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Oral Ciprofloxacin Compared with Parenteral Antibiotics in the Treatment of Osteomyelitis

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We undertook a prospective, randomized comparison of oral ciprofloxacin with standard parenteral therapies for the treatment of biopsy-proven osteomyelitis caused by susceptible organisms. Following surgical debridement, the ciprofloxacin patients received 750 mg twice a day, and the other patients received a broad-spectrum cephalosporin or a nafcillin-aminoglycoside combination intravenously (i.v.). There were 31 evaluable patients in the ciprofloxacin group, treated an average of 56 days, and 28 in the i.v. group, treated an average of 47 days. Clinical success rates were 24 of 31 (77%) for the ciprofloxacin group and 22 of 28 (79%) for the i.v. group. Of the seven failures in the ciprofloxacin group, one was due to a persistent *Klebsiella pneumoniae* infection and six were due to relapse of the infection within 1 year of therapy. Of the six failures in the i.v. group, one was due to an *Enterobacter aerogenes* strain which emerged resistant and five were due to relapse. The most troublesome etiology was polymicrobial osteomyelitis involving *Pseudomonas aeruginosa*, in which five of six (83%) regimens failed. Adverse reactions occurred infrequently, i.e., in 1 of 31 (3%) of the ciprofloxacin patients and in 4 of 28 (14%) of the i.v. patients, yet all reactions responded to therapy and none required protocol deviation. Our data indicate that oral ciprofloxacin monotherapy is as safe and effective as conventional parenteral therapy in cases of osteomyelitis caused by susceptible organisms.

Osteomyelitis is recognized as one of the most serious complications of severe bone trauma and is also a dreaded complication of contiguous spread of infection to bone from the elective placement of orthopedic prostheses or appliances. Chronic osteomyelitis in this setting is likely to be caused by nosocomial gram-positive strains such as *Staphylococcus aureus* as well as by gram-negative bacteria such as *Pseudomonas aeruginosa*. Chronic osteomyelitis is often accompanied by a sequestrum that requires surgical debridement, and successful therapy requires the use of appropriate antibiotics for 4 to 6 weeks or longer (3).

The usual therapy for osteomyelitis is a broad-spectrum cephalosporin or a penicillinase-resistant penicillin-aminoglycoside combination, all given parenterally (5). However, extended regimens of parenteral antibiotics are often compromised by toxicity, the inconvenience of intravenous access, and high costs. The ideal antimicrobial agent for the treatment of a deep-seated infection such as osteomyelitis would be one which has low toxicity and good tissue penetration and can be administered orally.

Ciprofloxacin (Miles Pharmaceuticals, West Haven, Conn.) is the first broad-spectrum oral antibiotic active in vitro against *P. aeruginosa* and *S. aureus*, including some methicillin-resistant strains (1). Ciprofloxacin is rapidly absorbed after oral administration, penetrates well into bone, and has an extended half-life which permits dosing every 12 h (2). It is also well tolerated for long periods of administration. Ciprofloxacin is a particularly promising agent for the treatment of osteomyelitis. Therefore, we undertook a prospective, randomized comparison of oral ciprofloxacin with parenteral antibiotics for the treatment of osteomyelitis.

MATERIALS AND METHODS

The study was undertaken between 1985 and 1987 at St. Luke's Episcopal Hospital, Houston, Tex., and the Hospital Mexico, San Jose, Costa Rica. Hospitalized adult patients with bone biopsy-confirmed osteomyelitis which required antimicrobial therapy were eligible for the study. Patients excluded from the study were those with a history of allergy to quinolones, those with renal impairment, pregnant women, those in whom septicemia was a likely complication of the osteomyelitis, those whose infection was caused by an organism resistant to ciprofloxacin (in particular, anaerobes), and those whose overall condition was poor or who could not tolerate prolonged oral therapy.

We made the decision not to enroll methicillin-resistant *S. aureus* osteomyelitis cases into this study, even if in vitro data indicated susceptibility to ciprofloxacin, because of our concerns about possible bacteremias and the relative sparsity of in vivo data for ciprofloxacin monotherapy for methicillin-resistant *S. aureus*.

Prior to enrollment, all infections had been surgically debrided, and all foreign metallic material was removed. After informed consent was given, patients were randomly assigned to receive oral or parenteral therapy. Patients assigned to the ciprofloxacin group received 750 mg twice daily, while those assigned to the parenteral group were treated with either a broad-spectrum cephalosporin (usually ceftazidime) or a nafcillin-aminoglycoside (usually amikacin) combination, selected by the investigator on the basis of culture and sensitivity results and ability to tolerate extended aminoglycoside therapy. Within the parenteral group, specific antibiotics and dosing could be modified because of toxicity, and these courses remained evaluable.

Before treatment, evaluation consisted of a medical history, physical examination, and laboratory studies which included a hematologic analysis, blood chemistry analysis, and urine analysis. These laboratory tests were repeated weekly during treatment and 48 h after the last dose of the study drug was given. All patients were evaluated weekly to document the clinical status of the infection, ophthalmologic status, therapeutic efficacy, and adverse reactions.

Specimens for culture were obtained by open biopsy of

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TABLE 1. Characteristics of patients

Therapy	No. of evaluable patients	Mean age (yr)	No. of:		No. with underlying DM[a] (%)	Avg no. of days of therapy (range)[b]
			Males	Females		
Ciprofloxacin	31	36	26	5	1 (3)	56 (28–96)
i.v. regimen	28	38	25	3	4 (14)	47[c] (8–77)

[a] DM, Diabetes mellitus. The total was 5 (8%) of 59.
[b] For both groups combined, the average number of days was 52 and the range was 8 to 96.
[c] $P < 0.05$.

bone. Routine aerobic cultures were performed, and the susceptibilities of all isolated pathogens were tested by the Kirby-Bauer method by using a 5-μg ciprofloxacin disk and a 30-μg cefotaxime disk. Anaerobic cultures were obtained on a non-routine basis from selected patients. Cultures were repeated during and after therapy, unless there was no further material to culture.

A full course of parenteral therapy was at least 4 and not more than 6 weeks, whereas a full course of ciprofloxacin therapy was 6 weeks. Patients who received ciprofloxacin and for whom there was concern on the part of the investigator that active osteomyelitis remained at 6 weeks received a prolonged course of therapy. The exact duration of therapy was based upon the clinical judgment of either investigator. Therapy was discontinued if an infecting pathogen developed resistance to the drug. At any time after 6 weeks, ciprofloxacin therapy was discontinued if, in the judgment of the investigator, signs and symptoms of infection failed to improve.

On completion of therapy and at a 1-year follow-up, if all signs and symptoms related to the infection had disappeared, the therapy was designated a clinical "success." "Failure" included courses in which signs and symptoms of infection and positive cultures failed to abate during therapy and those in which the infection relapsed within 12 months of the completion of therapy, as confirmed by repeat biopsy of bone. Relapse of infection due to the same pathogen at the same site was designated a "relapse," and relapse due to a different pathogen at the same site was designated a "reinfection."

The bacteriologic response was graded as "eradication" when either the causative organisms were absent from cultures taken at the end of therapy or the infection site was sufficiently improved in the judgment of the investigator that repeat biopsy was deemed unnecessary. "Persistence" indicated that causative organisms were present at the end of therapy. The designation eradication was retained even when the infection relapsed later. By definition, bacteriologic persistence resulted in clinical failure. "Superinfection" was defined as a new infection which appeared during therapy.

For the 1-year follow-up, the patients were contacted by telephone or letter and asked whether there had been a return of the symptoms of their infections. Those indicating any relapse returned to the hospital for an open biopsy of bone at no charge to the patient.

Patient courses were considered "inevaluable" if the antibiotic regimen was discontinued prior to 4 weeks for reasons other than clinical or bacteriologic failure or if the only organisms to be isolated from bone were coagulase-negative staphylococci.

Statistical comparisons between the two treatment groups were made using Fisher's exact test for categorical data and Student's *t* test for numeric data.

TABLE 2. Clinical responses

Clinical response	No. (%) with therapy		
	Ciprofloxacin (n = 31)	i.v. regimen (n = 28)	Overall (n = 59)
Success	24 (77)	22 (79)	46 (78)
Failure			
Poor response	1 (3)		1 (2)
Premature discontinuation		1	1 (2)
Relapse	6 (19)	5 (18)	11 (19)
Adverse reaction	1 (3)	4 (14)	5 (8)
Superinfection	4 (13)	2 (7)	6 (10)

TABLE 3. Infecting pathogens

Organism type and species	No. (%) isolated from patients with therapy		
	Ciprofloxacin	i.v. regimen	Overall
Gram positive			
Staphylococcus aureus	9 (22)	11 (28)	20 (25)
Streptococcus faecalis	2 (5)	5 (13)	7 (8)
Gram negative			
Pseudomonas aeruginosa	12 (29)	5 (13)	17 (21)
Proteus mirabilis	4 (10)	4 (10)	8 (10)
Klebsiella pneumoniae	3 (7)	4 (10)	7 (9)
Serratia marcescens	2 (5)	5 (13)	7 (9)
Enterobacter cloacae	3 (7)		3 (4)
Enterobacter aerogenes	1 (2)	1 (3)	2 (3)
Escherichia coli		2 (5)	2 (3)
Morganella morganii	1 (2)	1 (3)	2 (3)
Providencia stuartii	1 (2)	1 (3)	2 (3)
Acinetobacter calcoaceticus subsp. *anitratus*	1 (2)	1 (3)	2 (3)
Pseudomonas fluorescens	1 (2)		1 (1)

RESULTS

We considered 75 consecutive cases of chronic osteomyelitis, which were considered likely to benefit from antibiotic therapy, for enrollment into the study. We enrolled 67 patients, and 8 patients failed to give informed consent. From the 67 cases, we isolated no pathogens resistant in vitro to ciprofloxacin. In particular, all strains of *P. aeruginosa* evaluated were at least moderately susceptible to

TABLE 4. Clinical failures by etiology

Infection	No. failed/no. treated by:	
	Ciprofloxacin (n = 31)	i.v. regimen (n = 28)
S. aureus (single pathogen)	0/8	2/8
S. aureus (polymicrobial)		1/3
P. aeruginosa (single pathogen)	0/6	0/3
P. aeruginosa (polymicrobial)	3/4	2/2
S. aureus and *P. aeruginosa*	0/1	
Other single pathogen	4/9	1/6
Other polymicrobial	0/3	0/6

TABLE 5. Adverse reactions related to therapy

Therapy	No. of:				
	Patients with adverse reaction(s) (%)	Reactions[a]		Reactions receiving counter-measures	Resolved or improved cases[b]
		Total	Moderate or severe		
Ciprofloxacin (n = 31)	1 (3)	1	1		1
i.v. regimen (n = 28)	4 (14)	7	5	5	5

[a] Some patients had more than one adverse reaction.
[b] In no case of adverse reaction was therapy discontinued, and in no case did an adverse reaction lead to unchanged or worse condition or death.

ciprofloxacin. We did, however, exclude from consideration one case of methicillin-resistant *S. aureus* osteomyelitis, susceptible to ciprofloxacin in vitro, for reasons noted above.

Of the 67 patients enrolled into the study, there were 31 patients in the ciprofloxacin group and 28 patients in the parenteral group whose courses were considered evaluable.

Eight courses were deemed inevaluable. Five courses were inevaluable because of the lack of an identifiable pathogen other than coagulase-negative staphylococci, one was inevaluable because of the onset of renal failure unrelated to study drug therapy, and one patient died after informed consent was obtained but before study drug therapy could commence. One patient was mistakenly enrolled in this study despite a poor prognosis of almost certain amputation of the biopsy site due to lack of healing. This patient required a left-leg amputation, finished a 6-week ciprofloxacin course, and experienced no relapse within 1 year after treatment. However, we consider this course inevaluable because of the loss of the biopsy site.

Characteristics of patients in the two study groups are shown in Table 1. Most patients were nonelderly males, and few patients had underlying diabetes mellitus. The patients in the ciprofloxacin group were treated for an average of 9 days more than those in the intravenous (i.v.) group ($P < 0.05$).

Clinical responses to therapy are summarized in Table 2. Of 31 courses of ciprofloxacin therapy, 24 (77%) were determined to be successes, with the osteomyelitis cured at the end of therapy and at the 1-year follow-up; 1 (3%) failed prior to the end of therapy because of persistent *Klebsiella pneumoniae* infection; and 6 (19%) failed because of relapse within 1 year of the completion of therapy. Of 28 courses of parenteral therapy, 22 (79%) succeeded, 1 (4%) failed prior to the end of therapy because of an emergent resistant *Enterobacter aerogenes* strain, and 5 (18%) failed within 1 year of the completion of therapy.

Superinfections occurred in 4 patients (13%) on ciprofloxacin and 2 patients (7%) on i.v. therapy. It is noteworthy that none of the superinfecting organisms was resistant to the antibiotic, including one case in a patient who received extremely prolonged ciprofloxacin therapy (96 days). Two superinfections occurred in patients with diabetes mellitus, yet these patients were eventually cured without modifications of the antibiotic regimens. In one patient with osteomyelitis due to *Proteus mirabilis* and *P. aeruginosa*, there was a *K. pneumoniae* superinfection during therapy and there was relapse of *P. aeruginosa* infection within 1 year after completion of therapy. In our experience, superinfections usually reflected problems associated with wound healing.

Table 3 lists the infecting pathogens. For each group there were 40 organisms isolated from bone, an average of 1.4 per patient. The specific organisms were similar for the two groups. As mentioned above, one *K. pneumoniae* strain in the ciprofloxacin group persisted and one *E. aerogenes* strain in the i.v. group emerged resistant.

Clinical failures by etiology are shown in Table 4. The overall success rate was 78%. However, five of the six (83%) courses for polymicrobial osteomyelitis involving *P. aeruginosa* failed, despite the fact that all of the involved pathogens remained susceptible to the treatment antibiotics. It appears that polymicrobial osteomyelitis involving *P. aeruginosa* presents special difficulties, as none of the nine courses for single-pathogen *P. aeruginosa* osteomyelitis failed. Also, 5 of 15 (33%) courses for osteomyelitis due to a single gram-negative pathogen failed, 4 ciprofloxacin courses and 1 i.v. therapy course.

There were no significant differences in clinical success by etiology for the two different strategies for parenteral antibiotics, namely, a nafcillin-aminoglycoside combination or a broad-spectrum cephalosporin.

Adverse reactions probably or possibly related to drug therapy were rare in the ciprofloxacin group (Table 5). No adverse reaction resulted in a discontinuance of therapy, and all reactions resolved or improved. One of 31 (3%) patients who received ciprofloxacin developed pruritis, which later improved without intervention. In the i.v. group, 4 of 28 (14%) patients developed seven different reactions, usually rashes, of which five were serious enough to result in drug therapy modification. In the i.v. group, however, drug

TABLE 6. Ciprofloxacin therapy failures

Patient[a]:		Bone	Pathogen(s)	No. of days of therapy	Comment(s)
No.	Age (yr)				
7	49	Femur	*Proteus mirabilis*	87	Relapse
26	24	Ischium	*Proteus mirabilis*	88	Reinfection with *Pseudomonas aeruginosa* and *Citrobacter freundii*; inadequate debridement
29	29	Femur	*Proteus mirabilis*, *Pseudomonas aeruginosa*	96	*Klebsiella pneumoniae* superinfection during treatment; relapse of *Pseudomonas aeruginosa* infection
44	35	Tibia	*Acinetobacter calcoaceticus*	47	Relapse, inadequate debridement
70	19	Tibia	*Enterobacter cloacae*	44	Relapse and *Klebsiella pneumoniae* reinfection; inadequate debridement
72	33	Tibia	*Pseudomonas aeruginosa*, *Enterobacter aerogenes*	33	Relapse with resistant *Pseudomonas aeruginosa*; less than 6 wk of treatment due to patient noncompliance
74	25	Tibia	*Pseudomonas aeruginosa*, *Klebsiella pneumoniae*	36	*Klebsiella pneumoniae* persisted; less than 6 wk of treatment due to patient noncompliance

[a] None of the patients listed had diabetes mellitus.

TABLE 7. Parenteral therapy failures

Patient: No.	Patient: Age (yr)	DM[a]	Bone	Pathogen(s)	No. of days of therapy	Comment(s)
3	51	No	Femur	*Pseudomonas aeruginosa, Streptococcus faecalis*	79	Relapse
11	29	Yes	Femur	*Staphylococcus aureus, Enterobacter aerogenes*	8	*E. aerogenes* developed resistance to drug therapy
49	18	No	Femur	*Staphylococcus aureus*	77	Relapse, inadequate debridement
50	15	No	Femur	*Staphylococcus aureus*	44	Relapse and *Acinetobacter* reinfection
67	45	No	Tibia	*Klebsiella pneumoniae*	34	Relapse, inadequate debridement
73	62	No	Tibia	*Pseudomonas aeruginosa, Klebsiella pneumoniae*	29	Reinfection with *S. aureus*; less than 6 wk of treatment due to patient noncompliance

[a] DM, Diabetes mellitus.

therapy was frequently adjusted because of concerns over toxicity, yet these adjustments were permitted in the protocol and these patients remained evaluable.

Patient information for the clinical failures is summarized for ciprofloxacin in Table 6 and for parenteral therapy in Table 7. Neither age nor diabetes mellitus was a risk factor for clinical or bacteriologic failure in our patients. However, two of seven (29%) ciprofloxacin failures (one with persistent infection and one with relapse of infection) and one parenteral failure received slightly less than 6 weeks of therapy because of patient noncompliance; we chose to evaluate these courses because of the valuable bacteriologic data. For only one relapse was the pathogen, a *P. aeruginosa* strain, resistant to ciprofloxacin; subsequent combination therapy with nafcillin and amikacin was, however, completely successful.

For three of the seven (43%) ciprofloxacin failures and two of the six (33%) parenteral failures, we attributed radiographic evidence of a persistent sequestrum (the patient had completed a full course of therapy which resulted in remission and the pathogens at relapse remained susceptible to the drug therapy) to inadequate surgical debridement.

DISCUSSION

Surgery and effective antimicrobial agents do not overcome the need for prolonged drug therapy for chronic osteomyelitis. Parenteral regimens of 6 weeks or longer are not uncommon and may result in economic hardship to patients because of the high pharmacy and patient care charges and surgical insertion of a Broviac catheter. Furthermore, such regimens cause inconvenience and discomfort for the patient. Effective oral antibiotics would be welcome for chronic osteomyelitis.

We observed no statistically significant differences in clinical or bacteriologic efficacy between ciprofloxacin and parenteral therapies. Unfortunately, it would be impractical for our institution to conduct a similar trial free of the possibility of type II error. With clinical success rates for the two regimens of 77 and 79%, over 6,000 cases would need to be evaluated to give 80% power with a type I (significance) error of 5%.

Emergence of resistance to the quinolones is an issue of some concern (4). We observed no emergence of resistance to ciprofloxacin during therapy, despite regimens of over 12 weeks, although one strain of *P. aeruginosa* was resistant to ciprofloxacin at relapse. Furthermore, despite the fact that almost all of the patients in this study had received previous antibiotic therapy, methicillin resistance was noted in only 1 of 21 (5%) strains of *S. aureus* isolated. Resistant organisms were not a problem in this study, and our experience is that for most cases of chronic osteomyelitis, effective antibiotics are readily available and concerns about toxicity and hypersensitivity usually dictate selection.

Our analysis of the clinical failures in this study leads us to conclude that complete surgical debridement, not the particular antibiotic therapy chosen, is the most important factor for clinical success in osteomyelitis due to susceptible organisms. Our precision in biopsies of infected bones leads us to have some confidence in the otherwise difficult distinction we made between relapse and reinfection.

Our data have convinced us that oral ciprofloxacin is as safe and effective as parenteral antibiotics in cases of chronic osteomyelitis caused by susceptible organisms. We will continue to rely upon parenteral therapy for those infrequent cases of osteomyelitis caused by organisms resistant to ciprofloxacin as well as for patients who are unable to tolerate extended oral therapy. For the vast majority of cases of chronic osteomyelitis, however, oral ciprofloxacin offers an attractive alternative to traditional parenteral therapies.

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