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Postantibiotic Effects and Postantibiotic Sub-MIC Effects of Roxithromycin, Clarithromycin, and Azithromycin on Respiratory Tract Pathogens

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Pharmacodynamic parameters have become increasingly important for the determination of the optimal dosing schedules of antibiotics. In this study, the postantibiotic effects (PAEs), the postantibiotic sub-MIC effects (PA SMEs), and the sub-MIC effects (SMEs) of roxithromycin, clarithromycin, and azithromycin on reference strains of *Streptococcus pyogenes* group A, *Streptococcus pneumoniae*, and *Haemophilus influenzae* were investigated. The PAE was induced by 2× MICs (*S. pneumoniae*) or 10× MICs of the different drugs for 2 h, and the antibiotics were eliminated by washing and dilution. The PA SMEs were studied by addition of 0.1, 0.2, and 0.3× MICs during the postantibiotic phase of the bacteria, and the SMEs were studied by exposition of the bacteria to the drugs at the sub-MICs only. Growth curves were followed by viable counts for 24 h. The SMEs were generally very short. A PAE of 2.9 to 8 h was noted for all antibiotics against all strains. Clarithromycin induced a statistically significantly shorter PAE on *S. pneumoniae* than did roxithromycin and azithromycin and did so also against *H. influenzae* in comparison with azithromycin. The PA SMEs were long and varied at 0.3× MIC between 6.4 19.6 h. This pronounced suppression of regrowth of bacteria which are first treated with a suprainhibitory concentration of antibiotics and then reexposed to sub-MIC levels indicates that long dosing intervals for macrolides and azalides can be allowed.

Pharmacodynamic parameters have become increasingly important for the determination of optimal dosing schedules of antibiotics. For aminoglycosides and quinolones, which exhibit a long postantibiotic effect (PAE) and a concentration-dependent bactericidal effect, it has been shown both in vitro, in animal models, and in human studies that the parameters correlating best with clinical and bacteriological outcome are the area of the serum concentration-time curve/MIC ratio and the peak/MIC ratio (8, 12, 20, 33).

On the other hand, the efficacy of drug-bacterial combinations that lack a PAE and for which killing is predominantly independent of the antibiotic concentration, such as β-lactam antibiotics versus gram-negative pathogens, seems to be dependent on the time that concentrations in serum stay above the MIC (3, 7, 20, 33). Some studies on the PAEs of macrolides and azalides have been performed, but their pharmacodynamics have not been investigated in detail (6, 10, 16, 18).

In addition to the PAE, the success of discontinuous dosing regimens may be attributed both to the function of a normal host defense (1, 15, 29, 31, 35) and to the effects of subinhibitory antibiotic concentrations (sub-MICs) (14, 21, 22). We have earlier shown that there is a difference between the effects of sub-MICs following a suprainhibitory dose (postantibiotic sub-MIC effects [PA SMEs]) and the effects of sub-MICs (SMEs) alone. It seems that in antibiotic-bacterial combinations for which a PAE exists, very long PA SMEs are seen, whereas the effects of sub-MICs on bacteria which have not earlier been exposed to a suprainhibitory dose are minimal, with a few exceptions, as with the carbapenems versus *Pseudomonas aeruginosa* and amikacin versus *Escherichia coli* (2, 25–28). The aim of the present study was to investigate the PAEs, PA SMEs, and SMEs of roxithromycin, clarithromycin, and azithromycin on respiratory tract pathogens.

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MATERIALS AND METHODS

Cultures. The bacterial strains used in this study were as follows: *Streptococcus pyogenes* group A M12 NCTC P 1800, *Streptococcus pneumoniae* ATCC 6306, and *Haemophilus influenzae* 7002. The latter was a randomly selected clinical strain obtained from the Department of Clinical Microbiology, Uppsala University, Uppsala, Sweden. The gram-positive strains were grown in Todd-Hewitt broth for 6 h at 37°C in 5% CO_2 in air, resulting in approximately 5×10^8 CFU/ml. *H. influenzae* was cultured in PDM (Progressive Diagnostics Manufacturers) broth (Biodisk, Solna, Sweden) supplemented with 30 mg of hemin per liter and 1% IsoVitaleX for 6 h at 37°C, resulting in approximately 10^9 CFU/ml.

Antibiotics. The antibiotics were obtained as reference powders with known potencies from the indicated companies: roxithromycin, Roussel, Paris, France; clarithromycin, Abbott Laboratories, Queenborough, England; and azithromycin, Pfizer AB, Täby, Sweden.

Determination of MICs. MICs were determined by twofold macrodilution in broth with an inoculum of approximately of 10^5 CFU of the test strain per ml. Tubes were read after 24 h. The MIC was defined as the lowest concentration of the antibiotic allowing no visible growth. Determinations of MICs were performed in triplicate on separate occasions.

Induction of the postantibiotic phase and determination of the PAE. The antibiotics were studied against all three strains, and each combination was studied three times on different occasions. After an incubation of 6 h, the test strains in exponential-growth phase were diluted 10^{-1} to obtain a starting inoculum of 5×10^7 to 10^8 CFU/ml. Thereafter, the strains of *S. pyogenes* and *H. influenzae* were exposed to 10× MIC of the antibiotic for 2 h. Because of a pronounced killing during the induction, the postantibiotic phase of *S. pneumoniae* was instead induced by 2× MICs of all antibiotics. To eliminate the antibiotics, the strains were washed three times for 5 min at 1,400 × *g* and diluted into fresh medium. The control strains were treated similarly. To allow monitoring of growth after the 2-h exposure, and depending on the rate of killing, the exposed strains were either diluted by a factor of 10^{-2} in fresh medium or not diluted at all (the combinations of roxithromycin with *S. pneumoniae*, clarithromycin with *S. pneumoniae*, azithromycin with *S. pneumoniae*, and azithromycin with *H. influenzae* were not diluted). In order to obtain an inoculum as close to the exposed cultures as possible, the controls for *S. pneumoniae* were diluted by 10^{-4}, and the controls for the rest of the strains were diluted by 10^{-3}. The cultures with bacteria in the postantibiotic phase and the controls were thereafter

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TABLE 1. The MICs of roxithromycin, clarithromycin, and azithromycin against respiratory tract pathogens

Drug and organism	MIC (mg/liter)
Roxithromycin	
S. pyogenes P 1800	0.13
S. pneumoniae ATCC 6306	0.13
H. influenzae 7002	8.0
Clarithromycin	
S. pyogenes P 1800	0.016
S. pneumoniae ATCC 6306	0.008
H. influenzae 7002	4.0
Azithromycin	
S. pyogenes P 1800	0.10
S. pneumoniae ATCC 6306	0.037
H. influenzae 7002	1.0

divided into four different tubes. In order to determine the PAE, one tube of each culture was reincubated at 37°C for another 22 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, they were diluted in phosphate-buffered saline. In some experiments, samples were also taken at 15 h. Three dilutions of each sample were seeded on blood agar plates and counted for determination of the number of CFU. Only plates with 50 to 500 colonies were counted.

The PAE was defined according to the following formula (4): 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.

Determination of the PA SME and the SME. After washing and dilution, the remaining three tubes of the control cultures and the cultures in the postantibiotic phase were exposed to 0.1, 0.2, and 0.3× MICs, respectively, of the same antibiotic used for the induction of the PAE and reincubated at 37°C for another 22 h. Samples were withdrawn, and viable bacteria were determined as described above.

The PA SME was defined according to the following formula (24): PA SME = $T_{PA} - C$, where T_{PA} is the time for the cultures previously exposed to antibiotics, 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 as in the following formula (24): SME = $T_S - C$, where T_S is the time for the cultures exposed only to the sub-MICs to increase by one $\log_{10}$ unit above the counts observed immediately after washing and C is as defined above.

Statistics. The Student t test for unpaired samples was used to compare the durations of the PAEs, PA SMEs at 0.3× MIC, and SMEs at 0.3× MIC.

RESULTS

MICs. The MICs for the different strains are listed in Table 1.

PAEs, PA SMEs, and SMEs. Table 2 shows the PAEs, PA SMEs, and SMEs on all the strains studied. The results are based on the means from three experiments, and the ranges are given in parentheses. In the experiments in which the bacteria did not show an increase of 1 $\log_{10}$ unit of CFU after 24 h, only the ranges are given. To clearly distinguish the effects of sub-MICs added in the postantibiotic phase from the effects of sub-MICs alone, the PAE was also subtracted from the PA SME (PA SME − PAE). A PAE of 2.9 to 8 h was noted for all antibiotics against all strains. Azithromycin induced a statistically significantly longer PAE than did clarithromycin against *S. pneumoniae* and *H. influenzae* ($P < 0.05$). Roxithromycin also induced a statistically significantly longer PAE than did clarithromycin but only against *S. pneumoniae* ($P < 0.05$). Against *S. pyogenes*, there was no statistically significant difference in PAEs between the three antibiotics studied. The PA SMEs were generally long and varied at 0.3× MIC between 6.4 and 19.6 h. Roxithromycin and azithromycin induced a statistically significantly longer PA SME at 0.3× MIC than did

TABLE 2. The PAEs PA SMEs, and SMEs of roxithromycin, clarithromycin, and azithromycin on respiratory tract pathogens

Drug and organism	Duration (h) of indicated effect (mean; range in parentheses) at indicated fraction of MIC								
	PAE	PA SME			PA SME-PAE			SME		
		0.1	0.2	0.3	0.1	0.2	0.3	0.1	0.2	0.3
Roxithromycin										
S. pyogenes P 1800	5.0 (4.4–6.0)	6.3 (5.4–10.2)	13.2 (8.7–17.3)	14.6 (9.5–17.3)	1.3 (1.0–4.2)	8.2 (4.3–11.3)	9.6 (5.1–11.3)	0.1 (0–0.3)	0.1 (0–0.2)	0.1 (0–0.5)
S. pneumoniae ATCC 6306	8.8 (6–11.5)	10.5 (8.0–13.0)	*[a] (14.3–>21.3)	>21.3 (>21.3)	1.7 (1.5–2.0)	* (>10–>14.8)	>12.5 (>12.5)	0 (0–0)	0.6 (0.2–1.4)	4.0 (3.8–6.8)
H. influenzae 7002	6.0 (5.2–7.2)	8.3 (6.9–10.3)	10.4 (8.2–11.7)	12.1 (10.6–12.9)	2.3 (1.7–3.1)	4.4 (3.0–5.7)	6.1 (5.4–7.2)	0.4 (0.2–0.5)	0.6 (0.5–0.7)	1.3 (1.0–1.4)
Clarithromycin										
S. pyogenes P 1800	4.8 (4.5–5.3)	5.6 (5.2–6.0)	6.2 (6.0–6.5)	6.8 (6.3–7.7)	0.8 (0.4–1.3)	1.4 (0.7–1.8)	2.0 (1.0–3.0)	0.2 (0–0.3)	0.3 (0.3–0.4)	0.6 (0.5–0.8)
S. pneumoniae ATCC 6306	2.9 (2.7–3.3)	3.6 (2.7–4.6)	4.5 (3.6–5.0)	6.5 (5.4–7.0)	0.7 (0–1.3)	1.6 (0.9–2.3)	3.6 (2.1–4.3)	0.1 (0–0.3)	0.8 (0.5–1.4)	2.1 (0.7–5.0)
H. influenzae 7002	5.1 (4.3–6.2)	6.4 (6.1–6.7)	8.7 (7.6–10.9)	10.2 (9.1–11.9)	1.3 (0.5–1.8)	3.6 (2.7–4.7)	5.1 (4.2–5.7)	0.2 (0.1–0.3)	0.4 (0.1–0.5)	0.7 (0.6–0.7)
Azithromycin										
S. pyogenes P 1800	4.1 (4.0–4.3)	8.5 (6.7–9.5)	15.3 (14.8–15.7)	17.6 (16.7–19.2)	4.4 (2.4–5.5)	11.2 (10.7–11.5)	13.5 (12.6–14.9)	1.3 (1.0–1.5)	4.1 (3.0–4.8)	7.3 (5.8–9.4)
S. pneumoniae ATCC 6306	4.7 (3.7–5.5)	9.9 (7.1–11.8)	* (10.6–>22)	* (14.6–>22)	5.2 (3.4–6.8)	* (8.2–>16.5)	* (9.6–>18.9)	1.7 (1.4–1.9)	6.2 (3.6–11)	12.0 (10.1–14.3)
H. influenzae 7002	8.0 (6.6–9.5)	10.1 (8.6–11.2)	12.5 (10.5–13.5)	14.4 (13.2–15.3)	2.1 (1.7–2.6)	4.5 (3.9–5.7)	6.4 (5.8–7.0)	0.1 (0–0.2)	0.4 (0.2–0.5)	1.0 (0.8–1.3)

[a] The asterisks indicate experiments in which bacteria did not increase 1 $\log_{10}$ unit of CFU after 24 h.

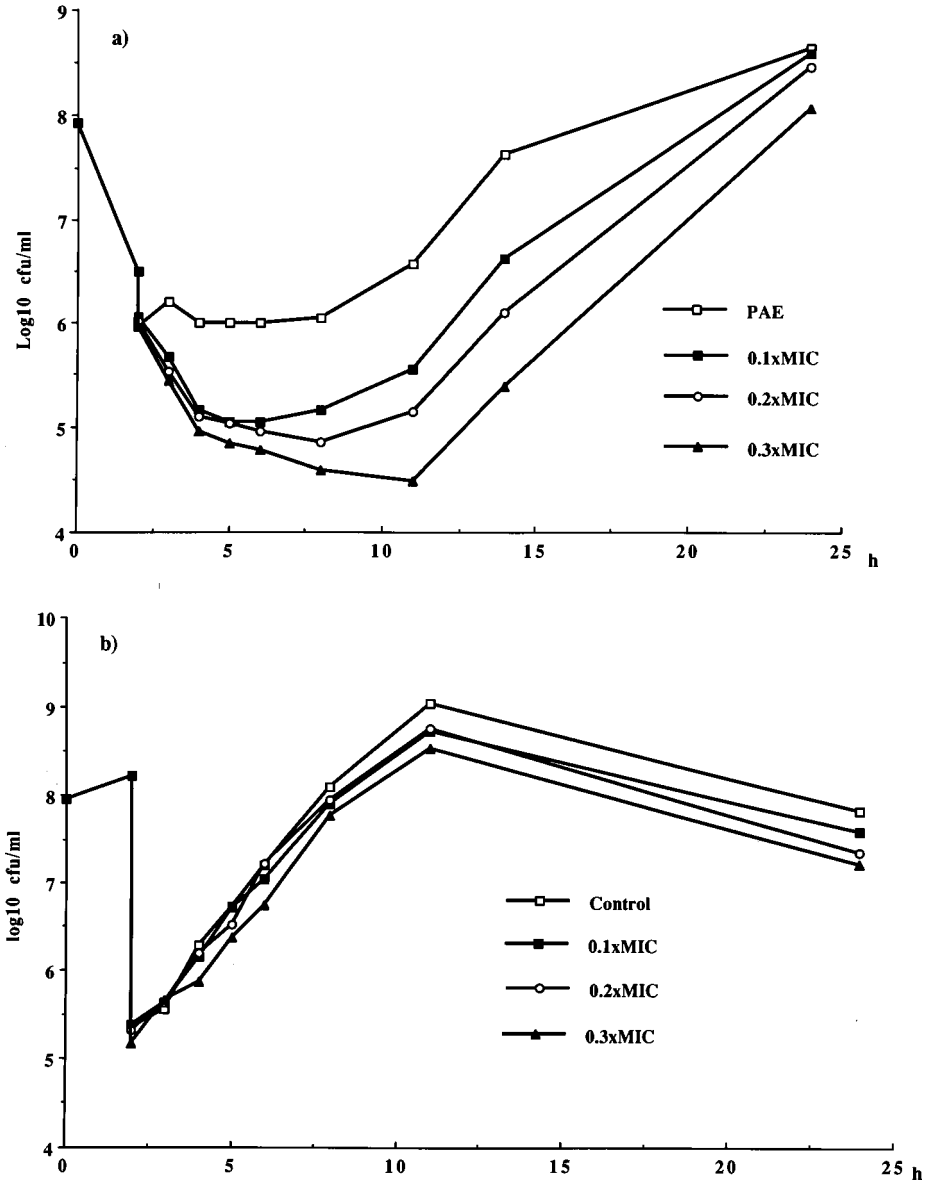

FIG. 1. PA SMEs (a) and SMEs (b) of azithromycin with *H. influenzae* 7002. The PAE was induced with 10× MIC.

clarithromycin against *S. pneumoniae* and *S. pyogenes* ($P < 0.05$). Against *H. influenzae*, only azithromycin induced a statistically significantly longer PA SME than did clarithromycin ($P < 0.05$), but there was no significant difference between clarithromycin and roxithromycin. Even if the PAEs were subtracted from the PA SME (PA SME − PAE), the effects of sub-MICs on previously exposed bacteria were longer than the effects of sub-MICs alone. Azithromycin induced statistically significantly longer SMEs against *S. pyogenes* and *S. pneumoniae* than did roxithromycin and clarithromycin, while otherwise, very short SMEs were noted.

Figure 1 shows the PAEs, PA SMEs, and SMEs of azithromycin on *H. influenzae*. Figure 2 shows the same parameters for roxithromycin on *H. influenzae*, and Fig. 3 shows the PAEs, PA SMEs, and SMEs of clarithromycin on *S. pyogenes* P 1800.

DISCUSSION

One of the primary objectives of antimicrobial therapy is to provide an optimal amount of active drug at the site of the infection. Determinations of MICs and the pharmacokinetics of antibiotics have hitherto been the major factors deciding the doses and dosage intervals of these drugs (19, 30). However, in the past decade the pharmacodynamics of antibiotics have stimulated greater interest. The postantibiotic effect is now a well-known parameter which may influence the effects of different dosing schedules (4, 5, 20, 33, 34). The success of discontinuous dosing regimens in spite of long periods of low antibiotic concentrations between doses could also be attributed to the function of a normal host defense (1, 15, 29, 31, 35). Already in the early work of Eagle et al., it was stated that during the prolonged recovery period (PAE) the damaged but still viable organisms continue to die under the impact of the

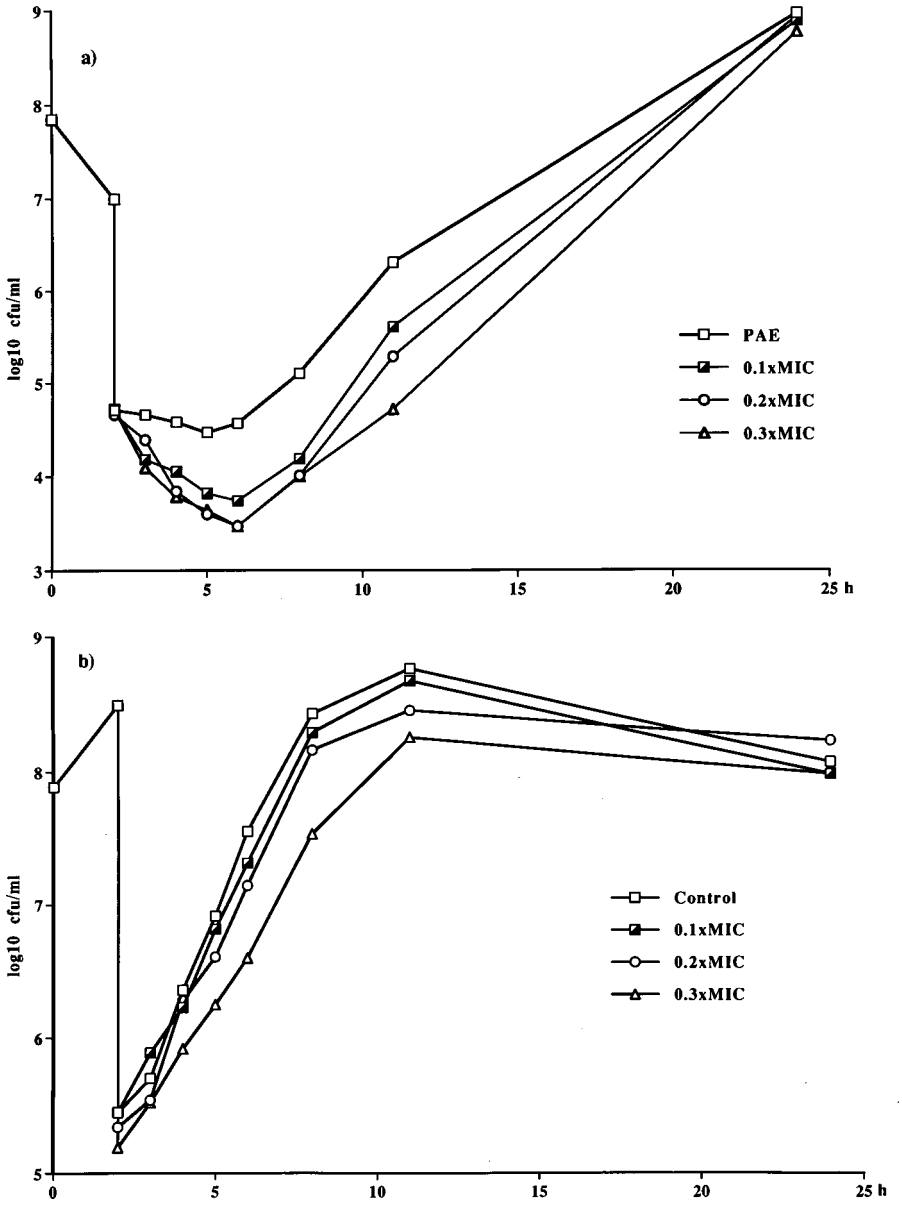

FIG. 2. PA SMEs (a) and SMEs (b) of roxithromycin with *H. influenzae* 7002. The PAE was induced with 10× MIC.

body's host defense mechanisms (9). However, even in neutropenic animals, lack of immediate bacterial regrowth when antibiotic concentrations fall under the MIC has been demonstrated (33). In addition to the PAE, the effectiveness of discontinuous dosing regimens could be explained by sustained effects of sub-MICs after a suprainhibitory dose (PA SME) (2, 25–28, 36). The difference between PAE and PA SME is not always obvious in small animals, in which there is a rapid elimination of the drug. However, in experiments in which the half-lives of antibiotics have been prolonged to stimulate human kinetics, the influence of the sub-MICs becomes more prominent (11).

A PA SME exists not only for β-lactam antibiotics. We have previously demonstrated long PA SMEs of vancomycin and sparfloxacin on *S. pneumoniae* and *S. pyogenes* (28). Winstanley et al. have also showed a prolongation of the PAE from 2.2 to 10.4 h after *Enterococcus faecalis* was exposed to 0.1× MIC of teicoplanin in the postantibiotic phase (36).

The pharmacodynamics of macrolides have not been examined thoroughly. There are some previous reports in the literature concerning the PAEs of macrolides. Gerber and Craig (16) reported a PAE of approximately 3 h both in vitro and in neutropenic mice for erythromycin against *S. pneumoniae*. A somewhat shorter PAE on *S. pyogenes* at 5× MIC was noted. Kuenzi et al. (18) studied the PAE of roxithromycin against the same bacterial species as in the present study. They found that the PAE was dependent on the exposure time and the concentration of the drug. At 5× MIC they noted a PAE of 3 h for roxithromycin against *S. pyogenes*, which can be compared with 5 h in our study at 10× MIC. Ebert et al. (10) reported a PAE of clarithromycin on *S. pneumoniae* of 5.5 h. In the present study, all the antibiotics studied induced PAEs of 2.9 to 8 h on all strains. The PAEs on *H. influenzae* were induced with 10× MIC to be able to compare earlier results. This concentration of the macrolides and azalides is not obtained in serum in the clinical situation. However, this concentration can be achieved

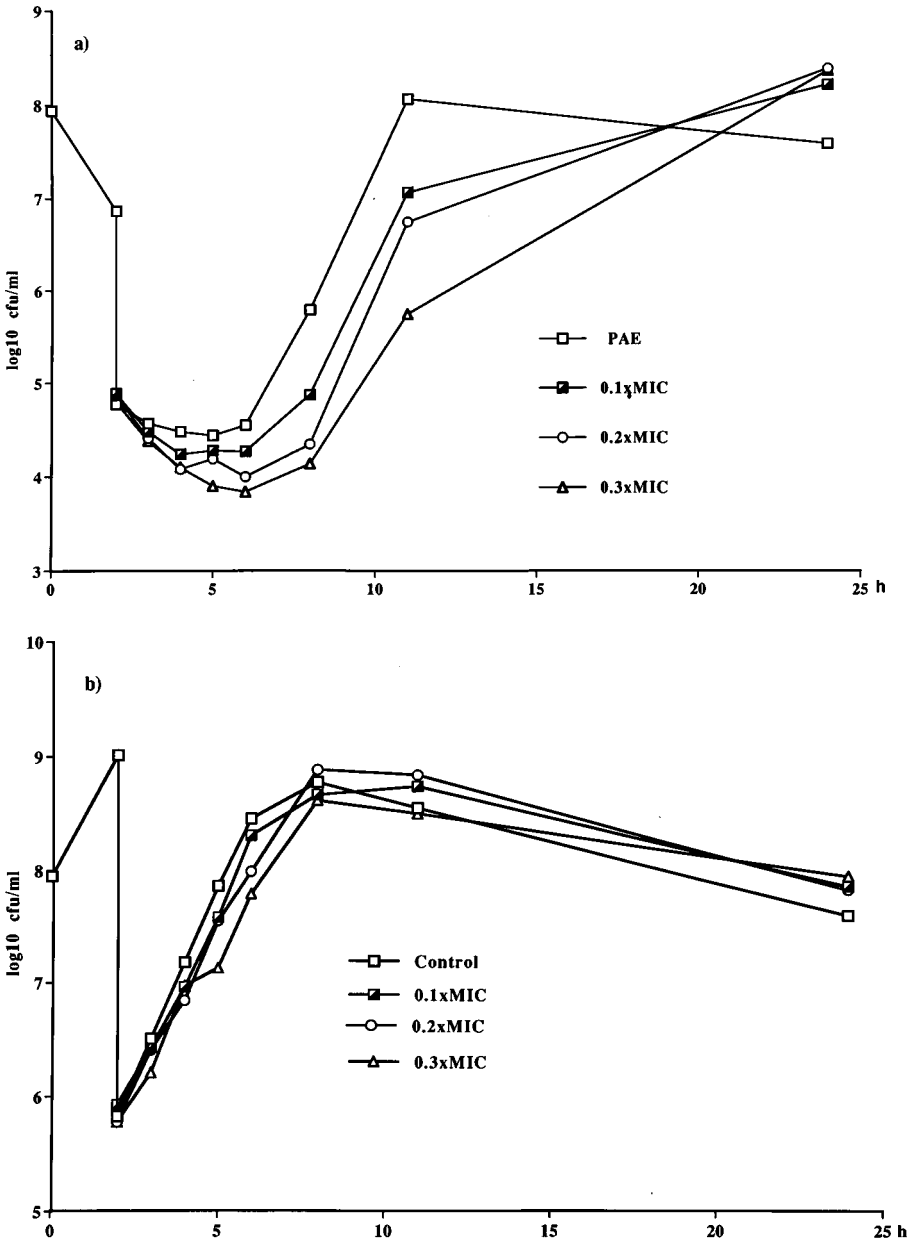

FIG. 3. PA SMEs (a) and SMEs (b) of clarithromycin with *S. pyogenes* M12 NCTC P 1800. The PAE was induced with 10× MIC.

intracellularly, and even if *H. influenzae* is not a obligate intracellular pathogen, it can reside at intracellular sites (13). Clarithromycin induced PAEs of 2.9 to 5.1 h on the studied strains, which were statistically significantly shorter against *S. pneumoniae* and *H. influenzae* than PAEs induced by azithromycin and significantly shorter against *S. pneumoniae* than those induced by roxithromycin. Clarithromycin also induced statistically significant shorter PA SMEs at 0.3× MIC against *S. pneumoniae* (6.5 h) and *S. pyogenes* (6.8 h) than did the other two antibiotics. The reason for this is unclear. Very little effect on bacterial growth was seen with sub-MICs alone.

Azithromycin, an azalide chemically related to the macrolides, yields very low concentrations in serum, but high levels are found in leukocytes and macrophages (23). In spite of this, clinical studies demonstrate efficacy in infections due to extracellular pathogens, which has been attributed to phagocytic delivery of azithromycin to the infection site (22). PAEs of azithromycin at 4× MIC against *S. pyogenes* of approximately 3.5 h and against *S. pneumoniae* of between 2.2 and 4.6 h (6) have been reported. These data correspond well with the results in our study (4.1 and 4.7 h, respectively, at 10× MIC). We could also demonstrate very long PA SMEs: that of azithromycin for *H. influenzae* was 14.4 h at 0.3× MIC and statistically significantly longer than that of clarithromycin but not that of roxithromycin. Azithromycin also showed statistically significantly longer SMEs than the other agents against *S. pyogenes* (7.3 h at 0.3× MIC) and *S. pneumoniae* (12 h at 0.3× MIC).

The mechanism behind the PA SME is not clearly understood, but a recently published paper by Yan et al. (37) suggests that the PAE of penicillin in *S. pyogenes* is caused by irreversible binding of penicillin to penicillin-binding proteins (PBPs) 1 through 3 and that the PAE represents the time

necessary for synthesis of new PBPs required for normal growth. It could be hypothesized then that only a small amount of the antibiotic is needed to inhibit these newly produced PBPs and that the PA SMEs represent this effect. In accordance with the theory of the mechanism of the PA SME for β-lactams, a similar explanation for protein synthesis inhibitors could be that the PAE stands for the time it takes for the protein translocation to be restored, and the PA SME could be due to the fact that only small amounts of the drug are necessary to maintain the inhibition of the translocation. On the other hand, the SMEs probably test the distribution of antibiotic susceptibility in the bacterial population, in which there are subpopulations that are inhibited by concentrations less than the MIC. The SME would then represent the time it takes for the population with higher MICs to become dominant.

The most effective dosage regimens for macrolides and azalides are still not determined, but data for erythromycin indicate that the predictive parameter for efficacy is the time the concentration in serum stays above the MIC (33). In clinical practice, once- and twice-daily doses give high efficacy rates, in spite of long periods of time in which the concentrations of the drugs will not exceed the MICs for the responsible pathogen. How much of this effect can be attributed to the postantibiotic effect, the sustained effects of sub-MICs, and/or the cofunction of the host defense is not known. However, a pronounced PAE and PA SME, as seen with the macrolides and azilides, may indicate that longer dosing intervals for these antimicrobial agents can be allowed.

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