Comparison of Difloxacin, Enoxacin, and Cefoperazone for Treatment of Experimental *Enterobacter aerogenes* Endocarditis

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This study compared difloxacin administered orally, enoxacin administered orally, and cefoperazone administered intramuscularly for the treatment of experimental *Enterobacter aerogenes* endocarditis. Difloxacin significantly reduced bacterial counts of vegetations, as compared with enoxacin and cefoperazone. Enoxacin and cefoperazone did not differ significantly. This study demonstrated that difloxacin was significantly more effective than enoxacin and cefoperazone for the treatment of *E. aerogenes* endocarditis in rabbits.

The development of oral antimicrobial agents with activity against resistant aerobic gram-negative bacilli will represent a major breakthrough in the treatment of deep-seated infections caused by these bacteria. The endocarditis model in rabbits is a severe test of the efficacy of antimicrobial agents for deep-seated infections. The purpose of this study was to compare the therapeutic efficacies of difloxacin administered orally, enoxacin administered orally, and cefoperazone administered intramuscularly for the treatment of experimental *Enterobacter aerogenes* endocarditis.

The *E. aerogenes* strain used in this study was a clinical isolate which has been previously studied (2). The MICs and MBCs of difloxacin, enoxacin, and cefoperazone were determined with an inoculum of 10² CFU of *E. aerogenes* per ml as previously described (6). The survival of a large inoculum (3 × 10⁷ CFU/ml) of *E. aerogenes* was studied in flasks with Mueller-Hinton broth (MHB) containing difloxacin at 12 μg/ml, enoxacin at 6 μg/ml, or cefoperazone at 170 μg/ml or with MHB alone as previously described (2). These concentrations of difloxacin, enoxacin, and cefoperazone were similar to peak levels achieved in serum in rabbits after a single dose of difloxacin or enoxacin at 100 mg/kg administered orally and after one dose of cefoperazone at 60 mg/kg administered intramuscularly. Concentrations of difloxacin, enoxacin, and cefoperazone in serum were measured by a paper disk agar diffusion method (1). The half-lives of the antimicrobial agents in serum were calculated by the method of least squares (7).

Female New Zealand White rabbits ranging from 2 to 2.7 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 10⁶ CFU of *E. aerogenes* in 1 ml of normal saline. Five days after inoculation, rabbits were randomly separated into an untreated control group and groups that were started on treatment with difloxacin or enoxacin at 100 mg/kg administered orally by syringe every 12 h or cefoperazone at 60 mg/kg administered intramuscularly every 6 h. Surviving rabbits were randomly sacrificed after 5 or 10 days of therapy 12 h after the last dose of antimicrobial agent. 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 calculated as 2 log₁₀ CFU/g because the smallest amount of vegetation plated was 10 mg.

Blood was taken from the ear veins of uninfected rabbits 0.5, 1, 2, 4, and 6 h after a single dose of difloxacin or enoxacin at 100 mg/kg administered orally and 0.25, 0.5, 1, 2, and 4 h after one dose of cefoperazone at 60 mg/kg administered intramuscularly. Concentrations of difloxacin, enoxacin, and cefoperazone in serum were measured by a paper disk agar diffusion method (1). The half-lives of the antimicrobial agents in serum were calculated by the method of least squares (7).

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FIG. 1. Rate of decrease in numbers of *E. aerogenes* in MHB containing difloxacin at 12 μg/ml, enoxacin at 6 μg/ml, or cefoperazone at 170 μg/ml.
A two-factor analysis of variance, followed by the Tukey-A post hoc procedure with the harmonic mean cell size, was used to determine significant differences in bacterial counts of vegetations. The independent variables were therapeutic agents and duration of therapy. The dependent variable was CFU per gram of vegetation.

The MICs and MBCs in micrograms per milliliter of each antimicrobial agent for an inoculum of 10⁶ CFU of the E. aerogenes strain used in this study per ml were 0.8 and 3.1 for difloxacin and enoxacin and 6.3 and 6.3 for cefoperazone, respectively. Figure 1 shows the rate of decrease in numbers of E. aerogenes in MHB containing difloxacin at 12 μg/ml, enoxacin at 6 μg/ml, or cefoperazone at 170 μg/ml with an inoculum of 3 × 10⁶ CFU/ml. Enoxacin and cefoperazone resulted in similar decreases in numbers of E. aerogenes in MHB, but the effect was greatest with difloxacin.

Table 1 shows the mean (± standard error) counts of E. aerogenes in log₁₀ CFU per gram of vegetation for the untreated control group and the three treatment groups of rabbits after 5 and 10 days of therapy. A two-factor analysis of variance revealed a significant main effect of antimicrobial agents on reducing bacterial counts of vegetations (P < 0.001). The main effect of duration of therapy, i.e., 5 versus 10 days, and the two-factor interaction of treatment and duration of therapy were not significant. The Tukey-A post hoc procedure with the harmonic mean cell size performed on the main effect of antimicrobial agents revealed that difloxacin significantly reduced bacterial counts of vegetations, as compared with enoxacin, cefoperazone, and no therapy (P < 0.01). Enoxacin significantly reduced bacterial counts of vegetations, as compared with no treatment (P < 0.01). Enoxacin and cefoperazone did not differ significantly, and cefoperazone and no therapy did not differ significantly.

Mortality during the treatment period (1 to 2 rabbits per group) did not differ among the four groups (difloxacin, enoxacin, cefoperazone, and no therapy).

The mean (± standard error) peak concentrations and elimination half-lives in serum after a single dose of difloxacin or enoxacin at 100 mg/kg administered orally and after one dose of cefoperazone at 60 mg/kg administered intramuscularly were 11.8 ± 1.8 μg/ml and 3.6 ± 0.5 h for difloxacin (four rabbits), 5.9 ± 0.5 μg/ml and 2.3 ± 0.3 h for enoxacin (three rabbits), and 171.5 ± 8.8 μg/ml and 0.6 ± 0.0 h for cefoperazone (four rabbits), respectively.

In the treatment of E. aerogenes endocarditis in rabbits, difloxacin significantly reduced bacterial counts of vegetations, as compared with enoxacin, cefoperazone, and no therapy. These in vivo results were predictable on the basis of the results of the in vitro time kill studies, which demonstrated the greater bactericidal activity against the E. aerogenes strain of difloxacin than of enoxacin and cefoperazone (when concentrations similar to peak levels in serum were used). Also, the superior in vivo results of difloxacin as compared with enoxacin were in part predictable on the basis of 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 than of many of the other quinolones administered orally (Abbott Laboratories, unpublished data).

Enoxacin significantly reduced bacterial counts of vegetations, as compared with no treatment, but enoxacin and cefoperazone did not differ significantly. In a previous study of endocarditis in rabbits with the same strain of E. aerogenes, enoxacin at 100 mg/kg administered orally every 6 h significantly reduced bacterial counts of vegetations, as compared with cefoperazone at 60 mg/kg administered intramuscularly every 6 h and no therapy (2). The reason that enoxacin was significantly better than cefoperazone in the previous study (2) but not in the present study is probably the different dosage intervals in the two studies (every 6 h versus every 12 h, respectively). In the present study and in the previous study (2), cefoperazone reduced bacterial counts of vegetations, as compared with no therapy, but not significantly.

In other studies, ciprofloxacin (another new quinolone antimicrobial agent) administered parenterally was effective for the treatment of experimental Pseudomonas aeruginosa endocarditis and chronic osteomyelitis (5, 8, 9). 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 E. aerogenes endocarditis in rabbits. Difloxacin was significantly more effective than enoxacin in equivalent doses. Therefore, the oral administration of quinolone antimicrobial agents may prove useful for the treatment of deep-seated infections caused by resistant aerobic gram-negative bacilli.

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**LITERATURE CITED**


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