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SESSION 23

Use of Quinolones for the Treatment of Osteomyelitis and Septic Arthritis

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The low minimal inhibitory concentrations and minimal bactericidal concentrations of the quinolones for most pathogenic gram-negative and many gram-positive organisms, the ease of their administration, and their good oral absorption make them good candidates for the treatment of chronic bone infections. Data presently available suggest that the quinolones are effective in the treatment of experimental osteomyelitis due to *Pseudomonas aeruginosa*, osteomyelitis due to other gram-negative organisms, and (when combined with rifampin) in the treatment of gram-positive osteomyelitides. Quinolones have also been shown to be effective in the treatment of experimental septic arthritis. These results were confirmed by clinical studies. Quinolones have been effective in the treatment of patients with gram-negative bacterial bone infections and have been as effective as conventional antistaphylococcal therapy in the treatment of osteomyelitis due to *Staphylococcus aureus*. Finally, it should be kept in mind that as yet quinolones have not been released for use as therapy for childhood infections.

Osteomyelitis and, to a lesser extent, some cases of septic arthritis represent a wide field of potential use for the new quinolones, since these diseases are characterized by a high frequency of failures of therapy and recurrence of infection due to short-term treatment, inadequate choice of antibiotic, formation of abscess and sequestrum, and other as yet unknown factors [1]. These failures of therapy are also partly influenced by the use of orthopedic fixation devices and prosthetic implants of various types that perpetuate the infectious process. Consequently, the development of a new group of antimicrobial agents that have better activity against microorganisms commonly isolated in patients with acute and chronic osteomyelitis and arthritis, that can be administered over prolonged periods either by the parenteral or oral routes, that have a low frequency of adverse effects, and that have high clinical efficacy has been the ultimate goal and secret hope of many orthopedic surgeons, microbiologists, and specialists in infectious disease. Whether the quinolones represent such a panacea is discussed in this presentation.

Microbiologic Aspects

The spectrum of microorganisms responsible for osteomyelitis and septic arthritis is summarized in table 1 [2–4]. In short, whether dealing with osteomyelitis of hematogenous type or of the contiguous type, *Staphylococcus aureus* and *Staphylococcus epidermidis* together are still the organisms encountered most frequently. Hematogenous osteomyelitis of the long bones can also be caused by group B streptococci (in neonates), *Haemophilus influenzae* (in infants), and, in the spine, by gram-negative organisms. Hematogenous disease, however, occurs most often at an age when the use of quinolones has, at this writing, been contraindicated, because of previous experience with nalidixic acid and new experimental data showing malformations due to exposure to quinolones during the development of limb buds.

In addition, adults are afflicted in two different ways by osteomyelitis. Vertebral osteomyelitis is due to both staphylococci and gram-negative rods [5]. Osteomyelitis contiguous to a focus of infection (such as those that occur after trauma or surgery) can be due to staphylococci and a variety of gram-negative rods, often in mixed cultures. One ideal property of any new agent (namely, low MIC or low MBC for these microorganisms) is certainly characteristic of the quinolones with respect to gram-negative organisms, including *Pseudomonas aeruginosa*, but to a lesser extent with respect to *S. aureus* and *S. epidermidis*—the MICs of quinolones are similar to, or sometimes higher than, those reported for the commonly used antibacterial agents. An ex-

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Table 1. Organisms most frequently encountered in patients with osteomyelitis.

Age group, organism	Type of osteomyelitis	
	*Hematogenous**	*Contiguous*
Children		
S. aureus	+ +	+ +
S. epidermidis	+	+ +
Group B streptococci (neonate)	+	(+)
H. influenzae (infant)	(+)	0
Adults		
S. aureus	+	+ +
S. epidermidis	+	+ +
Gram-negative organisms	+ +	+

NOTE. Frequency ranges from low (0) to high (+ +).
* Refers to osteomyelitis of the spine in adults.

ception to this rule may be the methicillin-resistant *S. aureus*; the MIC of quinolones for these organisms is only slightly higher than the MICs of their sensitive congeners. The search for new quinolones with lower MICs for staphylococci and other gram-positive organisms should be pursued in the future.

Another aspect to be discussed is whether the quinolones are active under the stringent physicochemical conditions of a focus of osteomyelitis or arthritis, characterized by a low pH [6] and low Po_2 [7]. Kill curves for difloxacin and A56620, determined under aerobic (100 mm Hg) and anaerobic (10 mm Hg) conditions have shown both antibiotics to be equally effective under both conditions [8]. Lowering of the pH dramatically increased the MIC of some, but not all, quinolones [9], a finding that suggests the influence of pH should be explored for each individual quinolone.

With respect to septic arthritis, the quinolones are certainly effective against *Neisseria gonorrhoeae* and the gram-negative rods isolated from septic joints, but the comments regarding osteomyelitis are applicable here—the available data concerning MICs for *S. epidermidis*, *S. aureus*, and streptococci show no great advantage of the quinolones when compared with the standard antibiotics presently used for the treatment of patients with bone and joint infections [10, 11].

Difficulties in Evaluating the Efficacy of the Quinolones

Problems in the evaluation of the efficacy of the quinolones arise because bone is a heterogeneous structure [12]. Differences in bone matrix and crystal density between cortex and medulla; differences in blood supply between cortex, medulla, and periosteum; and differences in fluid space between infected and noninfected bone will affect the measurement of levels of antibiotic in bone. This difficulty in measurement can be rectified in part by the introduction of correction factors such as assays of hemoglobin [13] or myoglobin [14] Extraction procedures, although well standardized, have shown either incomplete [14] or prolonged back diffusion of quinolones [15]. Finally, there are good reasons to believe that distribution of antibiotic is not uniform in a heterogeneous structure such as bone, and it can be hypothesized that the effects of nalidixic acid on developing bone or of quinolones on developing limb buds may be due to specific local accumulation of these compounds. In summary, small differences found in levels of quinolones in bone should not be attributed to the substances themselves, but rather to methodologic factors. In addition, interpretation of the data implies a careful evaluation of the extraction procedure, the control of blood contamination, and the standardization curves.

Other factors render the evaluation of the quinolones in clinical settings difficult [16]. For instance, none of the 25 studies reported by 1987 concerning the use of ciprofloxacin in the treatment of osteomyelitis have been controlled, despite the inclusion of more than 100 patients [16]. The reasons for the lack of data from controlled trials are evident and unavoidable: acute vs. chronic disease, the type of organisms involved, the mode of infection, the presence of foreign material, previous or concomitant surgery, and previous antibiotic therapy introduce so many variables into each individual patient that no clinical study will ever solve the statistical problem of the β error. This problem can be avoided in part by testing quinolones in experimental infections.

Experimental Osteomyelitis and Arthritis

In a recent study, Norden and Skinner [17] have shown a 95% cure rate of osteomyelitis due to *P. aeruginosa* after 4 weeks of treatment with ciprofloxacin vs. a 6% cure rate with tobramycin. Impressive as these results are, the investigators also showed that 20% of the organisms isolated at 2 weeks had a fourfold to 16-fold increase in the MIC of ciprofloxacin. Under similar experimental conditions, these in-

vestigators analyzed the efficacy of ofloxacin. Levels of drug in serum and bone of 5 mg/L at 2 hours and 1.7 mg/L at 6 hours, respectively, were achieved. They found that 94% of the rabbits had positive cultures before administration of drug and only 6% had positive cultures after 28 days of treatment. No increase in the MIC for the isolated strain of *P. aeruginosa* was observed in this study. These results were better than those recorded previously with carbenicillin, azlocillin, and sisomycin [18].

Experimental results are less convincing with respect to *S. aureus*. In two studies from the Mayo Clinic that were performed in rats, 3 weeks of treatment with ciprofloxacin led to the same results as those obtained with nafcillin on a methicillin-sensitive organism [19, 20]. A 3-week treatment with vancomycin or ciprofloxacin of osteomyelitis due to methicillin-resistant organisms gave equally poor results. Combination therapy with vancomycin plus rifampin was less effective than a combination of ciprofloxacin plus rifampin, the only effective mode of treatment. In a careful study on experimentally induced chronic osteomyelitis due to *S. aureus* in rabbits, Mader et al. [8] compared the effects of nafcillin (40 mg/kg four times daily) and two arylfluoroquinolones, A56619 (difloxacin) and A56620 (15 mg/kg or 20 mg/kg administered subcutaneously twice daily). All three treatments were started 2 weeks after induction of infection and continued for 4 weeks; the animals were killed 2 weeks after completion of therapy. The MIC for the strain of *S. aureus* used to cause the infection was the same for the quinolones and for nafcillin (0.39 mg/L). Thus, equivalent experimental conditions were created to compare a well-established antibiotic with the new quinolones. Identically good results were obtained with nafcillin (sterilizations, 12 of 20) and difloxacin (sterilizations, 14 of 20).

Taken together, these results suggest that the quinolone used was as effective as a β-lactamase-stable penicillin for the treatment of osteomyelitis due to methicillin-sensitive organisms. With respect to methicillin-resistant organisms, a combination of a quinolone and rifampin seemed to give the most favorable, albeit suboptimal, results. In the treatment of gram-negative osteomyelitis (for the most part due to *P. aeruginosa*) quinolones definitely fared better than other combinations.

In a recent study of experimental gram-negative arthritis in rabbits, the effect of ciprofloxacin was compared with the activity of gentamicin [21]. The offending organism was a pathogenic, serum-resistant strain of *Escherichia coli* isolated from a patient with neonatal meningitis. The joints of rabbits were injected with 10^8 organisms. Four days later the rabbits were randomly assigned to receive either intramuscular ciprofloxacin (80 mg/kg daily) or intramuscular gentamicin (5 mg/kg daily) for 17 days. Maximal levels of ciprofloxacin in serum and joint were always higher than the MBC for the strain of *E. coli*, whereas this was exceptionally the case for gentamicin. As expected, ciprofloxacin fared much better than gentamicin: ciprofloxacin was bactericidal in all cases at day 10 and in all but one case at day 17. In contrast, gentamicin was bactericidal in only six of 18 joint fluids at day 10 and in eight of 10 at day 17. Similar differences were obtained when synovial tissue was assessed. The comparison of ciprofloxacin vs. gentamicin showed the same beneficial effect of quinolones when the results were expressed in terms of residual colony-forming units.

Clinical Studies

A variety of studies have addressed the question of the efficacy of quinolones for treatment of patients with chronic osteomyelitis due to gram-negative aerobic organisms. In a study of 34 patients with gram-negative osteomyelitis who were treated with oral ciprofloxacin (750 mg twice daily for 6–24 weeks), Lesse et al. [22] reported on 23 evaluatable patients, nine of whom were still receiving treatment. These investigators found that 11 of 23 patients had polymicrobial infection – a disputed entity – five of these infections involved *S. aureus*, for which the patients received additional antistaphylococcal treatment. The authors reported an astonishing success rate of 23 of 23 patients, but, as mentioned above, only 14 patients had completed therapy and the follow-up period was short (mean, 6 months), while nine patients were still receiving treatment. A study of gram-negative chronic osteomyelitis in 20 patients was performed by Gilbert [23] with the same dosage of ciprofloxacin and a period of treatment of 6–10 weeks. Three patients had osteomyelitis of the sternum, and 17 patients had osteomyelitis of the lower extremities. *P. aeruginosa* was isolated from the site of infection in 13 patients; 15 patients underwent additional debridement. Results at 7–21 months follow-up showed a 65% clinical cure rate and a 70% microbiologic cure rate, with slightly less satisfactory results in cases of infection due to *P. aeruginosa*. The

MIC for strains of *P. aeruginosa* increased during therapy.

Two other series of patients with chronic gram-negative osteomyelitides who were given a similar regimen of ciprofloxacin (750 mg twice daily) have been published. In the study by Trexler [24], 22 of 24 patients were evaluatable, 16 patients also had surgical procedures performed, and eight patients were given additional antibiotic treatment. At follow-up after more than 6 months, 20 of 22 patients were determined to be cured on the basis of clinical, microbiologic, and radiologic findings. In the study by Slama [25], there were 10 acute and 20 chronic cases of osteomyelitis, including eight patients with sternal infections. Clinical and bacteriologic control was achieved in 22 of 30 patients; the eight recurrences of infection responded to a second course of ciprofloxacin therapy and debridement. Finally, Greenberg [26] performed as good a randomized study as possible in this disease with so many variables: he randomly assigned 30 patients to receive either ciprofloxacin (750 mg twice daily) or "appropriate chemotherapy" (most often a combination of two parenteral antibiotics, one of which was usually an aminoglycoside). The results were slightly better with combination therapy than with the quinolone. In 16 patients there were 11 "cures," four improvements, and one failure with combination therapy. In 14 patients there were seven "cures," three improvements, and four failures with quinolone therapy. The same trend was observed for infections due to *P. aeruginosa.* Noteworthy is the high rate of complications with combination therapy (five of 16 patients), which must be weighed against the good tolerance of ciprofloxacin. Overall, the occurrence of adverse effects with the quinolone [22–26] was rare and inconsequential. These results suggest that in patients with gram-negative osteomyelitis, treatment with quinolones—particularly ciprofloxacin—achieves cure rates >50% in most cases and represents an interesting alternative to conventional parenteral chemotherapy with its inherent complications.

The interpretation of the results achieved in osteomyelitis due to gram-positive organisms or of mixed etiology is more difficult. In an open study, Ramirez [27] treated and cured three cases of arthritis due to *N. gonorrhoeae* and *S. pneumoniae* with ciprofloxacin. Remarkable results were obtained by Desplaces et al. [28] with a combination of pefloxacin (400 mg twice daily) plus rifampin in patients with chronic osteomyelitis due to *S. aureus.* Fourteen of 14 patients were cured, with a follow-up of 9–24 months, results that confirm the experimental data described previously. Similar results were reported by Dellamonica [15] with the use of pefloxacin in 15 patients with chronic osteomyelitis, five of whom had infection due to *S. aureus.*

A long list of abstracts describing small numbers of cases of osteomyelitis treated with quinolones could be added to this enumeration. In addition, many investigators, deeply impressed by the favorable results obtained with quinolones, have expressed their enthusiasm by presenting the same data at several congresses, thereby artificially improving the overall cure rate. These studies do not help in the assessment of the efficacy of the quinolones for the treatment of chronic osteomyelitis. Care should also be given to an objective assessment, with adequate follow-up, of failures of treatment.

Conclusions and Remaining Problems

Quinolones have many characteristics (including their low MIC and MBC for most bone pathogens) that make them suitable as effective agents for the treatment of bone and joint infections due to gram-negative and gram-positive organisms. However, improved efficacy against *S. aureus* and *S. epidermidis* is a desirable attribute of compounds yet to be developed. Levels of drug in bone in experimental systems and in human bone biopsies are adequate to be effective against most bone pathogens, although efficacy may be limited by possible heterogeneous intraosseous distribution of the antibiotic. Experimental models of osteomyelitis have shown the quinolones to be effective, particularly in infections due to *P. aeruginosa*, but also in other bone and joint infections due to gram-negative organisms. These results suggest the use of combination therapy (with rifampin, for instance) for the treatment of infections due to gram-positive organisms. Clinical studies demonstrate that results of treatment with quinolones of bone infections due to gram-negative organisms are similar to or better than results of treatment with conventional parenteral combination therapy. Despite many anecdotal reports of the efficacy of quinolones for the treatment of staphylococcal infections, the pooled data are still inconclusive. Combination therapy with a quinolone plus another agent should be suggested until more studies are available. Large studies are still to be encouraged to further clarify the role of the quinolones in the treatment of bone and joint infections.

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