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Ofloxacin versus Parenteral Therapy for Chronic Osteomyelitis

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We conducted a randomized comparison of oral ofloxacin (400 mg twice a day) and parenteral agents (cefazolin, 1.0 g intravenously every 8 h, or ceftazidime, 2.0 g intravenously every 12 h) in biopsy-confirmed, nonprosthesis osteomyelitis. A total of 19 subjects received ofloxacin for an average of 8 weeks, and 14 received parenteral antibiotics for an average of 4 weeks; both therapies were well tolerated. Infections were due to *Staphylococcus aureus* (40%), *Enterococcus* spp. (3%), *Pseudomonas aeruginosa* (15%), and other gram-negative organisms (42%). At the completion of therapy, one *P. aeruginosa* infection in the ofloxacin group persisted and the organism acquired resistance, accompanied by a resistant *Acinetobacter* superinfection. In the parenteral group, one *S. aureus* infection persisted, and there was a resolved superinfection due to *S. aureus* as well. Eighteen-month follow-up data have been obtained. Among those treated with ofloxacin, four subjects whose initial response to therapy was successful suffered relapses of infection, three due to *S. aureus* and one due to *P. aeruginosa*, while in the parenteral group, one subject with a *P. aeruginosa* infection relapsed. Long-term response to therapy was successful for 14 of 19 (74%) subjects who received ofloxacin and 12 of 14 (86%) who received parenteral antibiotics; the difference was not significant. Oral ofloxacin appears comparable to parenteral antibiotics in chronic osteomyelitis due to susceptible organisms, and oral ofloxacin offers advantages in economics and convenience.

Twenty years ago, osteomyelitis was a disease typically associated with trauma, was caused by susceptible gram-positive organisms such as *Staphylococcus aureus*, and was curable with surgical debridement and a 4- to 6-week course of systemic therapy with a penicillinase-resistant penicillin such as nafcillin (8). Now, however, gram-negative pathogens such as *Pseudomonas aeruginosa* are found in more than one-half of all cases of chronic or recurrent osteomyelitis (6).

Polymicrobial osteomyelitis is common, and combination therapy involving the beta-lactam antibiotics and aminoglycosides has been popular. This approach is often compromised because of nephrotoxicity associated with prolonged regimens of aminoglycosides. In our center, aminoglycosides such as gentamicin are rarely used to treat chronic osteomyelitis. The beta-lactam antimicrobial agents, especially the cephalosporins, have been proven to be effective and safe as monotherapy for chronic osteomyelitis caused by susceptible organisms (1, 4).

With the development of the fluoroquinolones comes the hope for orally administered agents as effective as the parenteral cephalosporins, at less expense and inconvenience to the patient. Ofloxacin is a newer quinolone, with high bioavailability, excellent penetration into bone, and a broad spectrum of activity in vitro including activity against *S. aureus*, *P. aeruginosa*, and members of the family *Enterobacteriaceae* (7). Ofloxacin is pharmacodynamically similar to ciprofloxacin, which has been shown to be as effective overall as parenteral therapy in cases of chronic osteomyelitis due to susceptible organisms (6). We conducted a clinical trial comparing ofloxacin with standard parenteral therapies for cases of chronic osteomyelitis caused by susceptible organisms.

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MATERIALS AND METHODS

This was a randomized, parallel-group trial with adult patients with biopsy-confirmed osteomyelitis caused by susceptible organisms, conducted at our institutions in Houston, Tex., and San Jose, Costa Rica. Eligible subjects were randomized to receive either oral ofloxacin, 400 mg orally twice a day, or parenteral therapy consisting of either cefazolin, 1.0 g intravenously every 8 h, or ceftazidime, 2.0 g intravenously every 12 h (every 8 h for *P. aeruginosa* infections), with the particular parenteral regimen chosen according to the in vitro susceptibilities of the pathogens isolated from bone cultures. For the cefazolin-treated subjects, oral cloxacillin sodium (1.0 to 2.0 g orally every 6 h) could be administered following completion of cefazolin therapy for chronic suppression of *S. aureus* osteomyelitis in elderly subjects with histories of relapse of infection.

Both disk and MIC susceptibility tests were performed. Organisms were defined as susceptible to ofloxacin when the MIC was less than or equal to 2.0 μg/ml or when the zone size was greater than or equal to 16 mm, as moderately susceptible to ofloxacin when the MIC was between 2.0 and 8.0 μg/ml or when the zone size was between 13 and 15 mm, and as resistant to ofloxacin when the MIC was greater than or equal to 8.0 μg/ml or when the zone size was less than or equal to 12 mm. Standard susceptibility breakpoints were used for cefazolin and ceftazidime.

Patients excluded from the study were those with multiple sites of infection, with prosthetic material at the site of infection, with a pathogen resistant to ofloxacin or to both of the parenteral agents, with a history of allergy to the quinolones or cephalosporins, with impaired renal function, with amputation of the site of infection considered likely, with bacteremia or concomitant antimicrobial therapy likely because of another infection, or with arthritis. Female patients with childbearing potential were required to have a

TABLE 1. Profile of evaluable subjects

Treatment	No. of subjects				Age (yr)		Length of treatment (days)	
	Total	Male (%)	Female (%)	With diabetes mellitus (%)	Mean	Range	Mean	Range
Orally administered ofloxacin	19	11 (58)	8 (42)	2 (11)	40.9	20–73	54.2	21–86
Parenterally administered cephalosporin[a]	14	12 (86)	2 (14)	1 (7)	45.1	20–72	29.9[b]	15–55

[a] Either cefazolin or ceftazidime was administered, as described in Materials and Methods.
[b] Mean computed without considering four regimens of oral cloxacillin following initial cefazolin therapy for *S. aureus* osteomyelitis.

negative pregnancy test and to take effective measures to prevent pregnancy during the study.

The exclusion criteria eliminated coagulase-negative *Staphylococcus* osteomyelitis from this trial, since our established criteria for pathogenicity of this organism require either the presence of prosthetic material or positive blood cultures.

Informed consent was obtained. Surgical debridement, if necessary, was performed, and further surgical intervention was discouraged during the study. Upon admission of a subject, evaluation consisted of a physical examination with medical history, an ophthalmologic examination (fundoscopy, visual acuity, and color perception), an audiometric examination, laboratory screening (hematology, serum chemistry, erythrocyte sedimentation rate, and urinalysis), a radiologic examination, and a microbiologic examination (cultures of bone biopsy material or aspirate). Patients were reevaluated weekly and immediately following therapy.

For the ofloxacin-treated subjects, 6 weeks of therapy was considered a complete course, and for the parenteral group, 4 weeks was considered complete. Therapy was to be discontinued prior to a complete course only in the event of severe adverse experiences related to the therapeutic agent, obvious failure of therapy as indicated by a lack of improvement of signs and symptoms of osteomyelitis, or emergence of resistance to antibiotic therapy on the part of a pathogen. Therapy was to be continued past a complete course in the event of clinical improvement but not cure, while occasionally therapy was discontinued prior to a full course in the event of an early clinical cure.

Following the completion of therapy, microbiologic response by the pathogen was graded "eradication" when repeat cultures showed eradication of the pathogen or when clinical and radiographic resolution made further microbiologic evaluation inadvisable ("assumed eradication") and "persistence" when the pathogen could still be recovered from cultures following therapy. Infrequently during therapy, a new organism was isolated in biopsy material. Such organisms, when pathogenic, were defined as "superinfecting" and, when not pathogenic, as "colonizing."

Clinical response was initially evaluated immediately following therapy. "Cure" designated complete resolution of signs and symptoms of infection, "improved" designated substantial improvement in those signs, and "failure" designated little or no improvement. Adverse experiences were classified as "mild to moderate" or "severe," and they were designated as having "no relation" or "possible or probable relation" to drug therapy on the basis of the investigator's judgment and the available literature regarding the three antibiotic agents.

Long-term follow-up evaluations were conducted 18 months following the completion of therapy. The designation "relapse" indicated that pathogens were present at the original site of infection despite the fact that cultures immediately posttherapy in that same subject had been sterile or "assumed sterile." The long-term assessment of therapy reflected the most recent status of the infection; "successful" therapy was defined as continued bacteriologic eradication and resolution or improvement of clinical signs and symptoms of infection at least 18 months after completion of therapy, whereas "not successful" therapy was defined as therapy which failed to eradicate the pathogens or to abate the signs and symptoms of infection.

RESULTS

A total of 42 subjects were initially enrolled in this study, 9 of whose courses were inevaluable for the analysis of efficacy (7 because of the lack of growth of an identified pathogen, 1 because of a pathogen which was resistant to cefazolin and ceftazidime, and 1 who left the study early). Thirty-three courses of therapy were evaluable for the analysis of efficacy.

TABLE 2. Microbiologic profile and outcome

Organism	No. of strains[a]									
	Ofloxacin					Parenteral				
	N	E	S	P	R	N	E	S	P	R
S. aureus	10	6	2	0	2	6	4	1	1	0
Enterococcus faecalis	1	1	0	0	0					
P. aeruginosa	4	2[b]	0	1[c]	1	2	1	0	0	1[d]
E. coli						4	1	3	0	0
P. mirabilis	2	2	0	0	0	1	1	0	0	0
E. cloacae	2	1	1	0	0	1	1	0	0	0
M. morganii	1	1	0	0	0	1	1	0	0	0
K. pneumoniae						2	1	1	0	0
Enterobacter aerogenes						2	2	0	0	0
S. marcescens						1	1[e]	0	0	0
Total	20	12	3	1	4	20	13	5	1	1

[a] N, Number of strains isolated in original biopsy material; E, number of strains eradicated from bone during therapy, as confirmed by repeat biopsy following completion of study drug therapy and continued resolution of infection; S, number of strains assumed to have been eradicated during therapy, as indicated by continued clinical and radiographic resolution of all signs and symptoms of infection healing, yet without repeat bone biopsy; P, number of strains which persisted when study drug therapy was completed; R, number of strains which were reisolated from bone within 18 months of the completion of therapy, despite eradication or assumed eradication at the end of study drug therapy.
[b] One subject with eradicated *P. aeruginosa* suffered relapse due to *S. aureus*.
[c] Persistent *P. aeruginosa* infection in which the organism acquired resistance during therapy, accompanied by superinfection due to a resistant *Acinetobacter* strain.
[d] Relapse due to *P. aeruginosa* accompanied by *Enterobacter* infection.
[e] Eradicated *S. marcescens* infection accompanied by superinfection due to *S. aureus* which resolved during therapy.

TABLE 3. Response to therapy

Treatment	No. of evaluable subjects	No. of early relapses of infection	Organism causing early relapse	No. of late relapses of infection	Organism causing late relapse (no. of cases)	No. (%) of patients without relapse after 18 mo
Orally administered ofloxacin	19	1	*P. aeruginosa*	4	*S. aureus* (3), *P. aeruginosa*	14 (74)
Parenterally administered cephalosporin[a]	14	1	*S. aureus*	1	*P. aeruginosa*	12 (86)

[a] Either cefazolin or ceftazidime was administered, as described in Materials and Methods.

A profile of these subjects is seen in Table 1. There were 19 evaluable subjects treated with ofloxacin and 14 treated with parenteral therapy. Males outnumbered females in both groups; relatively more females were treated with ofloxacin. The mean ages were comparable for the two groups: 40.9 and 45.1 years. Diabetes mellitus, always a concern because of the possibility of poor wound healing, was present in two (11%) ofloxacin-treated subjects and one (7%) parenterally treated subject. Subjects who received ofloxacin received, on the average, 8 weeks of therapy (54.2 days), with a range of 3 to 12 weeks, whereas parenterally treated subjects were treated for an average of 4 weeks (29.9 days), with a range of 2 to 8 weeks. Chronic cloxacillin therapy was not included in this average. Of the 14 parenterally treated subjects, 4 received a course of cloxacillin sodium following a completed course of cefazolin (with durations of 28, 35, 42, and 42 days).

Gram-positive organisms accounted for 17 (43%) of the original isolates in bone, with 23 (57%) gram-negative isolates (Table 2). All but one of the gram-positive organisms were *S. aureus*. *P. aeruginosa* was the most common gram-negative pathogen, with six isolates. The etiologies were similar for the two groups, with the exception of the four *Escherichia coli* isolates in the parenterally treated group.

Clinical failure as evidenced by persistence of the original pathogen despite a full course of therapy was observed in one ofloxacin-treated subject with *P. aeruginosa* osteomyelitis, in whom the pathogen acquired ofloxacin resistance and in whom an accompanying superinfection due to a resistant *Acinetobacter* sp. was observed, and in one cefazolin-treated subject with *S. aureus* osteomyelitis. Also, in one ceftazidime-treated subject, *Serratia marcescens* osteomyelitis was accompanied by *S. aureus* superinfection; both organisms were eradicated following continued ceftazidime therapy.

Relapse of infection within 18 months of the completion of the study drug therapy was observed in two ofloxacin-treated subjects with *S. aureus* osteomyelitis, in one ofloxacin-treated subject with *P. aeruginosa* osteomyelitis in whom relapse was due to *S. aureus*, and in one ceftazidime-treated subject with *P. aeruginosa* osteomyelitis in whom relapse was accompanied by the presence of an *Enterobacter* sp. It is likely that the "new" *S. aureus* and *Enterobacter* sp. isolates were present in soft tissue upon admission to the study but were not detected at that time.

The response to therapy, as assessed 18 months following the study, was successful (i.e., resolution with no relapse) for 14 (74%) of 19 ofloxacin-treated subjects and 12 (86%) of 14 parenterally treated subjects (Table 3). Within the important subgroup of diabetic subjects, all three were cured; one had osteomyelitis due to *S. aureus* (requiring a 57-day course of ofloxacin), one had *Enterobacter cloacae* osteomyelitis (requiring a 43-day course of ofloxacin), and one had osteomyelitis due to *E. coli*, *Proteus mirabilis*, and *Klebsiella pneumoniae* (requiring a 37-day course of ceftazidime). There were no instances of untoward microbiological events (the emergence of resistance or superinfection with resistant organisms) in the diabetic subjects. We note that study drug therapy was not successful for four of six cases of osteomyelitis due to *P. aeruginosa* (three of four with ofloxacin and one of two with ceftazidime).

Despite extended courses of therapy, both ofloxacin and parenteral therapy were well tolerated (Table 4). Adverse experiences which were determined to be possibly or probably related to drug therapy were reported by seven (37%) ofloxacin-treated subjects (three cases of nausea, two cases of insomnia, two cases of a rash, and one adverse ophthalmologic reaction). One subject with *S. aureus* osteomyelitis suffered a severe rash on day 21 which required termination of therapy; this shortened course may have contributed to the later relapse of infection in this subject. In one subject who received a 29-day course of ofloxacin for *S. aureus* or *Morganella morganii* osteomyelitis, there was an unexplained loss of visual acuity in the left eye during therapy, from 20:40 to 20:100, while acuity in the right eye improved from 20:50 to 20:30. In no other subjects were there any significant changes in fundoscopy results, visual acuity, color perception, or audiometry results. One subject with *P. aeruginosa* osteomyelitis was initially enrolled for ceftazidime therapy, suffered a severe rash, and was subsequently reenrolled in the ofloxacin group to finish a successful 71-day course of ofloxacin. There were no clinically significant markedly abnormal laboratory values observed during the study.

TABLE 4. Adverse experiences which were possibly or probably drug related

Treatment	No. of subjects		No. of adverse experiences[a]				
	Total	With adverse experiences (%)	Total	Nausea	Insomnia	Rash	Ophthalmologic reaction
Orally administered ofloxacin	19	7 (37)	8	3	2	2 (1 severe)	1 (1 severe)
Parenterally administered cephalosporin[b]	14	4 (29)	4	2	0	2 (1 severe)	0

[a] There were no clinically significant abnormal laboratory values.
[b] Either cefazolin or ceftazidime was administered, as described in Materials and Methods.

DISCUSSION

Increasingly, physicians are relying upon outpatient clinics and home health care agencies for the continuing care of osteomyelitis patients (5). While long-term parenteral-access catheters provide reliable access for antibiotics delivered in these settings, the ideal agent for osteomyelitis care would be orally administered. From our data, ofloxacin appears to be an effective therapeutic alternative to parenteral therapy for many cases of chronic osteomyelitis due to susceptible organisms.

Appropriate agents for the treatment of chronic osteomyelitis must be extremely safe. It is known that antibiotic concentrations in bone may be far lower than the simultaneous concentrations in serum. For an antibiotic regimen to be effective in bone, the patient must be able to tolerate relatively high concentrations of antibiotics in serum for an extended duration. Ofloxacin, at a dosage of 400 mg orally twice a day, has been shown by our data to be safe in many subjects for prolonged courses of 12 weeks or longer.

Concerns have been expressed regarding the efficacy of ciprofloxacin for serious infections due to *S. aureus* (3). In this trial, there were no significant differences between ofloxacin and parenteral therapy for chronic osteomyelitis due to susceptible strains of *S. aureus*. Increasing use of ciprofloxacin has resulted in selection for ciprofloxacin-resistant strains of *S. aureus* (2, 3). Ofloxacin has an in vitro profile against *S. aureus* that is superior to that of ciprofloxacin (equivalent MICs for 90% of strains tested and higher levels in serum) (7), which may account for the lower number of superinfections due to *S. aureus* for ofloxacin, compared with results of our earlier trial with ciprofloxacin (6). Alternative oral agents such as cloxacillin have superior profiles against *S. aureus* compared with the quinolones but have not yet undergone comparative clinical trials.

When the economic and patient convenience benefits of oral therapy are accounted for (i.e., no surgical insertion of an intravenous-access catheter; reduced pharmacy, supply, and care-giver costs; and the ability of the patient to return to normal activities), it becomes apparent that effective oral agents such as ofloxacin may become widely used as monotherapy for chronic osteomyelitis due to susceptible organisms.

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