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Prospective Comparison of Cefoxitin and Cefazolin in Infections Caused by Aerobic Bacteria

MARC GURWITH,[1]* WILLIAM ALBRITTON,[1] BEVERLEY LANK,[1] GODFREY HARDING,[2] AND ALLAN RONALD[2]

Division of Infectious Diseases, Department of Medicine, University of Kansas Medical Center, Kansas City, Kansas 66103,[1] and Departments of Medicine, Pediatrics and Medical Microbiology, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada R3E 0W3[2]

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Intravenous cefazolin and cefoxitin were compared in a prospective randomized trial in infections where the suspected pathogen was expected to be susceptible to both antibiotics. In the cefazolin group (12 patients) the diagnosis was pneumonia in 4, including 2 with pneumococcal bacteremia, soft tissue infection in 5, *Staphylococcus aureus* bacteremia in 1, acute pyelonephritis in 1, and disseminated gonococcal infection in 1. In the cefoxitin group (10 patients) the diagnosis was pneumonia in 4, including 2 with pneumococcal bacteremia, soft tissue infection in 4, acute pyelonephritis in 1, and disseminated gonococcal infection in 1. In the cefazolin group receiving an evaluable course of therapy, a good clinical response was seen in 10 of 11 patients, and a bacteriological response was seen in 5 of 7. Cefazolin failed to eradicate *S. aureus* bacteremia in 1 patient and *S. aureus* in a skin ulcer of another patient. All 10 cefoxitin patients had good clinical and bacteriological responses, but in 1 patient *S. aureus* colonization of a postoperative wound recurred after discontinuation of the drug. Side effects in both groups included skin rash, phlebitis, and elevation of the serum alkaline phosphatase. Both cefoxitin and cefazolin appeared effective in infections caused by susceptible aerobic pathogens with the possible exception of *S. aureus*, although all 11 strains of *S. aureus* isolated in this study were susceptible in vitro to both antibiotics. Cefoxitin appeared to be equivalent to cefazolin in efficacy and occurrence of side effects.

Cefoxitin is a new semisynthetic cephamycin antibiotic that has antibacterial activity similar to that of most cephalosporin antibiotics but, in addition, includes increased activity against some aerobic gram-negative rods, especially indole-positive *Proteus* spp. and *Serratia marcescens* (3, 14) and activity against *Bacteroides fragilis* (12, 13). The object of the present study was to compare cefazolin, a commonly used cephalosporin antibiotic, with cefoxitin with respect to efficacy and side effects only in clinical situations where the pathogen was known or expected to be susceptible in vitro to either antibiotic.

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MATERIALS AND METHODS

Patients. Patients included in the study were hospitalized at the Health Sciences Centre, Winnipeg, Manitoba. Only patients without a history of allergy to penicillin or cephalosporin antibiotics and with documented or suspected infections where the infecting pathogen was thought to be susceptible to both cefoxitin and cefazolin were included. Informed verbal consent was obtained from patients or responsible relatives.

When an appropriate patient was identified and informed consent was obtained, the patient was treated with either cefoxitin or cefazolin, based on a previously generated table of random allocation. No other antibiotics were administered concomitantly with cefoxitin or cefazolin. Cefoxitin was administered either by scalp vein infusion or short catheter (Jellco). Two grams diluted in 100 ml of 5% dextrose-0.5 N saline were given over 20 to 40 min on a 8-h schedule. Cefazolin was given in an identical fashion except that 1.0 g was administered every 8 h. Infusion sites were checked daily and were changed by the hospital intravenous team every 24 to 72 h or at the first sign of inflammation. If phlebitis was present, its severity was estimated by one of the investigators (B.L.) seeing the patients daily. Mild phlebitis was defined as a small area of redness along the vein, moderate phlebitis was defined as a larger area of redness with some pain and tenderness, and severe phlebitis was defined as a larger area of redness, covering most of the circumference of the extremity and associated with pain, tenderness, and edema.

Toxicity studies, including complete blood count, urinalysis, serum glutamic oxalacetic transminase, bilirubin, alkaline phosphatase, potassium, sodium, creatinine, and blood urea nitrogen, were obtained before or at the initiation of therapy, at least once during therapy, and at the termination of therapy. Appropriate cultures were obtained from all patients before, during, and after therapy.

Bacteriology. Infecting pathogens were identified by standard microbiological techniques in the hospital clinical microbiology laboratory (7). In vitro susceptibility of clinical isolates was assayed by a modified Kirby-Bauer disk diffusion technique (1), using 30-μg cefoxitin and cephalothin disks. Zone diameter interpretations derived for cephalothin were also applied to the cefoxitin disk in determining in vitro susceptibility. Even though regression curves are not available for pneumococci and gonococci, diameters in excess of 20 mm for these strains were considered evidence of susceptibility. In the case of *Staphylococcus aureus* (11 strains), the minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) were determined by serial dilution in microtiter plates (Cooke) in Mueller-Hinton broth. Three different inocula, $10,^2$ $10,^4$ and 10^6 colony-forming units per ml, were incubated at 37°C, and results were read at 18 to 24 h. The MBC was defined as a three-$\log_{10}$ decrease in CFU from the 10^6-CFU/ml inoculum, as determined by sampling the MIC microtiter plate at 24 h with a 0.001-ml loop and failure to grow in a 200-fold dilution of Mueller-Hinton broth. The inoculum was from a log-phase growth adjusted to 10^8 *CFU/ml.* Inoculum checks were carried out at the 10^4-CFU/ml inoculum, and all dilutions were made from a single 10^8-CFU/ml tube.

RESULTS

A total of 22 patients were included in the trial, 12 in the cefazolin group and 10 in the cefoxitin group. In the cefazolin group, the patients ranged in age from 19 to 70 years with a mean of 46 and a median of 50 years (Table 1). There were five men and seven women. The infectious diagnoses were: pneumonia in four patients, including two with bacteremia; cellulitis and/or furunculosis in five; bacteremia with *S. aureus,* probably due to phlebitis secondary to an intravenous infusion, in one; acute pyelonephritis in one; and the disseminated gonococcal dermatitis/arthritis syndrome in one.

In the cefoxitin group, the age range was from 22 to 73 years with a mean of 39 and a median of 29.5 years (Table 2). There were five men and five women. The infectious diseases were: pneumonia in four patients, including two with bacteremia; cellulitis and/or furunculosis in three; acute pyelonephritis in one; *S. aureus* infection of a surgically removed hydatid lung cyst cavity as well as *Escherichia coli* urinary tract infection in one patient; and the disseminated gonococcal dermatitis/arthritis syndrome in one.

In eight patients there was a good clinical response to cefazolin therapy, and elimination of the infecting pathogen was demonstrated in five of the seven patients where follow-up bacteriological results could be evaluated (Table 1). There was one clinical and bacteriological failure, which occurred in a patient (CH) with *S. aureus* bacteremia. The patient did not respond clinically and died after 5 days of cefazolin therapy. Postmortem findings suggested widespread staphylococcal infection and cirrhosis, and postmortem blood cultures were positive for *S. aureus.* In one patient (EB) the results of therapy could not be evaluated because the drug was discontinued after only 1 day, when possible antibiotic-related vasculitis was noted. The vasculitis was histologically confirmed. In two other patients, both with an apparently good initial response, cefazolin was discontinued within 3 days. In one of these (TN) the cefazolin was discontinued because the patient developed suspected purulent pericarditis while on treatment. This latter finding proved to be nonbacterial, probably related to the patient's underlying vasculitis. In the other patient (VG), cefazolin was discontinued because of urticarial skin rash. In addition to the patient with persistent *S. aureus* bacteremia, one patient (NS) with cellulitis and a skin ulcer infected with *S. aureus* had an apparent clinical improvement of the cellulitis, but *S. aureus* was still present in the wound after 12 days of therapy.

In the cefoxitin group, a good clinical response was seen initially in all 10 patients and in all 9 patients where the bacteriological response could be evaluated (Table 2). In two patients, both with pneumococcal pneumonia and bacteremia, cefoxitin therapy was discontinued after 5 days. In one (LL), cefoxitin therapy was changed to penicillin when endocarditis was recognized as being present. This patient had responded clinically, and blood cultures were already negative. In the other patient (LS), persistence of fever and the isolation of an *E. coli,* resistant to cephalosporins, from a urine culture prompted the house staff to change to penicillin and gentamicin therapy. This patient had also shown clinical and bacteriological responses to cefoxitin therapy. A third patient (EL), with pneumonia due to *Klebsiella pneumoniae,* also with good clinical and bacteriological responses, developed an urticarial skin rash, and cefoxitin was discontinued after 4 days. In 1 (RS) of the 10 cefoxitin patients, after an initial good response, there was a bacteriological relapse. Both operative wound and urine cultures were sterile after 14 days of therapy, but *S. aureus* infection and/or colonization of her wound cavity recurred 4 weeks after discontinuation of therapy.

TABLE 1. *Patient characteristics, bacterial etiology, and results of therapy with cefazolin*

Patient	Sex	Age	Infectious diagnoses	Suspected pathogen	Underlying disease	Days of therapy	Results[a]	
							Clinical	Bacteriological
CL	F	33	Pneumonia, bacteremia	*Diplococcus pneumoniae*	Alcoholism	11	Response	Cure
GM	F	67	Pneumonia, bacteremia	*D. pneumoniae*	Lymphoma	7	Response	Cure
MP	F	70	Pneumonia	ND	Cerebrovascular accident	7	Response	ND
GP	M	59	Pneumonia	Group A streptococcus	Bronchiectasis	9	Response	Cure
RR	M	27	Cellulitis, furunculosis	ND	None	7	Response	ND
NS	F	54	Cellulitis, skin ulcer	*S. aureus*	Systemic lupus erythematosus	12	Response	Failure
TN	M	32	Cellulitis	Group A streptococcus, *S. aureus*	Vasculitis, pericarditis	3	Response	TD
VG	F	46	Cellulitis	Group A streptococcus, *S. aureus*	None	2	Response	TD
EB	F	63	Cellulitis, synergistic gangrene	Group A streptococcus, *S. aureus*	Multiple myeloma	1	TD	TD
CH	M	23	Bacteremia	*S. aureus*	Cirrhosis, gastrointestinal hemorrhage	5	Died	Failure
CW	M	59	Acute pyelonephritis	*Proteus mirabilis, P. morganii, S. faecalis*	Neurogenic bladder	6	Response	Cure
PC	F	19	Gonococcal dermatitis/arthritis syndrome, bacteremia	*Neisseria gonorrhoeae*	None	5	Response	Cure

[a] ND, Not determinable, infecting pathogen not definitively identified; TD, therapy discontinued early (see text).

TABLE 2. *Patient characteristics, bacterial etiology, and results of therapy with cefoxitin*

Patient	Sex	Age	Infectious diagnoses	Suspected pathogen	Underlying disease	Days of therapy	Results	
							Clinical	Bacteriological
LL	M	29	Pneumonia, bacteremia, (endocarditis)	*D. pneumoniae*	Alcoholism	5	Response	Cure, TD[a]
LS	F	44	Pneumonia, bacteremia	*D. pneumoniae*	Alcoholism	5	Response	Cure, TD
EL	M	66	Pneumonia	*K. pneumoniae*	Myocardial infarction	4	Response	Cure, TD
JK	F	73	Pneumonia	ND[b]	None	9	Response	Cure
RG	M	25	Cellulitis, furunculosis	*S. aureus*	None	13	Response	Cure
AW	M	50	Cellulitis	*S. aureus*, group A streptococcus	None	9	Response	Cure
FM	M	30	Cellulitis	Group A streptococcus	Alcoholism, trauma	7	Response	Cure
LW	F	24	Acute pyelonephritis	*E. coli*	None	4	Response	Cure, TD
RS	F	27	(i) Postoperative wound infection	(i) *S. aureus*	Hydatid cyst of lung	14	(i) Relapse	(i) Relapse
			(ii) Urinary tract infection	(ii) *E. coli*			(ii) Response	(ii) Cure
CS	F	22	Gonococcal dermatitis/ arthritis syndrome	*N. gonorrhoeae*	None	5	Response	Cure

[a] TD, Therapy discontinued early (see text).
[b] ND, Not determinable.

The side effects were similar in both groups (Table 3). In the cefazolin group, six patients had mild phlebitis, and one patient with *S. aureus* bacteremia had severe phlebitis. This patient had already had phlebitis associated with intravenous catheters before the institution of cefazolin therapy. An urticarial eruption was seen in two patients, and vasculitis probably associated with cefazolin was seen in a third patient. In two patients, both with mild phlebitis, an elevation in the serum alkaline phosphatase was noted. In one (CL), the alkaline phosphatase rose from 100 IU/dl on the initial day to 225 IU/dl on day 6 of therapy and fell to 165 IU/dl 3 days after discontinuation of therapy (normal range, 30 to 125 IU/dl). The patient's serum glutamic oxalacetic transaminase rose from 92 to 140 IU/dl, and the bilirubin rose from 2.0 to 2.8 mg/dl in this same period. This patient was one of the patients with alcoholism as an underlying disease. In another patient (GM), with pneumococcal bacteremia and lymphoma, the alkaline phosphatase rose from 293 IU/dl on day 2 of therapy to 425 IU/dl on day 4 and fell back to 286 IU/dl 1 day after therapy was discontinued.

In the cefoxitin group, mild phlebitis was seen in two patients and moderate phlebitis was seen in one. One patient (EL) developed an urticarial skin rash. In two patients, there was a rise in the serum alkaline phosphatase concomitant with cefoxitin therapy, with a return to normal after cefoxitin was discontinued. The alkaline phosphatase in LL rose from 45 IU/dl on day 1 of therapy to 450 IU/dl on day 5, falling to 186 IU/dl 2 days after discontinuation of therapy to 86 IU/dl 6 days after therapy was discontinued. The bilirubin remained normal throughout, and the serum glutamic oxalacetic transaminase, which was 136 IU/dl on day 1 of therapy, rose to 211 IU/dl on day 5 of therapy and fell to 67 IU/dl 6 days after therapy had been discontinued. In another patient (JK), the alkaline phosphatase rose from 135 IU/dl on day 1 of therapy to 410 IU/dl on day 6 of therapy, falling to 345 IU/dl 2 days after discontinuation of therapy and to 179 IU/dl 8 days after the end of therapy. There was no concomitant rise in bilirubin or serum glutamic oxalacetic transaminase.

All initial infecting pathogens tested, except a *Proteus morganii* resistant to cefazolin and *Streptococcus faecalis* resistant to both cefazolin and cefoxitin, were suceptible to both antibiotics. Because relatively poor clinical and bacteriological responses were seen in three of the *S. aureus* infections, all 11 *S. aureus* strains isolated from these 22 patients were further tested. The MICs and MBCs of cephalothin,

cefazolin, and cefoxitin were determined for these 11 strains (Table 4). The MICs, at all three inoculum sizes, were lowest for cephalothin and highest for cefoxitin, although all strains were susceptible to 4 μg of cefoxitin per ml. An inoculum effect on MIC was seen only with cephalothin and cefazolin, where a tendency for the MIC to increase was seen at the higher inoculum. The MBCs of the 11 strains were similar to the MICs for cefazolin and cefoxitin but were somewhat higher for cephalothin, where 4 strains had an MBC at least two dilutions greater than the MIC.

The MICs of the three strains of *S. aureus* isolated from patients with a poor bacteriological response to cefazolin or cefoxitin were similar to those of the rest of the strains. The MIC of the *S. aureus* causing persistent bacteremia was 0.25 μg/ml for cefazolin, whereas the other two strains had MICs of 2 μg/ml. All three of these strains had MICs of 4 μg/ml for cefoxitin. The MBC was the same as the MIC for cefazolin and cefoxitin for these three strains, and the same as that for cephalothin for two of the three strains. One strain had an MBC for cephalothin eight times greater than the MIC.

DISCUSSION

The purpose of this study was to compare cefazolin and cefoxitin in bacterial infections where the pathogen was expected to be susceptible to either antibiotic. This excluded anaerobic infections where *B. fragilis* was suspected. We felt that cefazolin was a good comparison antibiotic, since it resembles cefoxitin in its in vitro aerobic spectrum; that is, compared with other cephalosporins it has increased activity against some enteric aerobic gram-negative rods

TABLE 3. *Adverse reaction associated with cefazolin (CFZ) or cefoxitin (CXT)*

Patient	Treatment	Reaction			
		Phlebitis		Allergic	Increased alkaline phosphatase (× baseline)
		Severity	Days		
CW	CFZ	Mild	1		
CH	CFZ	Severe	5		
GM	CFZ	Mild	2		2
RR	CFZ	Mild	1		
GP	CFZ			Urticaria	
CL	CFZ	Mild	1		2
VG	CFZ	Mild	1	Urticaria	
PC	CFZ	Mild	1		
EB	CFZ			Immune vasculitis	
LL	CXT				10
RS	CXT	Moderate	4		
EL	CXT	Mild	1	Urticaria	
JK	CXT	Mild	4		4

TABLE 4. *MICs and MBCs of 11 strains of S. aureus to cephalothin, cefazolin, and cefoxitin*

Antibiotic	Inoculum (CFU/ml)	No. of strains with MIC or MCB (μg/ml) of:									
		≤0.03	0.06	0.125	0.25	0.5	1	2	4	≥8	≥16
MIC											
Cephalothin	10^2		2	1	8						
	10^4		1	2	8						
	10^6			1	4	6					
Cefazolin	10^2			2	5	4					
	10^4			2	4	5					
	10^6				4	2	1	4			
Cefoxitin	10^2						1	2	8		
	10^4						1	1	9		
	10^6							3	8		
MBC											
Cephalothin	10^6			1	3	3		1	3		
Cefazolin	10^6				3	2	1	5			
Cefoxitin	10^6							1	9	1	

and, possibly, decreased activity against penicillinase-producing *S. aureus* (4, 8). Since cefazolin has a longer half-life than cefoxitin, the cefoxitin dose chosen was twice the cefazolin dose. Cefoxitin or cefazolin serum levels were not done on any patients in the study, but we expected that the levels of both these antibiotics would be similar and well above the MICs of infecting strains. For example, in previous studies, the mean 4-h serum levels were approximately 20 μg/ml (6) after a 1-g infusion of cefazolin and 10 μg/ml after a 2-g infusion of cefoxitin (5).

The two antibiotics appeared equivalent in efficacy in the treatment of infections with susceptible pathogens. Clinical and bacteriological failure was seen in only one patient (CH) with *S. aureus* bacteremia treated with cefazolin. Probable persistent colonization of a wound with *S. aureus* was seen in two other patients, one in the cefazolin group and the other in the cefoxitin group. The serum alkaline phosphatase was elevated in four patients concomitant with the onset of antibiotic therapy, falling after antibiotic therapy had been discontinued, and otherwise unexplained in two patients in each group. This particular side effect has not been prominent in reports of toxicity after cefoxitin (5) but was noted with cefazolin (6). There was a slightly higher rate of phlebitis with cefazolin than with cefoxitin, but phlebitis was mild and not a significant problem except in one patient. Approximately one-third of the patients experienced phlebitis with cefoxitin, a rate similar to that noted by others (5). An allergic skin rash was seen in three patients in the cefazolin group and one in the cefoxitin group.

It is not possible to determine whether the apparent failures in achieving a bacteriological cure in the three *S. aureus* patients were due to failure of antibiotic or due to underlying host factors. The higher MICs and MBCs for most *S. aureus* isolates for cefoxitin and cefazolin in comparison with those for cephalothin, the fact that several instances of cefazolin treatment failures of *S. aureus* endocarditis have been reported (2, 9), and our own observations of failure of cefazolin in *S. aureus* infection (unpublished observations), make us favor parenteral methicillin, cloxacillin, or, when indicated, cephalothin for *S. aureus* infections. The instability of cefazolin in the presence of β-lactamase may account for cefazolin treatment failures in *S. aureus* infections (10). Nevertheless, the MICs and MBCs for *S. aureus* of cefoxitin and cefazolin are similar or lower than those of methicillin (11).

In conclusion, it appears that cefoxitin, a semisynthetic cephamycin antibiotic, is equivalent in efficacy and side effects to cefazolin in the treatment of infections caused by susceptible aerobic pathogens.

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