Comparison of Difloxacin, Enoxacin, and Cefazolin for the Treatment of Experimental *Staphylococcus aureus* Endocarditis

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This study compared difloxacin administered orally, enoxacin administered orally, and cefazolin administered intramuscularly for the treatment of experimental *Staphylococcus aureus* endocarditis. Difloxacin significantly reduced bacterial counts of vegetations compared with enoxacin. This study demonstrated that difloxacin was significantly more effective than enoxacin and as effective as cefazolin for the treatment of *S. aureus* endocarditis in rabbits.

The experimental endocarditis model is a severe test of the efficacy of antimicrobial agents for deep-seated infections. Several studies have evaluated the therapeutic efficacies of various quinolones administered parenterally (and we previously evaluated the therapeutic efficacy of enoxacin administered orally) for the treatment of experimental *S. aureus* endocarditis (2, 5, 8, 11). The pharmacokinetic profile of difloxacin administered orally appears to be better than that of many of the other quinolones administered orally (6; Abbott Laboratories, unpublished data). The purpose of this study was to compare the therapeutic efficacies of difloxacin administered orally, enoxacin administered orally, and cefazolin administered intramuscularly for the treatment of experimental *S. aureus* endocarditis.

The *S. aureus* strain used in this study was a clinical isolate. The MICs and MBCs of difloxacin, enoxacin, and cefazolin were determined with an inoculum of $10^6$ CFU of *S. aureus* per ml as previously described (7). The survival of a large inoculum ($4 \times 10^7$ CFU/ml) of *S. aureus* was studied in flasks with Mueller-Hinton broth (MHB) containing difloxacin at 12 µg/ml, enoxacin at 6 µg/ml, cefazolin at 150 µg/ml, or MHB alone as previously described (3). These concentrations of difloxacin, enoxacin, and cefazolin were similar to peak levels in serum achieved in rabbits after single doses of difloxacin or enoxacin at 100 µg/kg administered orally and after one dose of cefazolin at 25 mg/kg administered intramuscularly.

Female New Zealand White rabbits, ranging from 2 to 2.5 kg in weight, were anesthetized, and the right carotid artery of each was cannulated with advancement of the catheter across the aortic valve (4). Each rabbit was inoculated 24 h later through an ear vein with $10^7$ CFU of *S. aureus* in 1 ml of normal saline. At 24 h after inoculation, rabbits were randomly separated into an untreated control group (animals in this group were sacrificed) and groups that were started on treatment with difloxacin or enoxacin at 100 mg/kg administered orally by syringe every 12 h or with cefazolin at 25 mg/kg administered intramuscularly every 8 h. Endocarditis in rabbits caused by this strain of *S. aureus* produces a rapidly fatal infection killing almost 100% of untreated rabbits by 96 h. In this experiment all 10 untreated rabbits died by 96 h postinfection. Treated rabbits were sacrificed at 6 days after infection (5 days after the onset of treatment). Therefore, it was impossible to have untreated control rabbits at 6 days of infection. Surviving rabbits were sacrificed after 5 days of therapy 12 h after the last dose of antimicrobial agent was administered. All aortic valve vegetations from each sacrificed rabbit were excised, pooled, and titrated as previously described (3). In sterile vegetations, the number of CFU was recorded as $2 \log_{10}$ CFU/g because the largest amount of vegetations plated was 10 mg.

Blood was taken from the ear veins of uninfected rabbits 0.5, 1, 2, 4, and 6 h after single doses of difloxacin or enoxacin at 100 mg/kg administered orally and 0.5, 1, 2, and 4 h after one dose of cefazolin at 25 mg/kg administered intramuscularly. Concentrations of difloxacin, enoxacin, and cefazolin in serum were measured by a paper disk agar diffusion method (1). The elimination half-lives of the antimicrobial agents in serum were calculated by the least-squares method (9).

A one-way analysis of variance, followed by the Tukey-Kramer post hoc procedure, was used to determine significant differences in bacterial counts of vegetations. The independent variable was the antimicrobial agent and the dependent variable was the CFU per gram of vegetation. The MIC and MBC of each antimicrobial agent for an inoculum of $10^6$ CFU/ml of the *S. aureus* strain used in this study were 0.4 and 0.8 for difloxacin, 1.6 and 1.6 for enoxacin, and 0.8 and 3.1 for cefazolin, respectively. Figure 1 shows the rate of decrease in numbers of *S. aureus* in MHB containing difloxacin at 12 µg/ml, enoxacin at 6 µg/ml, or cefazolin at 150 µg/ml with an inoculum of $4 \times 10^7$ CFU/ml. Enoxacin and cefazolin resulted in similar decreases in numbers of *S. aureus* in MHB but the effect was greatest with difloxacin.

The mean (± standard error) counts of *S. aureus* in log$_{10}$ CFU per gram of vegetation were determined for the untreated control group after 1 day of infection (7.7 ± 0.4) and for the three treatment groups of rabbits after 5 days of therapy (difloxacin, 3.0 ± 0.4; enoxacin, 5.5 ± 0.6; cefazolin, 3.4 ± 0.6). A one-way analysis of variance revealed a significant main effect of antimicrobial agents on reducing bacterial counts of vegetations ($P < 0.001$). The Tukey-Kramer post hoc procedure performed on the main effect of antimicrobial agents revealed that difloxacin, enoxacin, and cefazolin treatment for 5 days significantly reduced bacterial counts of vegetations by 7.3 ± 0.4, 6.4 ± 0.3, and 5.8 ± 0.3, respectively.

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counts of vegetations compared with those in untreated control rabbits after 1 day of infection ($P < 0.01$, $P < 0.05$, and $P < 0.01$, respectively). Difloxacin significantly reduced bacterial counts of vegetations compared with enoxacin ($P < 0.05$). Difloxacin and cefazolin did not differ significantly and enoxacin and cefazolin did not differ significantly. Mortality during the treatment period (no more than one rabbit per group) did not differ among the three groups (difloxacin, enoxacin, and cefazolin).

The mean peak concentrations and elimination half-lives in serum after single doses of difloxacin or enoxacin at 100 mg/kg administered orally and after one dose of cefazolin at 25 mg/kg administered intramuscularly are shown in Table 1. Peak drug levels in serum occurred 60 to 120 min after administration of difloxacin and enoxacin and 30 min after administration of cefazolin.

In the treatment of *S. aureus* endocarditis in rabbits, difloxacin significantly reduced bacterial counts of vegetations compared with enoxacin. These in vivo results were predictable based on the results of the in vitro time-kill studies which demonstrated the greater bactericidal activity of difloxacin against the *S. aureus* strain used compared with enoxacin (when concentrations similar to peak levels in serum were used). Also, the superior in vivo results of difloxacin compared with enoxacin were in part predictable based on the better pharmacokinetic profile of difloxacin. The superior pharmacokinetic parameters of difloxacin administered orally compared with those of enoxacin administered orally are consistent with the better pharmacokinetic profile in other animals and humans of difloxacin administered orally (26-h elimination half-life in serum in humans) compared with that of many of the other quinolones administered orally (6; Abbott Laboratories, unpublished data).

Difloxacin and cefazolin were comparable in their ability to reduce bacterial counts of vegetations; cefazolin reduced bacterial counts of vegetations more than enoxacin, but not significantly. In a previous study of methicillin-resistant *S. aureus* endocarditis in rabbits, enoxacin administered orally was as effective as vancomycin administered intravenously in reducing bacterial counts of vegetations (5).

In other studies, ciprofloxacin and pefloxacin administered parenterally were effective for the treatment of experimental *S. aureus* endocarditis (2, 8, 11). Also, difloxacin administered parenterally was effective for the treatment of experimental *S. aureus* chronic osteomyelitis (10). The unique aspect of the present study was the demonstration that the oral administration of quinolone antimicrobial agents (difloxacin and enoxacin) was effective in reducing bacterial counts of vegetations in *S. aureus* endocarditis in rabbits. Difloxacin was significantly more effective than equivalent doses of enoxacin. Therefore, the oral administration of quinolone antimicrobial agents may prove useful for the treatment of deep-seated infections caused by *S. aureus*.

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**LITERATURE CITED**


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**TABLE 1. Peak concentrations and elimination half-lives of antimicrobial agents in serum**

<table>
<thead>
<tr>
<th>Antimicrobial agent (dose: no. of rabbits)</th>
<th>Peak level (µg/ml) in serum</th>
<th>Half-life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difloxacin (100 mg/kg; 6)</td>
<td>10.9 ± 1.3</td>
<td>3.7 ± 0.3</td>
</tr>
<tr>
<td>Enoxacin (100 mg/kg; 6)</td>
<td>7.3 ± 0.9</td>
<td>2.9 ± 0.3</td>
</tr>
<tr>
<td>Cefazolin (25 mg/kg; 4)</td>
<td>122.8 ± 7.4</td>
<td>0.4 ± 0.0</td>
</tr>
</tbody>
</table>

* Values are means ± the standard errors.
