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In Vivo Efficacies of Levofloxacin and Ciprofloxacin in Acute Murine Hematogenous Pyelonephritis Induced by Methicillin-Susceptible and -Resistant *Staphylococcus aureus* Strains

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Levofloxacin, the active L-isomer of ofloxacin, has demonstrated strong activity against *Staphylococcus aureus* both in vitro and in vivo. In a murine model of hematogenous pyelonephritis, the in vivo efficacies of levofloxacin and ciprofloxacin were evaluated against two methicillin-susceptible and two methicillin-resistant *S. aureus* strains. All four isolates had virtually identical susceptibilities to levofloxacin and ciprofloxacin. Pyelonephritis was induced in carrageenan-primed mice by an intravenous injection of 0.5 ml of 10^7 CFU of methicillin-susceptible *S. aureus* isolates per ml or 10^8 CFU of methicillin-resistant *S. aureus* isolates per ml. At 1 h postinfection, the mice were treated orally with levofloxacin or ciprofloxacin once a day or twice a day (total daily dose of 20 to 160 mg/kg of body weight) for 4 days. Mice were euthanized 24 h after the final treatment, and the kidneys were excised and weighed. The kidneys were prepared for histological examination or were homogenized to determine the numbers of CFU per gram of tissue quantitatively. The reduction in the mean $\log_{10}$ number of CFU per gram as a function of total daily dose was recorded. A dose-response analysis showed that levofloxacin was superior to ciprofloxacin for all four isolates at any dose or regimen tested, independent of the methicillin susceptibility of the isolates. By using an inverse prediction technique, the equivalent effective doses of levofloxacin (once a day) were less than those of ciprofloxacin (twice a day) by 5.2 and 3.2 times, respectively, for methicillin-susceptible *S. aureus* 9039 and 3087. For methicillin-resistant *S. aureus* 667 and 2878, the equivalent effective doses of levofloxacin (once a day) were less than those of ciprofloxacin (twice a day) by 4.1 and 6.4 times, respectively. In a separate study, histological examination of all infected, untreated mice showed moderate to marked hematogenous pyelonephritis. Levofloxacin-treated mice (40 mg/kg once a day) showed no evidence of pyelonephritis in the kidneys, whereas the kidneys of mice treated with the same dose of ciprofloxacin showed only a reduction in the severity of the lesions. Treatment with ciprofloxacin (80 mg/kg twice a day) demonstrated a histology comparable to that of treatment with levofloxacin (40 mg/kg once a day). Levofloxacin (40 mg/kg once a day) reduced the $\log_{10}$ numbers of CFU per gram by 5 $\log_{10}$; however, ciprofloxacin (80 mg/kg twice a day) reduced the numbers of CFU per gram by only 3 $\log_{10}$. In the present murine model of pyelonephritis, levofloxacin was superior to ciprofloxacin in preventing pyelonephritis and eradicating *S. aureus*.

The new fluoroquinolone agent levofloxacin is the optically active L-isomer of the racemate ofloxacin. The L-isomer is responsible for essentially all of the antibacterial efficacy observed with ofloxacin. Levofloxacin has demonstrated a wide range of activity against gram-positive, gram-negative, and atypical organisms both in vitro and in vivo (1, 8). Levofloxacin has been shown to have in vitro activity superior to that of ciprofloxacin against such gram-positive organisms as *Staphylococcus aureus* (1, 2, 8, 10–13, 18, 20, 21), *Streptococcus pneumoniae* (2, 8, 11, 13, 15, 18, 21), *Enterococcus faecalis* (8), and *Enterococcus faecium* (2, 10, 21). Moreover, levofloxacin has also shown greater efficacy than ciprofloxacin in vivo against *S. aureus* (8, 11–13, 18) when it was tested for its ability to protect against lethal systemic infections in mice. The greater activity of levofloxacin is believed to be due, in part, to its excellent pharmacokinetic and pharmacodynamic properties. Oral levofloxacin is essentially 100% bioavailable and achieves high levels in serum and tissue (1). Phase III clinical trials have been completed in the United States and Europe. Levofloxacin is available in both a solid oral dosage form and an intravenous preparation.

We conducted the study described here to compare the in vivo efficacy of levofloxacin or ciprofloxacin, administered orally once or twice a day, in treating *S. aureus* infections in a murine model of hematogenous pyelonephritis in which the in vitro activities of both fluoroquinolones were equivalent. A murine model of pyelonephritis (3, 8, 22), which had been used previously to assess the in vivo activities of fluoroquinolones (3–5, 8, 14) and cephalosporins (7), permitted us to assess several parameters in observing in vivo activity. The efficacies of levofloxacin and ciprofloxacin were compared by determining the reduction in the numbers of $\log_{10}$ CFU per gram of tissue in both kidneys as a function of the total daily dose of these agents. We also compared, macroscopically and microscopically, the morphologies of fluoroquinolone-treated mice versus those of untreated, but infected, mice. Our results indicate that levofloxacin is more efficacious than ciprofloxacin in eradicating *S. aureus* from infected mice.

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MATERIALS AND METHODS

Microorganisms. Four strains of *S. aureus* were used in these experiments: two methicillin-susceptible *S. aureus* (MSSA) isolates, *S. aureus* 9039 and 3087, and two methicillin-resistant *S. aureus* (MRSA) isolates, *S. aureus* 667 and 2878. All isolates were of clinical origin and were stored in The R. W. Johnson Pharmaceutical Research Institute culture collection at −70°C on porous beads in sterile Microbank cryovials (Pro-Lab Diagnostics, Richmond Hill, Ontario, Canada). The isolates were subcultured onto Trypticase soy agar (TSA; BBL Microbiology Systems, Cockeysville, Md.) at 37°C for 24 h prior to use.

Test compounds. Levofloxacin and ciprofloxacin were obtained from Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan. The potencies of levofloxacin and ciprofloxacin were 97.5 and 93.5%, respectively. To correct for the actual potencies of the fluoroquinolones for their use in the in vivo experiments, stock solutions of levofloxacin (10 mg/ml) and ciprofloxacin (20 mg/ml) were prepared by dissolving the fluoroquinolones in water at concentrations of 10.25 and 21.4 mg/ml, respectively. For studies carried out in vitro, both compounds were dissolved in sterile water at 2,560 μg/ml.

Determination of the MICs. Levofloxacin and ciprofloxacin MICs were determined in triplicate (three separate studies) by the broth macrodilution method with Mueller-Hinton agar (BBL Microbiology Systems) according to the guidelines established by the National Committee for Clinical Laboratory Standards (17). The MIC was defined as the lowest concentration of antibiotic that prevented visible growth at 24 h. The MBCs were determined by plating 0.01 ml of the resulting culture broth from the MIC determinations onto TSA containing 5% sheep erythrocytes (Becton Dickinson) (16). The concentrations plated included the MIC and concentrations up to four doubling dilutions higher than the MIC. The cultures were incubated for 48 h at 35°C. The MBC was defined as the lowest fluoroquinolone concentration that produced a 99.9% reduction in the numbers of viable bacteria.

Mice. Female CF-1 mice (Charles River Laboratories, Portage, Mich.) with a mean weight of 25 g were used. Mice were housed at five per cage and received food and water ad libitum throughout the duration of the experiment.

Preparation of the inoculum. Several *S. aureus* colonies from a pure culture were removed from a TSA plate and were suspended in 50 ml of brain heart infusion broth (BBL Microbiology Systems). The liquid culture was incubated at 37°C for 18 h under ambient air and was agitated at 100 rpm. After incubation, the cells were collected by centrifugation at 2,500 × *g* for 15 min in a Sorvall RT 6000D instrument (Dupont Co., Wilmington, Del.). The pellet was suspended in 25 ml of sterile 0.85% saline, and the wash step was repeated. The resulting pellet was suspended in 25 ml of sterile 0.85% saline and was further diluted 1:5 or 1:50 with sterile saline to yield a final concentration of 2×10^8 or 2×10^7 CFU/ml for the MRSA or MSSA strains, respectively. The actual numbers of CFU per milliliter were determined by serially diluting the inoculum and plating aliquots of the serial dilutions onto TSA. After 24 h of incubation at 37°C, the colonies were counted and the initial numbers of CFU per milliliter were determined.

Murine model of hematogenous pyelonephritis. The murine model of hematogenous pyelonephritis, which has been described previously (3, 22), was modified for use in our laboratory (8, 9). Mice were injected intravenously with 0.5 ml of a 2-mg/ml sterile solution of carrageenan type 2 (Sigma Chemical, St. Louis, Mo.) in 0.85% saline. One week following the administration of carrageenan, hematogenous pyelonephritis was induced with an intravenous injection of 0.5 ml of either 2×10^7 CFU of MSSA per ml or 2×10^8 CFU of MRSA per ml. Fluoroquinolone treatment was initiated 1 h after injection of the bacteria. The infected mice were dosed orally by gavage once a day or twice a day for 4 days. For the twice-a-day treatments, the doses were given 3 h apart. Test fluoroquinolones were administered to cover a range of concentrations, generally 5 to 160 mg/kg of body weight, to yield a dose-response curve. Groups of 10 infected mice were used to test each concentration of fluoroquinolone in the once-a-day and twice-a-day dosing regimens. Ten control mice were primed with carrageenan and were infected but were not treated with either fluoroquinolone. Twenty-four hours after the final treatment (5 days after infection), all of the mice, including the controls, were euthanized. The kidneys from each mouse were excised aseptically and weighed, placed in 4 ml of 0.1% peptone water (BBL), and homogenized. An Omni TH tissue homogenizer (Omni International, Marietta, Ga.) with sterile disposable probes was used to process the tissues. The numbers of CFU in the homogenate (numbers of CFU per gram) were determined by plating aliquots of the serially diluted homogenate onto TSA plates. The reduction in the mean $\log_{10}$ number of CFU per gram as a function of the total daily dose was recorded.

Statistical analysis. Dose-response curves for levofloxacin and ciprofloxacin were estimated with the use of SAS PR NLIN, version 6.08. Dose-equivalent ratios were obtained by determining the precise levofloxacin dose necessary to achieve the maximum ciprofloxacin response (reduction in the number of $\log_{10}$ CFU per gram). Doses were obtained through the use of inverse prediction techniques applied to dose-response models as described previously by Schwenke and Milliken (19).

Histopathology. Two carrageenan-primed mice that had been infected with 0.5 ml of 2×10^7 CFU of *S. aureus* 3087 per ml were sacrificed 5 days after infection. Two carrageenan-primed but uninfected mice and two naive mice were sacrificed at the same time for comparison. The kidneys were removed, fixed in 10% neutral buffered formalin, trimmed, routinely processed, embedded in paraffin, and sectioned at 5 to 7 μm. Tissue sections were stained with hematoxylin and eosin-phloxine and were evaluated by light microscopy.

To correlate the histologic findings with the bacterial load in the kidneys after fluoroquinolone treatment, five carrageenan-primed, *S. aureus*-infected mice were treated for 4 days with levofloxacin or ciprofloxacin at 40 mg/kg once a day or with ciprofloxacin at 80 mg/kg twice a day. The kidneys were removed 24 h after the final treatment. Kidneys from two mice treated with each fluoroquinolone by each dosing regimen were processed as described above for microscopic examination. The kidneys from the remaining three mice were used to quantify the viable counts, as described above for the dose-response analysis. Three infected, untreated mice were used as controls.

TABLE 1. Levofloxacin and ciprofloxacin MICs[a] and MBCs for selected strains of MRSA and MSSA

Isolate	MIC (μg/ml)/MBC (μg/ml)	
	Levofloxacin	Ciprofloxacin
9039 (MSSA)	0.5/0.5	0.5/2
3087 (MSSA)	0.5/1	1/2
667 (MRSA)	0.5/2	0.5/4
2878 (MRSA)	0.5/0.5	0.5/0.5

[a] Values are expressed as the average, based on three determinations.

RESULTS

In vitro activity. For all four *S. aureus* isolates used in the present murine pyelonephritis model experiment, the in vitro inhibitory activities of levofloxacin and ciprofloxacin were nearly identical for the MSSA and MRSA strains (Table 1). For these isolates, the susceptibility to either fluoroquinolone agent was not affected by the degree of methicillin resistance. The MICs of levofloxacin and ciprofloxacin were determined three separate times, and any deviation in MICs from a single test was within 1 doubling dilution of the value presented in Table 1. The MBCs of levofloxacin were within 2 doubling dilutions of the MIC, and the MBCs of ciprofloxacin were all within 3 doubling dilutions of the MIC.

Dose-response analysis of murine model of hematogenous pyelonephritis. The dose-response curves of levofloxacin and ciprofloxacin, indicated by a decrease in the $\log_{10}$ numbers of CFU per gram that correlated with an increase in the total daily dose (5 to 160 mg/kg), are presented in Figures 1, 2, 3,

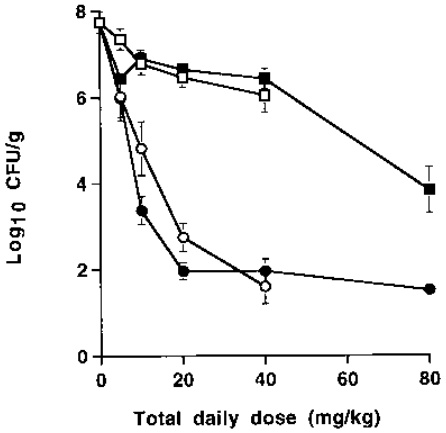

FIG. 1. Dose-response curves of viable cell counts in the kidneys ($\log_{10}$ CFU per gram) as a function of the total daily dose of levofloxacin or ciprofloxacin. The infecting organism was *S. aureus* 9039, a methicillin-susceptible strain. Values are expressed as means ± standard errors. Fluoroquinolone treatments included levofloxacin once a day (○) or twice a day (●) and ciprofloxacin once a day (□) or twice a day (■).

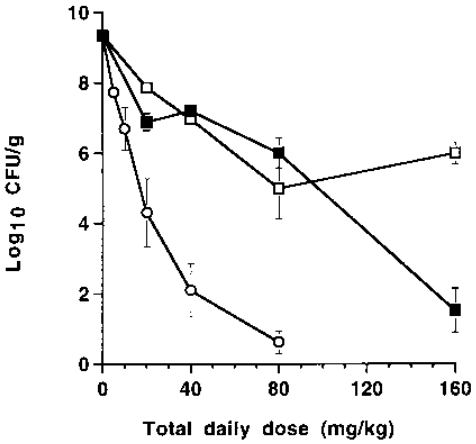

FIG. 2. Dose-response curves of viable cell counts in the kidneys ($\log_{10}$ CFU per gram) as a function of the total daily dose of levofloxacin or ciprofloxacin. The infecting organism was *S. aureus* 3087, a methicillin-susceptible strain. Values are expressed as means ± standard errors. Fluoroquinolone treatments included levofloxacin once a day (○) and ciprofloxacin once a day (□) or twice a day (■).

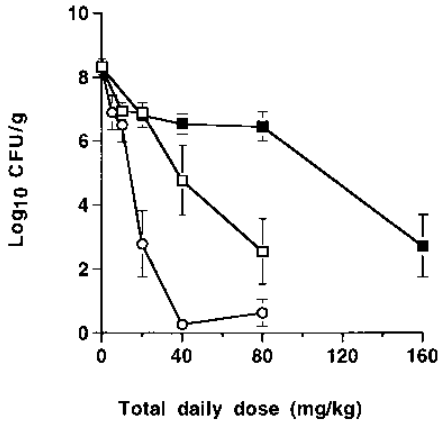

FIG. 4. Dose-response curves of viable cell counts in the kidneys ($\log_{10}$ CFU per gram) as a function of the total daily dose of levofloxacin or ciprofloxacin. The infecting organism was *S. aureus* 2878, a methicillin-resistant strain. Values are expressed as means ± standard errors. Fluoroquinolone treatments included levofloxacin once a day (○) and ciprofloxacin once a day (□) or twice a day (■).

and 4 for *S. aureus* isolates 9039, 3087, 667, and 2878, respectively. For *S. aureus* 667, 3087, 9039, and 2878, a reduction from control levels of 5, 7, 6, and 8 $\log_{10}$ CFU/g occurred at a dose of 40 mg of levofloxacin per kg given once a day. The dosage regimen for ciprofloxacin had been extended to cover 80 mg/kg once or twice a day to determine if ciprofloxacin could achieve the efficacy of levofloxacin observed at the lower doses. Overall, levofloxacin administered once a day for 4 days was more efficacious than a regimen of ciprofloxacin administered once or twice a day (the same total daily dose for both fluoroquinolones) against the MSSA or MRSA strains. Although levofloxacin was tested twice a day against *S. aureus* 9039 and 667 (Fig. 1 and 3), it was tested only once a day against 3087 and 2878 (Fig. 2 and 4) because of its greater efficacy compared with that of ciprofloxacin. When the twice-a-day dosage regimen of levofloxacin was dropped for strains 3087 and 2878, the dosage of levofloxacin was extended to cover 80 mg/kg once a day (Fig. 2 and 4). Therefore, all comparisons of dose-responses were based on once-a-day doses of levofloxacin.

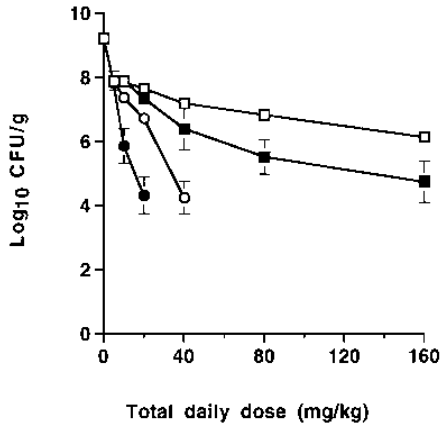

FIG. 3. Dose-response curves of viable cell counts in the kidneys ($\log_{10}$ CFU per gram) as a function of the total daily dose of levofloxacin or ciprofloxacin. The infecting organism was *S. aureus* 667, a methicillin-resistant strain. Values are expressed as means ± standard errors. Fluoroquinolone treatments included levofloxacin once a day (○) or twice a day (●) and ciprofloxacin once a day (□) or twice a day (■).

Against methicillin-susceptible *S. aureus* 9039, levofloxacin at 20 mg/kg once a day resulted in a decrease of 5 $\log_{10}$ CFU/g from the control levels in untreated mice (Fig. 1). Ciprofloxacin at 20 mg/kg once a day and twice a day resulted in decrease of only 1.25 $\log_{10}$ CFU/g from the control levels. Against methicillin-susceptible *S. aureus* 3087, levofloxacin at 40 mg/kg once a day resulted in a decrease of nearly 7 $\log_{10}$ CFU/g from the control levels (Fig. 2), whereas ciprofloxacin at 40 mg/kg once a day and twice a day resulted in decreases of only 2.4 and 3.4 $\log_{10}$ CFU/g, respectively.

Against methicillin-resistant *S. aureus* 667, levofloxacin at 40 mg/kg once a day resulted in a decrease of about 5 $\log_{10}$ CFU/g from the control levels (Fig. 3). Ciprofloxacin at 40 mg/kg once a day and twice a day decreased the numbers of CFU per gram by 2 and 3.7 $\log_{10}$, respectively, from the control levels. Against methicillin-resistant *S. aureus* 2878, levofloxacin at 20 mg/kg once a day resulted in a decrease of about 5.5 $\log_{10}$ CFU/g from the control levels (Fig. 4). Ciprofloxacin given once a day at 20 mg/kg resulted in a decrease of 1.5 $\log_{10}$ CFU/g, while once-a-day doses at 40 mg/kg resulted in a decrease of only 3.5 $\log_{10}$ CFU/g decrease from the control levels.

Upon examination of the dose-response curves, it was clear that the $\log_{10}$ numbers of CFU per gram declined exponentially as a function of the total daily dose for the levofloxacin-treated mice, whereas there was a much flatter and more linear decline for the ciprofloxacin-treated mice (Fig. 1 to 4). In addition, the ciprofloxacin-treated mice often did not experience a 50% reduction in the $\log_{10}$ numbers of CFU per gram from the control levels. As a result, the 50% effective doses and relative potencies were not calculated; however, a statistical analysis that estimated ratios for equivalent doses was implemented. For that analysis, we selected the dose of ciprofloxacin that yielded the maximal response, as indicated by the greatest reduction in the $\log_{10}$ numbers of CFU per gram. Using inverse prediction techniques, we calculated the equivalent dose of levofloxacin that would achieve the same result. A summary of the values for equivalent effective doses of levofloxacin or ciprofloxacin is provided in Table 2. On the basis of the total daily dose of either fluoroquinolone, for MSSA strains 9039 and 3087, the equivalent effective levofloxacin (once a day) dose was less than the equivalent effective ciprofloxacin (twice

TABLE 2. Equivalent effective doses of levofloxacin and ciprofloxacin

Isolate	Ciprofloxacin concn (mg/kg)[a]	Levofloxacin concn (mg/kg)[b]
9039 (MSSA)	40	15.5 (14.1–16.9)
3087 (MSSA)	80	49.5 (41.1–61.5)
667 (MRSA)	80	39.1 (36.3–42.0)
2878 (MRSA)	80	24.9 (21.2–29.5)

[a] Ciprofloxacin was administered twice a day.
[b] Levofloxacin was administered once a day. Values in parentheses are 95% confidence intervals.

a day) dose by about 5.2 and 3.2 times, respectively. For MRSA strains 667 and 2878, the equivalent effective levofloxacin (once a day) dose was less than the equivalent effective ciprofloxacin (twice a day) dose by 4.1 and 6.4 times, respectively.

Histologic examination of the murine model of pyelonephritis. A kidney from a naive mouse was compared with a kidney from a carrageenan-primed, infected mouse (data not shown). The infected kidney, removed 5 days following infection with *S. aureus* 3087, had numerous multifocal cortical abscesses, as indicated by multiple tan foci visible from the capsular surface. A gross examination showed that the kidneys of mice treated for 4 days with levofloxacin at 40 mg/kg once a day or ciprofloxacin at 80 mg/kg twice a day were normal macroscopically (data not shown). The kidneys of mice treated with ciprofloxacin at 40 mg/kg once a day appeared slightly mottled, with occasional tan foci and pale areas.

A microscopic comparison of kidney sections from a naive mouse and a carrageenan-primed, uninfected mouse is shown in Fig. 5a and b, respectively. No morphological changes were observed in the kidney from the carrageenan-primed mouse, and therefore, it was concluded that any morphological changes observed in the kidneys following infection with any of the *S. aureus* strains were the result of the bacterial infection. A kidney section from a mouse obtained 5 days postinfection is shown in Fig. 5c. The kidney exhibited multifocal cortical abscesses and large wedge-shaped areas of pyelonephritis. Microabscesses were characterized by focal infiltrations of inflammatory cells, primarily mononuclear, which sometimes surrounded bacterial colonies (Fig. 5d). The distribution of the cortical microabscesses was consistent with a hematogenous origin. Some microabscesses became confluent to produce large areas of inflammation in the cortex, with associated tubular necrosis. Extension into the medulla resulted in pyelonephritis with papillary necrosis, sometimes containing bacterial colonies. Overall, moderate to marked hematogenous pyelonephritis was present 5 days following an intravenous injection of *S. aureus* in carrageenan-primed mice. Microscopic examination of the kidneys confirmed that the morphological changes were due to the infection caused by *S. aureus.*

In a separate study, kidney sections from levofloxacin- or ciprofloxacin-treated mice were also evaluated to compare the effect of oral fluoroquinolone treatment on the morphology of an infected kidney. Sections of a kidney from an infected mouse treated with levofloxacin and a mouse treated with ciprofloxacin (40 mg/kg once a day) are shown in Fig. 5e and f, respectively. The severity of pyelonephritis was reduced in the kidneys of mice treated with ciprofloxacin; however, no evidence of pyelonephritis was found in the kidneys of mice treated with levofloxacin. At the same dosage, levofloxacin was superior to ciprofloxacin in reducing the number and severity of lesions in the kidneys of infected mice. When mice were treated with ciprofloxacin (80 mg/kg twice a day), no evidence of pyelonephritis was found in the kidneys of the infected mice (data not shown).

Kidneys obtained from the mice treated with levofloxacin or ciprofloxacin at 40 mg/kg once a day or treated with ciprofloxacin at 80 mg/kg twice a day were used to quantify viable cell counts following treatment and allowed for the direct comparison of cell counts with histologic findings. Levofloxacin at 40 mg/kg once a day reduced the viable counts 5 $\log_{10}$ from control levels of 9.39 $\log_{10}$ CFU/g in untreated, infected mice. A similar dosage and regimen of ciprofloxacin (40 mg/kg once a day) was not as effective and reduced the viable counts by only 1.92 $\log_{10}$ CFU/g. Ciprofloxacin at 80 mg/kg twice a day was slightly more effective and reduced the viable counts by 2.9 $\log_{10}$ CFU/g. The morphologic assessment was in agreement with the quantitation of the numbers of CFU per gram, which demonstrated that levofloxacin is superior to ciprofloxacin not only in reducing viable bacterial counts but also in reducing the number and severity of lesions in the kidneys of infected mice.

DISCUSSION

The superior potency of levofloxacin compared with that of ciprofloxacin against *S. aureus*-induced infections has been demonstrated in mouse protection studies (8, 11–13, 18). However, mouse protection studies rely on a single parameter, death, to measure potency. The murine pyelonephritis model described here allows for the evaluation of efficacy by two methods: a quantifiable method (measured by a decrease in bacterial load in the kidneys) and an observational method (macroscopic and microscopic pathology of morphology). The murine hematogenous pyelonephritis model has been used by several investigators (3, 4, 8, 14) to assess the activities of antimicrobial agents against gram-negative and gram-positive organisms. In particular, this model has been used previously to evaluate in vivo antistaphylococcal activity (8). Therefore, we chose this model to compare the efficacy of levofloxacin and ciprofloxacin against an *S. aureus*-induced infection.

Prior to the use of the murine pyelonephritis model, we evaluated the effect of an intravenous injection of carrageenan (type 2; primarily iota) on kidney morphology. No major histologic changes were found in the kidneys of mice 12 days after the injection of 1 mg of iota carrageenan compared with the kidneys of control mice. In fact, the microscopic evaluation could not differentiate these kidneys from those of the controls. Our findings are consistent with those of Fowler and colleagues (6), who reported the lack of renal histologic changes 24 h following the intravenous administration of 2 mg of iota carrageenan into mice. More than half of the mice injected with iota carrageenan showed no pathologic changes in either kidney at 28 weeks postinjection.

Our experiments show that levofloxacin is more effective than ciprofloxacin in treating *S. aureus*-induced hematogenous pyelonephritis in mice. Although levofloxacin and ciprofloxacin had equal inhibitory activities and similar bactericidal activities against the four *S. aureus* isolates tested in vitro, this model demonstrated that levofloxacin is superior in vivo. Depending on the *S. aureus* strain used, ciprofloxacin had to be given at concentrations 3.2 to 6.4 times the dose of levofloxacin to achieve a similar reduction in the numbers of CFU per gram of tissue. Viable bacterial cell counts from the kidneys of the infected, fluoroquinolone-treated mice and the histologic findings in these mice were in agreement with the dose-response analysis and showed that levofloxacin was superior to ciprofloxacin in eradicating *S. aureus*, even when ciprofloxacin was dosed at a level four times that of levofloxacin. Clinically, a

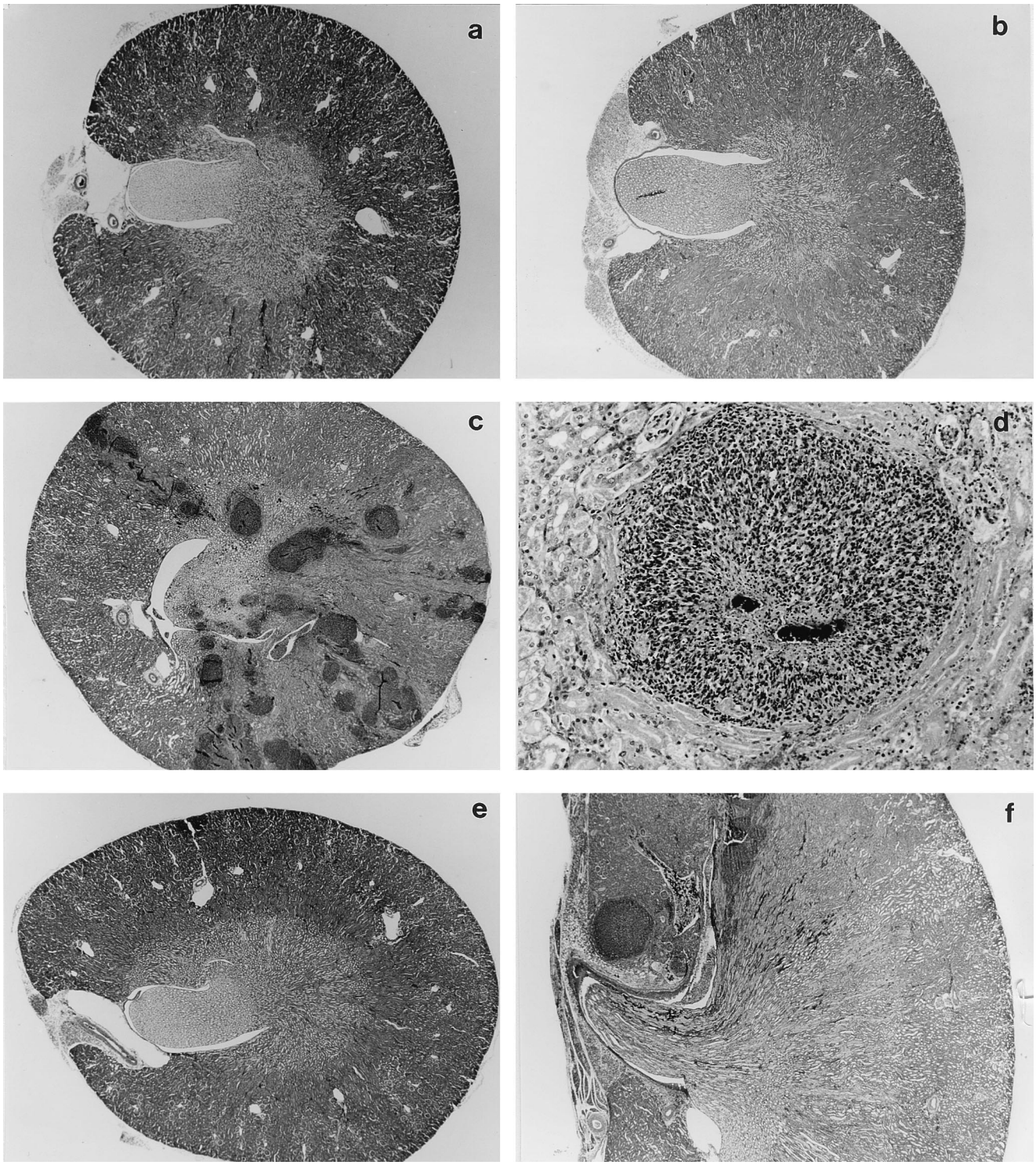

FIG. 5. Tissue section of a kidney from a naive mouse (hematoxylin and eosin-phloxine stains; magnification, ×16) (a) compared with those of a carrageenan-primed, uninfected mouse (hematoxylin and eosin-phloxine stains; magnification, ×16) (b) and a carrageenan-primed, infected mouse (hematoxylin and eosin-phloxine stains; magnification, ×16) (c). The kidney from the infected mouse was removed 5 days after intravenous injection of *S. aureus* 3087. A higher magnification of a focus of infection is shown in panel d (hematoxylin and eosin-phloxine stains; magnification ×150). The lesion is a well-circumscribed area of inflammatory cells, primarily mononuclear, surrounding bacterial colonies. Kidney sections of infected mice treated for 4 days with levofloxacin at 40 mg/kg once a day (hematoxylin and eosin-phloxine stains; magnification, ×16) (e) or ciprofloxacin at 40 mg/kg once a day (hematoxylin and eosin-phloxine stains; magnification, ×16) (f).

much greater dose of ciprofloxacin may be required to achieve the same effect as a much lower dose of levofloxacin.

The greater effectiveness of levofloxacin may be explained in part by the greater bioavailability of levofloxacin. For these studies, we determined by high-pressure liquid chromatography the profiles of levofloxacin and ciprofloxacin in serum following the administration of a single oral dose of 20, 40, 80, or 160 mg/kg to healthy and carrageenan-primed mice (unpublished data). Peak levels of both fluoroquinolones were achieved within 30 min. In healthy mice given an oral dose of levofloxacin of 20, 40, and 80 mg/kg, peak levels reached 3.84, 4.63, and 12.83 μg/ml, respectively. Levofloxacin levels in serum remained above 1 μg/ml for more than 1 h in mice given the drug at 40 and 80 mg/kg. In healthy mice given an oral dose of ciprofloxacin of 20, 40, 80, and 160 mg/kg, peak levels reached 0.47, 1.43, 3.10, and 3.31 μg/ml, respectively. Peak levels remained above 1 μg/ml for 30 min in mice given the drug at 40 and 80 mg/kg and for more than 1 h in mice given the drug at 160 mg/kg. The profiles of both levofloxacin and ciprofloxacin in the sera of carrageenan-primed mice were similar to those profiles obtained from healthy mice, although the peak levels appeared to be slightly higher. In healthy mice, the levels of both levofloxacin and ciprofloxacin in serum at all doses tested were <1 μg/ml after 3 h. Only in carrageenan-primed mice, at the highest dose of levofloxacin (80 mg/kg) or ciprofloxacin (160 mg/kg) tested, were the levels in serum between 1 and 2 μg/ml at 3 h. All other doses resulted in levels in serum of <1 μg/ml at 3 h in carrageenan-primed mice.

These data are in agreement with results from previous studies in which this same model of pyelonephritis was used (8). In those previous studies, it was shown by bioassay that after the administration of a single oral dose of 20 mg/kg, levofloxacin achieved higher concentrations than ciprofloxacin at the same dose in the serum and kidneys of mice. Thirty minutes after administration of drug, peak levels in serum were observed for both levofloxacin and ciprofloxacin at 2.5 and 0.5 μg/ml, respectively. Levofloxacin levels in blood remained above 1 μg/ml for 1 h, whereas ciprofloxacin never achieved levels of 1 μg/ml. After 3 h, the levels of levofloxacin and ciprofloxacin in serum dropped to 0.125 and 0.075 μg/ml, respectively. The maximum concentrations of drug in kidneys were observed at 15 min for both levofloxacin and ciprofloxacin at 4.55 and 0.59 μg/g, respectively (8). Within 3 h, levofloxacin levels had decreased to 0.59 μg/g and ciprofloxacin levels had decreased to 0.03 μg/g. Elimination of the fluoroquinolones from the kidneys closely paralleled elimination from serum.

Goto and colleagues (13) also found that after the administration of an oral dose of levofloxacin of 2 mg per mouse, levofloxacin achieved higher levels than ciprofloxacin in the serum, lungs, and kidneys. Levofloxacin levels remained above 1 μg/ml for more than 4 h, while ciprofloxacin levels were only above 1 μg/ml for about 2.5 h. Klesel et al. (16) found that 1 h after the administration of a 50-mg/kg oral dose, levofloxacin and ciprofloxacin levels in the blood were 5.4 and 1.97 μg/ml, respectively. After 2 h, levofloxacin levels were slightly less than 2 μg/ml and ciprofloxacin levels had dropped to 1 μg/ml. After 6 h, the levels had decreased to 0.57 and 0.29 μg/ml, respectively.

On the basis of these favorable results, it appears that levofloxacin may have potential in clinical practice as a therapeutic option in place of ciprofloxacin for the treatment of staphylococcal infections caused by susceptible strains of *S. aureus.*

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