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Worldwide Antimicrobial Susceptibility Patterns and Pharmacodynamic Comparisons of Gatifloxacin and Levofloxacin against *Streptococcus pneumoniae*: Report from the Antimicrobial Resistance Rate Epidemiology Study Team

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The use of fluoroquinolones for the treatment of community-acquired respiratory tract infection is increasing. Since for *Streptococcus pneumoniae* a ratio of the 24-h area under the concentration-time curve (AUC_{24}) for the agent to the MIC (AUC_{24}/MIC) greater than 30 for the fraction of unbound drug (f_u) is the major pharmacokinetic-pharmacodynamic (PK-PD) parameter correlating with bacterial eradication by fluoroquinolones in nonclinical models of infection and in infected patients, the Antimicrobial Resistance Rate Epidemiology Study Team systematically compared the in vitro susceptibility patterns and estimated the probability of attainment of the PK-PD target ratios for gatifloxacin and levofloxacin against pneumococci worldwide. Monte Carlo simulation was used to estimate the probability that gatifloxacin or levofloxacin would achieve an f_u AUC_{24}/MIC ratio of 30 or greater. A total of 10,978 *S. pneumoniae* isolates collected from 1997 to 2000, each indexed by site of infection and geographic region (North America, Latin America, Europe, and Asia-Pacific), were used to estimate the probability mass functions of the microbiological activities for each region considered in the analysis. f_u AUC_{24} probability distribution functions were estimated by using data that were part of each product's submission accepted by the Food and Drug Administration. A 10,000-patient simulation was performed for each drug-organism-region combination. The percentages of strains susceptible to each drug by region were as follows: for gatifloxacin, North America, 99.6%; Latin America, 99.8%; Europe, 99.9%; and Asia-Pacific, 99.2%; for levofloxacin, North America, 99.6%; Latin America, 99.8%; Europe, 99.8%; and Asia-Pacific, 99.1%. The MIC at which 50% of isolates are inhibited (MIC_{50}) and the MIC_{90} of each drug by region were as follows: for gatifloxacin, North America, 0.25 and 0.5 mg/liter, respectively; Latin America, 0.25 and 0.5 mg/liter, respectively; Europe, 0.25 and 0.5 mg/liter, respectively; and Asia-Pacific, 0.25 and 0.5 mg/liter, respectively; for levofloxacin, North America, 1 and 2 mg/liter, respectively; Latin America, 1 and 2 mg/liter, respectively; Europe, 1 and 1 mg/liter, respectively; and Asia-Pacific, 1 and 1 mg/liter, respectively. The probabilities of attaining an f_u AUC_{24}/MIC ratio greater than 30 for each drug by region were as follows: for gatifloxacin, North America, 97.6%; Latin America, 98.3%; Europe, 99.1%; and Asia-Pacific, 98.8%; for levofloxacin, North America, 78.9%; Latin America, 84.1%; Europe, 87.1%; and Asia-Pacific, 86.5%. These results for a very large collection of recent clinical strains demonstrate that, globally, gatifloxacin is two- to fourfold more active than levofloxacin against *S. pneumoniae* and that gatifloxacin has an overall 14.3% higher probability of achieving clinically important PK-PD target ratios than levofloxacin.

The Antimicrobial Resistance Rate Epidemiology Study Team (ARREST) Program was established as a collaborative effort among microbiologists, clinicians, statisticians, and other interested parties in an effort to use antimicrobial surveillance data and analytical techniques to better guide drug therapy and to understand factors predictive of antimicrobial resistance. In the analyses described herein, the ARREST Program used antimicrobial surveillance data from the SENTRY Antimicrobial Surveillance Program. The SENTRY Antimicrobial Surveillance Program contains a robust set of data for a large collection of isolates from around the world and associated information on the MICs for the isolates.

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Although MICs are important, the MIC of a drug for a microorganism is a relatively imprecise index for prediction of clinical outcome, largely because the pharmacokinetic (PK) properties of the drug are not considered. The integration of MIC and PK data by use of PK-pharmacodynamic (PD) models has proved more useful for prediction of the outcome of infection than the use of either PKs or MICs alone. Over the last two decades, it has been established in nonclinical models of infection and in patients that antibacterial effects can usually be correlated to outcome by the use of at least one of three PK-PD indices: first, the time of exposure of the pathogen to concentrations exceeding the MIC of the drug for the pathogen; second, the ratio of the peak concentration of the agent to the MIC for the pathogen; and third, the ratio of the 24-h area under the concentration-time curve (AUC_{24}) for the agent to the MIC for the pathogen (AUC_{24}/MIC ratio) (1, 5, 9).

Most recently, the application of Monte Carlo simulation

with PK data for patient populations, the distributions of MICs for target organisms, and PK-PD target ratios from nonclinical models of infection or clinical data has refined the paradigm for the PD evaluation of antimicrobial compounds (2, 7, 10). In essence, Monte Carlo simulation is a sampling experiment during which the variability or uncertainty in the input variables is taken into consideration. The uncertainty accounted for when Monte Carlo simulation is applied to antimicrobial PDs includes interpatient variability in drug exposure and microbiological susceptibility. Since for *Streptococcus pneumoniae* AUC_{24}/MIC ratios greater than 30 for the fraction of unbound drug (f_u) are the major PK-PD parameter correlating with bacterial eradication by fluoroquinolones in nonclinical models of infection (14, 15; W. A. Craig and D. R. Andes, Abstr. 40th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 289, 2000) and in infected patients (3), the ARREST Program compared contemporary in vitro susceptibilities and estimated the probability of PK-PD target ratio attainment for gatifloxacin and levofloxacin (two prominently used fluoroquinolones) against pneumococci worldwide.

MATERIALS AND METHODS

Simulation plan. The simulation described here was designed to assess the probability of PK-PD target ratio attainment against *S. pneumoniae* for gatifloxacin at a dose of 400 mg once daily and levofloxacin at a dose of 500 mg once daily. The planned simulations used PK data from patient population analyses and microbiological gatifloxacin and levofloxacin susceptibility data for 10,978 strains of *S. pneumoniae* from the SENTRY Program from 1997 to 2000.

The planned simulation size was 10,000 patients for each drug-organism combination by geographical region described below. Sensitivity analyses were planned to determine which input variable (PK data, microbiological susceptibility data) contributed most strongly to the output variable (f_u AUC_{24}/MIC ratio). To estimate the accuracy of each 10,000-patient simulation, the mean, standard deviation, and percentile error around the PK-PD target were calculated with a 95% confidence interval.

Microbiological data. A total of 10,978 *S. pneumoniae* isolates were gathered globally by the SENTRY Program between 1997 and 2000. Isolates were primarily gathered for the following study objectives: objective A, evaluation of isolates from patients with bloodstream infections; objective B, evaluation of isolates from patients with community-acquired respiratory tract infections caused by *S. pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*; and objective C, evaluation of isolates from hospitalized patients with pneumonia. Isolates were forwarded to regional monitors for reference-quality antimicrobial susceptibility testing and confirmation of organism identification.

Participants and monitors. Three reference laboratories functioned as monitor sites during the study period. These included the University of Iowa College of Medicine (for the North American and Latin American regions for isolates collected from 1997 to 2000 and for the European region for isolates collected from 1999 to 2000); Utrecht University, Utrecht, The Netherlands (for the European region for isolates collected from 1997 to 1998); and the Women's and Children's Hospital in Adelaide, Australia (for the Asia-Pacific region for isolates collected from 1998 to 2000). Common reagents and data-processing systems were used.

The number of participating laboratories varied slightly by year and included the following: 5 to 8 sites in Canada (North American region); 26 to 28 sites in the United States (North American region); 10 sites in the Latin American region; 12 to 23 sites in Europe, Israel, and Turkey (the European region); and 17 sites in the Asia-Pacific region (which also includes 1 site in South Africa).

Isolate identification. The species identities of all isolates were confirmed in monitoring laboratories on the basis of Gram stains and colony morphologies, patterns of growth on sheep blood and enriched chocolate agars, catalase reactivities, and the results of sodium deoxycholate solubility tests.

Determination of MIC. Gatifloxacin and levofloxacin powders for susceptibility testing were obtained from their U.S. manufacturers and dispensed into dry-form broth microdilution trays (for isolates collected in 1997, MicroScan; for isolates collected from 1998 to 2000, TREK/Sensititre). Each lot of trays was shared among all monitoring sites, and quality control or validation results were satisfactory in all cases.

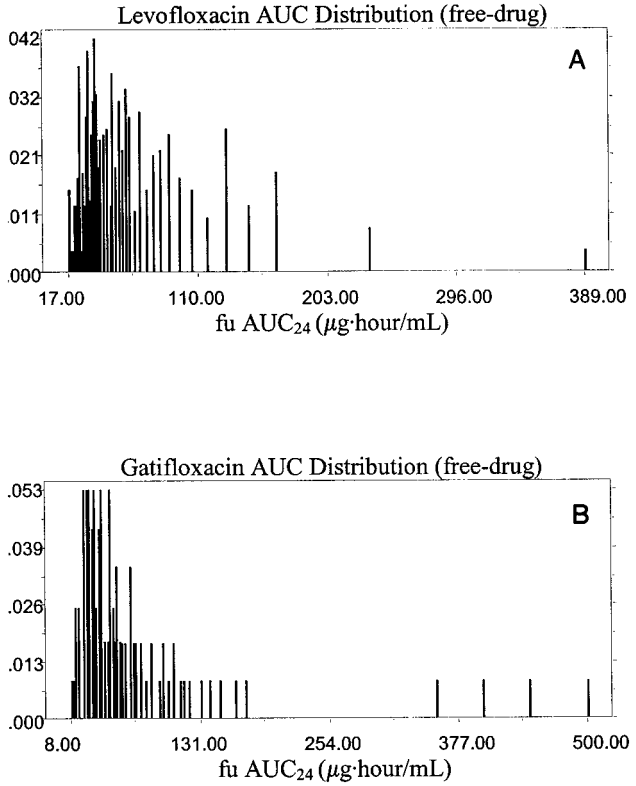

FIG. 1. Estimated probability density functions of f_u AUC_{24} for levofloxacin (A) and f_u AUC_{24} for gatifloxacin (B).

MICs were determined by the broth microdilution method described by the National Committee for Clinical Laboratory Standards (NCCLS) (16). The trays were incubated in ambient air at 35 to 37°C for 20 to 24 h before visual determination of the MICs. A final inoculum concentration of $\sim 5 \times 10^5$ CFU/ml was used and was confirmed by colony counts. The medium used was Mueller-Hinton broth plus 3 to 5% lysed horse blood. Daily quality control testing was conducted with *S. pneumoniae* ATCC 49619 (American Type Culture Collection). The interpretation of results was directed by present NCCLS standards (17).

PK data. Gatifloxacin PK data were obtained for adult patients (ages, 18 years or older) enrolled in a clinical trial conducted at multiple centers. The trials were designed in part to determine the disposition of gatifloxacin in infected patients. The data set included data for 64 acutely ill patients, all of whom had community-acquired infections and were treated with gatifloxacin at a dose of 400 mg every 24 h (2).

Similarly, levofloxacin PK data were obtained for adult patients (ages, 18 years or older) enrolled in clinical trials conducted at multiple centers. The trials were designed in part to determine the disposition of levofloxacin in infected patients, as published previously (18; Levaquin package insert; Ortho-McNeil Pharmaceutical Corporation, Raritan, N.J., 1996). The data set included data for 172 acutely ill patients, all of whom had community-acquired infections and were treated with levofloxacin at a dose of 500 mg every 24 h. The f_u AUC_{24} probability density functions for gatifloxacin and levofloxacin used in the PD analyses are presented in Fig. 1.

Monte Carlo simulation. PK-PD target ratio attainment analyses were done by Monte Carlo simulation. A 10,000-patient population simulation was performed with Crystal Ball 2000.1 software (Decisioneering, Inc., Denver, Colo.) by using the aforementioned PK data in conjunction with the following structural model:

$$f_u\,\mathrm{AUC}_{24}/\mathrm{MIC} = \frac{f_u \cdot \mathrm{AUC}_{24}}{\mathrm{MIC}} \quad (1)$$

The f_u assumed for gatifloxacin was 0.80, and that assumed for levofloxacin was 0.70. Two PK-PD targets were considered in these analyses: an f_u AUC_{24}/MIC ratio of 30 and an f_u AUC_{24}/MIC ratio of 120.

TABLE 1. In vitro activities of levofloxacin and gatifloxacin against 10,978 strains of *S. pneumoniae* stratified by four geographic regions[a]

Region (no. of isolates tested) and drug	Cumulative % of isolates inhibited at MIC (mg/ml) of:							
	≤0.03	0.06	0.12	0.25	0.5	1	2	4
Asia-Pacific (747)								
Gatifloxacin	0.0	0.0	13.0	91.6	99.1	(99.2)[b,c]	99.7	99.9
Levofloxacin	0.0	0.0	0.0	0.0	37.0	98.8	(99.1)[b]	99.3
Europe (2,176)								
Gatifloxacin	0.6	1.9	20.1	87.8	99.7	(99.9)	99.9	99.9
Levofloxacin	0.1	0.1	0.2	0.4	35.8	97.2	(99.8)	99.9
North America (6,700)								
Gatifloxacin	0.2	0.6	8.4	72.8	99.0	(99.6)	99.6	99.9
Levofloxacin	0.1	0.2	0.3	0.5	28.1	89.1	(99.5)	99.5
Latin America (1,355)								
Gatifloxacin	0.5	1.0	8.8	78.2	99.7	(99.9)	99.9	99.9
Levofloxacin	0.1	0.1	0.1	0.4	33.7	93.6	(99.8)	99.8

[a] The susceptibility data for the strains were from the SENTRY Program from 1997 to 2000.
[b] Cumulative percentages at the susceptibility breakpoint criteria of the NCCLS are in parentheses.

Random-number generator. The random-number generator (*r*) routine (multiplicative congruential generator) used the following iterative formula:

$$r < -(630,360,016 \cdot r) \bmod(2^{31} - 1) \quad (2)$$

The generator has a period length of 2,147,483,646, meaning that the cycle of random numbers repeats after approximately 2.15-billion trials.

Sensitivity and numerical stability analyses. Sensitivity analyses for all simulation inputs represented by a distribution (i.e., AUC_{24} and MIC) were carried out in order to determine which variable contributed most strongly to the output variable. The mean and standard deviation error were calculated with 95% confidence to estimate the accuracy of each 10,000-patient simulation.

RESULTS

Antimicrobial potency comparisons. Table 1 lists the comparative activities of gatifloxacin and levofloxacin (cumulative percentages of isolates inhibited over an 8-$\log_2$ dilution range) for each geographic region. Between regions, very modest (twofold) variations in the MICs at which 50% of isolates are inhibited (MIC_{50}s) and MIC_{90}s were noted for each fluoroquinolone; however, the concentration at which >99% of strains were susceptible was identical for each drug. The overall MIC_{50} of gatifloxacin (0.25 μg/ml) was fourfold lower than that of levofloxacin (1.0 μg/ml); and the proportions of strains susceptible at the NCCLS breakpoint for gatifloxacin were 99.2 to 99.9% (average, 99.7%), which were essentially the same as those for levofloxacin (99.1 to 99.8%; average, 99.6%). If equal breakpoint concentrations were used for each drug (≤1.0 μg/ml), the spectrum for gatifloxacin remains the same (99.7%), but the levofloxacin coverage of *S. pneumoniae* would be somewhat lower (89.1% for the North American region to 98.8% for the Asia-Pacific region; average, 94.9%). The numbers of fluoroquinolone-resistant *S. pneumoniae* isolates were detected in the following order, from highest to lowest: Asia-Pacific region (0.8 to 0.9%) > North America (0.4 to 0.5%) > Europe = Latin America (0.1 to 0.2%).

PK-PD comparisons. Figure 2A through D provide the f_u AUC_{24}/MIC ratio frequency distributions from the simulations for gatifloxacin and levofloxacin stratified by geographic region.

Summary statistics for each gatifloxacin simulation stratified by geographic region were similar. Across the four geographic regions the mean f_u AUC_{24}/MIC ratio ranged from 245 to 309 and the median f_u AUC_{24}/MIC ratio ranged from 144 to 184. Additionally, each f_u AUC_{24}/MIC ratio distribution was leptokurtic (peaked) and highly skewed to the right (>1.0). The precision of the mean, the median, and the percentile that included the PK-PD target f_u AUC_{24}/MIC ratio of 30 were consistently high across geographic regions (range of precision around the mean, 2.54 to 3.14%; range around the median, 0.01 to 5.96%; range of percentile that included the PK-PD target ratio, 0.01 to 7.22%).

Similarly, summary statistics for each levofloxacin simulation stratified by geographic region were comparable between regions. Across the four geographic regions the mean f_u AUC_{24}/MIC ratio ranged from 72 to 78 and the median f_u AUC_{24}/MIC ratio ranged from 51 to 58. Like those for gatifloxacin, each f_u AUC_{24}/MIC ratio distribution was leptokurtic and highly skewed to the right (>1.0). The precision of the mean, the median, and the percentile that included the PK-PD target f_u AUC_{24}/MIC ratio of 30 were consistently high across geographic regions (range of the precision around the mean, 1.71 to 3.77%; range around the median, 1.53 to 4.09%; range of the percentile that included the PK-PD target ratio, 0.46 to 3.18%).

The overall level of precision across the simulations for gatifloxacin and levofloxacin suggests a robust and accurate sampling experiment. Output distributions (f_u AUC_{24}/MIC ratios) were more sensitive to MIC input probability mass functions than AUC_{24} input probability distribution functions. This is expected, since considerably more variability is inherent in the MIC distributions than in the AUC_{24} distributions.

The probabilities of attaining an f_u AUC_{24}/MIC ratio greater than 30 were as follows for each drug by region: for gatifloxacin, North America, 97.6%; Latin America, 98.3%; Europe, 99.1%; and Asia-Pacific, 98.8%; for levofloxacin, North America, 78.9%; Latin America, 84.1%; Europe, 87.1%; and Asia-Pacific, 86.5%. Across geographic regions, the overall probability of attaining an f_u AUC_{24}/MIC ratio of 120 or greater for gatifloxacin was 67.2%, and that for levofloxacin was 14.6%.

DISCUSSION

The PD properties of fluoroquinolones have been well elucidated. Data obtained from animal models of sepsis, in vitro PD experiments, and clinical outcome studies indicate that the magnitude of the AUC_{24}/MIC ratio can be used to predict response. For instance, we have previously demonstrated that for gatifloxacin and levofloxacin an f_u AUC_{24}/MIC ratio of ≥33.7 is associated with the best bacterial eradication rates in the treatment of patients with respiratory tract infections involving *S. pneumoniae* (3). At an f_u AUC_{24}/MIC ratio of <33.7 the probability of a positive response was 64%, and at an f_u AUC_{24}/MIC ratio of ≥33.7 the probability of a positive response was 100% ($P < 0.01$). These observations are supported by numerous in vitro and animal infection model data that support a PK-PD f_u AUC_{24}/MIC ratio target of approximately ≥30 (14, 15; Craig and Andes, 40th ICAAC; N. A.

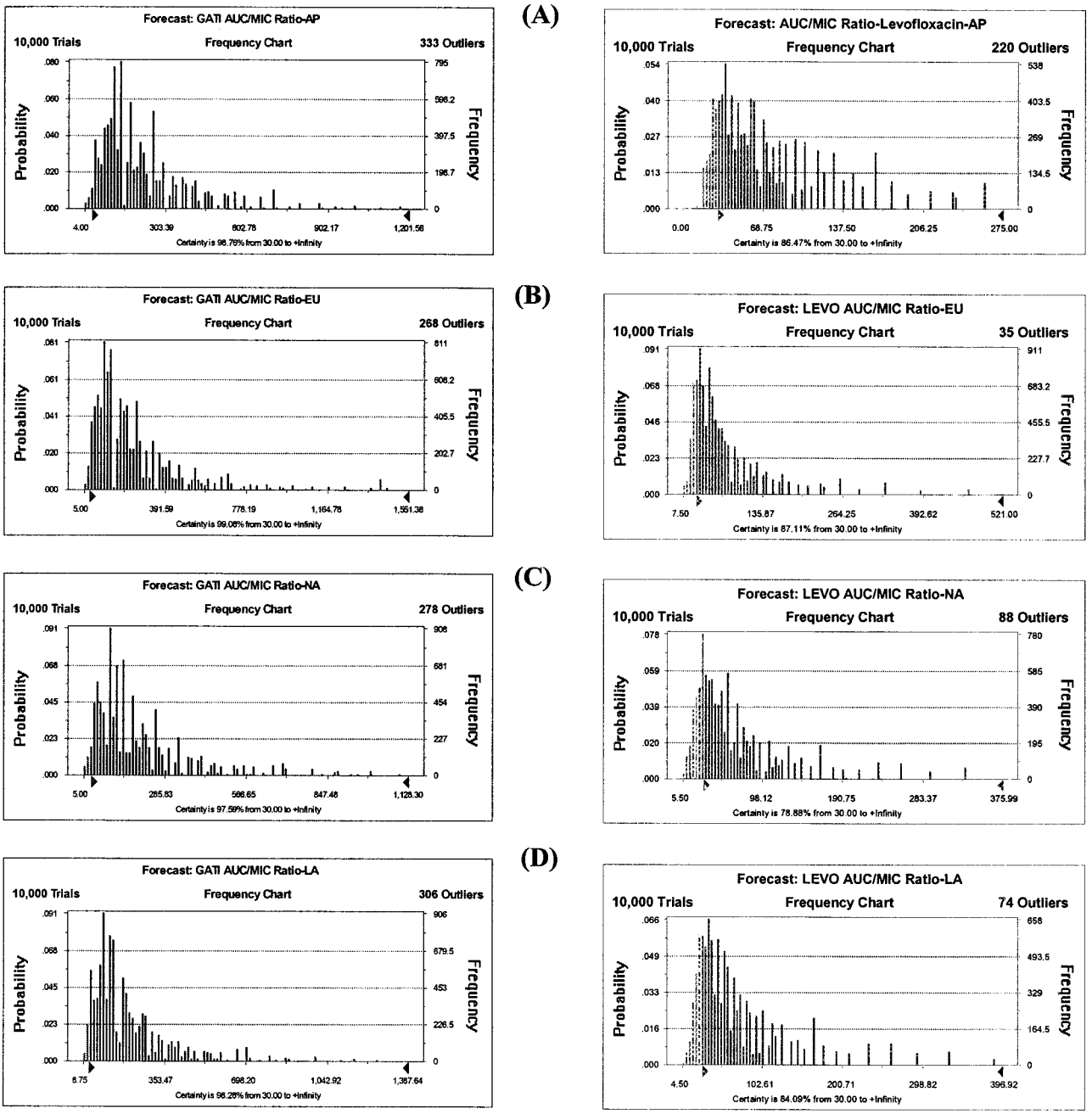

FIG. 2. f_u AUC_{24}/MIC ratio frequency distributions for gatifloxacin (GATI; left panels) and levofloxacin (LEVO; right panels) against *S. pneumoniae* isolates from the Asia-Pacific (AP) (A), Europe (EU) (B), North America (NA) (C), and Latin America (LA) (D). In each panel, the lighter bars represent the simulated patients for whom f_u AUC_{24}/MIC ratios were <30 and the darker bars represent simulated patients for whom f_u AUC_{24}/MIC ratios were ≥30.

Jumbe, A. Louie, W. Liu, M. Deziel, M. H. Miller, and G. L. Drusano, Abstr. 40th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 291, 2000).

The probability of attaining an f_u AUC_{24}/MIC ratio of at least 30 against *S. pneumoniae* is approximately 12.0 to 18.7% higher for gatifloxacin than for levofloxacin. These findings are consistent with observations from similar regional analyses (2; R. C. Owens, P. G. Ambrose, D. Piper, and S. Thomas, Abstr. 40th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 285, 2000).

Fluoroquinolone-resistant pneumococcal mutants are already a reality in certain parts of the world (4, 11, 12). Many factors are likely associated with the development of resistance, including high levels of use (both human and agricultural uses), the use of many derivatives in the same class with various PD profiles, the inappropriate use of the agents or the

use of inappropriate dosages, and, in some instances, poor manufacturing control and product quality. It is therefore crucial that compounds be evaluated not only by considering microbiological MIC distributions but also by considering the probabilities of attaining critical PK-PD targets that may minimize the emergence of resistance.

Resistance to quinolones in *S. pneumoniae* usually occurs in a stepwise manner (6, 8). Mutations which occur in the quinolone resistance-determining regions of *gyrA* and/or *parC* tend to increase MICs by about fourfold, and multiple mutations involving both genes are generally required to raise MICs past the breakpoint for clinical resistance. Coverage against isolates with increased resistance conferred by any single mutation step would therefore be expected to reduce the likelihood of emergence of high-level quinolone resistance. Conceptually, one may think of this exposure as a resistance prevention exposure. The probability of attaining an f_u AUC_{24}/MIC ratio of at least 120 for gatifloxacin against *S. pneumoniae* averaged 67.2%, whereas the probability for levofloxacin averaged 14.6%. This is an important observation. Since gatifloxacin has a high probability of attaining a fourfold higher target f_u AUC_{24}/MIC ratio (i.e., 120) relative to the probability for levofloxacin, it is expected that it will be clinically more effective against these mutants and thereby decrease the likelihood of the emergence of second-step mutants, which are highly resistant to nearly all marketed quinolones. This may be the single most important difference between these two compounds.

The microbiology presented here for gatifloxacin (MIC_{50}, 0.25 μg/ml) directly compared to that for levofloxacin (MIC_{50}, 1 μg/ml) confirms data presented in earlier reports (11, 12) that show a fourfold advantage for gatifloxacin in its central tendency of potency against *S. pneumoniae*, regardless of the geographic source of the strains tested. Also, fluoroquinolone-resistant strains are emerging at a higher rate in the Asia-Pacific and North American regions (4, 11, 13, 19).

In conclusion, choices among newer fluoroquinolones with enhanced activities gram-positive organisms can be difficult since their spectrums at published NCCLS breakpoints (16, 17) remain very similar. Evaluating fluoroquinolone antimicrobial agents on the basis of their abilities to attain PK-PD exposure targets that are associated with clinical efficacy and resistance prevention may prolong the usefulness of these important agents. In this study, gatifloxacin was consistently more potent than levofloxacin against *S. pneumoniae* and had a higher probability of achieving important PK-PD target exposure ratios.

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REFERENCES

1. **Ambrose, P. G., R. C. Owens, and D. M. Grasela.** 2000. Antimicrobial pharmacodynamics. Med. Clin. N. Am. **84:**1431–1446.
2. **Ambrose, P. G., and D. M. Grasela.** 2000. The use of Monte Carlo simulation to examine the pharmacodynamic variance of drugs: fluoroquinolone pharmacodynamics against *Streptococcus pneumoniae*. Diagn. Microbiol. Infect. Dis. **38:**151–157.
3. **Ambrose, P. G., D. M. Grasela, T. H. Grasela, J. Passarell, H. B. Mayer, and P. F. Pierce.** 2001. Pharmacodynamics of fluoroquinolones against *Streptococcus pneumoniae* in patients with community-acquired respiratory tract infections. Antimicrob. Agents Chemother. **45:**2793–2797.
4. **Chen, D. K., A. McGeer, J. C. de Azavedo, and D. E. Low.** 1999. Decreased susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. N. Engl. J. Med. **341:**233–239.
5. **Craig, W. A.** 2001. Pharmacodynamics of antimicrobials: general concepts and application, p. 1–22. *In* C. H. Nightingale, T. Murakawa, and P. G. Ambrose (ed.), Antimicrobial pharmacodynamics in theory and clinical practice. Marcel-Dekker, Inc., New York, N.Y.
6. **Davies, T. A., G. A. Pankuch, B. E. Dewasse, M. R. Jacobs, and P. C. Applebaum** 1999. In vitro resistance of five quinolones and amoxicillin-clavulanate in *Streptococcus pneumoniae*. Antimicrob. Agents Chemother. **43:**1177–1182.
7. **Drusano, G. L., S. L. Preston, C. Hardalo, R. Hare, C. Banfield, D. Andes, O. Vesga, and W. A. Craig.** 2001. Use of preclinical data for selection of a phase II/III dose for evernimicin and identification of a preclinical MIC breakpoint. Antimicrob. Agents Chemother. **45:**13–22.
8. **Drusano, G. L., D. E. Johnson, M. Rosen, and H. C. Standiford.** 1993. Pharmacodynamics of a fluoroquinolone antimicrobial agent in a neutropenic rat model of *Pseudomonas* sepsis. Antimicrob. Agents Chemother. **37:**483–490.
9. **Dudley, M. N., and D. Griffith.** 2001. Animal models of infection for the study of antibiotic pharmacodynamics, p. 67–97. *In* C. H. Nightingale, T. Murakawa, and P. G. Ambrose (ed.), Antimicrobial pharmacodynamics in theory and clinical practice. Marcel Dekker, Inc., New York, N.Y.
10. **Dudley, M. N., and P. G. Ambrose.** 2000. Pharmacodynamics in the study of resistance and establishing in vitro susceptibility breakpoints: ready for prime time. Curr. Opin. Microbiol. **3:**515–521.
11. **Hoban, D. J., G. V. Doern, A. C. Fluit, M. Roussel-Delvallez, and R. N. Jones.** 2001. Worldwide prevalence of antimicrobial resistance in *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* in the SENTRY Antimicrobial Surveilance Program, 1997–1999. Clin. Infect. Dis. **32**(Suppl. 2)**:**S81–S93.
12. **Jones, R. N., and M. A. Pfaller.** 2000. In vitro activity of newer fluoroquinolones for respiratory tract infections and emerging patterns of antimicrobial resistance: data from the SENTRY Antimicrobial Surveillance Program. Clin. Infect. Dis. **31**(Suppl. 2)**:**S16–S23.
13. **Jones, R. N., and M. A. Pfaller.** 2000. Macrolide and fluoroquinolone (levofloxacin) resistances among *Streptococcus pneumoniae* strains: significant trends from the SENTRY Antimicrobial Surveillance Program (North America, 1997–1999). J. Clin. Microbiol. **38:**4298–4299.
14. **Lacy, M. A., W. Lu, X. Xu, P. R. Tessier, D. P. Nicolau, R. Quintiliani, and C. H. Nightingale.** 1999. Pharmacodynamic comparisons of levofloxacin, ciprofloxacin, and ampicillin against *Streptococcus pneumoniae* in an in vitro model of infection. Antimicrob. Agents Chemother. **43:**672–677.
15. **Lister, P. D., and C. C. Sanders** 1999. Pharmacodynamics of levofloxacin and ciprofloxacin against *Streptococcus pneumoniae*. J. Antimicrob Chemother. **43:**79–86.
16. **National Committee for Clinical Laboratory Standards.** 2000. Performance standards for antimicrobial susceptibility testing. Document M7-A5. National Committee for Clinical Laboratory Standards, Wayne, Pa.
17. **National Committee for Clinical Laboratory Standards.** 2001. Performance standards for antimicrobial susceptibility testing. Document M100-S11. National Committee for Clinical Laboratory Standards, Wayne, Pa.
18. **Preston, S. L., G. L. Drusano, A. L. Berman, C. L. Fowler, A. T. Chow, and B. Dornseif.** 1998. Levofloxacin population pharmacokinetics and creation of a demographic model for prediction of individual drug clearance in patients with serious community-acquired infection. Antimicrob. Agents Chemother. **42:**1098–1104.
19. **Weiss, K., C. Resteri, R. Gauthier, M. Laverdiere, A. McGeer, R. J. Davidson, L. Kilburn, D. J. Bast, J. de Azavedo, and D. E. Low.** 2001. A nosocomial outbreak of fluoroquinolone-resistant *Streptococcus pneumoniae*. Clin. Infect. Dis. **33:**517–522.