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Pharmacodynamics to combat resistance

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The ability to identify agents with the optimal combination of potency, pharmacokinetics and pharmacodynamics should help to maximize bacteriological cure and thus minimize the potential for selection and spread of resistance. Gemifloxacin demonstrated excellent correlation between efficacy and the $AUC_{0–24h}$/MIC ratio whereas there was little correlation with time above MIC. Thus, gemifloxacin is similar to other quinolones in that it is the amount of drug present, not the frequency of administration, that determines antibacterial effect. In a neutropenic murine thigh model of infection, caused by Gram-negative bacilli, a $AUC_{0–24h}$/MIC ratio of approximately 100 was necessary to protect >90% of the animals, which is similar to data reported previously for other quinolones. However, in order to achieve the same protection in an immunocompetent murine infection caused by *Streptococcus pneumoniae*, the $AUC_{0–24h}$/MIC ratio was approximately 25. The magnitude of this $AUC_{0–24h}$/MIC ratio did not alter for strains exhibiting penicillin or macrolide resistance. Importantly, when gemifloxacin was examined against strains of *S. pneumoniae* with well-characterized ciprofloxacin resistance (including mutations in gyrase, *parC* and *parE* as well as efflux strains) there was little impact on the *in vivo* efficacy. Overall, the data showed a trend towards a decrease in the $AUC_{0–24h}$/MIC ratio for these more resistant strains. The lower $AUC_{0–24h}$/MIC ratio was especially noticeable for the efflux mutants suggesting that the quinolone efflux mechanism may be down-regulated *in vivo* and may be of minimal relevance to the clinical activity of gemifloxacin against *S. pneumoniae*. The efficacy of gemifloxacin, in comparison with other oral agents used to treat respiratory infections, has also been evaluated in a rat model using doses, and therefore $AUC_{0–24h}$/MIC ratios, that approximate those in man. These data confirm the excellent activity of gemifloxacin against strains of *Haemophilus influenzae* and *S. pneumoniae*, including those demonstrating penicillin, macrolide and quinolone resistance.

Introduction

The pharmacodynamics of an antibiotic are determined by the concentration of the antibiotic achieved in the serum or at the site of infection in relation to the concentration required to inhibit the growth of the infecting pathogen. As the relationships between pharmacodynamics and clinical and bacteriological outcome continue to be defined, pharmacodynamics is emerging as a useful tool for predicting clinical efficacy.[1,2]

The pharmacodynamic parameters that determine antimicrobial efficacy depend on the mechanism of antimicrobial killing observed for the antibiotic, of which there are two primary patterns. Time-dependent killing is dependent on the time that an antibiotic exceeds the MIC, but is independent of the antibiotic concentration, provided that an inhibitory level has been reached.[3] Antibiotics that show time-dependent killing, such as β-lactams, usually have short to moderate post-antibiotic effects once the concentration falls below the MIC. For these drugs, the time for which the concentration in serum exceeds the MIC has been shown to be the key determinant of efficacy in a number of animal models of infection.[1,4,5] The second pharmacodynamic pattern is concentration-dependent killing, where higher concentrations of antibiotic kill the pathogen more quickly and more completely. Antibiotics that display concentration-dependent killing, such as aminoglycosides and fluoroquinolones, show prolonged post-antibiotic effects. For these compounds, it is the amount of drug at the site of infection, rather than the frequency of dosing, that is

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the primary determinant of efficacy.[1] The amount of antibiotic in serum can be represented by the area under the concentration (in serum) versus time (0–24 h) curve (AUC). This value can be compared with the MIC for the target bacterial pathogen to provide the pharmacodynamic parameter AUC/MIC. The magnitude of the AUC_{0-24h}/MIC ratio has been shown to correlate well with efficacy in animal models[6] and clinical studies[7,8] for antibiotics that demonstrate concentration-dependent killing. The ratio of peak serum concentration to MIC is also important, as mentioned below.

Gemifloxacin is a new fluoroquinolone that is extremely potent against Gram-positive bacterial pathogens, particularly *Streptococcus pneumoniae*.[9] Gemifloxacin is not yet available for general clinical use, but has been tested in a number of *in vitro* studies, animal models of infection and in clinical studies. The results of some of these studies are discussed here, with specific reference to their relevance in determining the pharmacodynamic parameters important in predicting the clinical efficacy of gemifloxacin.

Concentration-dependent killing

The type of antibacterial activity shown by gemifloxacin has been determined in a number of *in vitro* studies. Gemifloxacin produced *in vitro* post-antibiotic effects similar to those of ciprofloxacin against *Staphylococcus aureus*, *Staphylococcus saprophyticus*, *S. pneumoniae*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Proteus vulgaris* and *Escherichia coli*, demonstrating prolonged persistent effects against these organisms.[10–12] In addition, gemifloxacin was shown to be rapidly bactericidal against *S. aureus*, *E. coli* and *P. aeruginosa* at low concentrations (0.03–1.0 mg/L), which ranged from one to four times the MIC.[13] These *in vitro* time–kill studies demonstrated concentration-dependent killing by gemifloxacin against all three species tested. For example, against a strain of *S. aureus* (MIC 0.03 mg/L), gemifloxacin was rapidly bactericidal at the MIC and regrowth of the culture was prevented for at least 24 h, whereas at lower concentrations (0.5 × MIC) gemifloxacin was less rapidly bactericidal and regrowth of bacteria was seen. Against a strain of *E. coli* (MIC 0.13 mg/L), a gemifloxacin concentration of at least twice the MIC was required to prevent regrowth for 24 h and the most rapid bactericidal effect was seen using four times the MIC.

For gemifloxacin, concentration-dependent killing has also been shown against *S. pneumoniae*,[14] with a rapid bactericidal effect and lack of regrowth up to 24 h when tested at concentrations equivalent to, or greater than, the MIC (0.016 mg/L). Good bactericidal effects, with no regrowth up to 24 h, were also demonstrated against strains of *H. influenzae* (MIC 0.002 mg/L) and *M. catarrhalis* (MIC 0.016 mg/L) but, for these organisms, at least twice the MIC of gemifloxacin was required to produce this effect.[14] Since gemifloxacin shows concentration-dependent killing, the pharmacodynamic parameters expected to correlate with efficacy were AUC/MIC and the peak antibiotic concentration in serum (C_{max})/MIC.

Pharmacodynamic studies in animal models of infection

A mouse thigh infection model was used to examine the effects of different pharmacodynamic parameters on the efficacy of gemifloxacin in a number of *in vivo* studies.[15,16] Neutropenia was produced in mice by the administration of cyclophosphamide, four days and one day before infection. The animals were infected and, 2 h later, antibiotics were administered. In order to determine which pharmacokinetic parameters are important for *in vivo* efficacy, various doses of gemifloxacin were administered. At the end of 24 h, the thigh tissue was removed from the mice, processed and quantitative determination of the numbers of viable organisms remaining was performed. Irrespective of the frequency of dosing, the *in vivo* efficacy (measured as the numbers of organisms remaining at 24 h) correlated well with the AUC_{0-24h}/MIC for gemifloxacin (r^2 = 89%), whereas there was little correlation between *in vivo* efficacy and time above MIC (r^2 = 59%). The correlation between C_{max}/MIC and efficacy (r^2 = 72%) was higher than seen for time above MIC, but not as high as seen for AUC/MIC.[16] Thus, gemifloxacin was shown to be similar to other fluoroquinolones in that it is the amount of drug, not the frequency of administration, that is the important determinant for antibacterial efficacy.

The magnitude of the AUC_{0-24h}/MIC of gemifloxacin required to achieve maximal bacteriological efficacy was also assessed using the murine thigh infection model. The studies showed that, in order to obtain 90–100% survival in animal infection models, it was necessary to achieve an AUC_{0-24h}/MIC ratio of approximately 25 for *S. pneumoniae* infections in immunocompetent animals. For infections caused by Gram-negative bacilli, in immunocompromised animals, a AUC_{0-24h}/MIC ratio of approximately 100 was required to achieve maximal bacteriological efficacy with gemifloxacin. These findings were also consistent with those seen for other fluoroquinolones.[17,18]

Clinical relevance of pharmacodynamic parameters of fluoroquinolones

The clinical implication of pharmacodynamic parameters for fluoroquinolone efficacy has been examined by a number of workers. A study reported by Forrest *et al.*,[7] in 64 patients with serious infections, demonstrated a favourable clinical and bacteriological outcome following treatment with intravenous ciprofloxacin when the serum AUC_{0-24h}/MIC

was ⩾125. When the ciprofloxacin AUC/MIC ratio was <125, the clinical response was <50% and the bacteriological response was <30%. More recently, a prospective trial performed by Preston and co-workers,[8] in 134 patients treated with levofloxacin, showed favourable clinical and microbiological efficacy when the C_{max}/MIC ratio was at least 12.2, which is comparable to an $AUC_{0–24h}$/MIC ratio of approximately 100. Preston and Drusano have recently re-examined their data, focusing specifically on infections caused by *S. pneumoniae*. A favourable clinical and microbiological outcome was demonstrated for $AUC_{0–24h}$/MIC values <30, supporting the concept that lower AUC/MIC values achieve a high rate of clinical and bacteriological success in pneumococcal infections.

Pharmacodynamics of fluoroquinolones and quinolone resistance

It has been shown, in 170 patients with nosocomial lower respiratory tract infections,[19] that exposure of bacteria to adequate levels of antibiotic decreases the probability of development and emergence of resistance. The probability of antibiotic resistance emerging was shown to be <10% after 13 days of exposure to a given antibiotic if the $AUC_{0–24h}$/MIC ratio was >100, but >60% at 13 days for $AUC_{0–24h}$/MIC ratios <100. Pharmacodynamic parameters such as AUC/MIC, therefore, appear to have clinical relevance, not only in the efficacy of antibiotics, but also in their potential to select resistant organisms.

The $AUC_{0–24h}$/MIC ratio of gemifloxacin, required to produce a 2 $\log_{10}$ kill over 24 h in the neutropenic mouse thigh infection model, was examined using strains of *S. pneumoniae* with a range of susceptibility patterns, to determine the effect of reduced antibiotic susceptibility on this pharmacodynamic parameter. A 2 $\log_{10}$ kill over 24 h was used as the criterion for efficacy, since it was found to correspond to a high rate of survival when the animals were treated over a longer period of time. Penicillin and macrolide resistance did not alter the magnitude of the AUC/MIC ratio for gemifloxacin required for efficacy in comparison with penicillin and macrolide susceptible strains of pneumococci. These pneumococci were also susceptible to ciprofloxacin and had gemifloxacin MICs ranging from 0.008 to 0.016 mg/L. When three ciprofloxacin-resistant strains of *S. pneumoniae* were examined (ciprofloxacin MIC > 2 mg/L; gemifloxacin MIC 0.03–0.25 mg/L) the AUC/MIC ratios required to produce a 2 $\log_{10}$ kill over 24 h were similar to those required against ciprofloxacin-susceptible strains.[16]

A collection of 16 well-characterized strains of ciprofloxacin-resistant *S. pneumoniae* were also studied in the neutropenic mouse model.[15] These included 13 strains with gyrase, *parC* and *parE* mutations, some of which had multiple mutations. The MIC values of gemifloxacin against these strains ranged from 0.03 to 0.5 mg/L. Three strains were also included in these studies for which the MIC of gemifloxacin decreased eight-fold in the presence of reserpine, a potent inhibitor of the efflux mechanisms of Gram-positive bacteria, suggesting that they contained an efflux mechanism of quinolone resistance. The $AUC_{0–24h}$/MIC values required to produce a 2 $\log_{10}$ kill against the strains with single *ParC* or gyrase mutations and low gemifloxacin MIC values (0.03–0.06 mg/L) were similar to those required for ciprofloxacin-susceptible strains. Moreover, the $AUC_{0–24h}$/MIC values associated with efficacy did not increase for strains of *S. pneumoniae* less susceptible to gemifloxacin and even showed a trend towards a decrease in therapeutic AUC/MIC ratio. This was particularly true for strains with efflux-mediated resistance, where the lowest AUC/MIC ratios (mean = 27) produced a 2 $\log_{10}$ kill. This suggests that quinolone resistance mechanisms have little impact on the *in vivo* efficacy of gemifloxacin against *S. pneumoniae* and that the efflux mechanism of quinolone resistance may be significantly down-regulated *in vivo*, compared with the *in vitro* situation, and of minimal relevance to the activity of gemifloxacin in the clinical situation.

These data were produced using neutropenic mice and are similar to the $AUC_{0–24h}$/MIC ratios reported as necessary for efficacy with other fluoroquinolones.

Relationship of AUC/MIC ratios achieved in humans and efficacy in experimental animal models of respiratory tract infection

If the $AUC_{0–24h}$/MIC ratios achieved in humans following conventional oral dosages of the newer fluoroquinolones are calculated for *S. pneumoniae* (Table I), it is apparent that, although gemifloxacin has the lowest $AUC_{0–24h}$, its high *in vitro* potency and consequent low MIC values result in the highest AUC/MIC ratio (267), in comparison with other fluoroquinolones. This value is higher than that seen for trovafloxacin (138), gatifloxacin (69) and moxifloxacin (192), and similar to the value for sitafloxacin (235). Similarly, although gemifloxacin has the lowest C_{max} of the fluoroquinolones examined, it has the highest C_{max}/MIC ratio.

In order to compare the effects of different oral agents used to treat respiratory tract infections, at AUC/MIC ratios usually achieved in humans, studies were performed in a rat model of respiratory tract infection.[20–22] In these studies, rats were infected via intrabronchial instillation with approximately 6 $\log_{10}$ cfu of *S. pneumoniae* or *H. influenzae* per lung, followed by treatment with oral antibiotics for 96 h. The numbers of viable bacteria in the lung were then determined. The doses of antibiotics administered to the rats were chosen to approximate to the animal tissue (azithromycin only) or serum AUCs achieved in humans following conventional oral dosing. The doses used in the rat to achieve this are compared with data from humans in Table II.

Table I. Pharmacodynamic parameters achieved in humans following conventional oral doses of new fluoroquinolones

Fluoroquinolone	Conventional once-daily dose (mg)	AUC_{0-24h}/MIC_{90} for *S. pneumoniae*	C_{max}/MIC_{90} for *S. pneumoniae*
Gemifloxacin	320	8.0/0.03 = 266.7	1.2/0.03 = 40
Trovafloxacin	200	34.4/0.25 = 137.6	3.1/0.25 = 12.4
Gatifloxacin	400	34.4/0.5 = 68.8	4.2/0.5 = 8.4
Moxifloxacin	400	48.0/0.25 = 192	4.5/0.25 = 18
Sitafloxacin	500	29.4/0.125 = 235.2	4.9/0.125 = 39.2

Table II. Doses administered to rats to achieve AUC values similar to those seen in humans following conventional oral dosage

Antibiotic	Dosing frequency	Rat		Human	
		dose (mg/kg)	AUC (mg·h/L)	dose (mg)	AUC (mg·h/L)
Gemifloxacin	od	300	6.9	320	8.0
Ciprofloxacin	bid	200	13.8	750	14.9
Trovafloxacin	od	40	36.1	200	30.4
Levofloxacin	od	125	48.0	500	47.5
Tosufloxacin	bid	25	7.7	600	5.6
Grepafloxacin	od	200	17.0	600	19.7
Amoxycillin/ clavulanate	bid	350/50	44.1/4.9	875/125	45.1/7.8
Cefuroxime	bid	70	14.3	250	14.0
Azithromycin	od	40/20	3.4	1000/500	4.1

When these doses were tested in the rat model against a penicillin-resistant, macrolide-resistant, ciprofloxacin-susceptible strain of *S. pneumoniae*,[20] untreated animals contained a mean of approximately 6 $\log_{10}$ cfu/lungs at 96 h. Cefuroxime, azithromycin and ciprofloxacin were ineffective ($P > 0.05$; Figure 1). Levofloxacin, grepafloxacin and trovafloxacin reduced the mean numbers of viable bacteria to 3.2–4.3 $\log_{10}$ cfu/lungs but, in these treatment groups, some animals responded well whereas some showed no response to antibiotic treatment. Amoxycillin (+ clavulanate) also produced an overall reduction in bacterial numbers in the lungs even though this organism would be considered resistant to amoxycillin (MIC 8 mg/L). All of the rats treated with gemifloxacin, however, showed a good bacteriological response, with a mean number of viable pneumococci (1.8 ± 0.2 $\log_{10}$ cfu/lungs) around the limit of detection by 96 h after the start of dosing (Figure 1).

Azithromycin, despite having an MIC of 1.0 mg/L (below the breakpoint for susceptibility), was ineffective at reducing *H. influenzae* numbers recovered from the lungs in comparison with non-treated controls (Figure 2).[21] Ciprofloxacin, levofloxacin and gemifloxacin, on the other hand, were highly effective, with numbers of *H. influenzae* reduced below the limit of detection (1.69 $\log_{10}$ cfu/lungs) in all animals treated. Grepafloxacin and trovafloxacin were marginally less active than the other quinolones tested (Figure 2).

A ciprofloxacin-resistant strain of *S. pneumoniae* was also tested in the rat respiratory tract infection model.[22] This strain was susceptible to penicillin but was macrolide-resistant. Amoxycillin/clavulanate and cefuroxime were highly effective, but azithromycin was ineffective (Figure 3). Ciprofloxacin, levofloxacin, grepafloxacin and trovafloxacin showed poor activity against this ciprofloxacin-reisistant strain of *S. pneumoniae*, with the mean numbers of viable pneumococci per lung being similar to those for untreated mice following treatment with these antibiotics (Figure 3). Tosufloxacin was effective in some animals, with a mean of 4 $\log_{10}$ cfu/lungs remaining by 96 h. Gemifloxacin was the most effective quinolone tested, being significantly more active than trovafloxacin and reducing the numbers of viable pneumococci to approximately 2.6 $\log_{10}$ cfu/lungs after 96 h.[21]

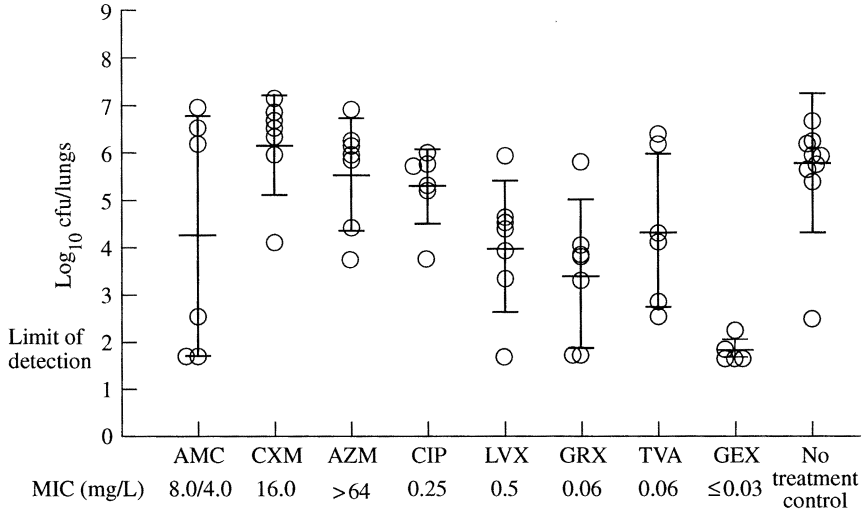

Figure 1. Efficacy of gemifloxacin and comparators against a respiratory tract infection in rats caused by a penicillin-resistant, macrolide-resistant, ciprofloxacin-susceptible strain of *S. pneumoniae*. Data are represented as mean and standard deviation of bacterial numbers in the lungs of individual animals. Abbreviations: AMC, amoxycillin/clavulanate; CMX, cefuroxime; AZM, azithromycin; CIP, ciprofloxacin; LVX, levofloxacin; GRX, grepafloxacin; TVA, trovafloxacin; GEX, gemifloxacin.

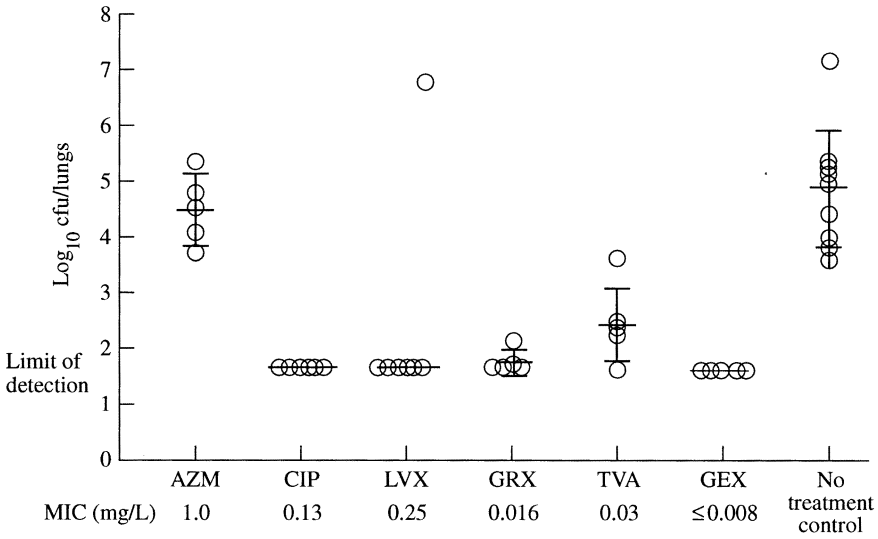

Figure 2. Efficacy of gemifloxacin and comparators against a respiratory tract infection in rats caused by *H. influenzae*. Data are represented as mean and standard deviation of bacterial numbers in the lungs of individual animals. Abbreviations: AZM, azithromycin; CIP, ciprofloxacin; LVX, levofloxacin; GRX, grepafloxacin; TVA, trovafloxacin; GEX, gemifloxacin.

Overall, gemifloxacin was the most active fluoroquinolone tested against quinolone-susceptible and quinolone-resistant strains of *S. pneumoniae in vivo*. It was also more effective than amoxycillin/clavulanate, cefuroxime and azithromycin against highly penicillin-resistant, macrolide-resistant *S. pneumoniae*. Gemifloxacin was more active than azithromycin and cefuroxime (data not shown) against *H. influenzae*, and showed similar activity to the other fluoroquinolones against this organism. In a model of skin and soft tissue infection in the rat, gemifloxacin was shown to be the most effective agent tested against *Streptococcus pyogenes* and *Staphylococcus* spp.[23]

Conclusion

In today's environment of high rates of antibiotic resistance amongst bacterial respiratory tract pathogens, it is important to use antibiotics with an optimum combination of potency, pharmacodynamics and pharmacokinetics, to

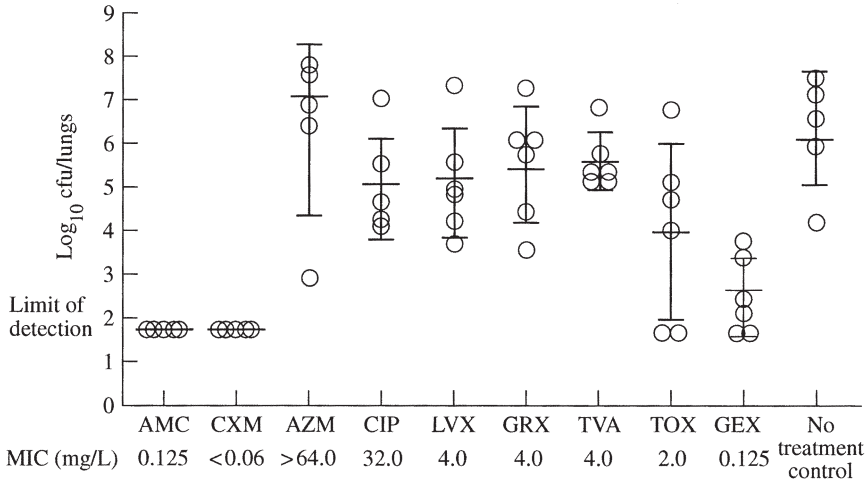

Figure 3. Efficacy of gemifloxacin and comparators against a respiratory tract infection in rats caused by a penicillin-susceptible, macrolide-resistant, ciprofloxacin-resistant strain of *S. pneumoniae*. Data are represented as mean and standard deviation of bacterial numbers in the lungs of individual animals. Abbreviations: AMC, amoxycillin/clavulanate; CMX, cefuroxime; AZM, azithromycin; CIP, ciprofloxacin; LVX, levofloxacin; GRX, grepafloxacin; TVA, trovafloxacin; TOX, tosufloxacin; GEX, gemifloxacin.

prevent bacteriological failure and the selection and spread of resistance. Pharmacodynamic parameters can predict bacteriological efficacy of quinolones and help to identify the most appropriate choice of agent. Pharmacodynamic parameters, such as AUC/MIC or C_{max}/MIC ratio, predict that gemifloxacin should be very effective against bacterial respiratory tract pathogens, including quinolone-resistant *S. pneumoniae*. Moreover, pharmacodynamic parameters for gemifloxacin against *S. pneumoniae* appear to be unaffected by quinolone resistance mechanisms. Gemifloxacin, therefore, may have an important role to play in the future therapy of bacterial infections, in particular those infections caused by *S. pneumoniae*.

References

1. Craig, W. A. (1998). Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clinical Infectious Diseases* **26**, 1–12.

2. Drusano, G. L. & Craig, W. A. (1997). Relevance of pharmacokinetics and pharmacodynamics in the selection of antibiotics for respiratory tract infections. *Journal of Chemotherapy* **9**, *Suppl. 3*, 38–44.

3. Craig, W. A. & Ebert, S. C. (1990). Killing and regrowth of bacteria *in vitro*: a review. *Scandinavian Journal of Infectious Diseases* **74**, *Suppl.*, 63–70.

4. Craig, W. A. (1995). Interrelationship between pharmacokinetics and pharmacodynamics in determining dosage regimens for broad-spectrum cephalosporins. *Diagnostic Microbiology and Infectious Disease* **22**, 89–96.

5. Craig, W. A. (1996). Antimicrobial resistance issues of the future. *Diagnostic Microbiology and Infectious Disease* **25**, 213–7.

6. Leggett, J. E., Fantin, B., Ebert, S., Totsuka, K., Vogelman, B., Calame, W. *et al.* (1989). Comparative antibiotic dose-effect relations at several dosing intervals in murine pneumonitis and thigh-infection models. *Journal of Infectious Diseases* **159**, 281–92.

7. Forrest, A., Nix, D. E., Ballow, C. H., Goss, T. F., Birmingham, M. C. & Schentag, J. J. (1993). Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. *Antimicrobial Agents and Chemotherapy* **37**, 1073–81.

8. Preston, S. L., Drusano, G. L., Berman, A. L., Fowler, C. L., Chow, A. T., Dornseif, B. *et al.* (1998). Pharmacodynamics of levofloxacin: a new paradigm for early clinical trials. *Journal of the American Medical Association* **279**, 125–9.

9. Cormican, M. G. & Jones, R. N. (1997). Antimicrobial activity and spectrum of LB20304, a novel fluoronaphthyridone. *Antimicrobial Agents and Chemotherapy* **41**, 204–11.

10. Moore, T., Kershner, K., Donald, B., Rittenhouse, S. & Coleman, K. (1999). Post-antibiotic effect (PAE) of gemifloxacin (SB-265805) and ciprofloxacin against Gram-positive and Gram-negative organisms. In *Program and Abstracts of the Thirty-Ninth Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, 1999*. Abstract 2298, p. 278. American Society for Microbiology, Washington, DC.

11. Credito, K. L., Clark, C. L., Jacobs, M. R. & Appelbaum, P. C. (1999). Post-antibiotic effect (PAE) of gemifloxacin (SB-265805) compared with five other quinolones against pneumococci. In *Program and Abstracts of the Thirty-Ninth Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, 1999*. Abstract 537, p. 21. American Society for Microbiology, Washington, DC.

12. Kim, M.-Y., Paek, K.-S. & Choo, Y. S. (1998). SB-265805 (LB20304a): Post-antibiotic effects on *Staphylococcus aureus* and *Escherichia coli*. In *Program and Abstracts of the Thirty-Eighth Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, CA, 1998*. Abstract F-088, p. 255. American Society for Microbiology, Washington, DC.

13. Paek, K.-S., Kim, M.-Y. & Choo, Y. S. (1998). SB-265805 (LB20304a): Bactericidal activity against *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*. In *Program and*

Abstracts of the Thirty-Eighth Interscience Conference of Antimicrobial Agents and Chemotherapy, San Diego, CA, 1998. Abstract F-091, p. 255. American Society for Microbiology, Washington, DC.

14. Paek, K.-S., Kim, M.-Y. & Choo, Y. S. (1998). SB-265805 (LB20304a): bactericidal activity against respiratory tract pathogens. In *Program and Abstracts of the Thirty-Eighth Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, CA, 1998*. Abstract F-094, p. 256. American Society for Microbiology, Washington, DC.

15. Andes, D. & Craig, W. A. (1999). Pharmacodynamics of gemifloxacin (GEM) against quinolone-resistant strains of *S. pneumoniae* (SP) with known resistance mechanisms. In *Program and Abstracts of the Thirty-Ninth Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, 1999*. Abstract 2032, p. 50. American Society for Microbiology, Washington, DC.

16. Andes, D. & Craig, W. A. (1999). In vivo pharmacodynamic activity of gemifloxacin (GEM) against multiple bacterial pathogens. In *Program and Abstracts of the Thirty-Ninth Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, 1999*. Abstract 27, p. 8. American Society for Microbiology, Washington, DC.

17. Andes, D. & Craig, W. A. (1999). In vivo pharmacodynamic activity of sitafloxacin (SIT) against multiple bacterial pathogens. In *Program and Abstracts of the Thirty-Ninth Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, 1999*. Abstract 28, p. 9. American Society for Microbiology, Washington, DC.

18. Andes, D. & Craig, W. A. (1999). In vivo pharmacodynamic activity of gatifloxacin (GAT) against multiple bacterial pathogens. In *Program and Abstracts of the Thirty-Ninth Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, 1999*. Abstract 191, p. 10. American Society for Microbiology, Washington, DC.

19. Thomas, J. K., Forrest, A., Bhavnani, S. M., Hyatt, J. M., Cheng, A., Ballow, C. H. *et al*. (1998). Pharmacodynamic evaluation of factors associated with the development of bacterial resistance in acutely ill patients during therapy. *Antimicrobial Agents and Chemotherapy* **42**, 521–7.

20. Berry, V., Page, R., Satterfield, J., Singley, C., Straub, R. & Woodnutt, G. (1999). Comparative efficacy of gemifloxacin against respiratory tract infection in rats caused by *Streptococcus pneumoniae*. *Journal of Antimicrobial Chemotherapy* **44**, *Suppl. A*, 148.

21. Berry, V., Page, R., Satterfield, J., Straub, R. & Woodnutt, G. (1999). Comparative efficacy of gemifloxacin against experimental RTI in rats caused by *Haemophilus influenzae*. *Journal of Antimicrobial Chemotherapy* **44**, *Suppl. A*, 146.

22. Berry, V., Page, R., Satterfield, J., Singley, C., Straub, R. & Woodnutt, G. (1999). Comparative efficacy of gemifloxacin (SB-265805) against experimental respiratory tract infection in rats caused by ciprofloxacin-resistant strains of *Streptococcus pneumoniae* and *Haemophilus influenzae*. In *Program and Abstracts of the Thirty-Ninth Interscience Conference of Antimicrobial Agents and Chemotherapy, San Francisco, CA, 1999*. Abstract 1548, p. 76. American Society for Microbiology, Washington, DC.

23. Berry, V., Page, R., Singley, C., Straub, R. & Woodnutt, G. (1999). Comparative efficacy of gemifloxacin against *S. pyogenes* and *Staphylococcus* spp. in skin and soft tissue infections in rats. *Journal of Antimicrobial Chemotherapy* **44**, *Suppl. A*, 148.