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Antistaphylococcal Effect Related to the Area under the Curve/MIC Ratio in an In Vitro Dynamic Model: Predicted Breakpoints versus Clinically Achievable Values for Seven Fluoroquinolones

Alexander A. Firsov,[1]* Irene Y. Lubenko,[1,2] Sergey N. Vostrov,[1] Yury A. Portnoy,[1] and Stephen H. Zinner[3]

Department of Pharmacokinetics & Pharmacodynamics, Gause Institute of New Antibiotics,[1] and Institute of Normal Physiology, Russian Academy of Medical Sciences,[2] Moscow, Russia, and Mount Auburn Hospital, Harvard Medical School, Cambridge, Massachusetts[3]

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Prediction of the relative efficacies of different fluoroquinolones is often based on the ratios of the clinically achievable area under the concentration-time curve (AUC) to the MIC, usually with incorporation of the MIC_{50} or the MIC_{90} and with the assumption of antibiotic-independent patterns of the AUC/MIC-response relationships. To ascertain whether this assumption is correct, the pharmacodynamics of seven pharmacokinetically different quinolones against two clinical isolates of *Staphylococcus aureus* were studied by using an in vitro model. Two differentially susceptible clinical isolates of *S. aureus* were exposed to two 12-h doses of ciprofloxacin (CIP) and one dose of gatifloxacin (GAT), gemifloxacin (GEM), grepafloxacin (GRX), levofloxacin (LVX), moxifloxacin (MXF), and trovafloxacin (TVA) over similar AUC/MIC ranges from 58 to 932 h. A specific bacterial strain-independent AUC/MIC relationship with the antimicrobial effect (I_E) was associated with each quinolone. Based on the I_E-log AUC/MIC relationships, breakpoints (BPs) that are equivalent to a CIP AUC/MIC ratio of 125 h were predicted for GRX, MXF, and TVA (75 to 78 h), GAT and GEM (95 to 103 h) and LVX (115 h). With GRX and LVX, the predicted BPs were close to those established in clinical settings (no clinical data on other quinolones are available in the literature). To determine if the predicted AUC/MIC BPs are achievable at clinical doses, i.e., at the therapeutic AUCs (AUC_{ther}s), the AUC_{ther}/MIC_{50} ratios were studied. These ratios exceeded the BPs for GAT, GEM, GRX, MXF, TVA, and LVX (750 mg) but not for CIP and LVX (500 mg). AUC/MIC ratios above the BPs can be considered of therapeutic potential for the quinolones. The highest ratios of AUC_{ther}/MIC_{50} to BP were achieved with TVA, MXF, and GEM (2.5 to 3.0); intermediate ratios (1.5 to 1.6) were achieved with GAT and GRX; and minimal ratios (0.3 to 1.2) were achieved with CIP and LVX.

Prediction of comparative efficacies among fluoroquinolones is often based on the ratios of the clinically achievable area under the concentration-time curve (AUC) to the MIC, usually with incorporation of the MIC_{50} or MIC_{90} (31). In fact, these antimicrobial effect predictors rather than the effect itself are often used in these comparisons. Such a replacement might seem appropriate, although it would be correct only if it were assumed that the AUC/MIC-response relationships are antibiotic independent. However, our in vitro pharmacodynamic studies that simulate quinolone pharmacokinetics (13, 18, 19, 43) did not support this assumption: a specific AUC/MIC-response relationship was shown to be inherent in each individual quinolone.

The present study was designed to compare the pharmacodynamics of seven pharmacokinetically different fluoroquinolones against *Staphylococcus aureus*, to delineate AUC/MIC-response relationships, and to predict the respective AUC/MIC breakpoints (BPs) relative to clinically achievable AUC/MIC ratios.

* Corresponding author. Mailing address: Department of Pharmacokinetics & Pharmacodynamics, Gause Institute of New Antibiotics, Russian Academy of Medical Sciences, 11 Bolshaya Pirogovskaya St., Moscow 119021, Russia. Phone: 7(095) 708-3341. Fax: 7(095) 245-0295. E-mail: firsov@dol.ru.

MATERIALS AND METHODS

Antimicrobial agents. Ciprofloxacin (CIP), gatifloxacin (GAT), gemifloxacin (GEM), grepafloxacin (GRX), levofloxacin (LVX), moxifloxacin (MXF), and trovafloxacin (TVA) were kindly provided by Bayer Corporation (West Haven, CT), Bristol-Myers Squibb Pharmaceutical (New Brunswick, NJ), SmithKline Beecham Pharmaceutical (Collegeville, PA), Glaxo-Wellcome (Research Triangle Park, NC) Ortho-McNeil Pharmaceutical (Raritan, NJ), Bayer Corporation, and Pfizer Inc. (Groton, CT), respectively.

Bacterial strains. Two clinical isolates of methicillin-resistant *Staphylococcus aureus*, *S. aureus* 944 and 916, were used in this study. Susceptibility testing was performed in triplicate by broth microdilution techniques at 24 h postexposure with the organism grown in Ca^{2+} (20 to 25 mg/liter)- and Mg^{2+} (10 to 12.5 mg/liter)-supplemented Mueller-Hinton broth (BBL, Becton Dickinson and Company, Sparks, MD) at an inoculum size of 10^6 CFU/ml. To determine precise values, the MICs of the quinolones were determined in parallel by using doubling dilutions with starting concentrations of 3, 4, and 5 mg/liter, as described previously (16). The MICs of the quinolones are presented in Table 1, and the respective weighted mean geometric values of the reported MIC_{50}s are presented in Table 2.

In vitro dynamic model and simulated pharmacokinetic profiles. A previously described dynamic model (17) was used in the study. The operation procedure, the reliability of the 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 (14).

A series of monoexponential profiles that mimic two consecutive 12-h doses of CIP and single-dose administrations of GAT, GEM, GRX, LVX, MXF, and TVA were simulated. The simulated half-lives (4, 7, 7.4, 11.6, 6.8, 12.1, and 10 h, respectively) represent the weighted medians of the values reported for humans: 3.2 to 5.0 h (4, 24), 6.0 to 8.4 h (30), 5.9 to 8.8 h (2), 10.1 to 12.7 h (10), 6.0 to 7.4 h (20), 9.3 to 14.0 h (38), and 7.2 to 9.9 h (41, 46), respectively. The simulated

TABLE 1. MICs of the fluoroquinolones for *S. aureus*

S. aureus strain	Quinolone MIC (μg/ml)						
	CIP	GAT	GEM	GRX	LVX	MXF	TVA
944	0.30	0.15	0.01	0.06	0.25	0.18	0.15
916	1.25	1.25	0.04	0.30	0.60	0.38	0.60

AUC/MIC ratios of CIP and LVX varied from 116 to 932 h; and those of GAT, GEM, GRX, MXF, and TVA varied from 58 to 466 h.

Quantitation of the time-kill curves. In each experiment multiple sampling of bacterium-containing medium from the central compartment was performed throughout the observation period. The duration of the experiments was defined in each case as the time until antibiotic-exposed bacteria reached the maximum numbers observed in the absence of antibiotic ($\geq 10^9$ CFU/ml). The procedure used to quantitate the viable counts has been reported elsewhere (14). The limit of accurate detection was 2×10^2 CFU/ml.

Quantitation of the antimicrobial effect and the relationships to its predictors. Based on the time-kill data, the intensity of the antimicrobial effect (I_E; which is the area between control growth and time-kill curves) (12, 17) was determined from time zero to the time that the effect could no longer be detected, i.e., the time after the last fluoroquinolone dose at which the number of antibiotic-exposed bacteria reached 10^9 CFU/ml.

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

The I_E-log AUC/MIC relationships were used to predict the effects of each individual quinolone on a hypothetical strain of *S. aureus* with MICs equal to the respective MIC_{50}s (Table 2) at therapeutic AUCs (AUC_{ther}s), i.e., the AUCs that correspond to two 500-mg doses of CIP, a 400-mg dose of GAT, a 320-mg dose of GEM, a 400-mg dose of GRX, a 500-mg dose of LVX, a 400-mg dose of MXF, and a 200-mg dose of TVA. In addition, the effect of LVX at the AUC that corresponds to that achieved with its 750-mg dose was predicted. The necessary AUC_{ther}s were calculated by using linear dose relationships (GEM [2], LVX [20], and MXF [38]) or curvilinear dose relationships (CIP [4], GAT [30], GRX [10], and TVA [41, 46]) of the AUC. To consider the different levels of protein binding of CIP, GAT, GEM, GRX, LVX, MXF, and TVA, the AUC_{ther}s were corrected by factors of 0.74, 0.80, 0.30, 0.57, 0.70, 0.60, and 0.28, respectively (the reported free fractions of the quinolones in plasma are presented in Table 2). Then, the unbound AUC_{ther}s ($AUC_{ther,f}$s) were related to the respective I_Es.

RESULTS

The time-kill curves for *S. aureus* 944 and 916 exposed to seven fluoroquinolones at one of the simulated AUC/MIC ratios are shown in Fig. 1. With each quinolone, bacterial regrowth followed the rapid killing of the bacteria during the first 3 to 4 h, which led to almost identical minimal numbers of surviving organisms. Despite similar initial killing rates, the times to regrowth were quinolone specific. For example, treatment with CIP resulted in the earliest regrowth of *S. aureus* 944, and this was 20 h shorter than that with treatment with GRX, with which the regrowth was the latest. Based on the time to regrowth, the quinolones may be arranged as follows: CIP < LVX < GAT ≤ GEM < TVA < MXF ≤ GRX. Similar patterns of quinolone pharmacodynamics were established at other simulated AUC/MICs with *S. aureus* 944 and 916 (data not shown).

With each quinolone, the antistaphylococcal effect expressed by I_E correlated well with the log AUC/MIC in a strain-independent ($r^2 \geq 0.98$) but quinolone-specific fashion (Fig. 2). The I_E-log AUC/MIC relationships were of different slopes: minimal with CIP and maximal with MXF and GRX. This resulted in distinct differences among the I_Es produced by a

TABLE 2. Quinolone doses, MIC_{50}s, clinically achievable AUCs, and AUC/MIC ratios

Quinolone	Dose (mg)	AUC_{ther} (μg · h/ml)	MIC_{50} (μg/ml)[a]	AUC_{ther}/MIC_{50} (h)	Free fraction (%)[b]	$AUC_{ther,f}$ (μg · h/ml)	$AUC_{ther,f}/MIC_{50}$ (h)
CIP	500	22	0.62	35	74	16	26
GAT	400	32.9	0.23	143	80	26	114
GEM	320	12.4	0.04	310	30	4	93
GRX	600	19	0.15	127	57	11	72
LVX	500	45.6	0.7	65	70	32	46
LVX	750	82.6	0.7	118	70	58	83
MXF	400	32.9	0.16	206	60	20	123
TVA	200	19	0.1	190	28	5	53

[a] Weighted geometric mean MIC_{50}s from reported data on CIP (1, 3, 8, 21, 27, 29, 37, 42, 44; F. Daschner, U. Frank, and K. Huber, Abstr. 6th Int. Symp. New Quinolones, abstr. S12.27, 1998; D. Felmingham, M. J. Robbins, I. Mathias, K. Ingley, H. Bhogal, and R. N. Gruneberg, Abstr. 20th Int. Congr. Chemother., abstr. 3276, 1997; F. H. Kayser, P. Santanam, and E. Huf, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. E-197, 1998; E. Loza, M. I. Morosini, F. Almaraz, M. C. Negri, F. Baquero, and Spanish Collaborative Group Microbiology Service, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. E-206, 1998; B. Minassian, G. Warr, B. Kolek, B. Ryan, J. Fung-Tomc, and D. Bonner, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. E-181, 1998; K. Paek, M.-Y. Kim, and Y. S. Choo, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-090, 1998; F. J. Schmitz, J. Verhoef, A. C. Fluit, H. P. Heinz, U. Hadding, and M. E. Jones, Abstr. 8th Int. Congr. Infect. Dis., abstr. 13.007, 1998; C. Torres-Viera, C. Wennersten, R. C. Moellering, Jr., and G. Eliopoulos, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. E-193, 1998; C. von Eiff and G. Peters, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. E-212a, 1998; B. Wiedemann, Abstr. 8th Int. Congr. Infect. Dis., abstr. 13.035, 1998) GAT (3, 26, 27; B. Minassian, G. Warr, B. Kolek, B. Ryan, J. Fung-Tomc, and D. Bonner, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. E-181, 1998; C. Torres-Viera, C. Wennersten, R. C. Moellering, Jr., and G. Eliopoulos, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. E-193, 1998), GEM (K. Paek, M.-Y. Kim, and Y. S. Choo, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-090, 1998; K. Paek, M.-Y. Kim, and Y. S. Choo, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-092, 1998), GRX (1, 21, 25, 29, 42, 44; F. Daschner, F., U. Frank, and K. Huber, Abstr. 6th Int. Symp. New Quinolones, abstr. S12.27, 1998; K. Paek, M.-Y. Kim, and Y. S. Choo, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-090, 1998; B. Wiedemann, Abstr. 8th Int. Congr. Infect. Dis., abstr. 13.035, 1998), LVX (3, 25, 35, 37; D. Felmingham, M. J. Robbins, I. Mathias, K. Ingley, H. Bhogal, and R. N. Gruneberg, Abstr. 20th Int. Congr. Chemother., abstr. 3276, 1997; F. Kayser, P. Santanam, and E. Huf, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. E-197, 1998; C. Torres-Viera, C. Wennersten, R. C. Moellering, Jr., and G. Eliopoulos, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. E-193, 1998), MXF (3, 21, 25, 28, 35, 37; J. Blondeau, R. Laskowski, and D. Vaughan, Abstr. 37th Intersci. Conf. Antimicrob. Agents Chemother., abstr. F155, 1997; J. Dubois and C. St-Pierre, Abstr. 6th Int. Symp. New Quinolones, abstr. S10.03, 1998; Kayser, F. H., P. Santanam, and E. Huf, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. E-197, 1998; E. Loza, M. I. Morosini, F. Almaraz, M. C. Negri, F. Baquero, and Spanish Collaborative Group Microbiology Service, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. E-206, 1998; F. Schmitz, J. Verhoef, A. C. Fluit, H. P. Heinz, U. Hadding, and M. E. Jones, Abstr. 8th Int. Congr. Infect. Dis., abstr. 13.007, 1998; L. Verbist and J. Verhaegen, Abstr. 8th Int. Congr. Infect. Dis., abstr. 13.015, 1998; C. von Eiff and G. Peters, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. E-212a, 1998; B. Wiedemann, Abstr. 8th Int. Congr. Infect. Dis., abstr. 13.035, 1998), and TVA (3, 8, 21, 25–28, 33; C. Torres-Viera, C. Wennersten, R. C. Moellering, Jr., and G. Eliopoulos, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. E-193, 1998; C. von Eiff and G. Peters, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. E-212a, 1998).

[b] Free fractions of CIP (5, 9, 45, 50), GAT (30), GEM (48), GRX (7, 11, 50), LVX (20, 50), MXF (36, 39, 40, 47), and TVA (6, 41, 50) in plasma.

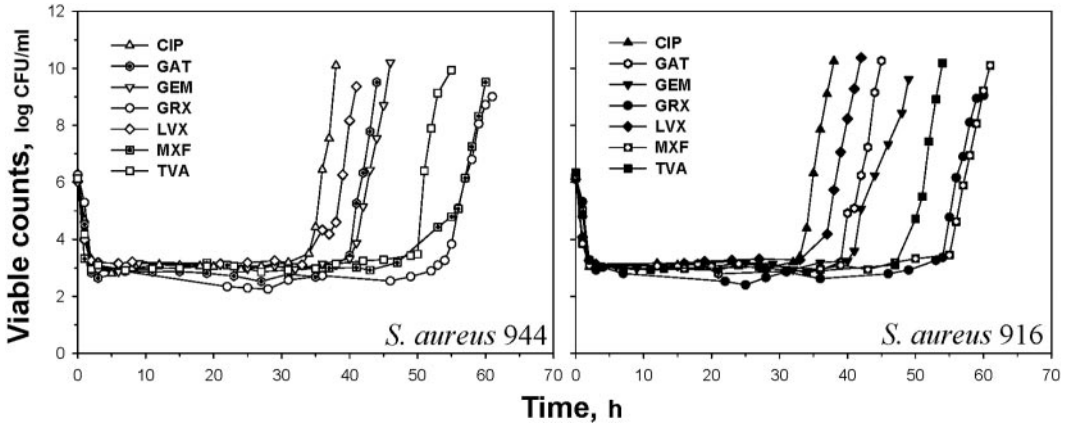

FIG. 1. Time-kill curves of quinolone-exposed *S. aureus* 944 and *S. aureus* 916 at comparable AUC/MIC ratios (466 h).

given AUC/MIC ratio of the different quinolones. For example, at an AUC/MIC of 125 h, the antistaphylococcal effects of GRX and MXF were 1.4 times greater than that of CIP.

On the other hand, the I_E-versus-log AUC/MIC plots allow prediction of the AUC/MIC ratios for new quinolones that may be equivalent to the clinically proven AUC/MIC BPs for an older quinolone. By using a 125-h AUC/MIC ratio of CIP as a reference, the BPs predicted for six other quinolones were estimated to be 75 h (GRX and MXF), 78 h (TVA), 95 h (GAT), 103 h (GEM), and 115 h (LVX) (Fig. 2, inset). Based on these predictions, 1.5-fold smaller AUC/MIC ratios of GRX, MXF, and TVA should provide the antimicrobial effect that is considered acceptable for CIP.

DISCUSSION

This study further demonstrates the bacterial strain-independent but quinolone-specific patterns of AUC/MIC relationships of the antistaphylococcal effect as expressed by the I_E parameter. Earlier, similar relationships were reported with GAT-exposed *Streptococcus pneumoniae* (49), CIP- and GAT-exposed *Escherichia coli* and *Klebsiella pneumoniae* (43), as

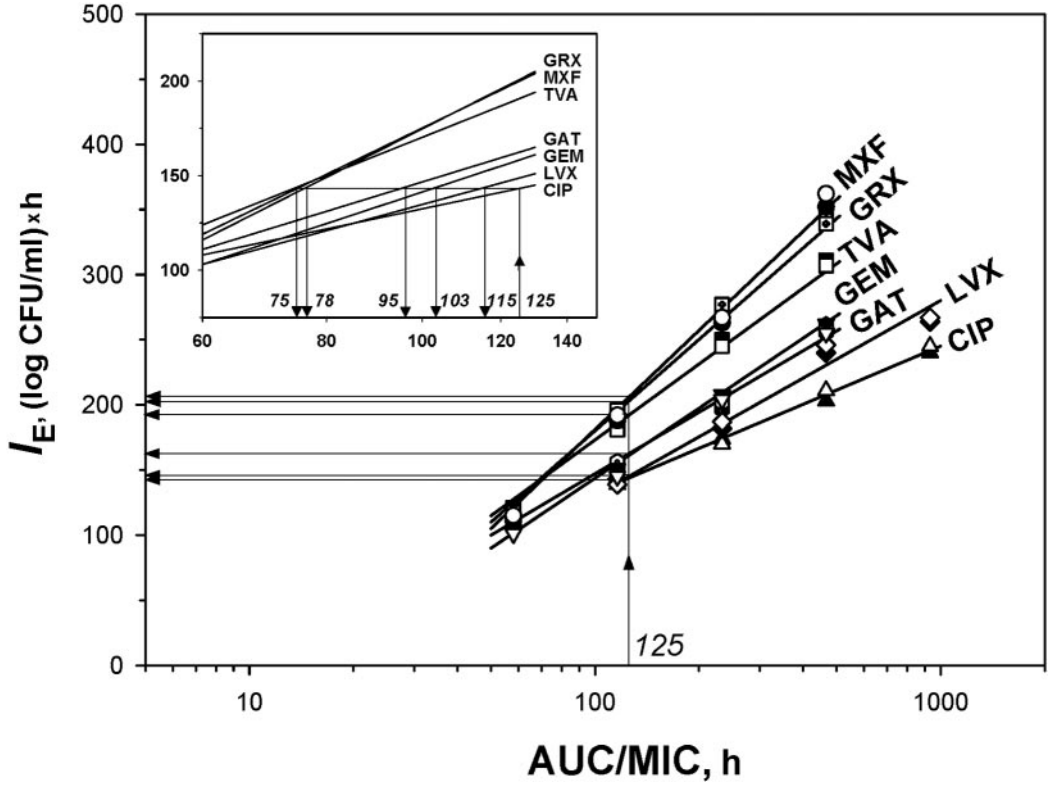

FIG. 2. AUC/MIC-dependent antistaphylococcal effects of seven quinolones. The equivalent AUC/MIC BPs are indicated by the italicized numbers in the inset. The symbols are the same as those in Fig. 1.

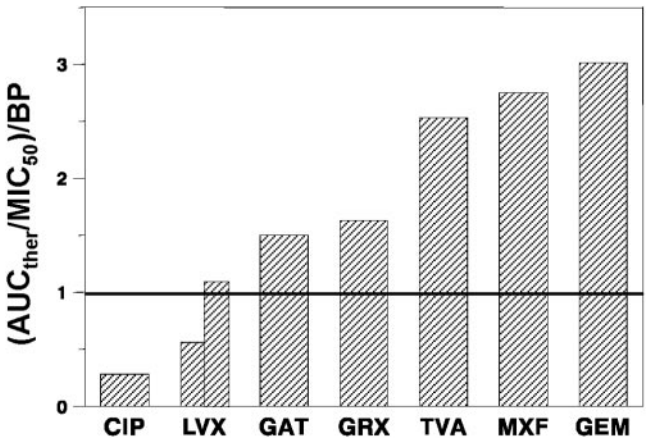

FIG. 3. Index of quinolone therapeutic potentials expressed as the clinically achievable ratio of AUC_{ther}/MIC_{50} related to the predicted AUC/MIC BPs. For LVX, the left bar reflects the 500-mg dose and the right bar reflects the 750-mg dose.

well as CIP- and TVA-exposed *Pseudomonas aeruginosa* (15). Based on the I_E-log AUC/MIC relationships that were established with seven pharmacokinetically different quinolones against *S. aureus*, equiefficient BPs of the AUC/MIC ratio were predicted. To achieve the same antistaphylococcal effect provided by a clinically proven 125-h BP of the CIP AUC/MIC (23), the respective AUC/MIC ratios of six other quinolones were shown to be lower: 75 to 78 h (GRX, MXF, and TVA), 95 to 103 h (GAT and GEM), and 115 h (LVX).

Are these predictions clinically relevant? To answer this question, the BPs predicted in vitro should be compared with proven BPs that have been reported from clinical studies. Unfortunately, such BPs have been established for only two novel quinolones. With GRX, the AUC/MIC BP was estimated to be 75 h (22); and with LVX, the respective peak concentration-to-MIC ratio (C_{max}/MIC) was estimated to be 12.2 (32), which corresponds to an AUC/MIC of 110 h (34). Based on the I_E-log AUC/MIC relationships established in the present study, the AUC/MIC BP for grepafloxacin (78 h) is very close to the 75-h value established in the clinical setting and the AUC/MIC BP (115 h) predicted for LVX is close to the 110-h value established in a clinical setting. There are only two examples of the in vitro-in vivo correlations. Further evidence is needed to confirm the clinical relevance of AUC/MIC breakpoints predicted in in vitro studies by the use of dynamic models.

Are the predicted AUC/MIC BPs attainable in patients treated with the recommended quinolone doses? More specifically, can these doses provide AUC/MICs above the BPs? By taking the therapeutic value of AUC (AUC_{ther}) related to the MIC_{50} (Table 2) as the clinically achievable AUC/MIC ratio, the respective AUC_{ther}/MIC_{50} ratios exceed the BPs for GAT, GEM, GRX, MXF, TVA, and LVX (750 mg) but not CIP and LVX (500 mg). The ratios of AUC_{ther}/MIC_{50} to BP can be considered an index of the quinolone therapeutic potential. As

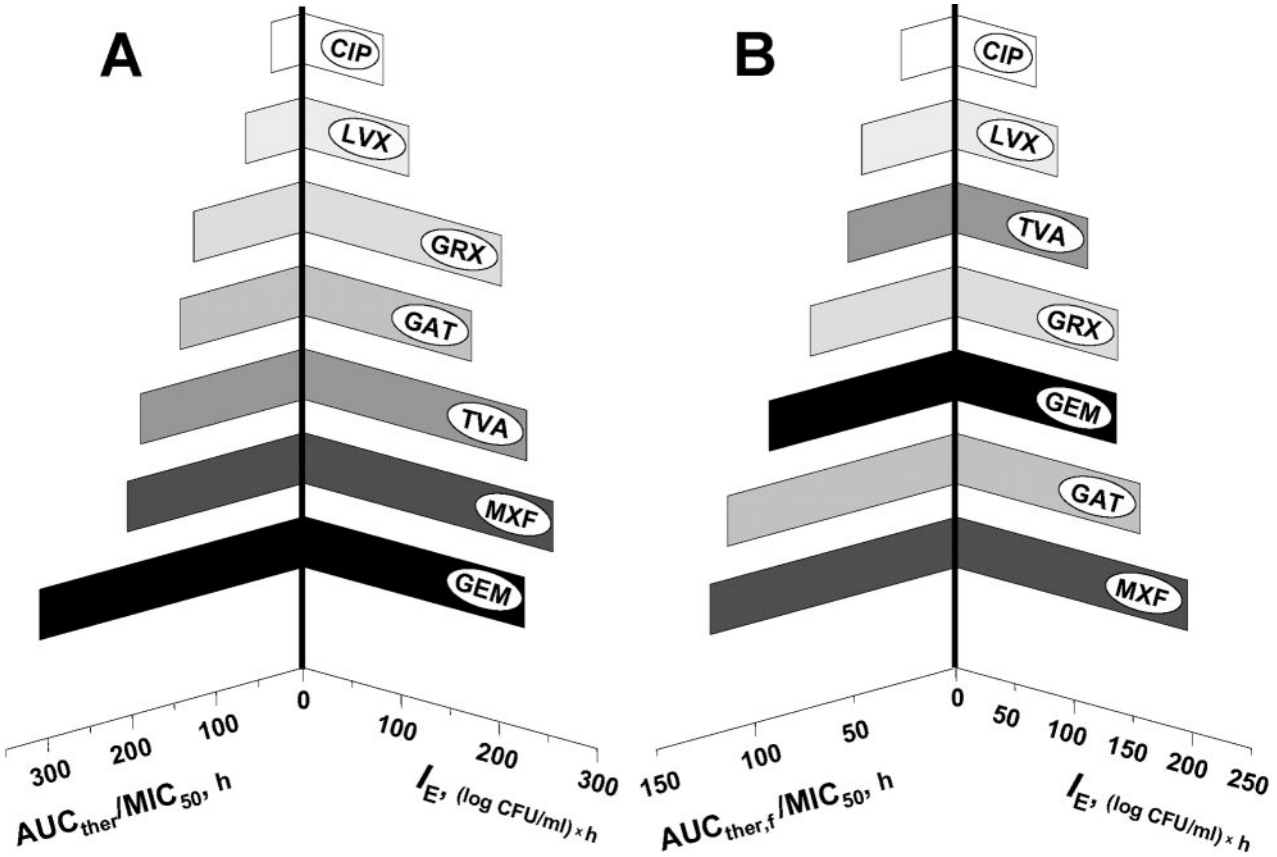

FIG. 4. AUC_{ther}/MIC_{50} (A) and $AUC_{ther,f}/MIC_{50}$ (B) compared with the respective I_Es.

seen in Fig. 3, the highest ratios of AUC_{ther}/MIC_{50} to BP are achieved with TVA, MXF, and GEM (2.5 to 3.0), intermediate values are achieved with GAT and GRX (1.5 to 1.6), and minimal values are achieved with CIP (0.3) and LVX (0.6 and 1.2 for 500- and 750-mg doses, respectively). This analysis predicts the greater therapeutic potentials of TVA, MXF, and GEM than GAT, GRX, and LVX (750 mg) but the lack of such potentials for LVX (500 mg) or CIP.

As pointed out in the introduction, the ratios of the AUC_{ther} or the therapeutic value of C_{max} to MIC_{50} or MIC_{90} rather than determination of the antimicrobial effect itself are often considered as a basis for the direct comparison of antibiotics: the greater that $AUC_{ther}/MIC_{50(90)}$ or $C_{max}/MIC_{50(90)}$ is, the better. Our study gives further evidence that different quinolones may produce different effects at a given AUC/MIC ratio. Quinolone-specific AUC/MIC-antimicrobial effect relationships are illustrated by comparing the AUC_{ther}/MIC_{50}s with their respective I_Es (Fig. 4A). Despite the similar AUC_{ther}/MIC_{50}s achieved with GRX and GAT, the predicted I_E of GRX appeared to be greater than that of GAT. Moreover, despite the higher AUC_{ther}/MIC_{50} ratio for GEM, its effect was less pronounced than that of MXF at a lower AUC_{ther}/MIC_{50} ratio. Therefore, plotting of the AUC_{ther}/MIC_{50} ratios versus I_Es results in a tree with asymmetric branches, and AUC_{ther}/MIC_{50} correlates rather loosely with I_E ($r^2 = 0.85$). This analysis demonstrates the lack of correspondence between the sequence of quinolones arranged by their AUC_{ther}/MIC_{50} ratios and the sequence of quinolones arranged by their antimicrobial effects. So, neither our in vitro study nor others' clinical studies (different BPs reported for CIP [23] and GRX [22]) support the replacement of the effect by its predictor in comparisons among the quinolones.

It is interesting that a tree of the quinolones arranged by the AUC_{ther}/MIC_{50} ratios that consider only free concentrations ($AUC_{ther,f}/MIC_{50}$) (Table 2) is almost symmetric (Fig. 4B). Furthermore, there is a stronger correlation between $AUC_{ther,f}/MIC_{50}$ and I_E (r^2 0.94). In this light, $AUC_{ther,f}/MIC_{50}$ (based on the free drug AUC) might be a better interquinolone predictor of the clinically achievable antimicrobial effect than AUC_{ther}/MIC_{50} (based on total drug AUC).

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