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MIC-Based Interspecies Prediction of the Antimicrobial Effects of Ciprofloxacin on Bacteria of Different Susceptibilities in an In Vitro Dynamic Model

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Multiple predictors of fluoroquinolone antimicrobial effects (AMEs) are not usually examined simultaneously in most studies. To compare the predictive potentials of the area under the concentration-time curve (AUC)-to-MIC ratio (AUC/MIC), the AUC above MIC (AUC_{eff}), and the time above MIC (T_{eff}), the kinetics of killing and regrowth of four bacterial strains exposed to monoexponentially decreasing concentrations of ciprofloxacin were studied in an in vitro dynamic model. The MICs of ciprofloxacin for clinical isolates of *Staphylococcus aureus*, *Escherichia coli* 11775 (I) and 204 (II), and *Pseudomonas aeruginosa* were 0.6, 0.013, 0.08, and 0.15 μg/ml, respectively. The simulated values of AUC were designed to provide similar 1,000-fold (*S. aureus*, *E. coli* I, and *P. aeruginosa*) or 2,000-fold (*E. coli* II) ranges of the AUC/MIC. In each case except for the highest AUC/MIC ratio, the observation periods included complete regrowth in the time-kill curve studies. The AME was expressed by its intensity, I_E (the area between the control growth and time-kill and regrowth curves up to the point where the viable counts of regrowing bacteria are close to the maximum values observed without drug). For most AUC ranges the I_E-AUC curves were fitted by an E_{max} (maximal effect) model, whereas the effects observed at very high AUCs were greater than those predicted by the model. The AUCs that produced 50% of maximal AME were proportional to the MICs for the strains studied, but maximal AMEs ($I_{E_{max}}$) and the extent of sigmoidicity (s) were not related to the MIC. Both T_{eff} and log AUC/MIC correlated well with I_E ($r^2 = 0.98$ in both cases) in a species-independent fashion. Unlike T_{eff} or log AUC/MIC, a specific relationship between I_E and log AUC_{eff} was inherent in each strain. Although each I_E and log AUC_{eff} plot was fitted by linear regression ($r^2 = 0.97$ to 0.99), these plots were not superimposed and therefore are bacterial species dependent. Thus, AUC/MIC and T_{eff} were better predictors of ciprofloxacin's AME than AUC_{eff}. This study suggests that optimal predictors of the AME produced by a given quinolone (intraquinolone predictors) may be established by examining its AMEs against bacteria of different susceptibilities. T_{eff} was shown previously also to be the best interquinolone predictor, but unlike AUC/MIC, it cannot be used to compare different quinolones. AUC/MIC might be the best predictor of the AME in comparisons of different quinolones.

Several predictors of the antimicrobial effect, including the ratio of the area under the concentration-time curve (AUC) to MIC (AUC/MIC), AUC above MIC (AUC_{eff}), time above MIC (T_{eff}), etc., have been examined in many studies published during the last decade (2, 3, 12, 14–18). Practical recommendations for rational antibiotic dosing derived from these studies have generally been accepted, despite some reported contradictions among actual comparisons of the predictors. We recently analyzed possible reasons for conflicting reports on some predictors of fluoroquinolone antimicrobial effects, including AUC/MIC, AUC_{eff}, and T_{eff} (10). Based on findings obtained with ciprofloxacin and trovafloxacin in our in vitro dynamic model and on the data reported by other investigators, we showed that the use of (i) inadequate experimental designs, (ii) inappropriately combined data with different quinolones and dosing regimens, and (iii) suboptimal quantitation of the effect itself all have contributed to this controversy.

We have suggested that it is useful to distinguish between intra- and interquinolone predictors of the antimicrobial effect. The intraquinolone predictors (AUC/MIC, AUC_{eff}, and T_{eff}) may be used to predict the effects of a given drug administered at various doses. The interquinolone predictor (T_{eff}) predicts the effect of one quinolone based on the predictor-response relationship established with another quinolone (10). This in vitro study was performed with pharmacokinetically different quinolones and discriminated between inter- and intraquinolone predictors. However, it did not discriminate among the several intraquinolone predictors, possibly because the bacterial strains studied had similar susceptibilities to the tested drugs. To verify this hypothesis, we examined the relative value of AUC/MIC, AUC_{eff}, and T_{eff} as intraquinolone predictors of the antimicrobial effect of ciprofloxacin on differentially susceptible bacteria.

MATERIALS AND METHODS

Antimicrobial agent. Ciprofloxacin lactate powder, kindly provided by Bayer AG, was used in the study. Stock solutions of the quinolone were prepared in sterile distilled water.

Bacterial strains. The clinical isolates of *Staphylococcus aureus* 452, *Escherichia coli* 11775 (I) and 204 (II), and *Pseudomonas aeruginosa* 48 were used in the study. Susceptibility testing was performed in duplicate in Ca^{2+}- and Mg^{2+}-supplemented Mueller-Hinton broth at an inoculum size of 10^6 CFU/ml at 24 h postexposure. The MICs for *S. aureus*, *E. coli* I and II, and *P. aeruginosa* were 0.6, 0.013, 0.08, and 0.15 μg/ml, respectively.

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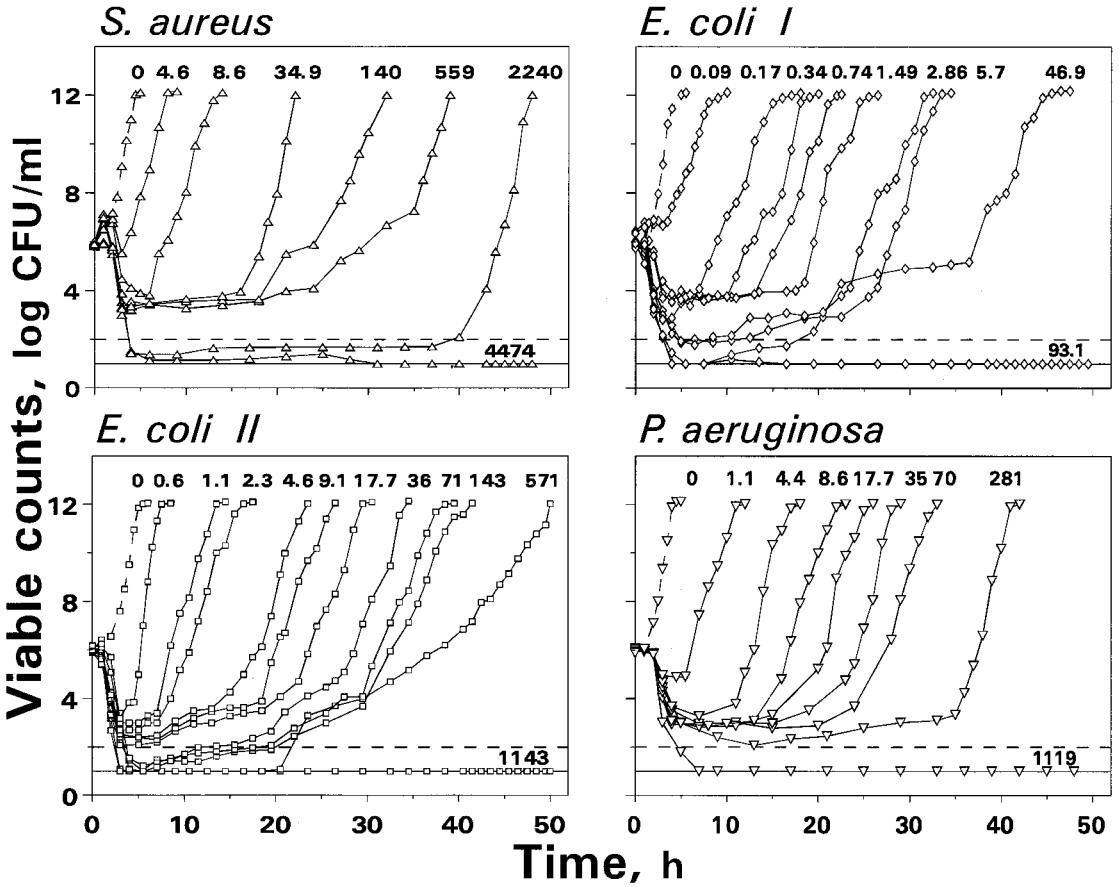

FIG. 1. Kinetics of killing and regrowth of different microorganisms exposed to ciprofloxacin. The simulated AUCs (in microgram · hours per milliliter) are indicated by the numbers at each curve. The dotted line indicates the low limit of accurate detection.

Simulated pharmacokinetic profiles. A series of monoexponential profiles mimicking the single-dose pharmacokinetics of ciprofloxacin were simulated. The simulated half-life ($t_{1/2}$) of 4 h was consistent with values reported in humans: 3.2 to 5.0 h (1, 13, 19). Regardless of the bacterial strain, the simulated initial concentrations of ciprofloxacin were designed to provide similar ≈1,000-fold ranges of the AUC/MIC for *S. aureus*, *E. coli* I, and *P. aeruginosa* and a 2,000-fold range for *E. coli* II. In each case the highest AUC/MIC provided complete bacterial killing with no regrowth. The respective AUC ranges in the experiments with *S. aureus*, *E. coli* I and II, and *P. aeruginosa* were 4.6 to 4474, 0.09 to 93.1, 0.6 to 1,143, and 1.1 to 1,119 μg · h/ml.

In vitro dynamic model and operating procedure. A previously described dynamic model (11) was used in the study. Briefly, the model consists of two connected flasks, one containing fresh Ca^{2+}- and Mg^{2+}-supplemented Mueller-Hinton broth and the other, the central unit, containing the same broth plus a bacterial culture (control growth experiments) or a bacterial culture plus antibiotic (killing and regrowth experiments). The central unit is incubated at 37°C in a shaking water bath. Peristaltic pumps (Minipuls 2; Gilson) circulate fresh nutrient medium to the bacterium-containing or bacterium- and antibiotic-containing medium and from the central 40-ml unit at a flow rate of 7 ml/h to simulate ciprofloxacin pharmacokinetics. Hence, the clearance provided by the designed flow rate plus the volume of the central unit ensure monoexponential elimination of ciprofloxacin and bacteria from the system with an elimination rate constant of 0.17 h^{-1} ($t_{1/2}$ = 4 h). Accurate simulations of the desired pharmacokinetic profiles are provided by maintaining constant flow rates and a constant volume of the central unit. Validation of the model by the determination of ciprofloxacin concentrations showed no systematic deviation of the observed values from the expected ones (10).

The system is filled with sterile Mueller-Hinton broth and is placed in a temperature-regulated incubator at 37°C. The central unit is inoculated with 18-h cultures of *S. aureus*, *E. coli* I or II, or *P. aeruginosa*, and after a further 2-h incubation, ciprofloxacin is injected into the central unit. The resulting exponentially growing cultures approach approximately 10^6 CFU/ml. The duration of the experiments is defined in each case as the time until the antibiotic-exposed bacteria (N_A) reach the maximum numbers observed in the absence of antibiotic (control growth [N_C]), i.e., the time when N_A becomes equal to N_C. In all cases experiments are stopped when N_A reaches $\geq 10^{11}$ CFU/ml. Since the experiments that simulate low AUC/MIC ratios meet this requirement earlier than those that simulate high AUC/MIC, the duration of the former experiments is shorter than the latter: the lower the AUC/MIC ratio, the shorter the observation period.

Quantitation of bacterial growth and killing. In each experiment 0.1-ml samples are withdrawn from the bacterium-containing media in the central unit throughout the observation period, at first every 30 min, later hourly, then every 3 h, and, during the last 6 to 7 h, again hourly. These samples are subjected to serial 10-fold dilutions with chilled, sterile 0.9% NaCl and are plated in duplicate on Mueller-Hinton agar. Antibiotic carryover at low counts is avoided by washing the bacteria with 0.9% NaCl. After overnight incubation at 37°C the resulting bacterial colonies are counted, and the numbers of CFU per milliliter are calculated. The lower limit of accurate detection is 10^2 CFU/ml. High within-day and interday reproducibilities of the results have been reported previously (10).

To reveal possible changes in susceptibility, the quinolone concentrations (C_{regrowth}) that correspond to the time when numbers of surviving organisms in the regrowth curves reached the level of the initial inoculum were determined in each run (9). The AUC/MIC-induced systematic increase in the C_{regrowth} that might relate to resistance was observed only with *E. coli* II at the two highest AUCs (143 and 571 μg · h/ml). Therefore, only negligible changes in the susceptibilities of the ciprofloxacin-exposed bacteria were assumed. Moreover, the appearance of regrowth of all four microorganisms was associated with ratios of the quinolone concentration to the MIC of unity. These data are consistent with previous findings of unchanged susceptibility of bacteria exposed to single doses of five fluoroquinolones in an in vitro dynamic model (20).

Quantitative evaluation of the antimicrobial effect and comparison of its predictors. The antimicrobial effect was expressed by its intensity (I_E), which describes the area between control growth and bacterial killing and regrowth curves from the zero point, the moment of drug input into the model, up to the time when viable counts on the regrowth curve are close to the maximum values observed without drug (8). The upper limit of bacterial numbers in the regrowth and control growth curves and the lower limit in the time-kill curve used to determine the I_E were 10^{11} CFU/ml (11) and 10 CFU/ml (the theoretical limit of detection), respectively. Also, the time to reduce the initial inoculum 100-fold (N_0) − $T_{99\%}$ (where $T_{99\%}$ is the time to reduce the starting inoculum 100-fold) and the difference between logarithms of N_0 and the numbers of surviving organisms at 24 h (N_τ) − $\Delta\log N_\tau$ were calculated in each case, if applicable.

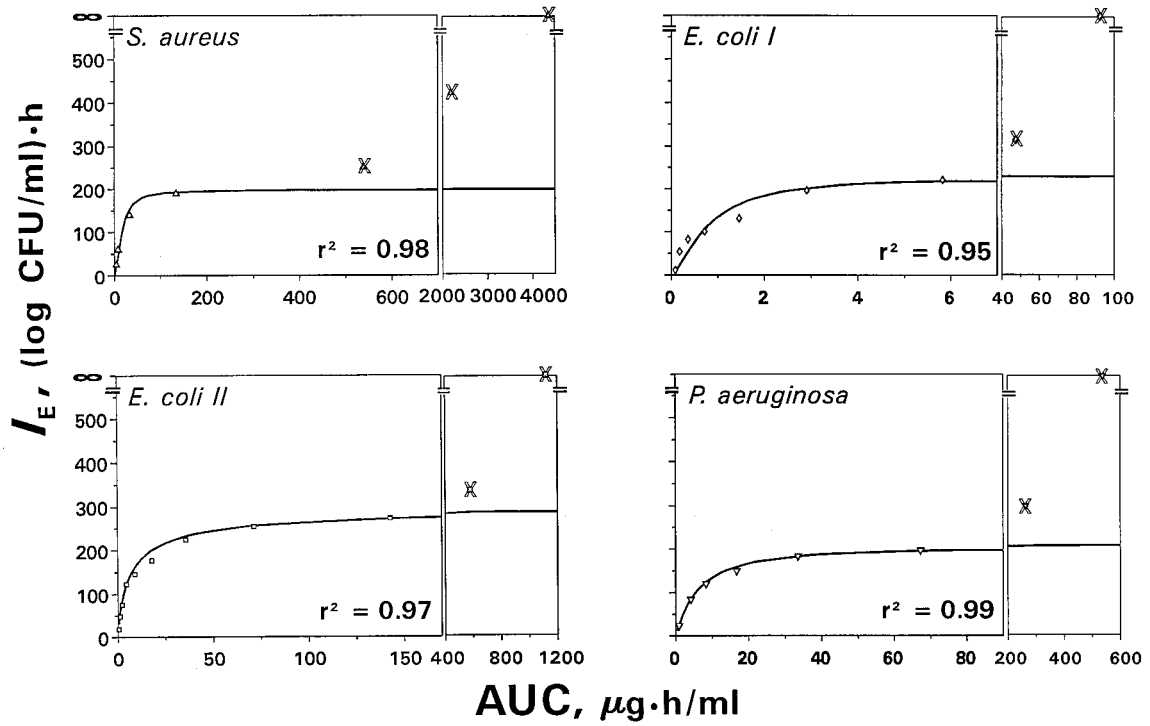

FIG. 2. AUC-dependent antimicrobial effects of ciprofloxacin as described by equation 1. The systematically diverging points are crossed out.

The I_E-AUC data sets obtained with each of the strains studied were fitted by an E_{max} model:

$$I_E = I_{E_{max}} AUC^s/(AUC_{50}{}^s + AUC^s) \quad (1)$$

where $I_{E_{max}}$ is the maximal value of I_E, AUC_{50} is the AUC associated with $I_{E_{max}}/2$, and s is a parameter reflecting the degree of sigmoidicity which is equivalent to the Hill coefficient.

To compare the predictive potentials of AUC/MIC, AUC_{eff}, and T_{eff}, the antimicrobial effects expressed by I_E were related to each predictor for each bacterial strain. Nonlinear regression analysis of the I_E-AUC data by equation 1 as well as correlation and regression analyses of the relationships between I_E and log AUC/MIC, log AUC_{eff}, or T_{eff} were performed with STATISTICA software (version 4.3; StatSoft, Inc.). Statistical comparison of the regressions was performed at P equal to 0.05.

RESULTS

The time courses of viable counts that reflect killing and regrowth of *S. aureus*, *E. coli* I and II, and *P. aeruginosa* exposed to monoexponentially decreasing concentrations of ciprofloxacin as well as the respective control growth curves are shown in Fig. 1. At all AUCs except for the maximum values, regrowth followed a considerable reduction in bacterial numbers. The time shift of the regrowth phase to the right along the time axis was distinctly dependent on the simulated AUC: the higher the AUC, the later the regrowth. Regardless of the bacterial strain, the appearance of bacterial regrowth was associated with ciprofloxacin concentrations which were close to the respective MICs.

As seen in Fig. 2, for most AUC ranges, the I_E-AUC data obtained with each organism were properly fitted by equation 1, although one to two points in each I_E-AUC plot systematically diverged from the respective theoretical curve. This might be interpreted as evidence for qualitative changes in drug-pathogen interactions at high AUCs resulting in complete killing of bacteria (I_E approaches infinity at the highest AUCs). Parameters of the E_{max} (maximal effect) model are presented in Table 1. At least one of the model parameters, the AUC that produced 50% of maximal antimicrobial effects (AUC_{50}), was directly proportional to the MIC, whereas no systematic relations could be established between MIC and $I_{E_{max}}$ or s. Therefore, regardless of the degree of sigmoidicity, saturation of the antimicrobial effect was observed at comparable I_Es but at distinctly different AUCs.

Model-fitted I_E-AUC curves were converted into linear I_E-log AUC plots for each of the strains studied (data not shown). Despite striking contrasts between I_E-AUC curves that reflect ciprofloxacin's effects against different organisms, the I_Es plotted against MIC-corrected AUCs appeared to be bacterial species independent. As seen in Fig. 3, the I_E-log AUC/MIC and I_E-T_{eff} data obtained with the four organisms were superimposed and fitted by the same linear regressions ($r^2 = 0.98$ in both cases).

Unlike AUC/MIC and T_{eff}, AUC_{eff} displayed MIC-dependent I_E-log AUC_{eff} relationships for each of the strains studied. As seen in Fig. 3, a specific relationship was inherent in each of them with reasonably high correlation coefficients. Statistically significant differences were established between *S. aureus* and *E. coli* I and II or *P. aeruginosa* in terms of the intercepts but not the regression coefficients. Moreover, the intercepts were distinctly dependent on the MICs: the higher the MIC, the

TABLE 1. Susceptibilities of bacteria and parameters of the E_{max} model

Microorganism and strain	MIC (μg/ml)	AUC_{50} (μg · h/ml)	$I_{E_{max}}$ [(log CFU/ml) · h]	s
S. aureus	0.60	17	198	1.8
E. coli I	0.013	0.8	230	1.5
E. coli II	0.08	7.0	295	0.8
P. aeruginosa	0.15	6.0	210	1.1

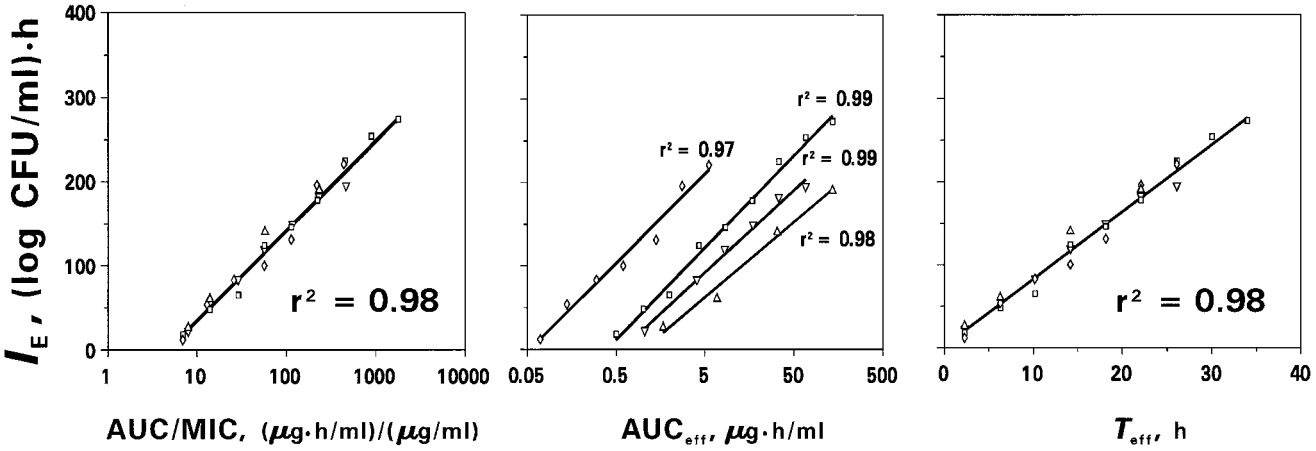

FIG. 3. Antimicrobial effects of ciprofloxacin related to the different predictors. △, *S. aureus*; ◇, *E. coli* I; □, *E. coli* II; ▽, *P. aeruginosa*.

lower the intercept. No differences were found between similarly susceptible strains of *E. coli* II or *P. aeruginosa*.

DISCUSSION

Regardless of the susceptibility to ciprofloxacin, all four bacterial strains used in this study displayed qualitatively similar saturable relationships between the antimicrobial effect as expressed by its intensity and the AUC of the antibiotic. For most AUC ranges studied, the I_E versus AUC data were fitted by the E_{max} model. However, in each case the I_Es observed at high AUCs diverged systematically from the model-predicted values. This limitation of the model is quite expected, since the maximal value of I_E approaches infinity when no regrowth occurs, and therefore, it should deviate from the plateau (Fig. 2). Among three parameters of the E_{max} model, $I_{E_{max}}$, s, and AUC_{50}, only the last one could be related to the MIC: the higher MIC, the higher the AUC_{50}.

This study suggests that intraquinolone predictors of the antimicrobial effect, AUC/MIC, AUC_{eff}, and T_{eff}, may be prop-

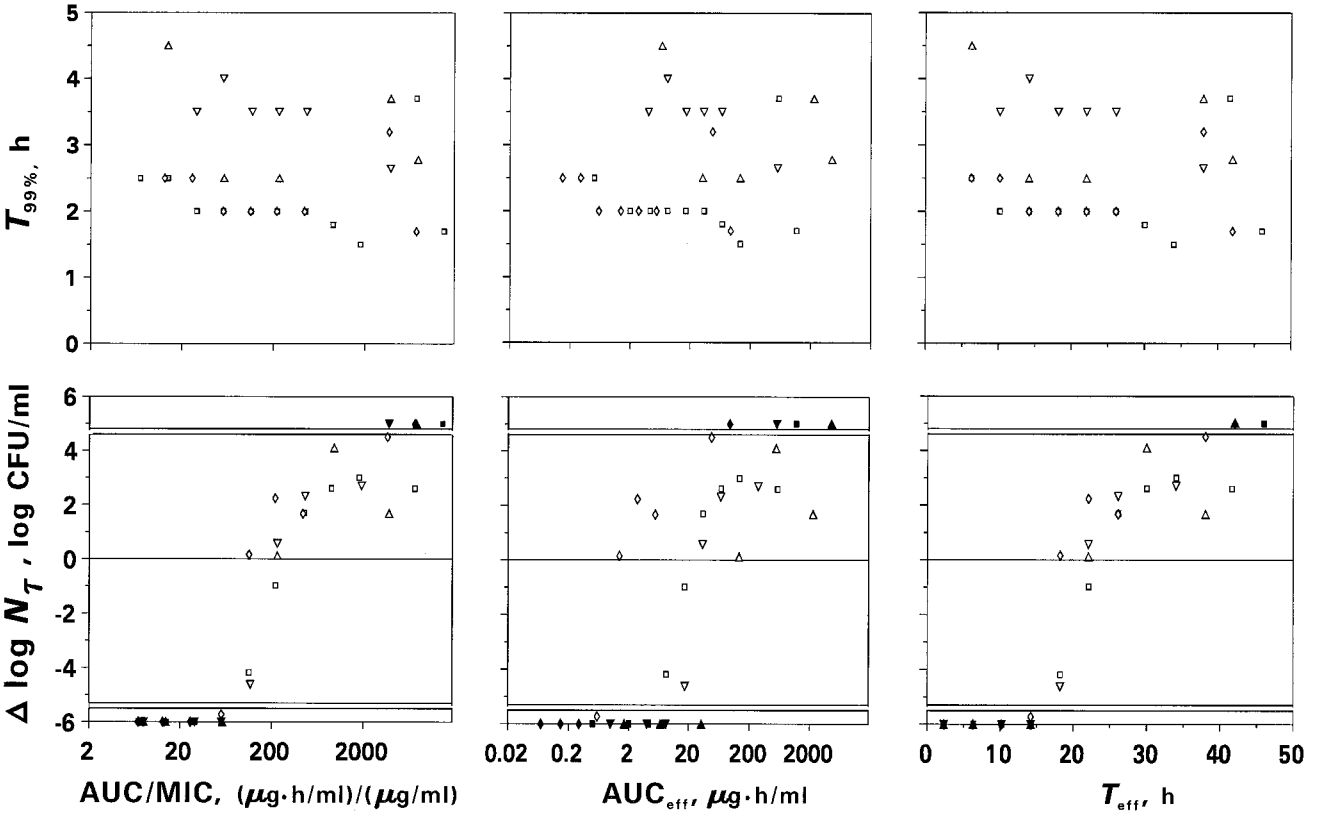

FIG. 4. Antimicrobial effects of ciprofloxacin expressed by $T_{99\%}$ and $\Delta\log N_\tau$ as related to the different predictors. The $\Delta\log N_\tau$ values which were near the upper ($\Delta\log N_\tau \rightarrow 5$) and lower ($\Delta\log N_\tau \rightarrow -6$) limits of accurate detection and which were therefore ignored in the correlation analysis are indicated by filled symbols. △, *S. aureus*; ◇, *E. coli* I; □, *E. coli* II; ▽, *P. aeruginosa*.

erly distinguished by examining them in terms of their respective I_E relationships established with bacteria of different susceptibilities. Although all three predictors covaried strongly for each organism taken separately, only log AUC/MIC and T_{eff} covaried for all four organisms taken together ($r^2 > 0.99$). Much looser correlations were established between AUC/MIC and AUC_{eff} ($r^2 = 0.56$) or between T_{eff} and log AUC_{eff} ($r^2 = 0.61$). Based on the data that were obtained, AUC/MIC and T_{eff} were better species-independent predictors of ciprofloxacin's effects than AUC_{eff}. Thus, the hypothesis formulated in the introduction appears to be true, and the approach described may be a reliable "test system" for selection of the optimal predictor(s) of the antimicrobial effects produced by a given fluoroquinolone.

However, AUC/MIC and T_{eff} cannot be considered similarly acceptable for the comparison of different quinolones. As reported earlier (10), unlike I_E-log AUC/MIC, the I_E-T_{eff} relationships could not distinguish pharmacokinetically different quinolones (ciprofloxacin and trovafloxacin) and the I_E-T_{eff} relationships cannot be used to compare them. Therefore, AUC/MIC, but not T_{eff} or AUC_{eff}, might be the most reliable predictor of the antimicrobial effects in a comparison of different quinolones. Recently, the effects of trovafloxacin and ciprofloxacin (4, 6, 7) and gatifloxacin and ciprofloxacin (5) were compared on the basis of the I_E-log AUC/MIC relationships established in in vitro dynamic models. Results similar to those reported here were observed.

The results of predictor examinations may be highly dependent on the endpoints used to quantitate the effect (10). In this study, the use of the intensity of the antimicrobial effect as an endpoint provided ultimate discrimination among AUC_{eff} and AUC/MIC or T_{eff}. It should be noted that more conventional endpoints, i.e., $T_{99\%}$ and $\Delta\log N_\tau$, did not properly distinguish the three predictors. As seen in Fig. 4, both $\Delta\log N_\tau$ and, especially, $T_{99\%}$ show predictor-response relationships that are much more erratic and scattered than those established with I_E. There is no correlation between $T_{99\%}$ and log AUC/MIC, log AUC_{eff}, or T_{eff} ($r^2 = 0.01$ to 0.02), and only weak correlations exist between each of the three predictors and $\Delta\log N_\tau$ ($r^2 = 0.34$ to 0.59). Moreover, $\Delta\log N_\tau$ could not be determined precisely at low values of AUC/MIC, AUC_{eff}, and T_{eff}. Also, there is a tendency toward saturation of the effect expressed by $\Delta\log N_\tau$ at high values of AUC/MIC and T_{eff}. The latter phenomenon was shown to be artificial and to misrepresent the true AUC-response relationship (11).

Overall, this and other (10) studies suggest that optimal intra- and interquinolone predictors as well as optimal predictors of antimicrobial effects in comparisons of different quinolones may be established in studies performed with in vitro dynamic models. Knowledge of optimal predictors might be useful in comparing new quinolone compounds in terms of their antimicrobial effect-predictor relationships.

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