for those patients with urinary tract infections to an average of 139-g total dose over 12 days of treatment (11.6 g/day) for patients with sepsis. The female-to-male ratio was 0.68. Eighty-one percent of the cefoxitin patient population had two or more significant background medical diseases, the most common of these being: (i) trauma or surgery during the 2 weeks before the study (25%); (ii) carcinoma (20%); and (iii) inadequately controlled diabetes (19%). Twenty-one percent of the patient population had two or more of the following physiological impairments: abnormal renal function, hypoxia, impaired immune responses, inadequate nutrition, or impaired consciousness. For the cephalothin population, the corresponding percentages were: two or more background medical diseases, 63%; trauma or surgery in the 2 weeks preceding the study, 17%; cancer, 7%; uncontrolled diabetes, 30%; and two or more physiological impairments, 17%. In the first comparative phase, the numbers of severely ill patients were: cephalothin, 17/28; cefoxitin, 14/29. Bacteremic patients in each group were: cephalothin, 2/28; cefoxitin, 3/29.

In the first comparative phase, 7% of the cefoxitin patients were unimproved, compared with 10% of the cephalothin-treated groups. Although the patients were not randomized for site of infection, the results were interpreted as permitting a continuing clinical trial of cefoxitin by using a larger number of patients.

Table 1 indicates the outcome of cefoxitin treatment for the entire patient population according to severity of illness. Of those patients who were severely ill, 91% were either cured or improved. In the entire patient population, 93% of those treated with cefoxitin were cured or improved.

In the seriously ill group of 20 patients with bacteremia, 95% were cured or improved by cefoxitin therapy, and bacteria were eliminated from the blood stream of all patients (*Escherichia coli*, eight; streptococci, five; *Haemophilus influenzae*, two; miscellaneous, four). In

this group were three patients with infective endocarditis: one caused by *Streptococcus viridans* and *H. influenzae*, and one each caused by *S. viridans* and *S. bovis*. All of these patients were cured bacteriologically. The patient with *S. viridans* endocarditis required aortic valvular replacement because of progressive aortic insufficiency; at the time of surgery the operative area was sterile.

The response to cefoxitin therapy was analyzed according to etiological agent producing the infection (Table 2). A satisfactory response was obtained in 60 of 62 (97%) of those patients whose infection was of staphylococcal or streptococcal etiology and in 63 of 67 (95%) with aerobic gram-negative rod infections. On entry into the study, 89% of these patients were judged to have severe illness. The bacteriological result in these 62 patients was eradication of the infecting staphylococcus or streptococcus in 53 of 62 treatment courses (85%). In 4 of 62 treatment courses (6%), the cocci were suppressed but not completely eradicated during therapy. Microbial colonization with organisms resistant to cefoxitin occurred in 5 of 62 treatment courses (8%) for coccal infection. Similar colonization occurred in 8 of 67 (12%) of treatment courses for gram-negative aerobic bacillary infection. The most common suprainfecting organism was *Pseudomonas aeruginosa*. None of the patients colonized with cefoxitin-resistant organisms developed clinical suprainfection.

The clinical and bacteriological result of the treatment of anaerobic infections is summarized in Table 2. Two classes of patients were included: those whose infection was caused by a single anaerobic species, and those whose infection was caused by several anaerobic species or by a mixture of anaerobic and aerobic bacteria. Anaerobic bacteria were suppressed in 2 of 14 and eradicated in the remaining 12. There were no treatment failures in this group. One of the 14 patients was colonized by a cefoxitin-resistant *Pseudomonas* species; this patient had extensive decubitus ulcer disease and fecal contamination of the infected area.

In another group of 44 patients with polymicrobial aerobic infections, the percentage of patients cured or improved was 85% (Table 3). It is in this group that the only deaths during treatment with cefoxitin occurred. All these patients had severe infection combined with three or more coexisting physiological impairments: one cirrhotic patient died of bilateral cavitating *Klebsiella* pneumonia; on the third day of cefoxitin treatment another patient developed massive gastrointestinal hemorrhage and irreversible shock associated with a polymicrobial gastrointestinal infection complicated by enterocutaneous fistulae and bile peritonitis; and the third patient with an improving polymicrobial lobar pneumonia expired from hepatorenal syndrome precipitated by shock due to gastrointestinal bleeding. (See Table 4 for further etiological data.)

TABLE 1. *Results of cefoxitin treatment: severity of infection*

Severity of infection	No. of patients				
	Cured	Improved	Unimproved	Died	Total
Severe	57	31	6	3	97
Moderate	28	14	2	0	44
Mild	1	1	0	0	2
Total	86 (60%)	46 (33%)	8 (6%)	3 (1%)	143

TABLE 2. *Results of cefoxitin treatment: etiological agent*

Organism	No. of patients			
	Cured	Improved	Unimproved	Total
Staphylococci[a]	27	5	1	33
Streptococci	22	6	1	29
Total gram-positive cocci	49	11	2	62
Aerobic gram-negative bacilli	43	20	4	67
Single anaerobic species	4	0	0	4
Mixed anaerobes, or anaerobes plus aerobes	6	4	0	10
Total	102 (71%)	35 (25%)	6 (4%)	143

[a] Includes five mixed staphylococci/streptococci infections.

Single-disk susceptibility testing of gram-positive and gram-negative organisms was routinely performed in the diagnostic microbiology laboratory throughout the study (Table 4). Of 875 strains of gram-positive cocci isolated, the percentages susceptible to cefoxitin were: *Staphylococcus* (coagulase positive), *Streptococcus pneumoniae*, group A, β-hemolytic streptococci, and non-group A, non-group D streptococci, 100%; *Staphylococcus* (coagulase negative), 96%; and group D *Streptococci*, 20%. Of 2,296 strains of aerobic gram-negative bacilli examined, the percentages of strains susceptible to cefoxitin were: *Proteus vulgaris*, 100%; *E. coli*, *Klebsiella* species, *H. influenzae*, and *Proteus mirabilis*, 99%; *Proteus morganii*, 85%; *Proteus rettgeri*, 64%; *Serratia* species, 64%; *Enterobacter* species, 6%; and *Pseudomonas* species, 3%.

Of particular interest were 25 patients infected by cefoxitin-susceptible but cephalothin-resistant organisms. The primary bacteria causing these infections were *E. coli*, 17: indole-positive *Proteus* species, 4; *Serratia marcescens*, *Enterobacter cloacae*, and *K. pneumoniae*, 1 each; and *Bacteroides fragilis*, 3. Multiple bacteria were isolated from infections in 7 of these 25 patients, 3 of whom were bacteremic. One death occurred in this group; the remaining 24 were cured.

TABLE 3. *Results of cefoxitin treatment: outcome of polymicrobial infections*

Clinical results	No. of patients
Cured	23
Improved	15
Unimproved	3
Died with infection	3
Total	44

Four patients in this study developed asymptomatic serum transaminase elevations. The peak SGOT value was 193 IU, and the peak SGPT value was 93 IU (normal ranges: SGOT, 1 to 40 IU; SGPT, 1 to 40 IU). The pretreatment serum of one of these patients contained an elevated level of alkaline phosphatase before cefoxitin treatment. Five patients developed an eosinophilia above 5% of the total leukocyte count during the course of treatment; the peak value was 9% (759/mm³). Four patients developed leukopenia (<4,500 leukocytes/mm³) during the course of cefoxitin therapy; the lowest count was 3,200/mm³. In all instances there was complete recovery after each of the adverse laboratory effects noted above; moreover, no long-term effects were encountered.

Two patients, neither of whom related a history of penicillin allergy, developed a maculopapular pruritic generalized rash during cefoxitin therapy. The eruptions regressed completely when cefoxitin was discontinued. Three

TABLE 4. *Etiology of infections of 143 patients treated with cefoxitin*

Infection	No. of strains of infecting bacteria																				Percent patients		
	No. of patients	*S. pneumoniae*	Staphylococci	Group A streptococci	Non-A or -D streptococci	Group D streptococci	Other cocci	*H. influenzae*	*E. coli*	*Klebsiella* species	*Proteus* species indole⁻	*Proteus* species indole⁺	*Serratia* species	Other gram-negative rods	*Neisseria meningitidis*	*N. gonorrhoeae*	*B. fragilis*	*Bacteroides* species	Anaerobic streptococci	*Clostridium* species	Other anaerobic bacteria	*Candida* species	Cured	Improved	Not improved
Skin, wound, and soft tissue	49		26	4	10	5			8	4	9	2	1	8			3	3	7	3	3	1	66	26	8
Pneumonia	48	23			3	1		20	4	5	1			3	2								63	33	4
Other respiratory infections	4				1			1						2	1								75	25	0
Urinary tract	21		1		2				15		2		1										52	40	8
Intraabdominal abscess	6					3			5	1		1	1					2		1			83	17	0
Sepsis from unidentified focus	4		1						3														75	25	
Endocarditis	3				2	1		1															100	0	0
Osteomyelitis	3		3																				100	0	0
Other	5		1				1	1								1				1			100	0	0
Total	143																								

patients (1.4%) developed thrombophlebitis at the site of infusion which was severe enough that cefoxitin therapy was discontinued. The incidence of milder thrombophlebitis occurring during the course of therapy and necessitating change of the infusion site was 3.4%. The number of patients with thrombophlebitis in the first comparative phase of the study was too small to evaluate for a difference in incidence of thrombophlebitis in those treated with cefoxitin compared with cephalothin.

DISCUSSION

Adjunctive supportive measures, including surgical drainage, were used whenever appropriate; the clinical results were attributable in part only to cefoxitin, since there was no significant pre-cefoxitin antibiotic therapy. Patients who received potentially effective antibiotics before or during the cefoxitin treatment were not included in these data.

When used against a polymicrobial anaerobic or aerobic-anaerobic infection in this study, cefoxitin treatment was associated with eradication or suppression of the infecting organisms and clinical cure. Since cefoxitin is effective in vitro against cephalothin-resistant gram-negative bacteria including *B. fragilis*, other investigators may wish to evaluate cefoxitin as a single antibiotic alternative to antibiotic combination regimens that would ordinarily involve an aminoglycoside and another antibiotic active against anaerobic organisms (4, 5, 11).

A previous suggestion that cefoxitin may not be effective against gram-positive coccal infections, particularly staphylococcal infections (15), is not completely resolved by this study. Although the results of cefoxitin treatment in this study were acceptable, the number of patients (62) was not large enough to permit definitive evaluation, especially since some of the staphylococcal infections of soft tissue may have responded to drainage alone, antibiotic therapy being adjunctive rather than determinative. However, there was no evidence of clinical or bacteriological relapse of gram-positive infections when cefoxitin was discontinued.

Thrombophlebitis requiring change of infusion site was encountered in only 3.4% of cases; in only 1.4% was thrombophlebitis so severe as to cause discontinuation of cefoxitin treatment. This is a lower rate than that previously reported (8). All infusions were managed by a small team of highly qualified intravenous team nurses, and the use of plastic indwelling intravenous catheters was minimal. Additional data must be acquired to verify the suggestion that thrombophlebitis is an infrequent complication during cefoxitin treatment.

Cefoxitin was stopped during treatment of two patients because of drug rash; otherwise, there were no adverse clinical or laboratory effects serious enough to warrant stopping treatment. Those adverse reactions reported here represent a rigorous evaluation of the role of cefoxitin, since in all instances there were alternative causes related to the infection, underlying physiological impairments, or concurrently administered drugs that could have produced the observed adverse reactions. The clinical cure/improved rate in this study was 93%, somewhat higher than the value of 71% recorded in a previous study with a smaller number of patients (8). Toxicity in this study, particularly eosinophilia and deterioration of renal function (which was not seen in this study), was less than that recorded by Hesseltine and co-workers (8). The reasons for these differences may be due to a different patient population.

We conclude that cefoxitin is a promising new cephamycin antibiotic that may represent a therapeutic advance in the treatment of serious gram-positive and gram-negative infections. Additional studies from other centers may modify this preliminary conclusion.

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