

## Comparative Pharmacodynamics of Gatifloxacin and Ciprofloxacin in an In Vitro Dynamic Model: Prediction of Equiefficient Doses and the Breakpoints of the Area under the Curve/MIC Ratio

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To demonstrate the impact of the pharmacokinetics of gatifloxacin (GA) relative to those of ciprofloxacin (CI) on the antimicrobial effect (AME), the killing and regrowth kinetics of two differentially susceptible clinical isolates each of *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumoniae* were studied. With each organism, a series of monoexponential pharmacokinetic profiles of GA (half-life [ $t_{1/2}$ ], 7 h) and CI ( $t_{1/2}$  = 4 h) were simulated to mimic different single doses of GA and two 12-h doses of CI. The respective eightfold ranges of the ratios of the area under the concentration-time curve (AUC) to the MIC were 58 to 466 and 116 to 932 ( $\mu\text{g} \cdot \text{h/ml}/(\mu\text{g/ml})$ ). The species- and strain-independent linear relationships observed between the intensity of AME ( $I_E$ ) and log AUC/MIC were not superimposed for GA and CI ( $r^2 = 0.99$  in both cases). The predicted AUC/MIC ratio for GA that might be equivalent to a clinically relevant AUC/MIC breakpoint for CI was estimated to be 102 rather than 125 ( $\mu\text{g} \cdot \text{h/ml}/(\mu\text{g/ml})$ ). The respective MIC breakpoints were 0.32  $\mu\text{g/ml}$  (for a 400-mg dose of GA) and 0.18  $\mu\text{g/ml}$  (for two 500-mg doses of CI). On the basis of the  $I_E$ -log AUC/MIC relationships, equiefficient 24-h doses ( $D_{24\text{h}}$ s) of GA and CI were calculated for hypothetical strains of *S. aureus*, *E. coli*, and *K. pneumoniae* for which the MICs were equal to the MICs at which 50% of isolates are inhibited. To provide an "acceptable"  $I_E$  equal to 200 (log CFU/ml)  $\cdot$  h, i.e., the  $I_E$  provided by AUC/MIC of 125 ( $\mu\text{g} \cdot \text{h/ml}/(\mu\text{g/ml})$ ) for ciprofloxacin, the  $D_{24\text{h}}$ s of GA for all three organisms were much lower (115, 30, and 60 mg) than the clinically proposed 400-mg dose. Although the usual dose of CI (two doses of 500 mg) would be in excess for *E. coli* and *K. pneumoniae* ( $D_{24\text{h}}$  = two doses of 40 mg and two doses of 115 mg, respectively), even the highest clinical dose of CI (two doses of 750 mg) might be insufficient for *S. aureus* ( $D_{24\text{h}}$  > two doses of 1,000 mg). The method of generalization of data obtained with specific organisms to other representatives of the same species described in the present report might be useful for prediction of the AMEs of new quinolones.

We recently described a new approach to the in vitro comparison of fluoroquinolones on the basis of an analysis of relationships between the intensity of the antimicrobial effect ( $I_E$ ; the area between control growth and bacterial killing and regrowth curves [4, 8]) and the ratio of the area under the concentration-time curve (AUC) to the MIC as established over a wide range of AUC/MIC ratios (9). This approach allowed accurate comparisons of the antimicrobial effects of trovafloxacin and ciprofloxacin in terms of the  $I_E$  versus log AUC/MIC relationships. On the basis of these relationships that were bacterial species and strain independent but that were specific for each quinolone, the equiefficient AUC/MIC breakpoint of trovafloxacin relative to that of ciprofloxacin was predicted (9). Later, the described approach was expanded to generalize the data obtained with specific bacterial strains to predict the equiefficient doses of the quinolones adjusted by the MIC at which 50% of isolates are inhibited ( $\text{MIC}_{50}$ ) (7).

A similar approach was applied in the present study to compare the antimicrobial effects of gatifloxacin and ciprofloxacin on *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneu-*

*moniae*. Also, an attempt to predict a clinical equiefficient dose of the newer quinolone was conducted.

### MATERIALS AND METHODS

**Antimicrobial agents.** Gatifloxacin and ciprofloxacin lactate powders (kindly provided by Bristol-Myers Squibb and Bayer Corporation, respectively) were used in the study.

**Bacterial strains.** Two clinical isolates each of *S. aureus* (methicillin-resistant *S. aureus* [MRSA] strains), *E. coli*, and *K. pneumoniae* were selected for the study. The MICs for these organisms were determined as described elsewhere (6) and are presented in Table 1. For the prediction of the antimicrobial effects of the quinolones on hypothetical representatives of the species mentioned above (see the Results section), weighted geometric means of the reported  $\text{MIC}_{50}$ s of gatifloxacin (1) and ciprofloxacin (1, 3, 15, 16; D. Adam, Proc. 20th Int. Congr. Chemother., abstr. 2237, 1997; S. Kocagoz, D. Gur, A. Karademir, H. Akalin, and S. Unal, Abstract 1st Eur. Congr. Chemother. and 7th Biennial Conf. Antiinfective Agents Chemother., abstr. F 148, 1997; M. Takahata, J. Mitsuyama, Y. Yamashiro, M. Yonezawa, H. Araki, H. Yamada, Y. Todo, S. Minami, Y. Watanabe, and H. Narita, Abstr. 37th Intersci. Conf. Antimicrob. Agents Chemother., abstr. F 159, p. 173, 1997; M. Visali, M. Jacobs, and P. Appelbaum, Proc. 20th Int. Congr. Chemother., abstr. 2233, 1997) were calculated. Since the  $\text{MIC}_{50}$ s for MRSA reported in one study (3) differed substantially from the estimates reported in five other studies (1, 15; Adam, Proc., 20th Int. Congr. Chemother., 1997; Kocagoz et al., Abstr. 1st Eur. Congr. Chemother. and 7th Biennial Conf. Antiinfective Agents Chemother., 1997; Takahata et al., 37th ICAAC), only  $\text{MIC}_{50}$ s for methicillin-susceptible strains reported in the study of Felmingham et al. (3) were considered. The respective geometric mean values of the  $\text{MIC}_{50}$ s of gatifloxacin for *S. aureus*, *E. coli*, and *K. pneumoniae* were 0.08, 0.02, and 0.04  $\mu\text{g/ml}$ , respectively, and those of ciprofloxacin were 0.52, 0.01, and 0.03  $\mu\text{g/ml}$ , respectively.

**In vitro dynamic model and simulated pharmacokinetic profiles.** A previously described dynamic model (8) was used in the study. The operation procedure,

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TABLE 1. MICs of gatifloxacin and ciprofloxacin

| Bacterial strain         | MIC ( $\mu\text{g}/\text{ml}$ ) |               |
|--------------------------|---------------------------------|---------------|
|                          | Gatifloxacin                    | Ciprofloxacin |
| <i>S. aureus</i> 944     | 0.15                            | 0.3           |
| <i>S. aureus</i> 916     | 1.25                            | 1.25          |
| <i>E. coli</i> 11557     | 0.2                             | 0.05          |
| <i>E. coli</i> 37        | 0.3                             | 0.2           |
| <i>K. pneumoniae</i> 56  | 0.2                             | 0.12          |
| <i>K. pneumoniae</i> 128 | 0.32                            | 0.4           |

reliability of simulations of the quinolone pharmacokinetic profiles, and the high degree of reproducibility of the time-kill curves provided by the model have been reported elsewhere (6).

A series of monoexponential profiles that mimic single-dose administration of gatifloxacin and twice-daily dosing of ciprofloxacin were simulated. The simulated half-lives (7 h for gatifloxacin and 4.0 h for ciprofloxacin) were consistent with values reported for humans: 6.0 to 8.4 h (10–12) and 3.2 to 5.0 h (2, 13, 17), respectively. The respective rates of fresh nutrient medium influx into the 40-ml central compartment and antibiotic- and bacterium-containing medium efflux from this compartment were 4 ml/h (gatifloxacin) and 7 ml/h (ciprofloxacin).

With both strains of *S. aureus* and with *E. coli* 37, the simulated AUC/MIC ratios for gatifloxacin were 58, 116, 233, and 466 ( $\mu\text{g} \cdot \text{h}/\text{ml}$ )/( $\mu\text{g}/\text{ml}$ ) and those for ciprofloxacin were 116, 233, 466, and 932 ( $\mu\text{g} \cdot \text{h}/\text{ml}$ )/( $\mu\text{g}/\text{ml}$ ). With *E. coli* 11557 or *K. pneumoniae* 56, the respective AUC/MIC ratios were 58, 116, and 233 and 116, 233, and 466 ( $\mu\text{g} \cdot \text{h}/\text{ml}$ )/( $\mu\text{g}/\text{ml}$ ). With *K. pneumoniae* 128, the AUC/MIC ratios for gatifloxacin were 58 and 233 ( $\mu\text{g} \cdot \text{h}/\text{ml}$ )/( $\mu\text{g}/\text{ml}$ ), and those for ciprofloxacin were 116 and 466 ( $\mu\text{g} \cdot \text{h}/\text{ml}$ )/( $\mu\text{g}/\text{ml}$ ). To provide comparable AUC/MIC ratios for gatifloxacin and ciprofloxacin, the latter of which has a shorter half-life, the sum of the peak concentration/MIC ratios produced by the two doses of ciprofloxacin was higher than the respective value for gatifloxacin at the same simulated AUC/MIC ratio. The overall range of the simulated peak concentration-to-MIC ratios for gatifloxacin was 5.8 to 46.4, and that for ciprofloxacin was 10.2 to 81.3 (Fig. 1). For ciprofloxacin, the designed AUC/MIC ratios reflect the sum of two AUC/MIC ratios provided by the two doses of the quinolone administered at 12-h intervals.

**Quantitation of time-kill curves and antimicrobial effect.** In each experiment multiple samples of bacterium-containing media from the central compartment were obtained throughout the observation period. The duration of the experiments was defined in each case as the time until regrowing antibiotic-exposed bacteria reached the maximum numbers observed in the absence of antibiotic ( $\geq 10^{10}$  CFU/ml). The procedure used for quantitation of viable counts has been reported elsewhere (6).

As described earlier (8), the antimicrobial effect ( $E$ ) at each time point ( $t$ ) was expressed by the difference between logarithms of the respective viable counts in the control growth curve ( $N_c$ ) and in the time-kill curve ( $N_t$ ):  $E(t) = \log N_c - \log N_t$  (Fig. 2). As seen in Fig. 2, either the area between the  $\log N_c$ - $t$  and  $\log N_t$ - $t$  curves (Fig. 2A) or the area under the  $E$ - $t$  curve (Fig. 2B) describes the total antimicrobial effect as expressed by  $I_E$ . The upper limit of bacterial numbers, i.e., the cutoff level on the regrowth and control growth curves used to determine the  $I_E$ , was  $10^{11}$  CFU/ml. In case of lower counts, they were extrapolated to the cutoff level by using a logistic function (STATISTICA software, version 4.3; StatSoft, Inc.).

**Relationships between effect and AUC/MIC or dose.** The  $I_E$ -versus- $\log$  AUC/MIC data sets obtained with each quinolone against *S. aureus*, *E. coli*, and *K. pneumoniae* were fitted by the equation  $I_E = a + b \log \text{AUC/MIC}$  (equation 1).

When predicting the AUC/MIC breakpoint for gatifloxacin, the reported breakpoint value for ciprofloxacin, 125 ( $\mu\text{g} \cdot \text{h}/\text{ml}$ )/( $\mu\text{g}/\text{ml}$ ), that correlated with bacterial eradication in patients with respiratory tract infections (14) was used. This reference breakpoint reflects the critical value of the area under the inhibitory curve that is very similar to the AUC/MIC.

To express the antimicrobial effects as a function of quinolone dose ( $D$ ), the AUC in the linear relationship between  $I_E$  and  $\log$  AUC that corresponds to equation 1 written for a given quinolone-pathogen pair was replaced by  $D$  according to the polynomial equation  $\text{AUC} = c + dD + eD^2$  (equation 2). The values of  $c$ ,  $d$ , and  $e$  for gatifloxacin ( $0$ ,  $7.0 \times 10^{-2}$ , and  $3.6 \times 10^{-5}$ , respectively) and for ciprofloxacin ( $0.10$ ,  $1.4 \times 10^{-2}$ , and  $7.5 \times 10^{-6}$ , respectively) were calculated by considering the curvilinear pattern of the AUC- $D$  plots constructed from pharmacokinetic data for gatifloxacin (AUCs at  $D$ s from 100 to 600 mg [10–12]) and ciprofloxacin (AUCs at  $D$ s from 100 to 1,000 mg [2]).

Correlation and regression analyses of the relationships between  $I_E$  and  $\log$  AUC/MIC for each quinolone were performed at a level of significance of  $P$  equal to 0.05.

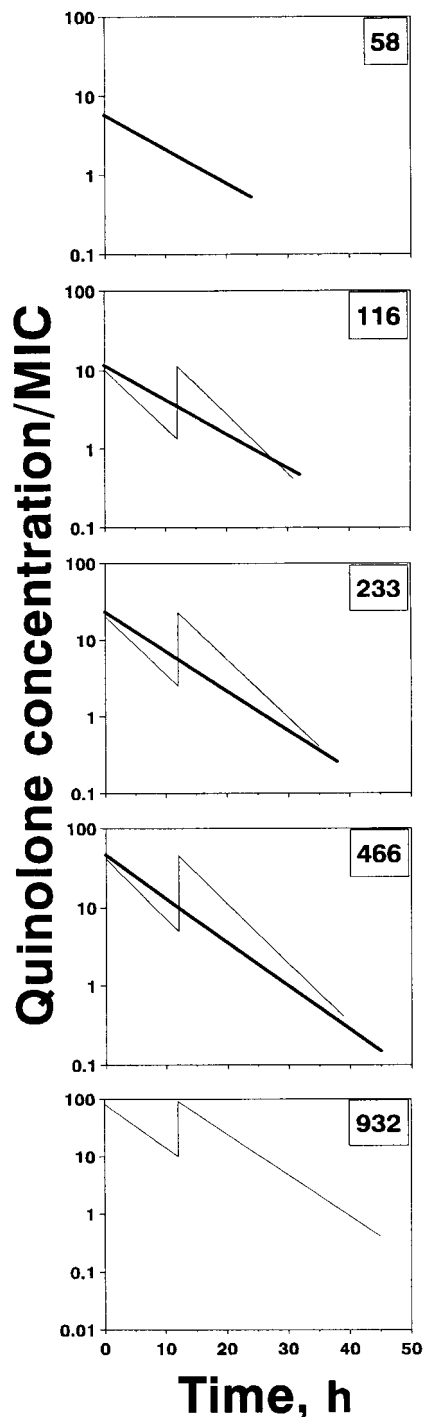


FIG. 1. In vitro simulated pharmacokinetic profiles of gatifloxacin (bold line) and ciprofloxacin (thin line). The simulated AUC/MIC ratios [in ( $\mu\text{g} \cdot \text{h}/\text{ml}$ )/( $\mu\text{g}/\text{ml}$ )] are indicated by the boxed numbers.

## RESULTS

The time courses of viable counts that reflect killing and regrowth of *S. aureus*, *E. coli*, and *K. pneumoniae* exposed to monoexponentially decreasing concentrations of gatifloxacin and ciprofloxacin yielded similar patterns. At the AUC/MIC ratios studied, regrowth followed a rapid and considerable reduction in bacterial numbers. The rapid onset of the anti-

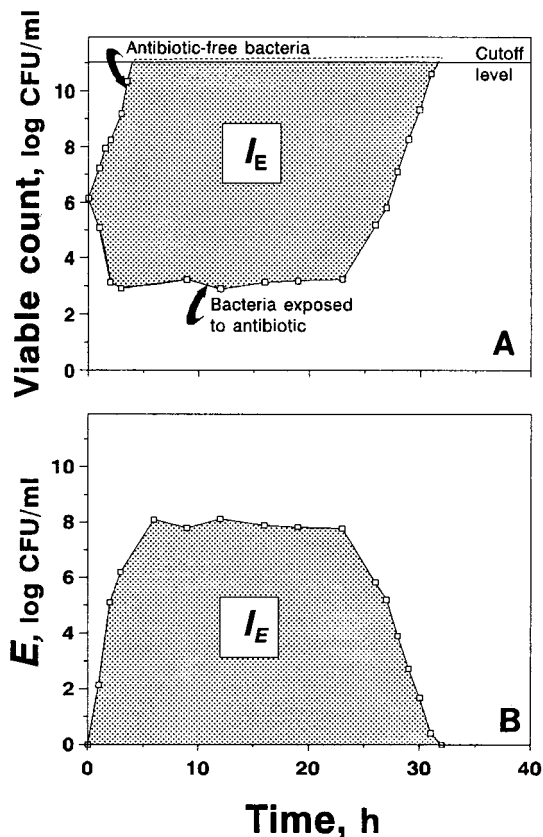


FIG. 2. Determination of  $I_E$ : *S. aureus* 944 was exposed to gatifloxacin at an AUC/MIC of 116 ( $\mu\text{g} \cdot \text{h/ml}$ )/( $\mu\text{g/ml}$ ).  $I_E$  describes the dashed area between the control growth and time-kill curves (A) or under the  $E-t$  curves (B).

crobial effect is reflected by steep ascending branches of the  $E-t$  curves (Fig. 3). As a rule, the maximal  $E_s$  ( $E_{\text{max}S}$ ) produced by both quinolones were greater at higher AUC/MIC ratios, although the AUC/MIC-induced differences in  $E_{\text{max}S}$  were less pronounced than those in the descending branches of the  $E-t$  curves. As seen in Fig. 3, these shifts were distinctly dependent on the simulated AUC/MIC: the higher the AUC/MIC, the later the disappearance of the antimicrobial effect.

The respective  $I_E S$  correlated well with  $\log$  AUC/MIC ratios for both gatifloxacin and ciprofloxacin (Fig. 4). The  $I_E$ - $\log$  AUC/MIC plots fitted by equation 1 were linear, bacterial species and strain independent, but quinolone specific. As seen in Fig. 4, at AUC/MIC ratios of  $>75$  ( $\mu\text{g} \cdot \text{h/ml}$ )/( $\mu\text{g/ml}$ ), the effects produced by gatifloxacin were greater than those produced by ciprofloxacin at the same AUC/MIC ratio. For example, at an AUC/MIC ratio of 250 ( $\mu\text{g} \cdot \text{h/ml}$ )/( $\mu\text{g/ml}$ ), the  $I_E$  of gatifloxacin was 14% higher than that of ciprofloxacin. Furthermore, an equivalent AUC/MIC ratio for gatifloxacin which corresponds to a clinically established AUC/MIC ratio of 125 ( $\mu\text{g} \cdot \text{h/ml}$ )/( $\mu\text{g/ml}$ ) for ciprofloxacin (14) and which produces the same  $I_E$  of 200 ( $\log$  CFU/ml)  $\cdot$  h was lower, 102 ( $\mu\text{g} \cdot \text{h/ml}$ )/( $\mu\text{g/ml}$ ). This estimated value might be proposed as an equivalent AUC/MIC breakpoint that in turn might be used to predict the MIC breakpoint of gatifloxacin. As follows from equation 2, a clinically accepted dose of gatifloxacin (400 mg) provides an AUC of 33  $\mu\text{g} \cdot \text{h/ml}$ . So, the MIC breakpoint is equal to 33/102, which is equal to 0.32  $\mu\text{g/ml}$ . The respective value for two 500-mg doses of ciprofloxacin estimated by using

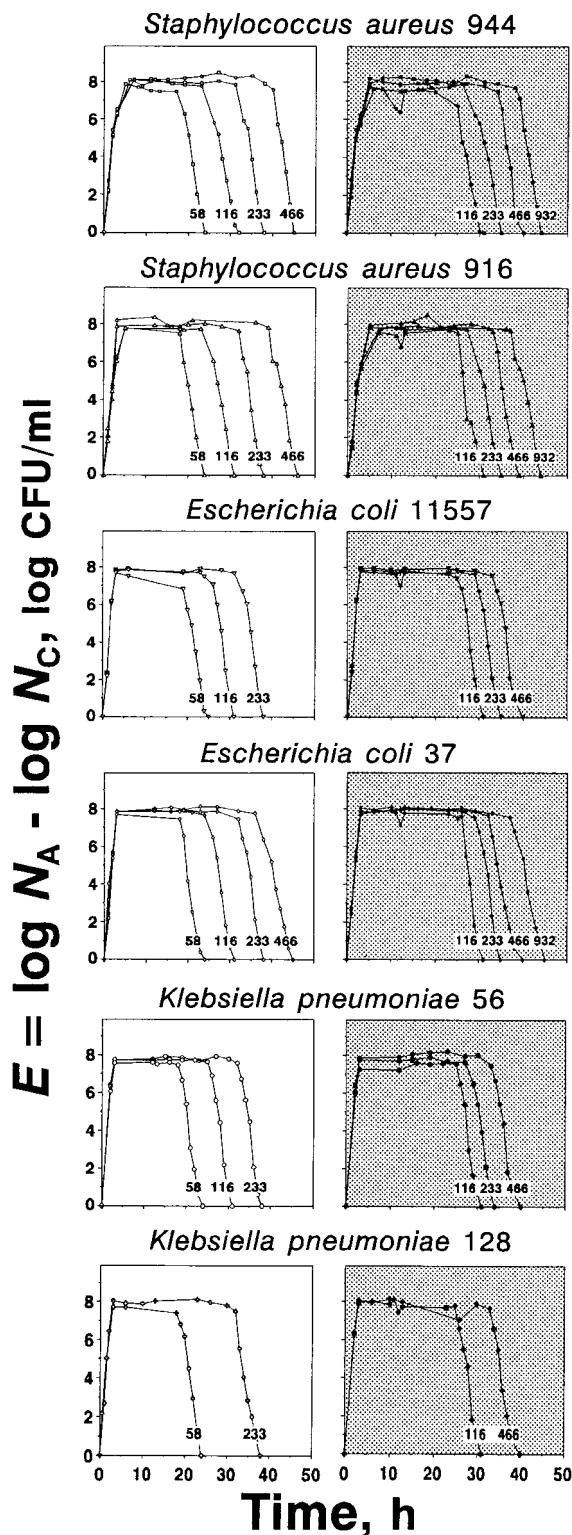


FIG. 3. Kinetics of the antimicrobial effect of gatifloxacin (left panels) and ciprofloxacin (right panels). The simulated AUC/MIC ratio [in ( $\mu\text{g} \cdot \text{h/ml}$ )/( $\mu\text{g/ml}$ )] is indicated by the number on each curve.

equation 2 is lower: 22/125, which is equal to 0.18  $\mu\text{g/ml}$ . As shown in Fig. 5, the MIC ranges limited from above by the respective  $\text{MIC}_{50S}$  for *E. coli* and *K. pneumoniae* are lower than the MIC breakpoint lines for both gatifloxacin and ciprofloxacin.

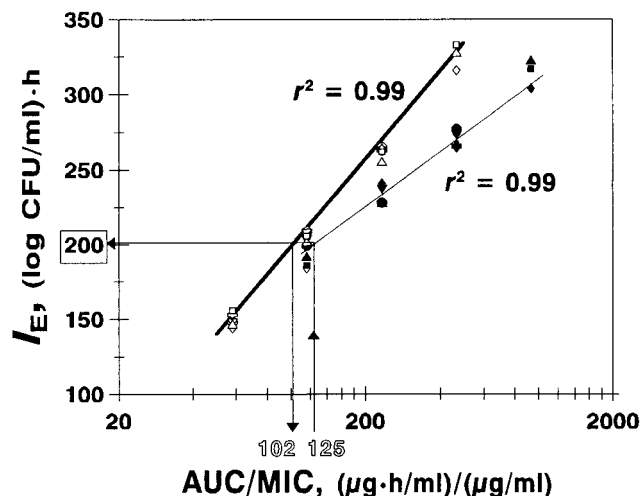


FIG. 4. AUC/MIC-dependent antimicrobial effects of gatifloxacin (bold line) and ciprofloxacin (thin line) on *S. aureus*, *E. coli*, and *K. pneumoniae* as fitted by equation 1, in which *a* is equal to -190 and *b* is equal to 194 for gatifloxacin and *a* is equal to -53 and *b* is equal to 121 for ciprofloxacin. The transparent numbers indicate the equivalent AUC/MIC.

cin. Unlike the two gram-negative bacteria, the usual clinical dose of ciprofloxacin (two 500-mg doses) might be insufficient to kill many strains of *S. aureus*, including those for which the MIC is less than the MIC<sub>50</sub>, whereas the proposed dose of gatifloxacin (400 mg) might kill any strain for which the MIC is less than or equal to the MIC<sub>50</sub>.

DISCUSSION

This comparative study demonstrating a bacterial species- and strain-independent but quinolone-specific pattern of the *I<sub>E</sub>*-log AUC/MIC relationships is consistent with our earlier findings for trovafloxacin and ciprofloxacin (7, 9). A similar strain-independent AUC/MIC-response relationship can be derived from another dose-range study with gatifloxacin (A.

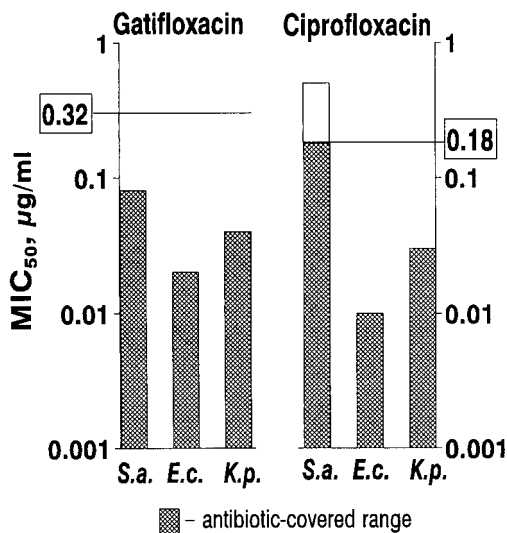


FIG. 5. MIC<sub>50</sub>s for *S. aureus* (*S.a.*), *E. coli* (*E.c.*), and *K. pneumoniae* (*K.p.*) compared with the MIC breakpoints of gatifloxacin and ciprofloxacin as predicted in this study.

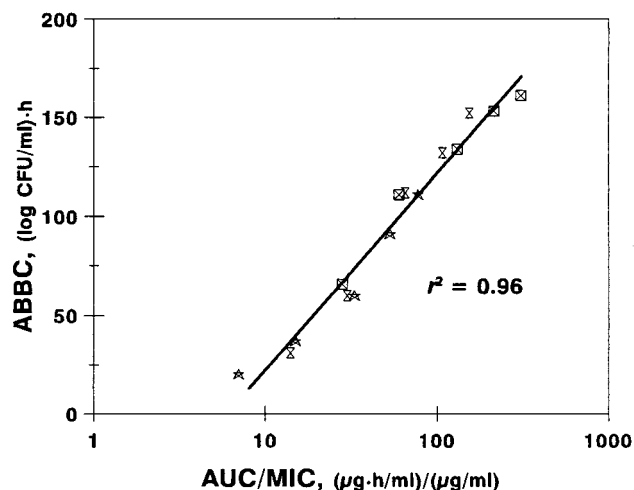


FIG. 6. AUC/MIC-dependent antimicrobial effects of gatifloxacin on *S. pneumoniae* constructed from reported data (Bauernfeind et al., Abstr. 2nd Eur. Congr. Chemother. and 7th Biennial Conf. Antiinfective Agents Chemother., 1996). The data obtained with three strains of *S. pneumoniae* are indicated by different symbols.

Bauernfeind, E. Eberlein, and I. Schneider, Abstr. 2nd Eur. Congr. Chemother. and the 7th Biennial Conf. Antiinfective Agents Chemother., poster T 135, 1996). To establish the respective relationship, on the basis of reported data (Bauernfeind et al., Abstr. 2nd Eur. Congr. Chemother. and 7th Biennial Conf. Antiinfective Agents Chemother., 1996), the antimicrobial effects of gatifloxacin against three differentially susceptible strains of *Streptococcus pneumoniae* (MICs, 0.25, 0.5, and 1 μg/ml) were expressed by areas between the control growth and time-kill curves (ABBC) (5), i.e., by *I<sub>E</sub>* determined within 24 h, when regrowth may or may not be seen. The AUC/MIC ratios that correspond to the doses used in the study by Bauernfeind et al. (Abstr. 2nd Eur. Congr. Chemother. and 7th Biennial Conf. Antiinfective Agents Chemother., 1996), from 100 to 800 mg, were calculated by using equation 2. As seen in Fig. 6, ABBC correlates well with log AUC/MIC in a strain-independent fashion. So, these data confirm the interstrain predictability of the antimicrobial effects of gatifloxacin in terms of the AUC/MIC-response relationship.

Due to the strain-independent pattern of the *I<sub>E</sub>*-log AUC/MIC relationships that were established in the present study with gatifloxacin and ciprofloxacin, equation 1 may be applied to any strain of a given species, including a hypothetical strain for which the MIC is equal to the MIC<sub>50</sub>. In this case equation 1 may be rearranged as follows: *I<sub>E</sub>* = *a'* + *b* log AUC (equation 3), where *a'* is *a* - *b* log MIC<sub>50</sub>. With the MIC<sub>50</sub>s specified in the Materials and Methods section, a specific *a'* can be calculated and the respective species-specific AUC/MIC relationship of *I<sub>E</sub>* can be obtained for each quinolone-bacterial species pair. Then, by combining equations 3 and 2, the respective MIC<sub>50</sub>-adjusted dose-response relationships, *I<sub>E</sub>* = *a'* + *b* log (*c* + *dD* + *eD*<sup>2</sup>) (equation 4), can be derived. The plots of the dose-dependent *I<sub>E</sub>*s that might be produced by gatifloxacin and ciprofloxacin for hypothetical representatives of the three bacterial species for which MICs are equal to the respective MIC<sub>50</sub>s are shown in Fig. 7.

As seen in Fig. 7, the *I<sub>E</sub>*-log *D* plots for gatifloxacin are positioned to the left of those for ciprofloxacin, showing that the same antimicrobial effect might be provided by much lower absolute doses of the new quinolone. For example, to provide

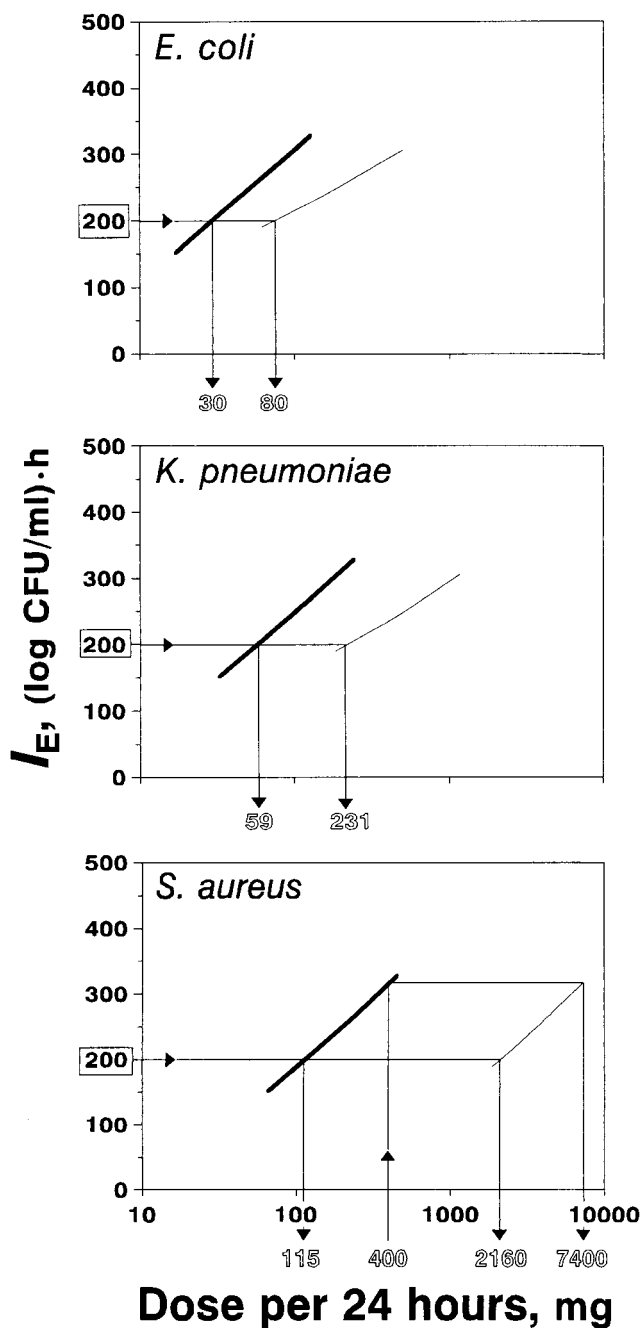


FIG. 7. Dose-dependent antimicrobial effects of gatifloxacin (bold curves) and ciprofloxacin (thin curves) on hypothetical strains of *E. coli*, *K. pneumoniae*, and *S. aureus*. The doses that provided the same  $I_E$  are indicated by the transparent symbols.

an  $I_E$  of 200 (log CFU/ml) · h that corresponds to an AUC/MIC of 125 ( $\mu\text{g} \cdot \text{h}/\text{ml}$ )/( $\mu\text{g}/\text{ml}$ ) for ciprofloxacin for the gram-negative organisms, the 24-h doses ( $D_{24\text{h}}$ ) of gatifloxacin might be 2.7-fold (*E. coli*) and 3.9-fold (*K. pneumoniae*) lower than the respective  $D_{24\text{h}}$ s of ciprofloxacin. Due to the more striking contrast between the intrinsic activities of the quinolones against *S. aureus* ( $\text{MIC}_{50\text{s}}$ , 0.08  $\mu\text{g}/\text{ml}$  for gatifloxacin and 0.52  $\mu\text{g}/\text{ml}$  for ciprofloxacin), the difference between the equiefficient  $D_{24\text{h}}$ s is even more pronounced: 115 mg versus two doses of 1,080 mg, respectively. On the other hand, to

provide the  $I_E$  of 314 (log CFU/ml) · h produced by the clinically accepted 400-mg  $D_{24\text{h}}$  of gatifloxacin against *S. aureus*, a  $D_{24\text{h}}$  of two doses of 3,700 mg of ciprofloxacin would be necessary, and this dose exceeds the ciprofloxacin  $D_{24\text{h}}$ s that might be given clinically. As the extrapolated relationship between  $D$  and AUC of ciprofloxacin, two doses of 3,700 mg, which is equal to a  $D_{24\text{h}}$  of 7,400 mg, is out of the actual  $D$  range in the AUC- $D$  set fitted by equation 2, the latter estimate is more conditional than the estimates for the other organisms. However, it does reflect the order of difference between the quinolone doses that might be necessary to provide the same antimicrobial effect.

The  $\text{MIC}_{50}$ -adjusted relationships between  $I_E$  and  $D_{24\text{h}}$  may be useful for the generalization of the findings obtained with specific representatives of a given species. However, they may or may not predict a clinical  $D_{24\text{h}}$  of the newly developed quinolone that should be at least as efficient as a clinically accepted  $D_{24\text{h}}$  of the older quinolone against similarly susceptible species, i.e., against gram-negative bacteria. Indeed, the estimated equiefficient  $D_{24\text{h}}$ s of gatifloxacin and ciprofloxacin against *E. coli* and *K. pneumoniae* strains for which the  $\text{MICs}$  are equal to the  $\text{MIC}_{50\text{s}}$  appeared to be much lower (Fig. 7) than, for example, the clinical  $D_{24\text{h}}$  of ciprofloxacin. With *E. coli*, the gatifloxacin and ciprofloxacin equiefficient  $D_{24\text{h}}$ s were 30 mg and two doses of 40 mg, respectively, and with *K. pneumoniae* they were 60 mg and two doses of 115 mg, respectively, which are much lower than a 400-mg dose for the  $D_{24\text{h}}$  of gatifloxacin or two doses of 500 mg for the  $D_{24\text{h}}$  of ciprofloxacin. Moreover, even if the  $D_{24\text{h}}$ s were compared at the highest level of  $I_E$  observed in our experiments [ca. 300 (log CFU/ml) · h for ciprofloxacin], they would still be lower, i.e., 100 mg of gatifloxacin and two doses of 220 mg of ciprofloxacin for *E. coli* and 190 mg of gatifloxacin and two doses of 520 mg of ciprofloxacin for *K. pneumoniae*, than the clinically relevant  $D_{24\text{h}}$ s, at least of gatifloxacin. These differences are so substantial that any extrapolation of the estimated equiefficient  $D_{24\text{h}}$ s to the clinical  $D_{24\text{h}}$ s would be quite speculative.

To avoid incorrect extrapolations, the antimicrobial effects of the quinolones might be compared by using bacteria for which the  $\text{MIC}_{50\text{s}}$  are comparable to the established MIC breakpoint for ciprofloxacin (0.18  $\mu\text{g}/\text{ml}$ ). Among the organisms studied, *E. coli* 37 ( $\text{MIC}_{50\text{s}}$ , 0.3 and 0.2  $\mu\text{g}/\text{ml}$  for gatifloxacin and ciprofloxacin, respectively) and *K. pneumoniae* 56 ( $\text{MIC}_{50\text{s}}$ , 0.2 and 0.12  $\mu\text{g}/\text{ml}$  for gatifloxacin and ciprofloxacin, respectively) meet this requirement most easily. On the basis of the respective dose-response curves, the predicted  $D_{24\text{h}}$ s of gatifloxacin (354 mg with *E. coli* 37 and 330 mg with *K. pneumoniae* 56) that might produce the same effects [ $I_E$ s of 194 and 221 (log CFU/ml) · h, respectively] as two doses of 500 mg for the  $D_{24\text{h}}$  of ciprofloxacin are close to the proposed 400-mg dose for the  $D_{24\text{h}}$  of the new quinolone. A similar analysis might also be applied not only to the specific strains studied but also to a more representative organism for which the  $\text{MIC}_{50}$  meets the requirement described above. *Serratia marcescens* may be an appropriate example: susceptibility testing performed with both quinolones in the same experimental setting (1) reported  $\text{MIC}_{50\text{s}}$  of gatifloxacin (0.25  $\mu\text{g}/\text{ml}$ ) and ciprofloxacin (0.13  $\mu\text{g}/\text{ml}$ ) which are comparable to ciprofloxacin's MIC breakpoint (0.18  $\mu\text{g}/\text{ml}$ ). By assuming species-independent patterns of the  $I_E$ -log AUC/MIC relationships, the  $D_{24\text{h}}$  of gatifloxacin that might produce the same effect [ $I_E = 217$  (log CFU/ml) · h] as two doses of 500 mg for the  $D_{24\text{h}}$  of ciprofloxacin is also close to the proposed 400-mg dose for the  $D_{24\text{h}}$  of the new quinolone (380 mg). Perhaps the estimated  $D_{24\text{h}}$ s of trovafloxacin, equivalent to two doses of 500 mg for the  $D_{24\text{h}}$  of ciprofloxacin, appeared to be so close to the clinically accepted

trovafloxacin  $D_{24h}$ , 199, 226, and 203 mg versus 200 mg (9), because for the three gram-negative strains studied the MICs were comparable (0.18  $\mu\text{g/ml}$ ). However, the apparent similarity of the predicted and clinically accepted quinolone doses may only be a chance observation, as the results depend highly on the MICs for arbitrarily selected organisms. Additional in vitro-in vivo correlations are needed to verify the clinical relevance of these predictions.

It should be noted in the present study that greater antimicrobial effects of gatifloxacin were demonstrated both in terms of  $D$ -response and AUC/MIC-response relationships. As with trovafloxacin and ciprofloxacin (7, 9), a given AUC/MIC ratio of the longer-acting quinolone (gatifloxacin) provided a more pronounced antimicrobial effect than the same AUC/MIC ratio of the shorter-acting quinolone (ciprofloxacin). These data highlight the important role of the longer half-lives of the newer extended-spectrum quinolones whose pharmacokinetic profiles result in a greater antimicrobial effect.

In conclusion, this study supports the applicability of our approach to the prediction of equivalent AUC/MIC breakpoints and equiefficient doses of quinolones on the basis of the species- and strain-independent AUC/MIC relationships of the antimicrobial effect over a wide range of in vitro simulated AUC/MIC ratios (7, 9). Further studies with other pharmacokinetically different quinolones are needed to verify this approach.

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