ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 1985, p. 128–132
0066-4804/85/070128-05$02.00/0

Vol. 28, No. 1

Open, Prospective Study of the Clinical Efficacy of Ciprofloxacin

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Received 5 November 1984/Accepted 23 April 1985

One hundred patients with infections mostly outside of the urinary tract were studied in a prospective, open manner to ascertain the effectiveness and safety of ciprofloxacin in a variety of clinical situations. There were 41 instances of bacteremia, including 38 with *Salmonella typhi*, and 21 respiratory, 17 skin and skin structure, 11 bone or joint, 6 gastrointestinal, and 4 urinary tract infections. The patients were given 500 mg of ciprofloxacin orally every 12 h for 2 to 107 days (mean, 15.1 days). Microorganisms isolated disclosed susceptibilities comparable to those reported previously, with a MIC for 90% of the strains of 0.25 μg/ml. For *Streptococcus pneumoniae* the MIC for 90% of the strains was 0.03 μg/ml, and it was higher for *Pseudomonas aeruginosa* (0.5 μg/ml), although still in the therapeutic range. Levels in blood were lower than those reported in other series, and no accumulation of the drug during treatment was detected. In 88 instances there was resolution of the infectious process, in 7 there was improvement, in 3 there was a failure to respond, and in 2 the clinical response was indeterminate. Bacteriological eradication was documented in 87 infections. Despite extensive clinical and laboratory examinations before, during, and after therapy, no major abnormalities related to therapy were seen; only one patient required discontinuation of ciprofloxacin due to gastrointestinal intolerance. Ciprofloxacin is an effective and safe therapeutic alternative in many tissue infections caused by susceptible microorganisms.

Ciprofloxacin (Bay o 9867) is a new quinoline carboxylic acid derivative with greater antibacterial activity than earlier related compounds, such as nalidixic, oxolinic or pipemidic acids, or norfloxacin (12). This agent is active against both gram-positive and gram-negative bacteria, with MICs generally in the range of 0.005 to 2.0 μg/ml (1, 3). Against anaerobic organisms mixed results have been reported, with MICs for *Bacteroides* spp. ranging from 0.8 to 16 μg/ml (2; S. M. Smith, D. M. Sylvester, and R. H. K. Eng, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother., 24th, Washington, D.C., abstr. no. 397, 1984). Ciprofloxacin has a rapid onset of action and is bactericidal, being particularly active against members of the family *Enterobacteriaceae* and strains of *Pseudomonas aeruginosa*. No cross-resistance occurs between ciprofloxacin and penicillins, cephalosporins, or aminoglycosides (3), and no increased resistance has been found among microorganisms resistant to earlier quinolones (11). Experimental data from animal protection studies demonstrated the effectiveness of ciprofloxacin, in particular against gram-negative bacteria. In early human pharmacokinetic and safety studies, no major adverse reactions have been observed with the drug (4; Ciprofloxacin Investigator's Brochure, Miles Pharmaceuticals, West Haven, Conn.). Crump, Wise, and Dent have shown good penetration into blister fluid in humans, as well as a long half-life, which suggests adequate levels with dosing every 12 h (4).

The purpose of the present study was to evaluate the effectiveness and safety of ciprofloxacin when used in the treatment of selected infections caused by susceptible gram-negative or gram-positive bacteria.

MATERIALS AND METHODS

Of the 104 patients initially included, 100 were evaluable for clinical or bacteriological response, or both. A total of 50 were studied at Roosevelt Hospital and 50 at San Juan de Dios Hospital in Guatemala City. Patients severely ill and requiring parenteral therapy were not included. Also excluded were: (i) patients with history of allergy to other quinoline derivatives; (ii) patients likely to require additional antimicrobial agents; (iii) patients with renal impairment, considered to be the presence of serum creatinine at ≥1.6 mg/dl or a creatinine clearance of less than 70 ml/min per m^2; and (iv) pregnant women or women in whom pregnancy could not be ruled out. Patients unsuccessfully treated with other antimicrobial agents were included if there was bacteriological reconfirmation of infection with an organism which was susceptible to ciprofloxacin. Patients with the following infections were considered eligible: bacteremia, defined as the isolation of a pathogenic microorganism from one or more blood or bone marrow cultures from a patient with a clinical picture consistent with such diagnosis and without a removable focus as primary site; skin or soft tissue infection, considered to be the presence of inflammatory changes or discharge, or both, from a discrete site and from which an appropriate sample could be studied by a Gram-stained smear and culture; gastrointestinal infection, as demonstrated by the presence of diarrhea (three or more loose stools per day), usually associated with other signs of alimentary tract (nausea, vomiting) or systemic (fever) compromise and with the presence of a pathogenic microorganism from stool cultures; bone or joint infection, or both, defined as the presence of inflammatory changes in such structures by clinical findings (pain or tenderness, swelling, erythema, discharge) along with radiological signs supportive for that diagnosis, and from which an uncontaminated sample could be cultured (sinus cultures were not considered acceptable); lower-respiratory-tract infection, defined as the presence of cough, sputum production, and fever, sometimes associated with other signs of respiratory tract compromise (pleuritic chest pain, chills), with physical findings supportive of the diagnosis (i.e., presence of rales, rhonchi, dullness to percussion)

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TABLE 1. Clinical response to ciprofloxacin treatment according to the type of infection

Type of infection	No. of cases showing:			
	Resolution	Improvement	Failure	Indeterminate response
Bacteremia	38	0	1	2
Skin and soft tissue	15	2	0	0
Gastrointestinal	6	0	0	0
Bone and joint	8	3	0	0
Respiratory	19	0	2	0
Urinary	2	2	0	0
Total	88	7	3	2

and with X-ray changes consistent with it (presence of an infiltrate); and urinary tract infection, considered to be the presence of $\geq 10^5$ CFU/ml in a clean catch, midstream specimen of urine from a patient with dysuria and fever.

After eligibility was ascertained, written informed consent was obtained. A complete clinical evaluation was performed, and cultures of the appropriate materials and baseline laboratory determinations were obtained. Chest or other X-rays, Gram stains, biopsies, and other tests were performed whenever indicated.

Antimicrobial effectiveness was evaluated by means of conventional clinical and laboratory parameters, including cultures of all infected sites taken before, during, and after therapy. The following tests were performed before therapy, every 4 to 5 days during therapy, and at the completion of treatment to ascertain the safety of the drug: a complete blood count, including platelets; complete urinalysis; and serum chemistries, including SMA-12, creatinine, alanine aminotransferase, triglycerides, sodium, potassium, and chloride. Daily clinical evaluations and a detailed opthalmological examination, including visual acuity, color perception, direct examination of the fundi, and search for subjective complaints before, during, and after treatment, were also performed. Isolates were identified using conventional methods (8); gram-negative rods were identified by using the API-20E system (Analytab Products, Inc., Plainview, N.Y.). Antibiotic susceptibility testing was performed by using a standardized disk method (9); quality control strains were run weekly. MICs of ciprofloxacin were determined by a macrobroth method in Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.) or in brain-heart infusion broth (BBL Microbiology Systems, Cockeysville, Md.) for streptococci, in a final volume of 1 ml with an inoculum of 10^5 to 10^6 CFU/ml and incubation for 18 to 24 h at 35°C in air (10). The MIC was defined as the lowest concentration of antimicrobial agent inhibiting visible growth after incubation.

Levels of ciprofloxacin in serum were determined in 71 patients; peak levels were obtained 1.5 h after drug administration, and trough levels were obtained 12 h after drug administration. They were determined by a microbiological assay with *Klebsiella pneumoniae* ATCC 10031 as the test organism in antibiotic medium II (Difco Laboratories, Detroit, Mich.). Ciprofloxacin standard was prepared in pooled human serum (GIBCO Laboratories, Grand Island, N.Y.) or distilled water, as indicated.

Ciprofloxacin was given as a single 500-mg tablet taken every 12 h with at least 200 ml of water and separated by at least 1 h from the closest meal. It was intended to be given for at least 5 days, usually 7 to 14 days, and longer in some cases, according to the clinical and bacteriological responses and the site and severity of the infection.

Clinical response was defined as disappearance of all signs and symptoms of infection; improvement was defined as disappearance of some of these signs and symptoms; and failure was defined as the persistence or worsening of those symptoms present. Bacteriological eradication was considered to be the documentation of disappearance of the original microorganism from the infected site during and after therapy (the complete healing of the infected site in a patient for whom no cultures could be obtained after therapy was considered to represent eradication); reduction was the persistence of lower numbers of the same microorganisms at the original site; recurrence was the reappearance of the original bacteria; and superinfection was the isolation of a new pathogen during or after therapy from the infected site. This protocol was approved by the Human Investigation Committees of both hospitals.

RESULTS

One hundred patients, aged 18 to 84 years (mean, 38.1 years), were studied. A total of 67 were males and 33 were females. Illnesses lasted from 2 to 123 days before initiation of therapy (mean, 13.1 days). The standard dose of ciprofloxacin given corresponded to 12 to 25 mg/kg of body weight per day (mean, 18.7 mg) and was received by the patients for 2 to 107 days (mean, 15.1 days). The drug was well tolerated, as only four patients (4%) developed adverse reactions. Fever, nausea, rash, and severe vomiting were each seen once; discontinuation of therapy and treatment with intravenous fluids was required in only the last case. Two other patients with the diagnosis of typhoid fever had their therapy stopped earlier than planned: one developed an intestinal perforation on day 9 of therapy, and the other signed out against medical advice on day 4 after becoming afebrile. Twenty infections were hospital acquired, and 14 patients had antecedent surgery recently (bone curettage in 4, amputation in 2, cholecystectomy in 2, and other procedures in 6). Associated illnesses were seen in 33 patients: diabetes mellitus and anemia in 7 each, alcoholism in 3 (one with alcoholic hepatitis), chronic obstructive pulmonary disease, congestive heart failure, paraplegia, and cholelithiasis in 2 each, and other problems in 8.

Bacteremia. Of the 41 episodes of bacteremia, 39 were *Salmonella* spp. (1 *Salmonella enteritidis* bioser. *choleraesuis* and 38 *Salmonella typhi*), 1 was *Escherichia coli*, and 1 was *Staphylococcus aureus*. All the nontyphoid bacteremias occurred in patients in poor condition, and one was hospital acquired. Patients with typhoid fever were younger (mean age, 26.7 years) and healthier (11 were in good condition and 14 were in fair condition before treatment) than the remainder of the patients in the series. Diagnosis was confirmed by the isolation of *Salmonella typhi* from blood (9 cases), bone marrow (14), or both (15); blood cultures were falsely negative in eight cases and bone marrow in one case. Therapy was given for 2 to 15 days (mean, 13.7 days), and there was one failure and two nonevaluable patients (the duration of therapy of 2 and 4 days was judged insufficient) (Table 1). Improvement was prompt and fever disappeared between days 3 and 6 of therapy (mean, 4.2 days). Proteinuria was observed in 73.9% of the patients with typhoid and disappeared during therapy; the degree of proteinuria on admission was significantly greater in typhoid patients than in the remainder of the patients in the series (Student's t test = 2.75; $P < 0.005$). The clinical failure occurred in a patient with acute cholecystitis

and *E. coli* bacteremia who cleared his blood cultures but still had chills and fever after 10 days; he responded to ampicillin and sisomicin and later underwent cholecystectomy uneventfully. Two indeterminate responses occurred in patients who did not complete 5 days of therapy because of gastrointestinal intolerance (*Salmonella enteritidis*) or discharge against advice (*Salmonella typhi*); both had indeterminate bacteriological responses due to short therapy and no control blood cultures being obtained, respectively.

Skin and soft tissue infections. A total of 17 patients were treated; in 14 the infection was hospital acquired, in 16 it was judged to be of moderate severity, and in 4 it was judged to be chronic. Eight patients had postsurgical wound infections, four had skin or leg ulcers, two had posttraumatic wound infections, two had postneedle puncture infections, and one had cellulitis. Bacteria isolated were *Pseudomonas aeruginosa* in nine cases, *E. coli* and *Staphylococcus aureus* in three cases each, and other microorganisms in the remainder. Two patients with *Pseudomonas aeruginosa* in ulcers were culture positive at the end of therapy. Fever disappeared on days 1 to 4 of therapy (mean, 1.8 days) and discharge on days 1 to 12 (mean, 7.0 days). Two patients were classified as improved at the end of therapy; both had decubitus ulcers from which *E. coli* and *Proteus mirabilis* and *Pseudomonas aeruginosa* had been cultured. Two patients also had urinary tract infections related to chronic indwelling catheters (*Citrobacter freundii* and *E. coli*). Both were cured, but one superinfection (*Acinetobacter calcoaceticus*; MIC, 2.0 μg/ml) was seen.

Gastrointestinal infections. Six patients with *Shigella* spp. isolated from stools (five with *Shigella flexneri* and one with *Shigella sonnei*) had been acutely ill for 3 to 12 days before therapy (mean, 5.7 days). Although clinically and bacteriologically they were cured, diarrhea persisted for 2 to 4 days (mean, 2.7 days) after therapy was started; ciprofloxacin was given for 7 to 10 days (mean, 7.7 days).

Bone and joint infections. Three patients had septic arthritis and eight had osteomyelitis, of which two cases were chronic and three were recurrent. Two cases of arthritis were gonococcal and one was pneumococcal; all were cured after 10 days of therapy. Among the patients with osteomyelitis, six had surgery for their infection before or during therapy. Four of them had received antimicrobial agents previously, in some cases aminoglycosides for several weeks, without effect. Microorganisms isolated included *Pseudomonas aeruginosa* in four patients, *Staphylococcus aureus* in two patients, and *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *K. pneumoniae*, *Proteus vulgaris*, and *A. calcoaceticus* in one patient each. Three patients had two microorganisms isolated from bone at the time of surgery (*Pseudomonas aeruginosa* and *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Staphylococcus haemolyticus*, and *Proteus vulgaris* and *A. calcoaceticus*). Therapy was given for 14 to 107 days (mean, 53.7 days). In one case a superinfection with *Pseudomonas aeruginosa* (MIC to ciprofloxacin, 0.25 μg/ml) was documented by culture of bone biopsy and of discharge from the sinus tract. Fever disappeared in 1 to 5 days, but discharge persisted for 11 to 60 days. Three patients had improvement only. One had had a compound fracture and *K. pneumoniae* was isolated; he developed the superinfection mentioned above, which still persists with some drainage; another had a bacteriological cure (*Staphylococcus epidermidis*) but did not heal completely, and in the third, a small bone fragment was not removed, and *Staphylococcus aureus* infection reoccurred.

TABLE 2. MICs of ciprofloxacin for pathogens isolated[a]

Organism	*n*	Range	MIC_{50}	MIC_{90}
Gram-positive cocci	21	≤0.008–8.0	0.03	1.0
Streptococcus pneumoniae	10	≤0.008–0.12	≤0.008	0.03
Streptococcus pyogenes	2	≤0.008–2.0		
Staphylococcus aureus	7	0.03–1.0	0.12	0.25
Staphylococcus spp. (non-*aureus*)	2	0.03–8.0		
Gram-negative rods				
Enterobacteriaceae	58	≤0.008–0.25	0.015	0.12
Salmonella spp.	39	≤0.008–0.25	0.015	0.12
Shigella spp.	6	≤0.008–0.06	0.03	0.06
Escherichia coli	6	0.015–0.12	0.03	0.12
Klebsiella spp.	3	≤0.008–0.03		
Proteus/Providencia spp.	4	≤0.008–0.06		
Nonfermenters				
Pseudomonas aeruginosa	14	0.03–2.0	0.12	0.5
Acinetobacter calcoaceticus	2	0.03–0.12		
Neisseria gonorrhoeae	1	0.06		

[a] MIC_{50} and MIC_{90}, MICs for 50 and 90% of the strains, respectively.

Respiratory infections. Of the 21 cases, 1 patient had purulent bronchitis and was considered a clinical failure, although his sputum became negative for the original *Staphylococcus aureus* strain isolated; the remaining 20 had pneumonia which was lobar in 16 and segmentary in 4; 1 patient had a pleural effusion. The illness was considered acute in all cases, severe in 2 and moderate in 19 cases; all of the patients were in good or fair condition before treatment. Ten patients had *Streptococcus pneumoniae* isolated, and in six no pathogen could be recovered from purulent sputa. Therapy was given for 7 to 13 days (mean, 9.0 days), and fever disappeared on day 2 or 3 (mean, 2.4 days). One patient went on to cavitate; *Staphylococcus aureus* disappeared from his sputum, but clinical and bacteriological relapse occurred 1 week posttherapy; he was treated with intravenous cefazolin with improvement, but was cured only after it was determined that he had tuberculosis and specific therapy was given. Posttherapy X-rays showed marked improvement or normal results in 13 cases, some improvement in 6 cases, no change in the patient with bronchitis, and worsening in the patient who cavitated. The six patients with no pathogens isolated on pretherapy cultures were classified as having indeterminate bacteriological responses; all were considered cured of their pneumonic process by clinical and radiological evaluations.

Urinary tract infections. Four patients were studied; two had hospital-acquired infections. One patient had a kidney stone, one had diabetes mellitus, and one had anemia. Pathogens isolated included *E. coli* in two, *Pseudomonas aeruginosa* in two, and *Providencia stuartii* in one. All had failed to improve on aminoglycosides. Therapy was given for 8 to 10 days (mean, 9.5 days). In all cases pyuria disappeared or improved markedly during therapy; one patient developed a superinfection (*Proteus vulgaris*; MIC of ciprofloxacin, 0.015 μg/ml).

Susceptibility data, levels in serum, and overall evaluation. MICs of the microorganisms isolated are depicted in Table 2. The MIC of ciprofloxacin for 90% of the strains of gram-positive organisms was 0.25 μg/ml, although for *Streptococcus pneumoniae* it was only 0.03 μg/ml; The MIC for 90% of the strains for gram-negative bacteria was also 0.25 μg/ml, and 0.12 μg/ml if *Pseudomonas aeruginosa* is excluded. Levels of the drug in serum were obtained in 71 patients; at

TABLE 3. Bacteriological response to ciprofloxacin treatment according to the type of infection

Type of infection	No. of cases showing:				
	Eradication	Reduction	Recurrence	Failure	Indeterminate response
Bacteremia	39	0	0	0	2
Skin and soft tissue	14	3	0	0	0
Gastrointestinal	6	0	0	0	0
Bone and joint	10	0	1	0	0
Respiratory	15	0	0	0	6
Urinary	3	1	0	0	0
Total	87	4	1	0	8

least 25 had more than four determinations at the first, fourth, and last days of therapy. There was no evidence of accumulation of the drug in those cases. Peak levels in serum were 0.77 ± 0.43, 0.79 ± 0.49, and 0.80 ± 0.41 μg/ml, and trough levels in serum were 0.29 ± 0.24, 0.34 ± 0.32, and 0.29 ± 0.24 μg/ml on the days mentioned. Overall, 88 patients experienced resolution, 7 experienced improvement, 3 experienced failures, and 2 had indeterminate responses (Table 1). Bacteriological eradication occurred in 87 cases, 4 had reduction, 1 had recurrence, and in 8 the response was indeterminate (Table 3). There were three instances of superinfection documented, one in bone and two in the urine. Despite extensive laboratory surveillance, no significant abnormalities clearly or possibly related to therapy were seen, except for one patient with pneumonia who developed elevated creatinine and hyaline and amorphous casts in the urine. No deaths occurred in this series.

DISCUSSION

This report documents the effectiveness and safety of ciprofloxacin in the treatment of a variety of tissue infections. It is important to note that the drug was exceedingly well tolerated, even after prolonged courses of therapy as seen in some of our osteomyelitis patients. In fact, discontinuation of therapy because of drug intolerance occurred in one case only. This contrasts markedly with our previous experience with other quinolones, in particular nalidixic acid.

The excellent results obtained in the treatment of typhoid fever are of note, especially in view of the occurrence of strains resistant to the commonly used antimicrobial agents in some parts of the world (5). Rapid clinical and bacteriological responses were the rule and were comparable to those observed with the use of chloramphenicol in our population (C. Ramirez, K. Ordoñez, and J. Sabbaj, Program Abstr. Intersci. Conf. Antimicrobial. Agents Chemother. 16th, Chicago, Ill., abstr. no. 376, 1976).

Our results in the treatment of skin and soft tissue infection are very encouraging, especially since half of the patients in this group had diabetes mellitus or were paraplegics with lower extremity or sacral ulcerations which were grossly infected. In particular, the effectiveness of ciprofloxacin against *Pseudomonas aeruginosa* makes it an attractive agent since it avoids the use of aminoglycosides in certain high-risk cases.

Patients with shigellosis had been ill for several days before therapy was started. Despite this, treatment with ciprofloxacin was effective, as diarrhea disappeared within 2.7 days, which contrasts with the 3.2 to 4.1 days reported recently for pivmecillinam and ampicillin in patients ill for a shorter period of time at the onset of therapy (3.5 to 3.8 days) (7).

Bone infection is a dreadful complication of trauma and surgery to the bone. It often requires prolonged hospitalization at high cost and frequently exposes the patient to serious toxicity due to prolonged administration of parenteral antibiotics, especially when gram-negative rods are involved. All of our patients had satisfactory responses, despite the fact that five of them had chronic or recurrent infections. The follow-up, however, is still short at this time (1 to 16 weeks).

Two of the superinfections observed in this series occurred in the urinary tract of patients with chronic indwelling catheters, a well-recognized complication. The other instance was seen in the bone of a patient with an osteomyelitis initially caused by *K. pneumoniae* and probably developed because of the repeated surgeries that he required.

The MICs of ciprofloxacin for the organisms isolated from patients in this study were comparable to those reported previously by other investigators (1, 3, 6). On the other hand, our levels of the drug in blood were lower than previously reported (4; R. Ziegler, K.-H. Graefer, W. Wigender, W. Gau, H.-J. Zeiler, U. Lietz, and P. Schacht, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 23rd, Las Vegas, Nev. abstr. no. 851, 1983). Although the reasons are not clear at this time, influence of meals and possible differences in genetic make-ups are areas that need to be explored. The quinolone class of antibiotics has previously been used for the treatment of urinary tract infections. Ciprofloxacin, however, represents a distinct advance because of its excellent activity, particularly against problem gram-negative bacilli often resistant to β-lactam and aminoglycoside antibiotics. In this study, we determined the effectiveness and safety of this new quinolone against a variety of infections, mostly outside the urinary tract. The results we observed were very encouraging, as ciprofloxacin was effective and well tolerated, and emergence of resistant organisms did not occur with any unusual frequency. The data from this study will clearly need to be expanded in controlled clinical trials comparing this agent with recognized effective agents in specific clinical situations.

ACKNOWLEDGMENTS

We gratefully acknowledge Rosa Mejia for her excellent technical assistance and help in the organization of the study. The help of the technologists at the clinical microbiology laboratories in the primary isolation and procurement of the strains is appreciated.

This work was supported by a grant from Bayer AG, Wuppertal, Federal Republic of Germany.

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