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Gatifloxacin Efficacy in Treatment of Experimental Methicillin-Sensitive *Staphylococcus aureus*-Induced Osteomyelitis in Rabbits

Mark E. Shirtliff,[1,2]* Jason H. Calhoun,[3] and Jon T. Mader[4,5]

Center for Biofilm Engineering, Montana State University, Bozeman, Montana 59717-3980,[1] and Department of Microbiology and Immunology,[2] The Marine Biomedical Institute,[4] Division of Infectious Diseases, Department of Internal Medicine,[5] and Department of Orthopaedic Surgery,[3] The University of Texas Medical Branch, Galveston, Texas 77555-1115

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The effectiveness of oral gatifloxacin was compared to that of standard parenteral antibiotic therapy (nafcillin) for the treatment of experimental methicillin-sensitive *Staphylococcus aureus*-induced osteomyelitis in a rabbit model. Gatifloxacin was as effective as nafcillin in clearing the infection. Therefore, oral gatifloxacin treatment of osteomyelitis may be an effective alternative to intravenous nafcillin treatment.

Osteomyelitis refers to infection of the bone. *Staphylococcus* spp. cause the majority of cases of osteomyelitis, but *Streptococcus* spp., *Pseudomonas aeruginosa*, and anaerobes are also major pathogens that have been isolated (12–14; M. E. Shirtliff, M. W. Cripps, and J. T. Mader, Abstr. 99th Gen. Meet. Am. Soc. Microbiol. 1999, abstr. C410, 1999). Surgery for debridement and parenteral antibiotic treatment lasting from 4 to 6 weeks remain the cornerstones of treatment of osteomyelitis (3). Because of the ease of administration, oral antibiotic treatment would represent a significant advantage in the efficient treatment of this disease. Gatifloxacin is a recently developed fluoroquinolone (see the work of Perry et al. [10] for a review of gatifloxacin therapy) and may be an attractive alternative for the treatment of osteomyelitis. The purpose of the present study was to compare the effectiveness of oral gatifloxacin to that of a standard parenteral antibiotic (nafcillin) for the treatment of experimental osteomyelitis caused by methicillin-sensitive *Staphylococcus aureus* (MSSA) (4–6, 9, 11).

The MSSA strain used in the present study was obtained from a patient with osteomyelitis. The sensitivities of this *S. aureus* strain to gatifloxacin and nafcillin were measured by the tube dilution method (1). Osteomyelitis was induced in the left tibia of rabbits as reported previously (6, 9, 11). The rabbits were randomly placed into one of three groups at the time of infection (day zero), and treatment began 14 days later, after infection was confirmed by radiography (see below). Infected but untreated rabbits (group 1; $n = 12$) were included as controls. Rabbits in group 2 ($n = 15$) received oral gatifloxacin (approximately 40 mg/kg of body weight) dissolved in 0.5% methylcellulose every 12 h (7), and rabbits in group 3 ($n = 15$) received parenteral subcutaneous nafcillin at 30.0 mg/kg every 6 h (6). The antibacterial agents were given from day 14 through day 42 (28 days total). Gatifloxacin was administered orally through a syringe coated with sugar (7), and the nafcillin was given subcutaneously into the backs of the rabbits' necks (5). Following completion of the treatment regimens, the rabbits were observed for 2 weeks before they were killed in order to allow the regrowth of any remaining *S. aureus* organisms that were not eliminated by the antibiotic treatment. Roentgenograms of both tibias were taken at the time of initiation of antibiotic treatment (day 14), and the severity of the infection was determined by roentgenographic appearance by a well-established rating system (6) (Table 1). At the conclusion of the study, the rabbits were killed. Both tibias were removed, dissected free of all soft tissue, and processed for bacterial cultures (11). Tenfold serial dilutions were performed, and 20 μl of each dilution was applied to tryptic soy agar (5% defibrinated sheep blood) plates to quantitate the concentrations of bacteria in the bone (dilutions and plating were each performed in triplicate). The plates were incubated overnight at 37°C.

A single oral dose of gatifloxacin (approximately 40 mg/kg) dissolved in 0.5% methylcellulose solution was administered to a group of rabbits (group 4; $n = 6$) (7). A single subcutaneous dose of nafcillin (30.0 mg/kg) was administered to another group of rabbits (group 5; $n = 6$) (5). Serum gatifloxacin and nafcillin concentrations were determined with blood drawn at 1, 3, 6, 12, and 24 h after administration of the dose. The serum and bone gatifloxacin concentrations were simultaneously determined for another group (group 6; $n = 3$) 1.5 h after the administration of a single oral dose of gatifloxacin. The serum and bone nafcillin concentrations were simultaneously determined for another group (group 7; $n = 3$) 1.5 h after the administration of a single subcutaneous dose of nafcillin. An agar disk diffusion bioassay (with *Sarcina lutea* ATCC 9341 and *Bacillus subtilis* as the test organisms for the assays with nafcillin and gatifloxacin, respectively) was used to measure the nafcillin and gatifloxacin concentrations in both serum and bone eluates (6, 11). Blood was drawn from each rabbit prior to antibiotic administration, and no inhibitors were detected.

Fisher's exact test was used to compare the numbers of infected rabbits between each group. In order to determine if there was a significant difference in the concentrations of bacteria in the bones of treated but still infected animals at the end of the study compared to those in untreated, infected controls, we used a two-tailed Student's *t* test. Differences between

* Corresponding author. Mailing address: Center for Biofilm Engineering, 366 EPS Building, P.O. Box 173980, Montana State University, Bozeman, MT 59717-3980. Phone: (406) 994-4770. Fax: (406) 994-6098. E-mail: mshirtliff@erc.montana.edu.

TABLE 1. Criteria for grading severity of *S. aureus*-induced osteomyelitis in Rabbits

Gross pathology		Radiographic findings	
Grade	Criteria	Grade	Criteria
0	Normal	0	Normal
1+	No bone involvement; soft tissue swelling at proximal tibial metaphysis	1+	Elevation or disruption of periosteum, or both; soft tissue swelling
2+	Soft tissue abscess; <10% widening of proximal tibial metaphysis	2+	<10% disruption of normal bone architecture
3+	>10% widening of proximal tibial metaphysis	3+	10–40% disruption of normal bone architecture
4+	Disruption or pitting of normal bone architecture	4+	>40% disruption of normal bone architecture

groups were deemed statistically significant if P was ≤ 0.05. This test was also used to compare the radiographic scores for the different groups of rabbits at 14 days postinfection. Differences between groups were deemed statistically significant if P was ≤ 0.05. The MIC and minimal bactericidal concentration of gatifloxacin and nafcillin for this strain of *S. aureus* were <0.39 and <0.39 mg/liter and 0.39 and 0.78 mg/liter, respectively. No animals except those in the group treated with nafcillin died from the time of treatment initiation to the time of study termination. Five of the 15 animals in the group treated with nafcillin died during the treatment phase of the study due to excessive dehydration and gastrointestinal inflammation (2). The average radiographic scores and standard deviations at the initiation of therapy were 3.37 ± 0.74, 3.33 ± 0.72, and 3.4 ± 0.82 for the infected, untreated controls, the gatifloxacin-treated group, and the nafcillin-treated group, respectively. No statistically significant difference in the severity of infection was detected between the rabbits in each group.

All tibias from infected, untreated control rabbits ($n = 12$) were culture positive for *S. aureus*. Compared to untreated controls (rate of infection, 100%), the gatifloxacin-treated ($n = 15$) and nafcillin-treated ($n = 10$) rabbits demonstrated significantly lower rates of *S. aureus* infection posttreatment (6.7 and 0%, respectively) ($P < 0.05$). The differences in sterilization percentages between the treated groups were not statistically significant. The bacterial concentration found in infected, untreated rabbits was 1.07×10^6 CFU/g of bone. Since only one rabbit in the gatifloxacin-treated group demonstrated a detectable bacterial concentration (2.64×10^5 CFU/g bone) and no rabbits in the nafcillin-treated group had detectable levels of infection ($<5.0 \times 10^1$ CFU/gram bone), statistical analyses were not applied to the concentrations of bacteria in the groups.

The concentrations of gatifloxacin (40 mg/kg) and nafcillin (30 mg/kg) in the sera of rabbits after administration of the respective drugs are shown in Fig. 1. The elimination of the antibiotics from the serum was fastest for nafcillin, followed by gatifloxacin. Figure 2 compares the simultaneous concentrations in the sera and bones of the animals 1.5 h after administration of a single oral dose of gatifloxacin (40 mg/kg). Data for a nafcillin-treated (30 mg/kg) group 1.5 h following subcutaneous administration are also shown in Fig. 2. The highest antibiotic concentrations in serum were obtained with nafcillin. However, the concentrations of both antibiotics tested in the present study in tissue were approximately equal.

Oral gatifloxacin and parenteral nafcillin were equally effective in the treatment of *S. aureus*-induced osteomyelitis in rabbits. Each treatment group demonstrated infection clearance percentages that were significantly greater than that for

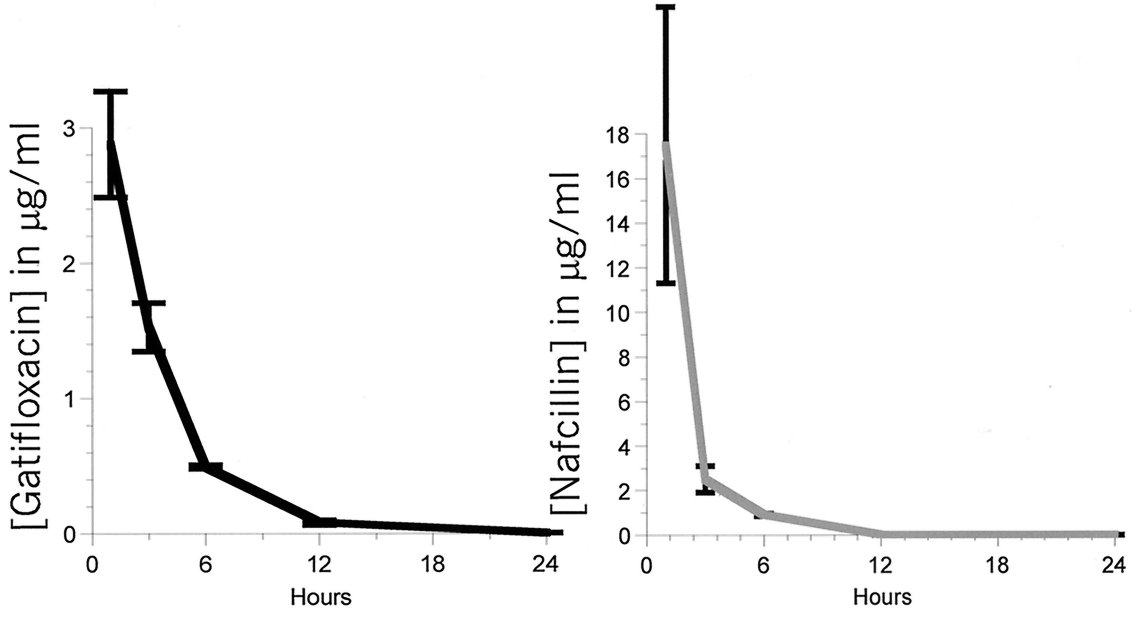

FIG. 1. Concentrations of gatifloxacin (40 mg/kg dose; $n = 6$) and nafcillin (30 mg/kg; $n = 6$) in the sera of rabbits 1, 3, 6, 12, and 24 h after antibiotic administration.

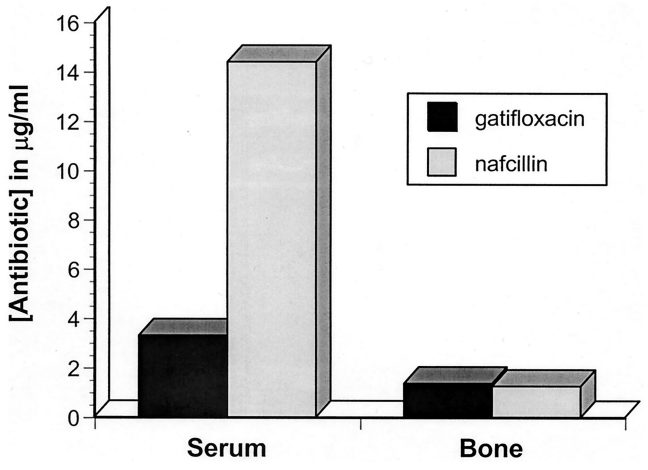

FIG. 2. Simultaneous concentrations of gatifloxacin (40 mg/kg) ($n = 3$) and nafcillin (30 mg/kg) ($n = 3$) in the sera and bones of rabbits 1.5 h after administration of a single dose of antibiotic.

the untreated controls ($P < 0.05$). Approximately 93.3 and 100% of the rabbits treated with gatifloxacin and nafcillin, respectively, had tibial bacterial concentrations below the level of detection after treatment. Furthermore, the dosages of gatifloxacin and nafcillin used in the present study resulted in concentrations of antibiotics in serum similar to those achieved in humans with standard doses (8) The differences observed for tibial sterilization percentages and concentrations of viable bacteria in bone were not statistically significant between the treatment groups.

In the present study, oral antibiotic therapy was as effective as parenteral antibiotic therapy in eradicating experimental *S. aureus*-induced osteomyelitis. Parenteral antibiotic therapy often requires hospitalization of the patient for the duration of the antibiotic treatment in order to ensure correct administration of the antibiotic(s). Effective oral antibiotic treatment represents a significant development in the treatment of osteomyelitis. Also, health care providers may choose to initiate therapy with a standard parenteral regimen, followed by a switch to therapy with an oral regimen. While fluoroquinolones are not traditionally used as single agents for the treatment of osteomyelitis due to gram-positive pathogens, our results indicate that oral gatifloxacin may be an attractive alternative to parenteral therapy for the treatment of *S. aureus* osteomyelitis. When one considers the high degree of tolerability, the wide spectrum of activity, easy oral dosing once per day, and good pharmacokinetic profile of gatifloxacin, clinical evaluation of gatifloxacin in the treatment of osteomyelitis should necessarily follow.

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