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Ciprofloxacin Therapy of Infections Caused by *Pseudomonas aeruginosa* and Other Resistant Bacteria

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Ciprofloxacin was administered orally to 48 patients with 24 *Pseudomonas aeruginosa* infections and 13 other infections caused by cephalothin-resistant gram-negative bacilli. The types of infections treated included those of skin or skin structure, bone, urinary tract, and respiratory tract. In 83% of *P. aeruginosa* infections, a favorable clinical outcome occurred, compared with 85% for all infections. Failure to achieve a cure correlated with the emergence of resistant *P. aeruginosa* and *Acinetobacter calcoaceticus* strains in four instances and superinfection with *Candida* (two cases) and *Streptococcus* (two cases) species. Therapy was discontinued in three patients because of the development of nausea. Ciprofloxacin appears to be safe and effective in the therapy of infections caused by resistant gram-negative bacilli.

The therapy of gram-negative bacterial infections may require parenteral antibiotic therapy owing to intrinsic resistance to orally administered antibiotics as well as the need to achieve high levels of drug in serum with respect to MICs. Ciprofloxacin is a new quinolone carboxylic acid that achieves levels in serum after oral administration that are well above the MICs for such gram-negative bacilli as *Pseudomonas aeruginosa*, *Serratia* species, and *Enterobacter* species (10). In the expectation that infections with some of these organisms might be successfully treated by oral ciprofloxacin, we undertook an open therapeutic trial.

MATERIALS AND METHODS

Patient selection. This study was conducted in outpatients (five were hospitalized for a small portion of their therapeutic course) who had symptoms and signs of infection which were confirmed by the isolation of ciprofloxacin-susceptible bacteria. When cultures were initially sterile (three patients) or yielded resistant organisms (one patient), the patient was dropped from the study while safety testing was continued. Soft tissue infections consisted of draining wounds surrounded by cellulitis. To help differentiate between colonizers and pathogens among organisms cultured, Gram-stained specimens from wound drainage were examined for the presence of polymorphonuclear leukocytes and homogeneous populations of organisms (except for polymicrobial infections). Bone infections showed inflammatory changes within bone on gross inspection, histopathology of biopsied material, or roentgenogram examination. Urinary tract infections were defined by the presence of greater than 10^5 bacterial colonies per ml on a clean voided or catheterized specimen of urine. Prostatitis was noted if the prostate was indurated and tender on exam and yielded a purulent urethral exudate on massage. Respiratory tract infections consisted of cases of pneumonia and sinusitis. In both cases, roentgenographic changes were noted, and either expectorated sputum or sinus irrigations were cultured and examined with Gram stain for polymorphonuclear leukocytes and organisms.

Patient treatment and evaluation. After written informed consent was obtained, ciprofloxacin was administered by mouth in doses of 5 to 10 mg/kg (median dose, 0.60 g) twice daily. Levels of drug in serum were monitored as described previously (5) to ensure compliance in these outpatients. They were examined initially, once weekly while on therapy, and at the conclusion of therapy. Laboratory tests (complete blood count, chemistry-24, and urinalysis) were performed at these times. Cultures were performed before therapy, 3 days after the initiation of therapy, and when possible, at the conclusion of therapy. In patients with osteomyelitis or respiratory infections, roentgenograms were also performed at the completion of therapy. Susceptibility to ciprofloxacin was determined by the Kirby-Bauer method with 5-μg ciprofloxacin disks. A zone of inhibition of 18 mm was considered to indicate susceptibility. The MICs were measured by a standard twofold serial dilution method with Mueller-Hinton broth as described previously (5). An organism with an MIC of 1 μg or less was regarded as susceptible. Levels of drug in serum were determined via bioassay as described previously (5).

Response to therapy was determined on microbiological and clinical grounds. Cure was defined as the complete resolution of signs of infection and sterilization of cultures in cases in which culture specimens could be obtained at the conclusion of therapy. For urinary tract infections, urine cultures were required to remain sterile for 1 week after completion of therapy. For osteomyelitis and respiratory infections, roentgenograms were required to show signs of improvement. Cases of osteomyelitis continued to be followed (minimum of 9 months) after the conclusion of therapy to ensure that they did not relapse. These cures are still provisional owing to the possibility of relapse of osteomyelitis years later. Clinical improvement was noted when signs of infection waned but further therapy was required. Failure was defined as nonimprovement in the signs of infection.

RESULTS

Forty-eight patients were treated with oral ciprofloxacin for a duration of 4 to 159 days (median, 34). There were 27 males and 21 females, ages 23 to 88 (median, 46). Underlying diseases that could be considered as interfering with normal host response were noted in 26 of the 48 patients. These included diabetes mellitus (10 cases), cirrhosis (six cases), and carcinoma (five cases). The types of infections treated are listed in Table 1. There were 30 skin or skin structure

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TABLE 1. Clinical results of infections treated with ciprofloxacin

Infection	No. of patients			
	Total	Cured	Improved	Failed
Skin or skin structure	26	16	5	5
Urinary tract	12	10	2	0
Respiratory tract	2	0	1	1
Osteomyelitis	4	3	1	0
Intraabdominal	4	1	2	1

infections, 12 complicated urinary tract infections, 2 respiratory tract infections, and 4 cases of osteomyelitis. In 24 of the 48 cases *P. aeruginosa* was isolated (median MIC, 0.33 μg/ml). In 13 other cases, cephalothin-resistant gram-negative rods were isolated, including *Serratia marcescens* (four cases), *Acinetobacter calcoaceticus* (five cases), and *Enterobacter cloacae* (four cases). Thus, 37 of the 48 infections were caused by cephalothin-resistant gram-negative bacilli (77%). Thirteen infections were polymicrobial. Levels of ciprofloxacin in serum drawn to ensure compliance varied from 0.5 (trough) to 4.2 (peak) μg/ml depending on the time at which serum was drawn, dosage, and renal function. Low levels in serum did not correlate with clinical failure.

Skin or skin structure infections consisted of seven wound infections, eight cases of pustular cellulitis (due to *P. aeruginosa*), two scrotal abscesses, four infected plantar ulcers in diabetics, and five infected foot ulcers in patients with peripheral vascular disease. The cases of pustular cellulitis were bona fide infections of the lower extremities and one case of stubborn "hot-tub dermatitis," unresponsive to local measures for 1 week. The four intraabdominal infections included one case of a subphrenic abscess due to *E. cloacae* in a leukemic patient, a subhepatic abscess due to *Escherichia coli* in a patient with a traumatically lacerated liver, and two cases of cholangitis in patients with cancer and obstructed biliary ducts requiring percutaneous indwelling biliary catheters. One of these latter two patients was infected with *Klebsiella pneumoniae* and *Serratia rhubidaea*, and the other was infected with *Enterobacter aerogenes*.

The four cases of osteomyelitis were all chronic (recurrent therapeutic episodes). Patients were infected with *P. aeruginosa* in three cases, and diphtheroids (present on Gram-stained specimens of a bone abscess) in one case. In the one case of *P. aeruginosa* osteomyelitis of the talus, screws were present which were stabilizing the fracture site.

The infections of the urinary tract were all complicated. In four cases, they were associated with indwelling nephrostomy tubes, in two cases with neurogenic bladders, in four cases with chronic recurrent infections due to organisms resistant to all other oral antibiotics, and in one case with prostatitis. Bacteria causing these infections included *P. aeruginosa* (five cases), *S. marcescens* (one case), *E. cloacae* (one case), *Morganella morganii* (one case), *Streptococcus faecalis* (two cases), *Proteus rettgeri* (one case), *A. calcoaceticus* (var. *antitratus*) (one case), *E. coli* (one case), and *Proteus mirabilis* (one case). Two cases were polymicrobial, and both were catheter associated. Multiple specimens revealed both organisms.

The two respiratory infections were both caused by *P. aeruginosa*. One was a case of chronic maxillary sinusitis, and the other was pneumonia in a patient with cystic fibrosis.

Efficacy. Bacteria were eradicated in 51 of the 61 isolates (84%), or in 41 of the 48 patients (85%) (Table 2). The eradication rate was lowest for *P. aeruginosa*, in which 19 of the 24 initial isolates were eliminated (79%). In two of the five *P. aeruginosa* strains which persisted, the MICs for the initial (0.5 and 1.0 μg/ml, respectively) and final isolates (2.0 and 8.0 μg/ml, respectively) were noted to increase. Since these isolates were not typed, it could not be ascertained whether this resulted from superinfection or from mutation in the original isolate. Increase in the MIC was also noted in one infection due to *A. calcoaceticus* var. *anitratus*, in which the MIC increased from 0.125 μg/ml initially to 7.0 μg/ml in the final isolate. The three resistant organisms emerged from two foot infections of diabetics after 26 and 44 days, respectively, and from an infected stump of a nondiabetic after 36 days. The persisting pseudomonads were isolated from a complicated urinary tract infection, from the respiratory tract of a patient with cystic fibrosis, and from a diabetic foot infection.

Superinfection occurred in four cases, two with *Candida* and two with *Streptococcus* species. The *Candida* sp. superinfections contributed to therapeutic failure in two urinary tract infections with indwelling nephrostomy tubes. Two superinfections due to *Streptococcus* species were noted, one due to an *S. faecalis* strain which was ciprofloxacin

TABLE 2. Bacteria isolated from patients treated with ciprofloxacin

Organism	No. of isolates			MIC (μg/ml)	
	Total	Eradicated	Persisted	Mean	Range
Staphylococcus aureus	3	2	1	0.18	0.125–0.25
Staphylococcus epidermidis	2	2	0	0.75	0.5–1.0
Streptococcus faecalis	4	4	0	0.75	0.5–1.0
Streptococcus sp.	2	1	1	0.25	
Pseudomonas aeruginosa	24	19	5	0.33	0.06–1.0
Serratia marcescens	4	4	0	0.42	0.06–1.0
Enterobacter cloacae	4	3	1	0.04	0.008–0.06
Acinetobacter calcoaceticus	5	4	1	0.14	0.06–0.25
Morganella morganii	2	2	0	0.03	
Proteus sp. (indole positive)	2	2	0	0.07	0.016–0.125
Escherichia coli	4	4	0	0.028	0.008–0.06
Klebsiella sp.	1	1	0	0.25	
Proteus mirabilis	1	1	0	0.06	
Clostridium sp.	1	1	0	—[a]	
Diphtheroids	1	1	0	0.06	
Mycobacterium chelonei	1	0	1	4	

[a] —, Not done.

resistant (MIC, 6.0) and one due to beta-hemolytic *Streptococcus* sp. not group A, B, or D (MIC, 0.5).

Cure or improvement was noted in 41 of the 48 cases (85%), as shown in Table 1. Of the 24 patients with *P. aeruginosa* infections, 20 responded satisfactorily to ciprofloxacin (83%). Seven therapeutic failures were noted: five skin or skin structure infections, one patient with cystic fibrosis and a *P. aeruginosa* pneumonia, and one patient with cancer and a subphrenic abscess due to *E. cloacae*. Of the five patients with skin or skin structure infections who failed ciprofloxacin therapy, three were diabetics with *P. aeruginosa* infections of the lower extremities. The fourth patient had a scrotal abscess due to *Staphylococcus aureus* which became superinfected with *Streptococcus* (not group A, B, or D) and *Acinetobacter* species. The fifth patient was infected with *Mycobacterium chelonei* with multiple furuncles and carbuncles in the perineum. The organism appeared susceptible by disk testing but had an MIC of 4 μg/ml.

Of the 11 patients who improved on ciprofloxacin therapy but were not completely cured, 6 required additional surgical therapy. Two patients who were improving prematurely terminated therapy as they were unwilling to cooperate with the requirements of the study. Three other patients judged to be improved discontinued taking the drug because of adverse drug reactions (nausea). One patient with indwelling nephrostomy tubes and a urinary tract infection initially responded but suffered a superinfection due to *Candida* sp. Two patients with cholangitis and an indwelling biliary catheter for obstructed biliary ducts due to cancer improved but could not be cured of their infections.

The drug was well tolerated except for gastrointestinal symptoms (mainly nausea) in 9 of the 48 patients, which required discontinuation of the drug in three patients. Mild reversible leukopenia was noted in one patient taking 0.5 g of ciprofloxacin twice daily whose leukocyte count dropped to 2,500/mm^3 (with 39% neutrophils). When the dose was dropped to 0.25 g twice daily, the count rose to 3,500 with 57% neutrophils. A macular rash was noted in one case but did not require discontinuation of the drug. In one patient the uric acid rose from 6.9 to 14.7 mg/dl during therapy, but this reversed on discontinuation of the drug. No joint or skeletal complaints were noted nor was toxicity referable to the central nervous system noted.

DISCUSSION

The quinolone carboxylic acid derivatives offer the opportunity to treat resistant gram-negative bacillary infections by the oral route with a drug with reduced nephrotoxic potential compared with aminoglycosides. Ciprofloxacin is one of the most potent agents in this class, especially with regard to cephalothin-resistant gram-negative bacilli such as *Pseudomonas*, *Serratia*, *Enterobacter*, and *Acinetobacter* species (10). We utilized this drug in 48 infections, more than three-quarters of which were caused by these bacteria. Cure or improvement was noted in 85% of all cases and in 83% of *P. aeruginosa* infections, with 15 of 24 cured and 5 of 24 improved. It was generally well tolerated except for gastrointestinal side effects in nine patients and mucocutaneous *Candida* sp. infections in four.

Failure to achieve a cure correlated with the emergence of resistant strains of *P. aeruginosa* in three cases and *A. calcoaceticus* in one case and with superinfection due to *Streptococcus* species in two others (one *S. faecalis*, the other not group A, B, or D). One patient with a skin or skin structure infection due to a resistant *M. chelonei* (MIC, 4.0 μg/ml) also failed. Success in the treatment of this group of organisms with ciprofloxacin has been suggested by in vitro susceptibility testing (6), although the MICs for *M. chelonei* appear to be greater than those for *Mycobacterium fortuitum*.

Ciprofloxacin achieved a degree of efficacy in the treatment of cephalothin-resistant gram-negative bacillary infections comparable with that of new β-lactam antibiotics and aminoglycosides. Since cases reported herein were in outpatients, they are therefore milder than those in inpatients reported in trials with parenteral β-lactams and aminoglycosides. Nonetheless, it may be interesting to compare the efficacies, keeping this point in mind. The 83% efficacy for ciprofloxacin in *P. aeruginosa* infections is similar to those for piperacillin (72 [4] and 56% [9]), moxalactam (67 [2], 62.5 [7], and 50% [8]), ceftazidime (92 [3] and 88% [5]), imipenem (95% [2]), and tobramycin (83% [1]). Moreover, its oral administration will allow antibiotic administration in outpatient settings, as it circumvents the need for hospitalization for parenteral drug administration in certain situations. Comparative trials of ciprofloxacin with these drugs (β-lactams and aminoglycosides) appear warranted.

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