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Randomized Comparative Study of Moxalactam and Cefazolin in the Treatment of Acute Urinary Tract Infections in Adults

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Eighty-nine patients with clinical and laboratory evidence of acute urinary tract infection were randomized to therapy with either moxalactam (500 mg) or cefazolin (1 g) every 12 h. *Escherichia coli* was the predominant pathogen in both groups (92.6 versus 90.2%). Therapy was continued for 3 days after the patient defervesced. The minimum hospital stay was 5 days. Sequential urine cultures were obtained on day 3, at discharge, and 5 to 10 days after the cessation of therapy. The average duration of hospital stay was 5.6 days for both groups of patients. The incidence of recurrent infection was similar in uncomplicated patients (9.1 versus 10%) and in complicated patients with a condition predisposing them to urinary tract infections (43 versus 42%). Moxalactam-treated patients had a higher incidence of reversible hepatic enzyme elevation (36%) and *Streptococcus faecalis* superinfections (12.2%). Moxalactam is as effective as cefazolin for the elimination of gram-negative pathogens from the urine of patients with acute urinary tract infections, but it is associated with a higher incidence of reversible side effects.

The antimicrobial spectrum and pharmacokinetic properties of moxalactam suggest that it should be a useful agent for the empirical treatment of urinary tract infections in patients with normal renal function (2, 4–6, 8–15, 17–20). In this prospective randomized study of patients with acute urinary tract infections, the efficacy of this new antibiotic was compared with that of cefazolin, an agent of proven usefulness in this clinical setting (3, 7). Patients were evaluated for clinical and bacteriological response, duration of hospital stay, and adverse drug reactions.

MATERIALS AND METHODS

The patients in this study were referred to the Infectious Disease Service from the emergency center or the inpatient medical and surgical services of the Ben Taub General Hospital, Houston, Tex. Each patient considered for inclusion carried a clinical diagnosis of acute pyelonephritis. Microscopic examination of the urinary sediment of each patient had to document the presence of bacteriuria or pyuria ($>10^5$ cells per high-power field) or both. Patients with abnormal renal function (a serum creatinine level of >2.0 mg/100 ml), indwelling Foley catheters, complete urinary tract obstruction, perinephric abscesses, staghorn calculi, and distant sites of infection were excluded from the study. Informed consent was obtained according to the guidelines of the Institutional Review Board for Human Research, Baylor College of Medicine, Houston, Tex. Patients were randomized to parenteral moxalactam (500 mg every 12 h) or cefazolin (1 g every 12 h) according to a computer-generated list.

A laboratory profile (hematocrit, hemoglobin, leukocyte count, blood urea nitrogen, creatinine, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, total bilirubin, and urinalysis), blood culture, and clean-catch midstream or catheterized urine for quantitative culture and susceptibility were obtained before the institution of therapy. Coagulation studies were not obtained routinely during the course of this investigation. Significant numbers ($>10^5$ colony-forming units per ml) of a sensitive bacterial pathogen had to be isolated from the admission urine sample. Organisms isolated from urine and blood were identified with an Analytical Profile Index 20E (Analytab Products, Plainview, N.Y.). Kirby-Bauer susceptibility testing was performed on Mueller-Hinton agar with a standard cephalothin disk and a 30-μg moxalactam disk (1).

Antibiotic therapy was continued for a minimum of 5 days and until the patient had remained afebrile for 72 h. The laboratory profile and urine culture were repeated on hospital day 3 and again at the end of therapy. Follow-up clean-catch midstream urine samples for culture and susceptibility were obtained between 5 and 10 days after discharge. A laboratory profile was obtained at that time only if hematological or chemical abnormalities attributable to antibiotic therapy had occurred during the treatment period.

The therapeutic effects of both agents were assessed on the basis of the sequential urine cultures obtained from each patient. The criteria were as follows: cure, absence of significant bacteriuria at follow-up; recurrence, significant bacteriuria with the initial organism at follow-up; reinfection, significant bacteriuria with a

different organism at follow-up; and superinfection, significant bacteriuria with a different organism while undergoing therapy.

Results were compared by using the chi-square test for discreet variables and Student's *t* test for continuous variables. A *P* value of less than 0.05 was considered significant.

RESULTS

Eighty-nine patients were entered in this study. Seven patients were excluded after 48 h of treatment due to sterile or contaminated admission urine cultures. The remaining 82 patients met all the clinical and microbiological criteria for the diagnosis of an acute urinary tract infection. Forty-one patients were treated with each of the study antibiotics. Both groups of patients were similar with regard to age, sex, predisposing conditions, admission temperature, and selected pretreatment laboratory tests, including leukocyte count, blood urea nitrogen, creatinine, serum glutamic oxalacetic transaminase, and alkaline phosphatase. The average weight of cefazolin-treated patients (127 lb [ca. 58 kg]) was greater than that of moxalactam-treated patients (103 lb [ca. 47 kg]).

Escherichia coli was the most common pathogenic organism in 38 (92.6%) moxalactam-treated patients and 37 (90.2%) cefazolin-treated patients. Five patients (12.2%) in each group were bacteremic with this pathogen. *Klebsiella pneumoniae* was the causative organism in one moxalactam-treated patient and two cefazolin-treated patients. *Enterobacter cloacae* and a group B streptococcus respectively, were the pathogenic organisms in two patients in the moxalactam group, and *Proteus mirabilis* accounted for two infections in the cefazolin group.

Fifty-five patients with no known predisposing condition for a urinary tract infection (uncomplicated patients) participated in this study. Of these, 29 received moxalactam and 26 received cefazolin. The length of hospital stay was similar for moxalactam-treated (5.6 days) and cefazolin-treated (5.5 days) patients. The causative bacterial pathogen had been eliminated from the urine of all these patients by the time of discharge. A total of 22 of the moxalactam-treated patients and 20 of the cefazolin-treated patients returned for follow-up urine cultures 5 to 10 days after the cessation of therapy (Table 1). Of the moxalactam group, two (9.1%) patients had recurrent infections and two (9.1%) had reinfections. One of the reinfections was due to a different organism, and the other was due to *E. coli* with a different susceptibility pattern. In the cefazolin group, two (10%) patients had recurrent infections and none had a reinfection. The difference in the recurrence rates between the two groups was not statistically significant.

Twenty-seven patients in this study had an underlying condition predisposing them to urinary tract infections (complicated patients). Of these, 12 belonged to the moxalactam group and 15 belonged to the cefazolin group. The length of hospital stay was 5.7 days for both groups of patients. The causative bacterial pathogen had been eliminated from the urine of all these patients by the time of discharge. Seven moxalactam patients and 12 cefazolin patients returned for follow-up culture 5 to 10 days after the cessation of therapy (Table 1). Three (43%) moxalactam-treated patients and five (42%) cefazolin-treated patients had recurrent infections. The difference in the recurrence rates between these two groups of patients was not statistically significant. There were no reinfections in either group.

During the course of this study, six patients developed significant bacteriuria with another organism while undergoing therapy (Table 1). Five (12.2%) patients in the moxalactam group developed superinfections with *Streptococcus faecalis*. This phenomenon was observed in 25% of the complicated patients and 6.9% of the uncomplicated patients in this group. None of these patients were symptomatic and in two cases the organism spontaneously disappeared

TABLE 1. Bacteriological response of complicated and uncomplicated patients treated with moxalactam and cefazolin

Patient group	Antibiotic	No. of patients/total no. of patients			
		Cure	Recurrence	Reinfection	Superinfection[a]
Uncomplicated	Moxalactam	18/22 (81.8)[b]	2/22 (9.1)	2/22 (9.1)	2/29 (6.9)
	Cefazolin	18/20 (90)	2/20 (10)	0	1/26 (3.8)
Complicated	Moxalactam	4/7 (57)	3/7 (43)	0	3/12 (25)
	Cefazolin	7/12 (58)	5/12 (42)	0	0

[a] The denominator for superinfections represents all patients entered in the study for each group, since these infections occurred during therapy.

[b] Numbers in parentheses are percentages.

within 1 week after the cessation of therapy. The remaining three patients never returned for follow-up cultures. One patient treated with cefazolin developed a *Pseudomonas aeruginosa* superinfection which required additional therapy.

Evidence of drug toxicity occurred in 23 (56%) patients treated with moxalactam and 16 (39%) patients treated with cefazolin (P = not significant). The elevation of one or more hepatic enzymes (serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, and alkaline phosphatase) to an abnormal level (at least twice the level at admission) occurred in 15 (36.5%) patients treated with moxalactam and 6 (14.6%) patients treated with cefazolin. This difference was statistically significant. There was no difference between the two groups when the incidence of leukopenia (fewer than 4,000 leukocytes per mm^3), eosinophilia (greater than 5%), thrombophlebitis, and pruritis was compared (Table 2). There was no evidence of hemolysis or nephrotoxicity in either group, and no patient required removal from either antibiotic due to an adverse drug reaction. All patients with evidence of drug toxicity who returned for follow-up examination experienced a complete reversal of their chemical and clinical abnormalities.

TABLE 2. Adverse reactions during therapy

Adverse reaction	No. of patients	
	Moxalactam (n = 41)	Cefazolin (n = 41)
Hepatic enzyme elevation	15 (36.5)[a,b]	6 (14.6)[a]
Eosinophilia	10 (24.4)	7 (17.7)
Leukopenia	3 (7.3)	2 (4.9)
Thrombophlebitis	2 (4.9)	1 (2.4)
Pruritis	1 (2.4)	0

[a] $P < 0.05$.
[b] Numbers in parentheses are percentages.

DISCUSSION

In this study we compared moxalactam with cefazolin, a cephalosporin with similar pharmacokinetic properties and proven efficacy in the treatment of acute urinary tract infections. We considered only those patients who had clinical signs of pyelonephritis in an attempt to exclude patients with uncomplicated cystitis and acute uretheral syndrome. We found that moxalactam (500 mg every 12 h) and cefazolin (1 g every 12 h) are equally effective in eradicating gram-negative bacteria from the urine of patients with acute urinary tract infections regardless of the presence or absence of a predisposing condition.

Moxalactam produced a greater incidence of reversible hepatic enzyme elevation, but there was no other difference in toxicity between the two agents. Of interest was the 12% incidence of *S. faecalis* superinfections in patients treated with moxalactam. Although this observation has been reported by other investigators, the clinical significance remains unknown (16, 21). None of our patients was symptomatic, and the organism disappeared spontaneously from the urine of both patients who returned for follow-up cultures.

This study demonstrates that moxalactam is effective in the treatment of acute urinary tract infections, caused by susceptible microorganisms, in which there are clinical signs of upper tract involvement. The use of this agent should not supplant the use of the less toxic drug, cefazolin, for the treatment of community-acquired urinary tract infections. The effectiveness of moxalactam against susceptible microorganisms and its in vitro activity against multiply drug-resistant gram-negative rods make it a possible alternative to the aminoglycosides for the treatment of serious urinary tract infections when the presence of resistant microorganisms is likely and the avoidance of nephrotoxicity is desirable. However, patients who are treated with moxalactam will be at risk for the development of enterococcal superinfections. Further studies comparing moxalactam with the aminoglycosides are needed to evaluate its usefulness in this clinical setting.

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