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Randomized, Double-Blind Comparison of Ceftazidime and Moxalactam in Complicated Urinary Tract Infections

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Sixty-seven patients with complicated urinary tract infections were randomized in double-blind fashion to ceftazidime or moxalactam (MOX). A total of 54 patients were evaluable, 27 in each group. Patients received 500 mg of antibiotic intravenously every 12 h, except for those with *Pseudomonas aeruginosa* randomized to MOX who received 2 g intravenously every 12 h. Toxic effects with ceftazidime were experienced by the following number of patients: pain with infusion, one; posttherapy diarrhea, one; liver function test elevations, two; and neutropenia, one. Toxic effects with MOX were experienced by the following number of patients: liver function test elevations, two; and prolonged prothrombin time, one. All resolved. At 1 week posttherapy, bacteriologic results were 74% cured, 11% relapsed, 15% reinfection with ceftazidime and 52% cured, 33% relapsed, and 19% reinfection with MOX. Ceftazidime was effective for infections caused by MOX-resistant *P. aeruginosa*. *P. aeruginosa* resistant to MOX and other beta-lactams was isolated from one patient after MOX therapy. Enterococcal reinfection was common in both groups.

Ceftazidime (CAZ) is a new 2-aminothiazolyl cephalosporin which has activity against a broad spectrum of both gram-positive and gram-negative organisms (4, 6). It has shown particular promise in the treatment of various *Pseudomonas* species, especially *Pseudomonas aeruginosa* (8). It is excreted unchanged by glomerular filtration and has a half-life of 1.8 h in patients with normal renal function (8).

In this study, CAZ and moxalactam (MOX) were compared for safety and efficacy in the treatment of complicated urinary tract infections. Susceptibility patterns of posttherapy isolates were studied to detect the development of antimicrobial resistance emerging during therapy. In addition, patients infected with MOX-resistant, CAZ-susceptible *Pseudomonas aeruginosa* were treated with CAZ and evaluated.

MATERIALS AND METHODS

Randomized study. Adult patients with a urinary tract infection requiring systemic antibiotic therapy were eligible if they had a urinary tract abnormality known to promote infection, to account for persistence of infection, or to promote recurrence. Infection was defined as (i) $\geq 10^5$ CFU/ml of fresh midstream, clean catch, or catheterized urine and (ii) two or more of the following: fever (temperature ≥37.8°C), signs and symptoms of urinary tract infection, ≥5 leukocytes per high-power field of urinary sediment. Exclusionary criteria were (i) sensitivity to cephalosporins or anaphylactic reaction to penicillin, (ii) pregnancy, (iii) serum creatinine > 3 mg/dl or total serum bilirubin > 3 mg/dl, (iv) serum aspartate aminotransferase > 200 U/ml, (vi) suspected or proven bacteremia, (vii) reception of any antibiotic to which the infecting organism was susceptible within the 48 h before collection, and (viii) presence of a chronic indwelling urinary catheter.

After written informed consent was obtained, patients were randomized in double-blind fashion to receive 500 mg of either MOX or CAZ intravenously every 12 h. Emergence of resistance in *Pseudomonas aeruginosa* during therapy with MOX has been reported (11). Therefore, a *Pseudomonas* isolate signalled the pharmacist to increase the dose to 2 g every 12 h for patients randomized to MOX. The usual length of treatment was 7 days. Four patients were treated for 9.5, 10, 10, and 11.5 days, respectively. One patient had pyelonephritis; the others had therapy extended through the performance of cystoscopy.

Nosocomial infection was defined as onset of symptoms after more than 48 h in the hospital.

Open study. A patient was considered for a nonblinded protocol with CAZ when the infecting organism was resistant to MOX. Enrollment, treatment, and follow-up were otherwise identical with the randomized study.

Laboratory studies. Urine cultures and susceptibilities (1) were repeated after 2 to 4 days of therapy and at 5 to 9 days posttherapy. When possible, cultures were obtained 4 to 6 weeks after therapy.

MICs of MOX and CAZ were determined by serial twofold dilutions in Mueller-Hinton broth (Difco Laboratories) in a final volume of 3 ml. Each tube was inoculated with a final bacterial population of 10^5 CFU/ml from an overnight Mueller-Hinton broth culture incubated for 24 h at 37°C in air. The MIC was defined as the lowest concentration of drug inhibiting macroscopic growth. Isolates were considered resistant when MICs were ≥64 μg/ml for either antibiotic.

Hematology, serum chemistry, and thyroid function tests were monitored before therapy, on day 3 of therapy, and 24 h after therapy.

Definitions of outcome. In this study the following definitions were used. Cure is $<10^5$ CFU/ml posttherapy. Persistence is $\geq 10^5$ CFU of the original isolate per ml during therapy. Superinfection is $\geq 10^5$ CFU of a different isolate per ml during therapy. Relapse is sterile urine during therapy with $\geq 10^5$ CFU of the original isolate per ml posttherapy. Reinfection is sterile urine during therapy with $\geq 10^5$ CFU of a new isolate per ml posttherapy.

Statistical analysis was performed with the Fisher exact

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TABLE 1. Summary of patients treated with CAZ or MOX

Characteristic	CAZ group (n = 27)	MOX group (n = 27)
Mean (range) age (yr)	70 (49–94)	71 (31–93)
Sex (no. of males/no. of females)	26/1	27/0
Diagnosis (no.)		
Cystitis	25	26
Pyelonephritis	2	1
Prostatitis	0	0
Fever (no. with temp of ≥38.7°C)	13	8
Pyuria (no. with ≥5 leukocytes per high-power field)	23	27
Mean no. of days of treatment	7.2	7.28
Hospital-acquired infection (no.)	15	13
Complication (no.)		
Benign prostatic hypertrophy	14	15
Neurogenic bladder	9	7
Indwelling catheter (removed)	5	3
External catheter	2	0
Urethral stricture	2	3
Intermittent straight catheter	3	2
Prostatic carcinoma	4	2
Calculi	1	1
Bladder diverticuli	1	0

test; $P = 0.05$ was chosen as the level of statistical significance.

RESULTS

Comparative results. Of 67 patients enrolled, 13 were excluded. Four received another antibiotic, four had negative pretherapy cultures, and one had bacteremia. Four with pretherapy isolates resistant to MOX received CAZ in an open protocol.

Of the 54 evaluable patients, 27 received CAZ and 27 received MOX. The two groups were clinically comparable (Table 1). Pretherapy isolates and susceptibility to study drugs are given in Table 2. Susceptibility among members of the family *Enterobacteriaciae* was similar, but MICs of MOX were higher than MICs of CAZ against *Pseudomonas aeruginosa*. Resistance to other antimicrobial agents was common among initial isolates of both groups (Table 3).

All patients had resolution of signs and symptoms while on therapy (Table 4). No patients had persistence or superinfection during therapy. At 5 to 9 days posttherapy, the difference between cure rates (CAZ, 74%; MOX, 52%) was not statistically significant ($P = 0.079$). Differences in relapse rates (CAZ, 11%; MOX, 33%) were significant ($P = 0.0497$). CAZ treatment relapses were with *Escherichia coli* (two) and *Citrobacter diversus* (one). MOX treatment relapses were with *E. coli* (three), *Klebsiella pneumoniae* (two), *Pseudomonas aeruginosa* (two), *Proteus mirabilis* (one), and *Serratia marcescens* (one). Reinfecting isolates in the CAZ group were enterococci (three) and a *Candida* species (one). Reinfecting isolates in the MOX group were enterococci (four) and *E. coli* (one). CAZ had higher cure rates than MOX in both nosocomial (60 versus 38%) and community-acquired (92 versus 64%) infections, but these differences were not statistically significant.

One patient with *Pseudomonas aeruginosa* (not serotypable) treated with MOX became reinfected with a second strain of *Pseudomonas aeruginosa* (serotype 11) which was resistant to MOX, cefotaxime, ceftriaxone, carbenicillin,

TABLE 2. MICs of CAZ and MOX for initial isolates

Organism	Treatment group	No. of strains	Drug	MIC (μg/ml)	
				Range	50%
Escherichia coli	CAZ	16	CAZ	<0.06–1	0.25
			MOX	0.06–4.0	0.25
	MOX	9	CAZ	<0.06–0.25	0.25
			MOX	0.06–0.25	0.12
Pseudomonas aeruginosa	CAZ	4	CAZ	1.0–4.0	2
			MOX	16–32	16
	MOX	4	CAZ	1.0–2.0	1
			MOX	8–16	8
Klebsiella pneumoniae	CAZ	3	CAZ	0.12–4	0.25
			MOX	0.25–2	0.5
	MOX	5	CAZ	0.12–1	0.25
			MOX	0.12–4	0.5
Klebsiella oxytoca	MOX	1	CAZ	0.12	
			MOX	1	
Klebsiella ozaenae	MOX	1	CAZ	<0.06	
			MOX	0.06	
Citrobacter freundii	CAZ	3	CAZ	0.25–32	0.5
			MOX	0.12–0.5	0.12
	MOX	2	CAZ	0.25–0.5	0.25
			MOX	0.06–0.06	0.06
Proteus mirabilis	MOX	2	CAZ	<0.06–<0.06	<0.06
			MOX	0.12–0.12	0.12
Proteus vulgaris	CAZ	1	CAZ	0.12	
			MOX	0.25	
Providencia rettgeri	MOX	1	CAZ	4	
			MOX	<0.06	
Providencia stuartii	MOX	1	CAZ	1	
			MOX	0.25	
Serratia marcescens	MOX	1	CAZ	0.5	
			MOX	2	
Morganella morganii	CAZ	1	CAZ	0.25	
			MOX	<0.06	
Enterobacter cloacae	MOX	1	CAZ	4	
			MOX	8	

TABLE 3. Resistance among initial isolates in CAZ- and MOX-treated patients, as determined by disk diffusion

Antibiotic	% Resistant in patients treated with:	
	CAZ	MOX
Ampicillin	82	67
Carbenicillin	64	29
Cefazolin	46	46
Cefamandole	22	15
Gentamicin	18	19
Tobramycin	18	19
Amikacin	0	0
Co-trimoxazole	42	36

TABLE 4. Bacteriologic response

Posttherapy culture	Drug	No. of patients/total no.		
		Cure	Relapse	Reinfection
Days 5–9	CAZ	20/27	3/27	4/27
	MOX	14/27	9[a]/27	5[a]/27
Weeks 4–6	CAZ	5/12	4/12	3/12
	MOX	4/8	3/8	1/8

[a] One patient had relapse and reinfection.

mezlocillin, and aztreonam. This resistance was not due to the presence of a beta-lactamase.

Of the 34 patients bacteriologically cured at 5 to 9 days posttherapy, 20 had cultures obtained at 4 to 6 weeks posttherapy. Of these 20, 11 (55%) had $\geq 10^5$ CFU/ml. In the CAZ group, relapses were with *E. coli* (three) and *Pseudomonas aeruginosa* (one) and reinfections were with enterococci (two) and *Proteus mirabilis* (one). In the MOX group, relapses were with *Providencia stuartii* (one), *Klebsiella pneumoniae* (one), and *Klebsiella ozaenae* (one) and reinfection was with enterococcus (one).

Open study. Four patients with MOX-resistant *Pseudomonas aeruginosa* were treated with CAZ. All responded clinically. Posttherapy cultures at 1 week showed bacteriologic cure in three patients. One was reinfected with *Proteus vulgaris*.

Toxicity and side effects. No MOX patient had any symptomatic side effects. One CAZ patient complained of pain at the infusion site, but there was no erythema, warmth, or tenderness, and he completed the full course. Three days after his last dose, one CAZ patient developed apparent antibiotic-related colitis with up to 17 liquid stools per day. Proctoscopy showed hyperemic mucosa. He was unable to tolerate colonoscopy. Assay for *Clostridium difficile* toxin was positive. The diarrhea responded to symptomatic therapy; he did not receive vancomycin.

Two CAZ and two MOX patients had elevations of serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and gamma-glutamyl transpeptidase. None had hyperbilirubinemia, all were asymptomatic, and all resolved spontaneously. One MOX patient had a prothrombin time of 20.3 s (control < 13.2 s) on posttherapy day 1. This resolved with 10 mg of vitamin K. One CAZ patient had a peripheral leukocyte count of 2,400 on posttherapy day 1. This resolved spontaneously within 48 h.

DISCUSSION

Complicated urinary tract infections in hospitalized patients are commonly caused by organisms resistant to many antimicrobial agents (9). These infections contribute to patient mortality (10) and health-care costs (5). MOX and CAZ compare favorably with aminoglycosides in this setting (2, 9). In our study, CAZ produced higher cure and lower relapse rates than did MOX for infections due to urinary pathogens susceptible to both antibiotics. It also was effective for infections due to MOX-resistant *Pseudomonas aeruginosa*. Side effects were infrequent and have been reported previously with this class of antibiotics (7).

The high relapse and reinfection rates likely relate to the irreversible urinary tract abnormalities of our study population. A longer course of therapy might have produced more cures (3).

The enterococcus was the most common reinfecting organism in both groups. This phenomenon has been seen previously with MOX (14) and the new monobactam antibiotic aztreonam (13). The broad gram-negative enteric spectrum of these antibiotics presumably selects for this highly resistant family of gram-positive organisms. Of concern was the reinfection of one patient with a highly resistant *Pseudomonas aeruginosa* after MOX therapy. Microbial resistance after broad-spectrum antibiotic therapy is being reported with increased frequency (12). Selective use of these agents should be based upon relevant advantages of clinically effective spectrum, toxicity, and cost.

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