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Variation in Postantibiotic Effect of Clindamycin against Clinical Isolates of *Staphylococcus aureus* and Implications for Dosing of Patients with Osteomyelitis

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Initial measurements of postantibiotic effect (PAE) were made by a standard laboratory method (exposure to 1 mg of clindamycin per liter for 1 h). The range of PAE for 21 strains of *Staphylococcus aureus* isolated from osteomyelitis patients was 0.4 to 3.9 h, which markedly exceeded the coefficient of variation for the method (6 to 19%). Exposure of *S. aureus* to three doses of clindamycin at 8-h intervals had no consistent effect on either PAE or MIC. The PAE was dependent on both concentration and duration of exposure to clindamycin: for example, the PAEs for one strain were 1.7 h after exposure to 1 mg/liter for 1 h, 2.4 h after exposure to 4 mg/liter for 1 h, and 5.9 h after exposure to 4 mg/liter for 3 h. Pharmacokinetic simulations showed that the dose required to maintain free serum clindamycin concentrations above the MIC was 300 mg 6 hourly after oral administration (95% confidence interval, 243 to 301 mg) and 1.2 g 6 hourly (95% confidence interval, 305 to 1,145 mg) after intravenous (i.v.) administration. The duration of PAE would have to be at least 2.4 h to allow an increase in the oral dose interval to 8 h or to allow i.v. administration of 300 mg 6 hourly. Additional PAE experiments were performed with the three strains for which PAEs are the shortest after exposure to 1 mg/liter for 1 h (0.4 to 1.2 h). The PAE for these three strains increased markedly to 4.4 to 6.7 h following exposure to 2 mg/liter for 6 h (to mimic the area under the concentration-time curve from 0 to 6 h after a 300-mg dose). These data suggest that oral clindamycin could be administered at 300 mg 8 hourly in the treatment of *S. aureus* infection, whereas the i.v. dose interval should be 6 h. These suggestions should be confirmed by performing clinical trials.

A persistent suppression of bacterial growth after a short exposure to antimicrobial agents was first noticed in the early 1940s (2, 24, 25). It was not until the 1970s that the term postantibiotic effect (PAE) was introduced to describe this phenomenon (21). Since then, PAE studies have been conducted with many antibiotic-organism combinations in vitro, and most of these show some evidence of a PAE. The major exception is that some β-lactam drugs have either an insignificant PAE or even a negative PAE for gram-negative bacilli (4, 13, 14, 21, 23, 26–28, 30). Studies with animal models have shown that a PAE may also be demonstrated in vivo and that the PAE is generally more prolonged than it is in vitro (6, 11, 30).

Recently, it has been suggested that the PAE should be considered in designing antibiotic dosage regimens (5, 19). Turnidge proposed that the optimum dosing interval could be calculated as the sum of the time that the serum drug concentration exceeded the MIC plus the duration of the PAE (29). The optimum dosing interval could then be calculated mathematically by using the drug's pharmacological parameters and dose, the MIC for the organism, and the relationship between the area under the concentration-versus-time curve (AUC) and PAE. Obviously, this proposal is more convincing for concentration-independent antibiotics such as β-lactams and clindamycin rather than concentration-dependent antibiotics such as aminoglycosides. Other effects which might contribute to the PAE in vivo, such as the postantibiotic leukocyte effect and postantibiotic sub-MIC effect, are difficult to reproduce in vitro and are unlikely to enhance any PAE measured in the laboratory.

If PAE is to be used for dosage calculation, the following points must be considered. Firstly, the measurements must be robust, reproducible, and, hopefully, standardized. Secondly, the amount of interstrain variation must be known. If this is wide, ideally dosing should be based on measurement of the PAE for the infecting bacteria. However, measurement of PAE is a research procedure which is not available in routine laboratories. A more practical way to deal with interstrain variation of PAE would be to use a population statistic such as the PAE for at least 50% of strains (PAE_{50}) or the PAE for at least 90% of strains (PAE_{90}). Thirdly, there should be no reduction in PAE after multiple dosing (17, 18). Finally, the duration of PAE must be sufficiently long to have a significant impact on unit dose or dosing interval. The aims of this study were to address each of these points with respect to the PAE of clindamycin against *Staphylococcus aureus* and then to make a critical assessment of the likely impact of this information on dosing of clindamycin for treatment of osteomyelitis.

MATERIALS AND METHODS

Bacterial isolates. Twenty-one strains of *S. aureus* were used; 20 had been isolated from patients with osteomyelitis, and 1 was the standard Oxford *S. aureus* strain (ATCC 25923). The bacteria were identified by standard microbiological methods (1). The isolates were stored at −20°C on beads until use.

Inoculum. Each organism was subcultured onto blood agar and incubated overnight. The following day, a logarithmic-phase culture was obtained by inoculating two colonies into Muller-Hinton broth (MHB) (Difco) and incubating them in a shaking water bath at 37°C until the optical density was the same as a McFarland 0.5 standard (approximately 10^8 bacteria per ml).

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Antimicrobial agents. Clindamycin (Sigma Chemical Co.) stock solution (1,000 mg/liter) was prepared, aliquoted, and stored at −20°C for a maximum of 1 month. Dilutions (1, 2.25, and 4 mg/liter) were prepared in MHB (Difco) on the day of use.

Determination of PAE. The PAE in MHB was measured by the viable-count technique (7). The organism was exposed to 1 mg of clindamycin per liter for 1 h. Antibiotic concentration was then reduced to 0.01 mg/liter by a 100-fold dilution. The PAE was measured by calculating the difference in time required for the number of test and control bacteria to increase 1 $\log_{10}$ unit (10-fold) above the number present immediately after removal of antimicrobial agents from the test cultures.

Reproducibility of the PAE method. The PAE of clindamycin against four isolates (including three clinical isolates and the Oxford *S. aureus* strain) was measured six times on different days. The mean, median, standard deviation, and coefficient of variation (CV) were then calculated for the six separate measurements of PAE.

Interstrain variation of PAE. The PAE of clindamycin was measured against 21 strains of *S. aureus*. The exposure time was 1 h, and the concentration was 1 mg/liter.

Susceptibility test and relationship between PAE and MIC. The MIC was determined by a standard twofold agar dilution technique in Iso-Sensitest agar (National Committee for Clinical Laboratory Standards, 1985) (3). The MIC was defined as the lowest concentration of antibiotic that inhibited visible growth after 18 h of incubation.

Effect of duration of exposure and concentration on PAE. The PAE for two strains (for which the MIC was the same) was measured after exposure to concentrations of two times the MIC (2MIC), 8MIC, 16MIC, and 32MIC for 1, 2, and 3 h. The relationship between PAE and AUC (exposure time × exposure concentration) was tested by linear regression.

PAE and MIC following single and multiple exposures. PAEs for two strains were measured after exposure for 2 h to single and multiple doses of 2 mg of clindamycin per liter. PAE was measured after the first dose, and cultures were then allowed to continue regrowth. When 8 h from the time of its initial exposure to clindamycin had passed, the culture was diluted, if necessary, to approximately 10^8 to 10^{10} CFU/liter and reexposed to the same clindamycin concentration. This entire process was repeated once more 8 h later. In addition, MICs were measured for all cultures, just before each of the three exposures to clindamycin.

Impact of PAE on unit dose and interval of clindamycin dosing. Eleven groups of oral concentration-time data and eight groups of intravenous (i.v.) concentration-time data from healthy subjects were collected from publications describing studies with healthy volunteers (9, 22, 31). These data were then entered into TOPFIT (a commercial pharmacokinetic-dynamic software package) to perform kinetic simulations (15). Optimal dosing regimens were regarded as those which maintained the serum drug concentration above the MIC at which 90% of the isolates were inhibited (MIC_{90}) throughout the dosing interval. For these calculations, the MIC was corrected for protein binding. Studies suggested that protein binding of clindamycin decreases from 84 to 40% as the drug concentration increases from 0.4 to 40 mg/liter. According to the population simulation results, the concentration range of clindamycin in serum is 1 to 6 mg/liter after a 300-mg dose every 6 h orally or i.v. Protein binding of clindamycin is around 80% in this concentration range (8). The MIC_{90} of clindamycin against *S. aureus* is 0.25 mg/liter. Therefore, the MIC_{90} justified by protein binding should be $0.25/(1 - 0.8) = 1.25$ mg/liter. Allowance was made for the duration of the PAE by subtracting it from the initial dose interval. For these simulations, the PAE was set at 0, 1, 2, 3, and 4 h. For example, if the chosen dosing interval was 6 h, then the aim of the simulation was to calculate the dose of clindamycin which would maintain serum drug concentrations above 1.25 mg/liter for 6 h (PAE = 0), 5 h (PAE = 1 h), 4 h (PAE = 2 h), 3 h (PAE = 3 h), and 2 h (PAE = 4 h). The alternative way of manipulating dosing is to add the PAE to the dose interval, but the only practical increments are from 6 hourly to 8 hourly or 12 hourly dosing. Therefore, a 300-mg unit dose was simulated at different dosing intervals (6, 8, and 12 hourly). It was assumed that once the serum drug concentration fell below 1.25 mg/liter, only the PAE would prevent regrowth. Therefore, for each dosing interval, the number of hours during which serum drug concentrations were below 1.25 mg/liter was calculated because that indicates the duration of PAE required to prevent regrowth.

PAE after exposure to concentrations simulating the AUC of a 300-mg dose of clindamycin in vivo. The three strains of *S. aureus* for which the PAEs were the shortest after exposure to 1 mg of clindamycin per ml were selected. TOPFIT was used to simulate the steady-state AUC from 0 to 6 h for a dose of 300 mg of clindamycin administered orally or i.v. and to calculate the mean steady-state serum drug concentration. The PAE for the three strains of *S. aureus* was then remeasured after exposure to the mean steady-state serum drug concentration for 6 h.

Statistics. Nonparametric statistics were used for skewed distributions. Estimates of the population median, the population 90th percentile, and their 95% confidence intervals (CI) were made by standard methods (12). Estimates of the difference between medians and their 95% CI were made with Minitab for Windows.

TABLE 1. CV of PAE for six separate measurements with four strains of *S. aureus*

Strain	PAE (h)		SD	CV (%)	95% CI of mean PAE (h)
	Mean	Median			
Oxford	3.3	3.4	0.2	6	3.2–3.5
03872K	4.0	4.0	0.3	7	3.8–4.2
24097X	1.7	1.8	0.3	19	1.5–2.0
24129Q	1.8	1.7	0.3	15	1.4–1.9

RESULTS

Reproducibility of PAE. The mean and median of the repeated measurements of PAE were similar, so that parametric statistics were used (Table 1). The CV for each strain varied from 6 to 19% (Table 1). The PAEs for the Oxford *S. aureus* strain and one clinical isolate were reproducibly longer than the PAE for the other two clinical strains (Table 1).

Interstrain variation of PAE. The distribution of PAE was skewed (Fig. 1), and nonparametric statistics were used for the analysis. The sample PAE range was 0.4 to 3.9 h, and the mean was 2.0 h. The median (PAE_{50}) was 1.7 h, the 90th percentile (PAE_{90}) was 1.2 h, and the 95% CIs for the estimated population PAE_{90} (1.0 h) were from 0.4 to 1.4 h. The 95% CIs for the estimated population PAE_{50} (2.0 h) were from 1.4 to 2.8 h. The CV of these 21 strains' PAE is 45%, which is much higher than the interassay variation (from 6 to 19%). This suggests that the variation in PAE for 21 strains was not due to experimental error alone and that there is genuine variation in PAE among strains.

Relationship between MIC and PAE. The MIC for 10 of the 21 *S. aureus* isolates was 0.25 mg/liter, and the MIC for the remaining 11 was 0.125 mg/liter. The median PAE was longer for the 11 strains for which the MIC was lower, 0.125 mg/liter (2.3 versus 1.4 h; estimated difference in population medians, 0.6 h; 95% CI, 0 to 1.4 h; $P = 0.05$, Mann-Whitney test).

Effect of duration of exposure and clindamycin concentration on PAE. PAE increased with the exposure concentration and exposure time (Fig. 2). The relationship between AUC (exposure time × concentration) and PAE was approximately linear for both of the strains (Fig. 3). The coefficient of correlation between PAE and AUC was 0.99 for both of the strains. Although there was a strong linear relationship between PAE and AUC for both strains, the lines were not parallel (Fig. 3).

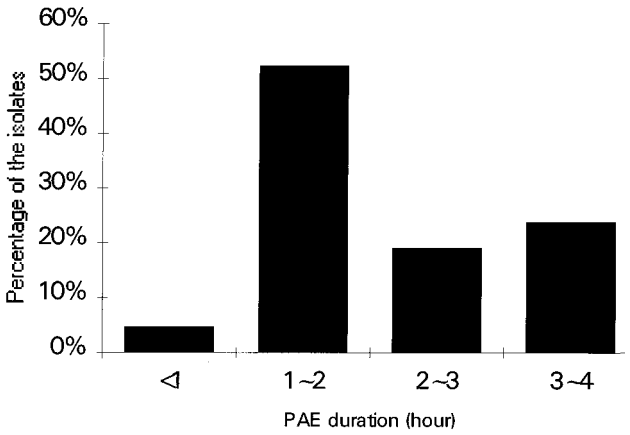

FIG. 1. PAE of clindamycin against 21 clinical *S. aureus* isolates (exposed to 1 mg/liter for 1 h).

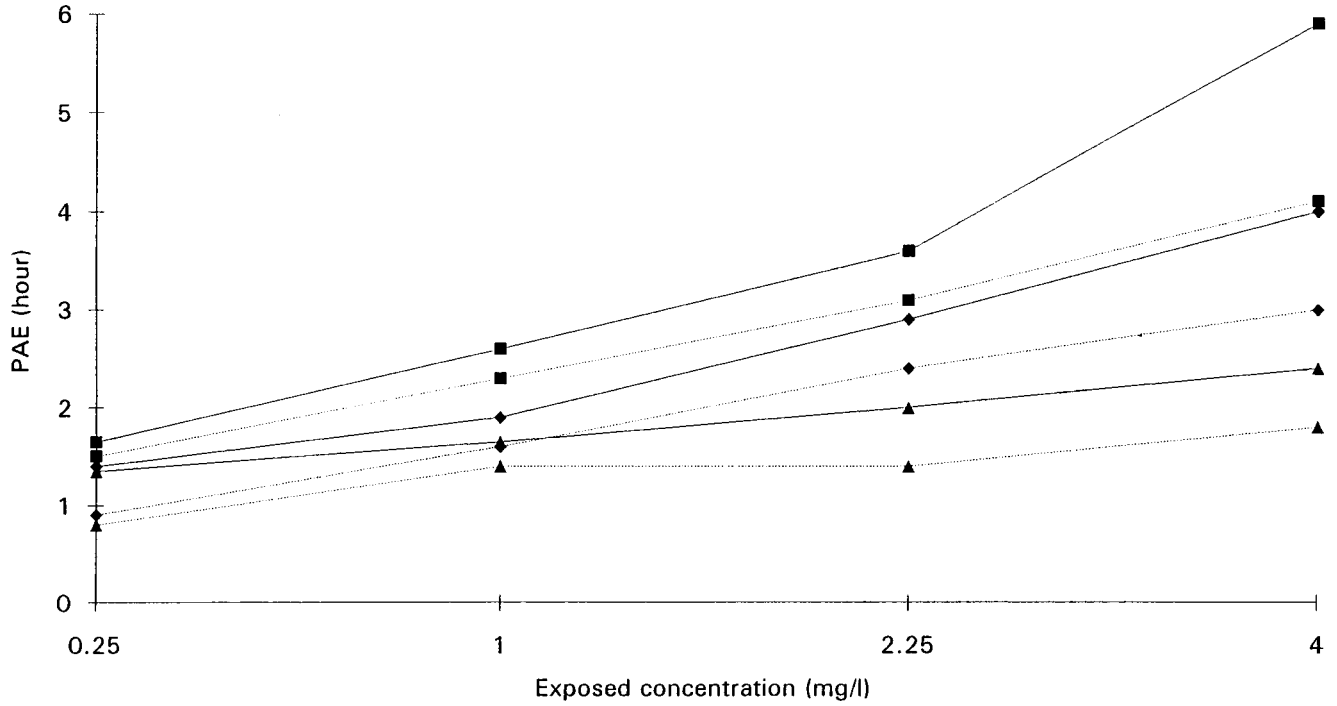

FIG. 2. Relationship among PAE, exposure concentrations, and exposure time. ■, Exposed for 3 h; ◆, exposed for 2 h; ▲, exposed for 1 h; ——, strain 1; . . . . . , strain 2.

Consequently, the difference between the PAEs for these two strains is both concentration and time dependent. For example, after exposure to clindamycin at 1 mg/liter for 1 h, the difference was 0.3 h (1.4 versus 1.7 h), whereas after exposure to 4 mg/liter for 3 h, the difference in PAE was 1.9 h (4.0 versus 5.9 h).

Impact of multiple doses on PAE and MIC. For the reference strain and one clinical strain of *S. aureus*, multiple expo-

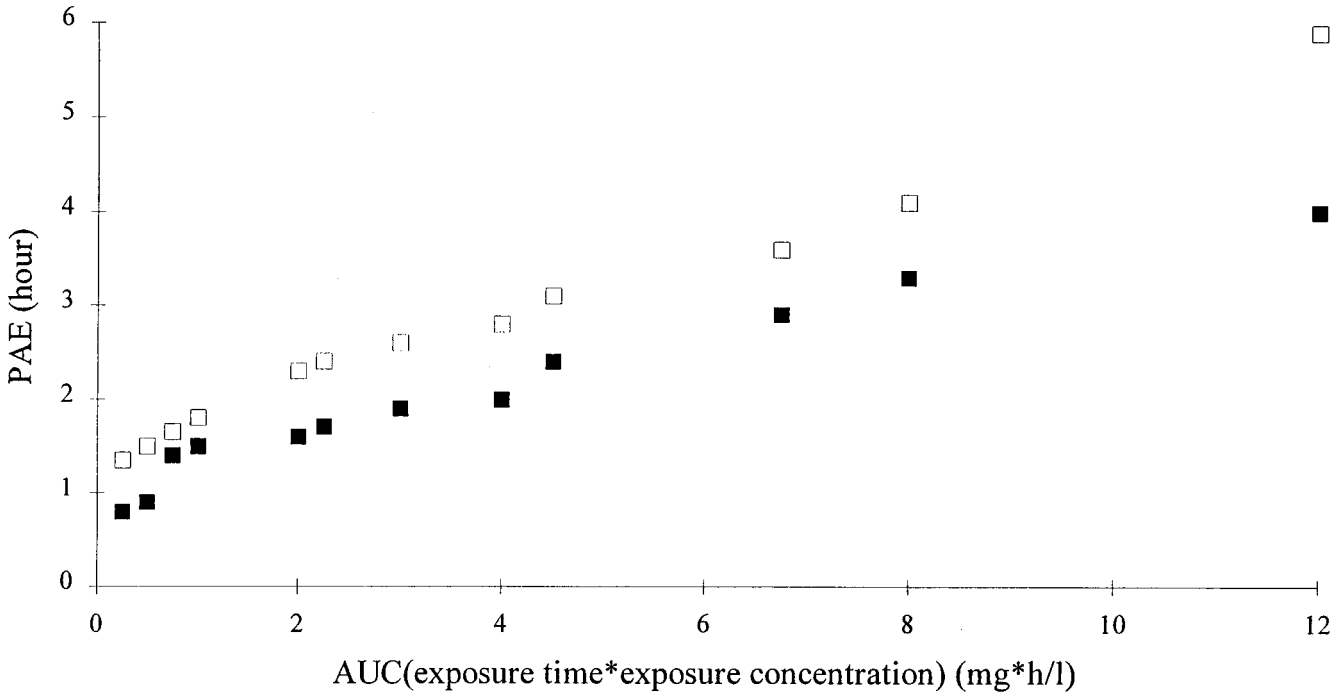

FIG. 3. Relationship between AUC (exposure time × exposure concentration) and PAE for two strains for which MICs are identical.

TABLE 2. PAE and MIC following single and multiple exposures of *S. aureus* to clindamycin at 2 mg/liter[a]

Time of measurement	PAE (h)		MIC (mg/liter)	
	Strain 1	Strain 2	Strain 1	Strain 2
Preexposure	NA[b]	NA	0.25	0.125
After first exposure	3	2	0.25	0.125
After second exposure	2.5	3	0.25	0.125
After third exposure	2.3	2.7	0.125	0.0625

[a] Approximately 10^8 CFU/liter was exposed to clindamycin for 2 h every 8 h over a 24-h period in vitro.
[b] NA, not applicable.

sures had no significant consistent effect on either PAE or MIC. The MICs after the third exposure are twofold lower, which cannot be regarded as a significant reduction (Table 2).

Impact of PAE on unit dose and dosing interval of clindamycin. For oral administration of clindamycin, the dose required to maintain serum drug concentrations above 1.25 mg/liter was approximately 300 mg 6 hourly (95% CI, 243 to 301 mg) (Table 3), whereas for i.v. administration, the dose required was much higher (mean, 725 mg; 95% CI, 305 to 1,145 mg) (Table 3). For oral administration, the only practical dose reduction is to 150 mg, as that is the next available dose formulation. For oral administration the dose could be reduced to 150 mg 6 hourly if the PAE is at least 3 h, because the 95% CI of the dose required to maintain free serum drug concentrations greater than the MIC would be 110 to 134 mg (Table 3). Alternatively, the oral dose interval could be extended to 8 hourly if the PAE is >2.4 h (95% CI, 1.6 to 2.4 h) (Table 4). Conversely, for i.v. administration the PAE would need to be 3 h for a dose of 300 mg 6 hourly to be used with confidence (95% CI, 156 to 276 mg 6 hourly) (Table 3). Each vial of the i.v. formulation contains 300 mg of clindamycin; therefore, reducing the unit dose below 300 mg would not save any drug unless the drug could be reused. Finally, the i.v. dose interval could be extended to 8 hourly for a 300-mg dose if the PAE is >4.6 h (95% CI, 2.6 to 4.6 h) (Table 4).

PAE after exposure to concentrations simulating the AUC of a 300-mg dose of clindamycin in vivo. PAEs after exposure to clindamycin at 2 mg/liter for 6 h were 4.4 to 6.7 h for the three strains for which PAEs were 0.4 to 1.2 h after exposure to 1 mg/liter for 1 h (mean for two experiments).

DISCUSSION

There is very little published information about interstrain variation in PAE. The reason may be that PAE experiments are time-consuming and laborious. As the mechanism of PAE is still unclear, it is difficult to speculate about the processes underlying the variation of PAE, although differences in MIC appeared to account for some of the variation in our sample. Whatever the mechanism, the degree of variation significantly increases the difficulty of using the PAE in the design of optimal dosing regimens. It is highly unlikely that any routine laboratory would undertake measurement of PAE for individual patients. Therefore, dose calculation must be based on population statistics. For a serious infection, like osteomyelitis, the PAE_{90} is probably the appropriate statistic. If calculations of the dosing regimens are to incorporate the PAE (29), then more information about interstrain variation is required. This is relatively easy for osteomyelitis because the range of causative organisms is small (10), but it may present formidable difficulties for other infections.

The healthy-volunteer population kinetics means were used in this study, and they might be different from the kinetics in real patients. This is one limitation of our study, and more data about kinetics in representative patient populations are necessary.

Previous studies suggested that the PAE of aminoglycosides or ciprofloxacin for gram-negative bacteria was markedly reduced following multiple exposures (17, 18) whereas the PAE of β-lactams was not affected by multiple exposure (18). Our data show that the PAE of clindamycin is not affected by multiple doses.

The complex relationship between PAE, drug concentration, and exposure time (Fig. 2) may explain some of the differences between in vitro and in vivo PAEs that have been observed. PAE is generally longer in vivo than in vitro (5, 11, 30). Besides the sub-MIC effect, postantibiotic leukocyte effect, and some other effects in vivo, differences in duration of exposure between in vivo and in vitro PAE experiments might contribute as well. It might be argued that a longer exposure time should be used routinely for in vivo PAE experiments. However, the experiments with a 6-h exposure took around 17 h of continuous work to perform. Automatic methods may make these experiments more practical (16, 20), but with less-sophisticated equipment these experiments are daunting. Consequently, information about interstrain variation for PAE after longer exposure time is likely to remain minimal.

The sequence of experiments described in this paper could be applied to the design of dosing regimens for other drugs. PAEs could be measured after standard short exposures to estimate the population variation in PAE. Once the strains for which PAEs are relatively short have been identified, they should be used in experiments with a longer exposure time, mimicking the in vivo steady-state concentration for a realistic dose interval. These PAEs are unlikely to overestimate the in

TABLE 3. Impact of PAE on dose of clindamycin[a]

PAE (h)	Oral clindamycin				i.v.-bolus clindamycin			
	Mean dose (mg)	95% CI of mean dose (mg)	Mean dose reduction by PAE (%)	95% CI of mean dose reduction (%)	Mean dose (mg)	95% CI of mean dose (mg)	Mean dose reduction by PAE (%)	95% CI of mean dose reduction (%)
0	272	243–301	NA[b]	NA	725	305–1145	NA	NA
1	209	189–230	23	25–21	514	254–774	24	30–18
2	161	146–177	40	44–36	336	204–468	46	53–39
3	122	110–134	55	59–51	216	156–276	59	69–49
4	97	86–109	64	68–60	144	117–171	72	80–64

[a] The mean dose is that required to maintain serum drug concentrations of >1.25 mg/liter for the whole duration of the dose interval (6 h) minus the PAE. The simulation was based on data from some references (9, 22, 31).
[b] NA, not applicable.

TABLE 4. Impact of PAE on dosing interval of oral and i.v. clindamycin[a]

Interval of 300-mg dose[b]	Oral		i.v. bolus	
	Mean time (h) during which serum drug concns are >1.25 mg/liter (95% CI)	Mean PAE required to prevent regrowth (h) (95% CI)	Mean time (h) during which serum drug concns are >1.25 mg/liter (95% CI)	Mean PAE required to prevent regrowth (h) (95% CI)
q6h	5.9 (5.8–6.0)	0.1 (0–0.2)	4.4 (3.6–5.3)	1.6 (0.7–2.4)
q8h	6.0 (5.6–6.4)	2.0 (1.6–2.4)	4.4 (3.4–5.4)	3.6 (2.6–4.6)
q12h	5.8 (5.3–6.2)	6.3 (5.8–6.7)	4.4 (3.6–5.2)	7.6 (6.8–8.4)

[a] The mean PAE is that required to prevent regrowth while the serum drug concentrations are lower than 1.25 mg/liter. The simulation was based on data from some references (9, 22, 31).
[b] q6h, q8h, and q12h, every 6, 8, and 12 h, respectively.

vivo PAE, and it could be inferred that the PAE for other strains will reliably be at least as long as this in vivo. Finally, it is necessary to ensure that the PAE is preserved after multiple dosing.

In conclusion, for clindamycin and *S. aureus*, we believe that the PAE would have to be at least 2.4 h to have an impact on the oral dosing regimen that we currently use for osteomyelitis. The results presented here provide us with evidence that the PAE_{90} is likely to be more than 3 h after exposure to 12 mg · h/liter, which can be achieved by oral administration of 300 mg of clindamycin; therefore, a change to 300 mg 8 hourly seems reasonable for oral administration. In contrast, for i.v. administration we would recommend a dose of 300 mg 6 hourly. Although the laboratory techniques used almost certainly underestimate PAE in vivo, the technical difficulties of more realistic simulation of in vivo concentration-time profiles are formidable. This situation is unlikely to change unless a practical technique which will allow both realistic kinetic simulation and testing of a representative number of strains can be devised.

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