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Postantibiotic, Postantibiotic Sub-MIC, and Subinhibitory Effects of PGE-9509924, Ciprofloxacin, and Levofloxacin

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Postantibiotic effects (PAEs), postantibiotic sub-MIC effects, and sub-MIC effects of the new nonfluoroquinolone PGE-9509924, ciprofloxacin, and levofloxacin against gram-positive and gram-negative strains were investigated. In comparison to ciprofloxacin and levofloxacin, PGE-9509924 exerted very similar PAEs against all strains except for both strains of *Streptococcus pneumoniae*, where longer PAEs were found for PGE-9509924. All three investigated quinolones showed no minimal PAEs against *Pseudomonas aeruginosa*.

Pharmacodynamic studies of antibiotics have aroused great interest in the past few years. Results from in vitro and animal studies have shown that different classes of antibiotics behave differently with regard to antibacterial activity (4–6). One of the pharmacodynamic parameters most studied is the postantibiotic effect (PAE), which describes the suppression of bacterial growth after a short exposure of bacteria to antimicrobials (3). The PAE has been one of many explanations for the success of intermittent dosing with drugs that exhibit short half-lives. Another explanation is the postantibiotic sub-MIC effect (PA SME), which also takes into account the effect of subinhibitory concentrations after exposure to suprainhibitory concentrations (2, 12–19). Nonfluorinated quinolones (NFQs) are agents where the 6-fluorine of the older quinolones has been replaced with a 6-H substitute. NFQs have an enhanced activity against gram-positive strains (J. L. Gray, J. K. Almstead, S. M. Flaim, C. P. Gallagher, X. E. Hu, N. K. Kim, H. D. Mckeever, C. J. Miley, T. L. Twinem, S. X. Zheng, and B. Ledoussal, Abstr. 40th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 1506, p. 209, 2000) and have shown potential for the treatment of infections caused by bacteria resistant to currently available fluoroquinolones (7). The aim of the present study was to investigate basic pharmacodynamic parameters such as the PAE, the PA SME, and the SME of the NFQ PGE-9509924 and compare them with those of ciprofloxacin and levofloxacin.

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The antibiotics were obtained as reference powders with known potency. Ciprofloxacin (Bayer AB, Stockholm, Sweden) and levofloxacin (Aventis, Romainville, France) were dissolved in 0.1 M sodium hydroxide. PGE-9509924 was obtained from Procter & Gamble Pharmaceuticals, Mason, Ohio, and dissolved in acetate buffer, pH 4.0. The antibiotics were thereafter diluted in Todd-Hewitt broth (in the experiments with *Streptococcus pneumoniae*) or Mueller-Hinton broth (in the experiments with *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*). The strains investigated in the study included *S. pneumoniae* ATCC 6306 (penicillin susceptible), one clinical isolate of *S. pneumoniae* 2151 belonging to a Spanish-Icelandic clone of serotype 6B isolated from a patient with pneumonia (penicillin resistant; MIC = 4 mg/liter), *S. aureus* ATCC 29213 (methicillin-susceptible *S. aureus*), *S. aureus* Col. 1881 (methicillin-resistant *S. aureus* [MRSA]), and *S. aureus* CCUG 35601 (Culture Collection of the University of Gothenburg; MRSA). The gram-negative strains studied were *E. coli* ATCC 25922, *K. pneumoniae* ATCC 13883, and *P. aeruginosa* ATCC 27853. The gram-negative strains and *S. aureus* were grown in Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.), supplemented with 50 mg of Ca^{2+}/liter and 25 mg of Mg^{2+}/liter, for 6 h at 37°C, yielding an initial inoculum of approximately 5×10^8 CFU/ml. The strains of *S. pneumoniae* were grown in Todd-Hewitt broth (Difco Laboratories) for 6 h at 37°C, resulting in approximately 5×10^8 CFU/ml.

The MICs of PGE-9509924 were determined both in fluid media by a macrodilution technique in triplicate on different occasions according to guidelines of the National Committee for Clinical Laboratory Standards (11) and with the BioScreen C (Lab Systems, Helsinki, Finland). The MICs of levofloxacin and ciprofloxacin were determined with the BioScreen C for all strains. The BioScreen C is a computerized incubating turbidometric reader, where growth curves are monitored continuously. Twofold serial dilutions of the antibiotics in broth were placed in microplates containing 400-μl wells, and the test strains were added to give a bacterial density of approximately 10^5 CFU/ml. The plates were then incubated in the BioScreen C. The MIC was defined as the lowest concentration that prevented growth, as determined by measuring optical density. The lowest detectable level of optical density corresponded to approximately 5×10^5 CFU/ml (9, 19).

The PAEs, PA SMEs, and SMEs of PGE-9509924 were determined with the BioScreen C and compared with those of levofloxacin and ciprofloxacin. After incubation for 6 h, the strains were diluted 1:2 to 1:10 to obtain an inoculum of approximately 5×10^7 CFU/ml at the beginning of the experiments. The gram-positive strains were thereafter exposed to 10 times the MICs of the antibiotics for 1 h at 37°C, and the

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TABLE 1. MICs of PGE-9509924, levofloxacin, and ciprofloxacin for the various strains

Strain	MIC (mg/liter)			
	PGE-9509924		Levofloxacin by BioScreen	Ciprofloxacin by BioScreen
	Macrodilution	BioScreen		
S. pneumoniae ATCC 6306	0.03	0.03	1	0.5
S. pneumoniae R 2151	0.03	0.06	1	0.5
S. aureus ATCC 29213	0.03	0.03	0.25	0.25
S. aureus Col. 1841	0.03	0.03	0.25	0.25
S. aureus CCUG 35601	0.03	0.03	0.5	0.5
E. coli ATCC 25922	0.125	0.06	0.03	0.016
K. pneumoniae ATCC 13883	0.5	0.125	0.06	0.03
P. aeruginosa ATCC 27853	2	2	2	0.5

gram-negative strains were exposed to 2 times the MICs for 1 h at 37°C due to a very fast initial killing (MICs determined with the BioScreen C). The unexposed control strains were washed similarly but were diluted 10^{-2}, 10^{-3}, 10^{-4}, and 10^{-5} to obtain inocula close to those of the exposed strains. Viable counts of the exposed cultures and the controls were measured before antibiotic exposure, after 1 h of induction, and after washing. Both the exposed strains and the different dilutions of the controls were then transferred at a volume of 40 μl and inoculated to microtiter wells with 360 μl of broth and incubated in the BioScreen C at 35°C. Growth curves were measured automatically as optical density (OD) at 540 nm in the computer every 10 min for 24 h. Earlier experimental studies have shown that the growth curves of the controls with different inocula are parallel. Therefore, in the experiments where the inocula of the exposed culture and the control did not quite match, a control curve for each strain and experiment, in which the control strain had the same initial inoculum as the corresponding exposed strain, could be constructed.

The PAE was calculated as the difference in the lengths of time for the exposed cultures and the corresponding control to grow to a defined point (A_{50}) on the OD curve, defined as 50% of the maximal OD of the control (9, 15, 16, 17, 19).

The PA SMEs for the same strains were determined as follows. The postantibiotic phase was induced as described above, and the controls were diluted (10^{-2}, 10^{-3}, 10^{-4}, and 10^{-5}) in the same way as in the PAE experiments. Viable counts were also used as described above. The strains in the postantibiotic phase and the different dilutions of the controls were then exposed to 0.1, 0.2, and 0.3 times the MICs of the quinolones and incubated in the BioScreen C. Growth curves were monitored automatically for 24 h.

The PA SME was defined as the difference in lengths of time for the exposed cultures, later exposed to sub-MICs, and the corresponding controls with the same initial inoculum as the exposed culture to reach A_{50} (defined as above) (9, 15, 16, 17, 19).

The SME was defined as the difference in lengths of time for the cultures exposed only to the sub-MICs and the controls to reach A_{50} (9, 15, 16, 17, 19). All experiments were performed twice for each antibiotic-bacterium combination.

To validate the data, the PAEs, PA SMEs, and SMEs of PGE-9509924 for all strains were also determined by the viable-count method. After incubation for 6 h, the test strains in exponential growth phase were diluted 10^{-1} to obtain a starting inoculum of approximately 5×10^7 CFU/ml. The gram-positive strains were thereafter exposed to 10 times the MICs (MICs determined on the basis of viable counts), and the gram-negative strains were exposed to 2 times the MICs, of PGE-9509924 for 1 h at 37°C. To eliminate the antibiotics, the cultures were washed three times, centrifuged each time for 5 min at 1,400 × *g*, and diluted 10^{-1} in fresh medium. The unexposed control strains were washed similarly and diluted in order to obtain an inoculum as close to that of the exposed strains as possible. The cultures with bacteria in the postantibiotic phase and the controls were thereafter divided into four different tubes. To determine the PAE, one tube of each culture was reincubated at 37°C for another 23 h after washing and dilution. To determine the SMEs and the PA SMEs, the remaining three tubes of the control cultures and the cultures

TABLE 2. PAEs of PGE-9509924, levofloxacin, and ciprofloxacin

Strain	PAE[a] (h)			
	PGE-9509924		Levofloxacin by BioScreen	Ciprofloxacin by BioScreen
	Viable counts	BioScreen		
S. pneumoniae ATCC 6306	4.3 (4.0–4.4)	6.8 (3.2–10.4)	2.2 (2.0–2.3)	1.2 (0.9–1.4)
S. pneumoniae R2151	4.0 (3.6–4.3)	6.9 (6.6–7.2)	1.7 (1.3–2.0)	0.4 (0.3–0.4)
S. aureus ATCC 29213	2.3 (1.8–3.0)	2.6 (2.0–3.2)	2.2 (2.0–2.3)	0.6 (0.3–0.8)
S. aureus Col. 1841	6.7 (4.6–9.0)	1.1 (0.3–1.9)	1.3 (1.2–1.3)	2.1 (1.1–3.1)
S. aureus CCUG 35601	3.8 (2.3–6.0)	0.3 (0–0.6)	1.2 (0.6–1.8)	2.3 (1.4–3.1)
E. coli ATCC 25922	3.7 (2.8–4.5)	2.3 (2.1–2.4)	2.8 (2.4–3.2)	2.5 (2.4–2.6)
K. pneumoniae ATCC 13883	2.2 (2–2.3)	0.9 (0.9–0.9)	0.7 (0.5–0.9)	0.7 (0.4–0.9)
P. aeruginosa ATCC 27853	0.9 (0.5–1.4)	0.1 (−0.9–1.0)	0.1 (−0.2–0.4)	0.6 (0.5–0.6)

[a] Values are means of two experiments, with ranges in parentheses.

TABLE 3. PA SMEs of PGE-9509924, levofloxacin, and ciprofloxacin

Strain	PA SME[a] (h) at indicated multiple of the MIC								
	PGE-9509924			Levofloxacin			Ciprofloxacin		
	0.1	0.2	0.3	0.1	0.2	0.3	0.1	0.2	0.3
S. pneumoniae ATCC 6306	11.4 (4.7–18.1)	12.4 (6.6–18.1)	15.9 (13.7–18.1)	3.0 (2.9–3.0)	4.4 (3.3–5.4)	19.6 (19.2–20)	1.9 (1.7–2.1)	4.0 (4.0–4.0)	7.3 (7.1–7.5)
S. pneumoniae R 2151	8.7 (8.1–9.3)	11.5 (11–12)	13.2 (12.14.4)	3.2 (3.0–3.3)	7.8 (5.4–10.1)	13.2 (10.9–15.4)	1.3 (1.0–1.5)	3.4 (2.4–4.4)	7.0 (4.6–9.4)
S. aureus ATCC 29213	4.5 (4.1–4.9)	14.3 (11.2–17.4)	18.3 (18.1–18.5)	2.8 (2.4–3.1)	5.8 (5.6–5.9)	14.4 (8.8–19.9)	1.0 (0.6–1.3)	2.3 (1.4–3.1)	5.3 (2.0–8.5)
S. aureus Col. 1841	2.8 (2.4–3.1)	5.0 (4.0–5.9)	11.3 (7.1–15.5)	1.8 (1.4–2.2)	2.9 (2.4–3.4)	4.7 (3.0–6.3)	2.6 (1.1–4.0)	6.2 (1.1–11.2)	10.3 (1.8–18.8)
S. aureus CCUG 35601	2.0 (1.4–2.5)	6.0 (5.1–6.9)	17.0 (16.6–17.3)	2.0 (1.3–2.6)	17.6 (17.6–17.6)	17.6 (17.6–17.6)	3.6 (3.0–4.2)	18.5 (18.1–18.9)	18.5 (18.1–18.4)
E. coli ATCC 25922	2.8 (2.6–3.0)	7.7 (4.3–11.1)	12.2 (4.9–19.4)	3.3 (2.8–3.7)	4.2 (3.4–4.9)	14.2 (7.3–21.1)	3.1 (2.5–3.6)	6.2 (4.4–7.9)	20.2 (19.4–21)
K. pneumoniae ATCC 13883	1.9 (1.9–1.9)	4.4 (4.4–4.4)	12.8 (9.4–16.1)	1.5 (1.2–1.8)	4.0 (3.2–4.8)	9.6 (6.9–12.2)	1.1 (0.6–1.5)	2.9 (2.9–2.9)	6.7 (6.5–6.9)
P. aeruginosa ATCC 27853	1.1 (0.6–1.6)	7.5 (7.5–7.5)	14.6 (14.0–15.1)	1.1 (0.8–1.4)	2.8 (2.2–3.3)	6.4 (5.6–7.1)	2.5 (2.0–3.0)	10.5 (9.4–11.5)	14.0 (13.6–14.4)

[a] Values are means of two experiments, with ranges in parentheses.

TABLE 4. SMEs of PGE-9509924, levofloxacin, and ciprofloxacin

Strain	SME[a] (h) at indicated multiple of the MIC								
	PGE-9509924			Levofloxacin			Ciprofloxacin		
	0.1	0.2	0.3	0.1	0.2	0.3	0.1	0.2	0.3
S. pneumoniae ATCC 6306	1.1 (0.6–1.6)	6.5 (2.4–10.5)	12.0 (5.3–18.6)	0.4 (0.3–0.4)	2.7 (2.3–3.1)	8.3 (7.5–9.0)	0.5 (0.5–0.5)	1.9 (1.8–2.0)	5.6 (4.6–6.5)
S. pneumoniae R2151	2.2 (2.0–2.4)	4.8 (3.0–6.6)	8.7 (3.8–13.6)	1.3 (1.0–1.6)	5.6 (3.1–8.0)	10.8 (5.9–15.6)	0.8 (0.3–1.3)	3.3 (1.9–4.9)	8.9 (3.8–14.0)
S. aureus ATCC 29213	1.3 (0.6–1.9)	7.4 (2.8–12.0)	15.8 (13.5–18.0)	0.3 (2.4–3.1)	1.3 (5.6–5.9)	9.9 (8.8–19.9)	0 (0–0)	0.5 (0.3–0.6)	1.0 (0.8–1.1)
S. aureus Col. 184	0.8 (0.6–0.9)	1.9 (1.3–2.5)	3.6 (2.8–4.4)	0.2 (0–0.3)	1.0 (0.9–1.1)	1.4 (1.1–1.6)	0 (0–0)	0.1 (0–0.2)	0.3 (0–0.5)
S. aureus CCUG 35601	0.9 (1.4–2.5)	2.0 (5.1–6.9)	8.9 (16.6–17.3)	0.6 (1.3–2.6)	10.5 (17.6–17.6)	18.7 (17.6–17.6)	0.7 (3.0–4.2)	9.7 (18.1–18.9)	18.3 (18.1–18.4)
E. coli ATCC 25922	0 (0–0)	0.2 (0–0.3)	1.0 (0.5–1.4)	0.1 (0–0.1)	0.4 (0.3–0.4)	1.2 (0.8–1.6)	0.3 (0.3–0.3)	1.2 (0.8–1.6)	13 (5–21)
K. pneumoniae ATCC 13883	0.4 (0.3–0.4)	2.4 (1.9–2.9)	13.4 (10.6–16.1)	0.2 (0–0.3)	2.0 (1.3–2.6)	9.4 (8.8–10.0)	0.5 (0.4–0.6)	1.9 (1.9–1.9)	6.4 (6.3–6.4)
P. aeruginosa ATCC 27853	0.9 (0.4–1.3)	9.9 (6.4–13.3)	14.4 (13.3–15.4)	0.6 (0.3–0.9)	2.3 (2.0–2.5)	4.0 (2.9–5.0)	1.0 (0–1.9)	8.4 (4.0–12.8)	13.4 (12.8–14.0)

[a] Values are means of two experiments, with ranges in parentheses.

in the postantibiotic phase were exposed to 0.1, 0.2, and 0.3 times the MIC of PGE-9509924 and reincubated at 37°C for another 23 h. Samples were withdrawn at 0 and 2 h (before and after dilution) and at 3, 4, 5, 6, 8, 11, and 24 h and if necessary diluted in phosphate-buffered saline. In some experiments, samples were also taken at 14 h. At least three dilutions of each sample were spread onto blood agar plates (Columbia agar base with 5% horse blood) and incubated at 37°C, and the colonies were counted after 24 h. The limit of detection of the method was 5×10^1 CFU/ml.

The PAE was defined according to the following formula (3): PAE = $T - C$, where T is the time required for the viable counts of the antibiotic-exposed cultures to increase by 1 $\log_{10}$ unit above the counts observed immediately after washing and C is the corresponding time for the controls.

The PA SME was defined according to the following formula (13): PA SME = $T_{PA} - C$, where T_{PA} is the time for the previously antibiotic-exposed cultures, which thereafter had been exposed to different sub-MICs, to increase by 1 $\log_{10}$ unit above the counts observed immediately after washing and C is the corresponding time for the unexposed control. The SME was defined by the formula (13) SME = $T_S - C$, where T_S is the time it takes for the cultures exposed only to sub-MICs to increase 1 $\log_{10}$ unit above the counts observed immediately after washing and C is the corresponding time for the unexposed culture.

The experiments were investigated in duplicate.

The MICs of the three quinolones for the various strains are presented in Table 1. Overall PGE-9509924 had the lowest MICs versus the gram-positive isolates in comparison to the other two quinolones. Against the gram-negative isolates, the MICs of PGE-9509924 were similar to those of levofloxacin and higher then those of ciprofloxacin. With the exception of the MICs of PGE-9509924 against *K. pneumoniae*, the difference between the macrodilution method and the determinations with BioScreen C was within 1 dilution step.

When comparing data for PGE-9509924 determined by the viable-count method to those obtained with the BioScreen C, it was found that there were only minor differences except for data for *S. aureus* Col. 1841 and CCUG 35601, where longer PAEs were noted with the viable-count method (Table 2). In comparison to ciprofloxacin and levofloxacin, PGE-9509924 exerted very similar PAEs against all strains except for both strains of *S. pneumoniae*, where PAEs of 3.2 to 10.4 h and 3.6 to 4.4 h were found by the BioScreen C and viable-count methods, respectively, in comparison to BioScreen C PAEs of 1.3 to 2.3 h for levofloxacin and 0.3 to 1.4 for ciprofloxacin (Table 2). Also, longer PA SMEs of PGE-9509924 at 0.1 and 0.2 times the MICs for these strains were noted (Table 3). This was also confirmed with the viable-count method. The three quinolones exerted a PAE of 0.3 to 2.6 h against the strains of *S. aureus*, and there was no apparent difference in PA SMEs at 0.1 times the MIC, where the compounds exerted a PA SME of 1.0 to 4.5 h. Overall, the longest PAE for the gram-negative strains was noted for *E. coli* (2.3 to 2.8 h by the BioScreen C) for all three quinolones. Short or minimal PAEs against *K. pneumoniae* (0.7 to 0.9 h by the BioScreen C) and *P. aeruginosa* (0.1 to 0.6 h by the BioScreen C) were seen. Also for these two strains short PA SMEs were noted at 0.1 times the MIC for all three antibiotics (Table 3).

In comparison to levofloxacin, PGE-9509924 exhibited longer SMEs at 0.2 and 0.3 times the MIC against *P. aeruginosa* but similar SMEs to those of ciprofloxacin. Otherwise there was no difference in SMEs between levofloxacin and PGE-9509924. In comparison to those of ciprofloxacin, longer SMEs of PGE-9509924 against *S. aureus* ATCC 29213, *S. aureus* Col. 1841, and *S. pneumoniae* ATCC 6306 were seen (Table 4). In almost all cases, the PA SMEs exceeded the sums of the PAEs and the SMEs, indicating a greater effect of sub-MICs on the exposed bacteria in comparison to that on the previously unexposed bacteria. We have previously investigated the influence of the effect of sub-MICs on bacteria in the postantibiotic phase and have found a very long delay in bacterial regrowth for many antibiotic classes and different bacterial species. For example in a study of sparfloxacin, a PA SME at 0.3 times the MIC of 5 to 6 h was found for the gram-positive strains and one of between 1.7 and 13 h was found for the gram-negative strains (14, 15). Licata et al. investigated the PAEs and PA SMEs of levofloxacin and ciprofloxacin against several strains of *S. pneumoniae* and *S. aureus* and found PAEs very similar to our results (8). They also found, as seen in our earlier studies, a pronounced prolonging of the PAE when bacteria in the postantibiotic phase were exposed to sub-MICs. In the present study, the PAEs and PA SMEs of PGE-9509924 were very similar to those of other fluoroquinolones (1, 8, 10, 18, 20, 21).

In conclusion, the PAEs and PA SMEs of PGE-9509924 against the strains of *S. pneumoniae* were, by both methods, longer than those of levofloxacin and ciprofloxacin but were very similar to those against the other investigated strains. All three investigated quinolones showed no or a minimal PAE against *P. aeruginosa*.

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