

## Bactericidal Activity of Low-Dose Clindamycin Administered at 8- and 12-Hour Intervals against *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Bacteroides fragilis*

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Twelve volunteers received 300 mg of clindamycin intravenously (i.v.) or orally (p.o.) administered every 8 h (q8h) or q12h by random assignment over four study periods. Serum bactericidal titers were determined for each regimen against two isolates each of *Staphylococcus aureus*, *Streptococcus pneumoniae* (one penicillin-sensitive isolate and one penicillin-resistant isolate), and *Bacteroides fragilis*. The duration of measurable bactericidal activity over the dosing interval (expressed as a percentage of the dosing interval) was determined for each isolate. No significant differences in the duration of activity were observed between i.v. and p.o. regimens dosed according to the same interval ( $P > 0.05$ ). All regimens provided bactericidal activity against *S. pneumoniae* for 100% of their respective dosing intervals. Against *B. fragilis*, bactericidal activity was observed for greater than 80% of the dosing interval for each of the regimens. Although a statistically significant difference favoring the q8h i.v. regimen ( $P < 0.05$ ) was detected, this difference is not believed to be clinically significant. The q8h and q12h regimens provided measurable bactericidal activity against *S. aureus* for greater than 85 and 50% of the dosing intervals, respectively ( $P < 0.001$ ). Clindamycin dosed at 300 mg i.v. or p.o., q8h or q12h, provides adequate coverage against *S. aureus*, *S. pneumoniae*, and *B. fragilis*.

Characterization of the pharmacodynamic properties of various antimicrobials, including the  $\beta$ -lactams and aminoglycosides, has had a significant influence on the dosing of these agents. Despite the drug's widespread clinical use, optimal dosing for clindamycin remains elusive (1–3, 5, 11–13). Recently, we described concentration-independent activity of clindamycin against five strains of *Bacteroides fragilis* (7). According to these data, the optimal dosing regimen for clindamycin is the lowest dose that yields concentrations in serum above the MIC for a variety of pathogens throughout the dosing interval. The objective of this study was to evaluate the activities of two low-dose (300-mg) clindamycin regimens administered intravenously (i.v.) and orally (p.o.) at 8- and 12-h intervals.

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### MATERIALS AND METHODS

**Healthy volunteers.** Twelve normal, healthy volunteers were recruited for participation in this randomized, open-label, four-way crossover trial. Study procedures and informed consent were reviewed and approved by the Institutional Review Board at Hartford Hospital prior to subject enrollment. Individuals were considered eligible for participation if they were at least 18 years of age, did not have a history of hypersensitivity to clindamycin or related compounds, and were not taking medications other than the study agents, oral contraceptives, or vitamins during the study period. Females were excluded if pregnant (verified by serum pregnancy test). Prior to the first study period, all potential subjects submitted to physical and laboratory (serum chemistry, complete blood count with differential, and urinalysis) evaluations. Volunteers were excluded from the trial if significant physical or laboratory abnormalities (e.g.,

serum creatinine greater than 2.0 mg/dl or liver transaminases greater than two times the upper limit of normal values) were detected on prestudy screening. Informed consent was obtained from each individual prior to participation. Consumption of alcoholic beverages and smoking were not permitted during the trial. Volunteers also refrained from strenuous activities during test periods. During study periods, subjects were housed in the hospital's Clinical Research Center. Posttrial laboratory evaluations were performed on each individual upon their completion of or withdrawal from the study.

**Study agents and administration.** Subjects were randomly assigned to receive 300 mg of clindamycin (Cleocin; The Upjohn Co., Kalamazoo, Mich.) i.v. or p.o. every 8 (q8h) or q12h during the first study period and received the remaining dosing regimens during subsequent study periods. There was a 6-day washout period between each arm of the study. Clindamycin for i.v. administration was diluted with 100 ml of 5% dextrose (USP) prior to infusion. The i.v. regimens were infused over 30 min via a SideKick infusion pump system (Solo Pak, Boca Raton, Fla.) through an i.v. cannula placed in the antecubital vein of each subject. The p.o. clindamycin regimens were administered as one 300-mg capsule given with an 8-oz glass of water. Prior to administration of clindamycin, subjects fasted overnight (at least 5 h) and remained in the fasted state for 2 h following administration of the dose. To ensure that steady-state concentrations in serum had been achieved, subjects were administered three doses of clindamycin prior to the initiation of sample collection.

**Sampling.** Venous blood samples were collected via an indwelling i.v. cannula placed in the antecubital vein of each subject. If the individual was receiving i.v. clindamycin, this cannula was placed in the arm contralateral to that used for medication administration. Samples were obtained prior to medication administration on the first day of each study period (predose) and at predetermined time points following the administration of select antimicrobial doses. A sample was obtained immediately prior to the administration of the third dose of clindamycin (time zero) and at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, and 8.0 h following dose administration. Additional samples were collected at 10.0 and 12.0 h from individuals receiving q12h regimens. Immediately following i.v. doses, prior to the collection of the 0.5-h sample, i.v. sites were flushed with 6 ml of normal saline to remove residual clindamycin from the administration site. At the time of each sample collection, 3 ml of blood was drawn from the i.v. access site and discarded. Ten milliliters of venous blood was then collected in serum separation tubes (Becton Dickinson Vacutainer Systems, Rutherford, N.J.) at each time point and allowed to clot at room temperature for 30 min. Serum was separated via centrifugation at  $1,600 \times g$  for 10 min and stored at  $-70^\circ\text{C}$  until the time of analysis. Following sample collection, cannulas were flushed with 3 ml of normal saline followed by instillation of 1.5 ml of heparin (100 U/ml) for maintenance of site patency.

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TABLE 1. Median MICs for study isolates

Isolate	Clindamycin MIC ( $\mu\text{g/ml}$ )	Clindamycin MBC ( $\mu\text{g/ml}$ )	Penicillin MIC ( $\mu\text{g/ml}$ )
<i>S. aureus</i> 1	0.25	0.25	
<i>S. aureus</i> 30	0.125	0.125	
<i>S. pneumoniae</i> 8	0.125	0.125	4.0
<i>S. pneumoniae</i> 23	0.125	0.125	0.125
<i>B. fragilis</i> 11	0.5	0.5	
<i>B. fragilis</i> 16	0.5	1.0	

**Test organisms.** Two clinical isolates each of *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *B. fragilis* were obtained from our institution's Department of Microbiology for evaluation of the bactericidal activity of subject serum. The MIC of clindamycin for each isolate of *S. aureus* was determined according to National Committee for Clinical Laboratory Standards (NCCLS) guidelines for aerobic microdilution techniques with cation-adjusted Mueller-Hinton broth (CAMHB; Difco Laboratories, Detroit, Mich.) as the growth medium (11). The MIC of clindamycin for each isolate of *S. pneumoniae* was determined according to NCCLS guidelines for aerobic microdilution techniques using CAMHB supplemented with 5% lysed horse blood as the growth medium (11). Additionally, the MICs of penicillin for *S. pneumoniae* isolates were determined. MICs for the two isolates of *B. fragilis* were conducted in accordance with NCCLS guidelines for anaerobic microdilution techniques (9). For anaerobic testing procedures, Schaedler broth (Becton Dickinson Microbiology Systems, Cockeysville, Md.) was utilized as the growth medium. The MBCs were subsequently determined by plating 3 to 5  $\mu\text{l}$  from each MIC sample onto a plate containing Mueller-Hinton agar (Difco Laboratories) for *S. aureus* and *B. fragilis* and Trypticase soy agar supplemented with 5% sheep blood (Becton Dickinson Microbiology Systems, Cockeysville, Md.) for *S. pneumoniae*. MIC and MBC determinations were repeated each day an isolate was utilized for serum activity testing. The median MIC was determined at the end of microbiologic testing. Prior to use in the determination of the bactericidal activity of subject samples, isolates were screened against subject drug-free (predose) serum to document lack of inhibition secondary to unidentified serum inhibitory factors.

**Bactericidal activity determinations.** Serum inhibitory and bactericidal titers (SIT, SBT) were determined for each of the clindamycin dosing regimens against each of the six study isolates. SITs and SBTs were determined in duplicate according to NCCLS guidelines (10). Briefly, for aerobic determinations 100  $\mu\text{l}$  of subject serum was placed in the first column of a microtiter tray. Samples were then serially diluted with 50  $\mu\text{l}$  of drug-free, heat-inactivated, normal pooled serum which had been demonstrated not to impair growth of the test isolates. Finally, 50  $\mu\text{l}$  of test microorganism solution, approximately  $10^6$  CFU/ml (isolates were grown in CAMHB for 3 h to ensure exponential growth, adjusted to a 0.5 McFarland turbidity standard, and diluted with CAMHB by a factor of 1:100), was added to each well of the microtiter tray. These procedures resulted in serial dilutions of clindamycin-containing volunteer serum samples of 1:2, 1:4, and 1:8, etc., up to 1:2,048. After incubation at 37°C for 24 h, SIT results were recorded. Subsequently, 3 to 5  $\mu\text{l}$  from each SIT sample was removed and plated on Mueller-Hinton agar (Difco Laboratories) for *S. aureus* and *B. fragilis* and Trypticase soy agar supplemented with 5% sheep blood (Becton Dickinson Microbiology Systems, Cockeysville, Md.) for *S. pneumoniae*. Following a 24-h incubation period at 37°C, SBTs were determined by identifying the largest dilution that resulted in a 99.9% reduction in bacterial growth compared with drug-free controls.

Similar procedures were followed during testing with *B. fragilis* with the following modifications. Incubation periods were extended to 48 h, and anaerobic conditions were maintained throughout by placing samples in an anaerobic jar equipped with a BBL GasPak Plus packet (Becton Dickinson Microbiology Systems, Towson, Md.). Additionally, SBT samples were plated on blood agar plates (Becton Dickinson Microbiology Systems, Cockeysville, Md.) rather than Mueller-Hinton agar plates.

**Analytical methods.** Serum clindamycin concentrations were determined with high-performance liquid chromatography methods using UV wavelength detection ( $\lambda = 198$  nm) and a Nova-Pak  $\text{C}_{18}$  column (4- $\mu\text{m}$  particles; 3.9 by 150 mm). The mobile phase consisted on 0.01 M phosphate-0.05% tetrabutylammonium buffer (pH 6.7) and acetonitrile in a 70.5:29.5 ratio (vol/vol) at a flow rate of 1.3 ml/min. The extraction procedure was as follows: 200  $\mu\text{l}$  of standard, check sample, or unknown was combined with 50  $\mu\text{l}$  of internal standard (triazolam, 5  $\mu\text{g/ml}$ ), vortexed, and centrifuged at  $3,000 \times g$  for 10 min. The aqueous solution was decanted, evaporated under nitrogen to a volume of 200  $\mu\text{l}$ , and centrifuged at  $3,000 \times g$  for 10 min. Twenty microliters was then injected onto the column. Pooled human serum was used to prepare the standards and check samples as well as to dilute unknown samples as required. The assay was linear over the range of 0.5 to 50  $\mu\text{g/ml}$ . Intraday coefficients of variation were 2.3 and 0.8%, and interday coefficients of variation were 2.2 and 2.0% for the low (2- $\mu\text{g/ml}$ ) and high (35- $\mu\text{g/ml}$ ) check samples, respectively.

**Pharmacokinetic analysis.** The pharmacokinetic parameters for clindamycin were calculated for each regimen by noncompartmental techniques. The elimination rate constant ( $k_{el}$ ) was determined via regression analysis of the terminal portion of subject concentration-versus-time profiles ( $r^2 \geq 0.95$ ). The serum half-life was calculated as  $0.693/k_{el}$ . Peak and trough serum drug concentrations were determined by visual inspection of the concentration-versus-time curves and standardized to 70 kg. The area under the serum drug concentration-versus-time curve ( $\text{AUC}_{0-\tau}$ ) was calculated for each dosing regimen by applying the trapezoidal rule to datum points. Bioavailability of the oral dosage form was calculated as  $\text{AUC}_{p.o.}/\text{AUC}_{i.v.}$ . Clindamycin total body clearance was calculated as  $\text{dose}/\text{AUC}$ .

**Pharmacodynamic analysis.** Median reciprocal SBTs were determined for each regimen-isolate combination and plotted as a function of time. From these plots, the duration of measurable bactericidal activity was determined. Duration of antibacterial activity was identified as the last time point for which measurable bactericidal activity (reciprocal SBT  $\geq 2$ ) was observed. This was then converted to a percentage of the dosing interval by dividing the last time point with measurable activity by the dosing interval and multiplying by 100. The length of time for which one-half of the observed serum drug concentrations remained above the MIC for each isolate was also determined. (One-half the serum concentration was selected because this is what is represented by the lowest SBT dilution [1:2].) This value was converted to the percentage of the dosing interval over which activity is predicted.

**Statistical analysis.** Statistical comparisons were made among treatment groups with respect to the duration of measurable bactericidal activity expressed as a percentage of the dosing interval. Comparisons were performed via an analysis of variance. If a statistical difference was detected among the treatment groups, an ad hoc pairwise comparison was performed with the Scheffe test for multiple comparisons. All statistical tests were performed with a  $P$  value of  $\leq 0.05$  considered significant. Statistical analysis was conducted with a statistical package from SYSTAT Inc., Evanston, Ill.

## RESULTS

**Subjects.** A total of 12 subjects, 6 male and 6 female, were enrolled in the study. Volunteers had a mean ( $\pm$  standard deviation) age of  $28.5 \pm 8.1$  years and weight of  $75.3 \pm 13.5$  kg. No adverse events were reported by subjects during the study period.

**Susceptibility testing.** Two clinical isolates each of *S. aureus*, *S. pneumoniae*, and *B. fragilis* were selected for evaluation of the bactericidal activity provided by the various clindamycin dosing regimens. Median MIC and MBC results are presented in Table 1. The MICs of clindamycin for the test isolates were consistent over the testing period.

**Pharmacokinetics.** Mean pharmacokinetic data are presented in Table 2. These data are consistent with those reported by other investigators (5, 6, 12).

TABLE 2. Observed pharmacokinetic parameters for i.v. and p.o. clindamycin (300 mg) administered q8h and q12h<sup>a</sup>

Dosing regimen	Concn ( $\mu\text{g/ml}$ ) in serum		$\text{AUC}_{0-\tau}$ ( $\mu\text{g/ml} \cdot \text{h}$ )	Half-life (h)	Total body clearance (liter/h)	Bioavailability (%)
	Peak	Trough				
i.v. q8h	$6.23 \pm 1.84$	$0.49 \pm 0.27$	$18.05 \pm 6.81$	$2.18 \pm 0.42$	$19.01 \pm 6.64$	
p.o. q8h	$3.06 \pm 1.82$	$0.38 \pm 0.20$	$10.29 \pm 5.27$	$2.51 \pm 0.68$		$55.07 \pm 12.17$
i.v. q12h	$5.93 \pm 1.86$	$0.24 \pm 0.12$	$18.78 \pm 7.38$	$2.42 \pm 0.54$	$18.50 \pm 6.77$	
p.o. q12h	$2.95 \pm 1.36$	$0.21 \pm 0.08$	$9.99 \pm 5.12$	$2.69 \pm 1.01$		$51.48 \pm 12.17$

<sup>a</sup> All values are means  $\pm$  standard deviations.

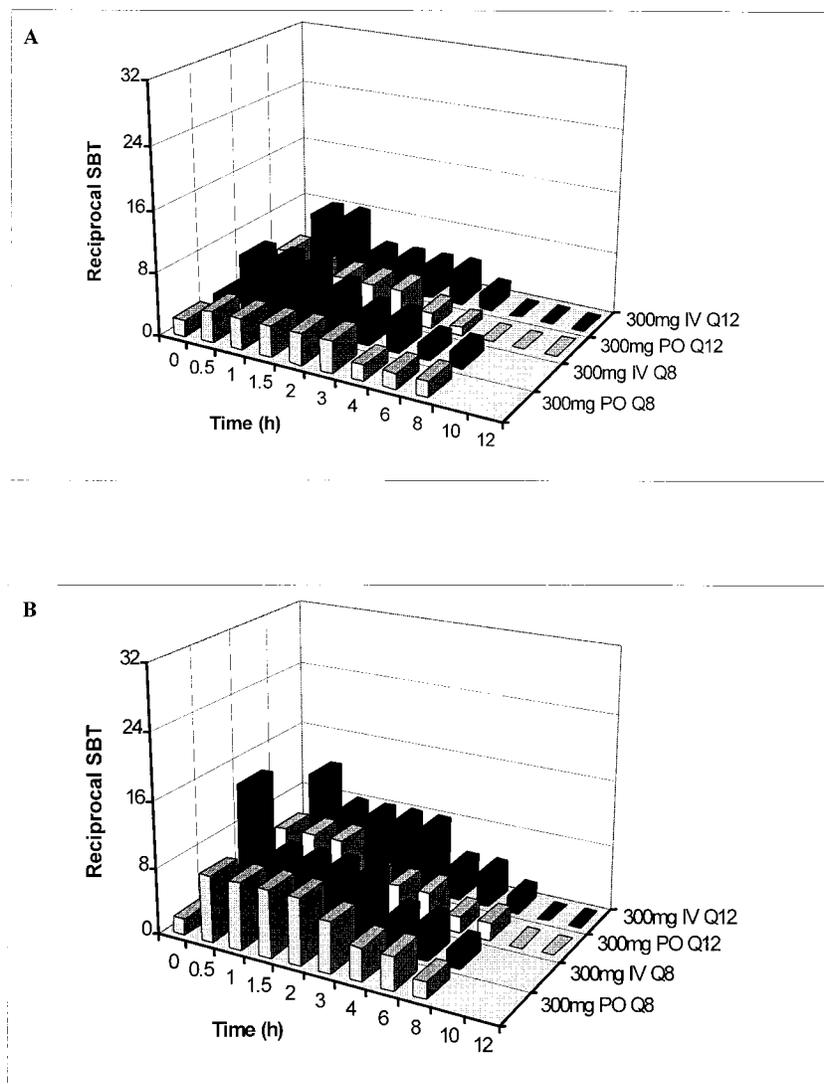


FIG. 1. Median reciprocal SBT-versus-time plots for *S. aureus* 1 (A), *S. aureus* 30 (B), *S. pneumoniae* 8 (C), *S. pneumoniae* 23 (D), *B. fragilis* 11 (E), and *B. fragilis* 16 (F).

**Bactericidal activity.** Plots of the reciprocal SBT versus time for each regimen-isolate scenario are presented in Fig. 1. Minimal trailing was observed with all of the isolates tested and was generally noted to be within 1 dilution of the recorded SBT. The percentage of the dosing interval over which bactericidal activity was detected for each regimen against test isolates is provided in Table 3. Against isolates of *S. aureus*, q8h regimens provided measurable bactericidal activity for a greater percentage of the dosing interval than q12h regimens (87.5 to 100% versus 49.6 to 77.1%,  $P < 0.001$ ). In contrast, clindamycin dosed on either an 8- or 12-h schedule yielded measurable activity for 100% of the dosing intervals when tested against penicillin-sensitive and penicillin-resistant isolates of *S. pneumoniae*. Results did not differ between the isolates of *S. pneumoniae*. Despite the existence of a statistically significant difference between the intravenous q8h regimen and the q12h regimens ( $P < 0.05$ ), all dosing regimens provided measurable bactericidal activity for greater than 80% of their respective dosing intervals against the two isolates of *B. fragilis*. No differences in the duration of activity among i.v. and

p.o. regimens dosed according to the same interval were detected for any of the isolates ( $P > 0.05$ ).

## DISCUSSION

Despite extensive clinical use, clindamycin remains highly active against a variety of gram-positive aerobic and anaerobic microorganisms. Additionally, clindamycin has a favorable pharmacokinetic profile which makes both i.v. and p.o. therapy viable therapeutic options. However, despite our wealth of clinical experience with clindamycin, it is only recently that the pharmacodynamic properties of this agent have been adequately described (7, 8, 14).

In this study, we derived two dosing regimens for clindamycin which take advantage of the pharmacokinetic and pharmacodynamic characteristics of clindamycin. Owing to the relatively long half-life and concentration-independent killing characteristics of clindamycin, regimens were developed with relatively low doses of clindamycin (300 mg) administered at extended intervals (q8h and q12h). We found both of these

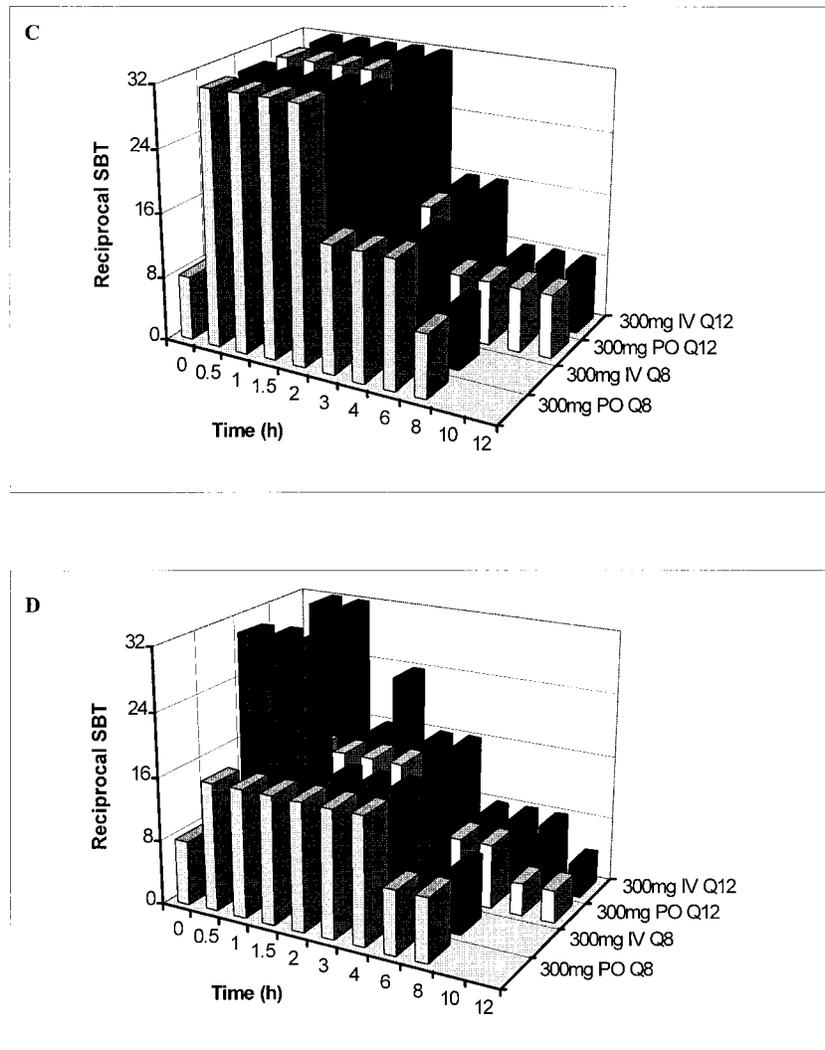


FIG. 1—Continued.

regimens to be effective against various gram-positive aerobic and anaerobic pathogens. Against *S. pneumoniae* and *B. fragilis* both regimens provided excellent activity throughout their respective dosing intervals. Although the q8h regimen yielded a greater percentage of the dosing interval with measurable bactericidal activity against study isolates of *S. aureus*, the q12h

regimens did provide coverage for approximately 50% of the dosing interval. For agents with concentration-independent activity, such as clindamycin, it has been suggested that regimens which provide bactericidal coverage for a minimum of 50% of the dosing interval are adequate to yield a positive clinical outcome (4).

TABLE 3. Percentage of the clindamycin (300 mg) dosing interval with measurable and predicted bactericidal activity

Dosing regimen	Mean ± SD % of dosing interval with measurable (predicted) bactericidal activity against:					
	<i>S. aureus</i> 1	<i>S. aureus</i> 30	<i>S. pneumoniae</i> 8	<i>S. pneumoniae</i> 23	<i>B. fragilis</i> 11	<i>B. fragilis</i> 16
i.v. q8h	87.5 ± 14.7 <sup>c,d</sup> (75)	100 <sup>c,d</sup> (100)	100 (100)	100 (100)	100 <sup>d</sup> (50)	97.9 ± 7.1 <sup>c,d</sup> (50)
p.o. q8h	92.7 ± 13.8 <sup>c,d</sup> (75)	100 <sup>c,d</sup> (100)	100 (100)	100 (100)	93.8 ± 13.3 (25)	92.2 ± 17.2 (25)
i.v. q12h	55.6 ± 12.7 <sup>a,b</sup> (50)	74.3 ± 16.3 <sup>a,b</sup> (83)	100 (83)	100 (83)	88.2 ± 18.0 (33)	81.3 ± 19.8 <sup>a</sup> (33)
p.o. q12h	49.6 ± 21.2 <sup>a,b</sup> (50)	77.1 ± 14.6 <sup>a,b</sup> (83)	100 (83)	100 (83)	87.5 ± 18.6 <sup>a</sup> (25)	80.2 ± 22.3 <sup>a</sup> (25)

<sup>a</sup> Significantly different (*P* < 0.05) from i.v. q8h result.  
<sup>b</sup> Significantly different (*P* < 0.05) from p.o. q8h result.  
<sup>c</sup> Significantly different (*P* < 0.05) from i.v. q12h result.  
<sup>d</sup> Significantly different (*P* < 0.05) from p.o. q12h result.

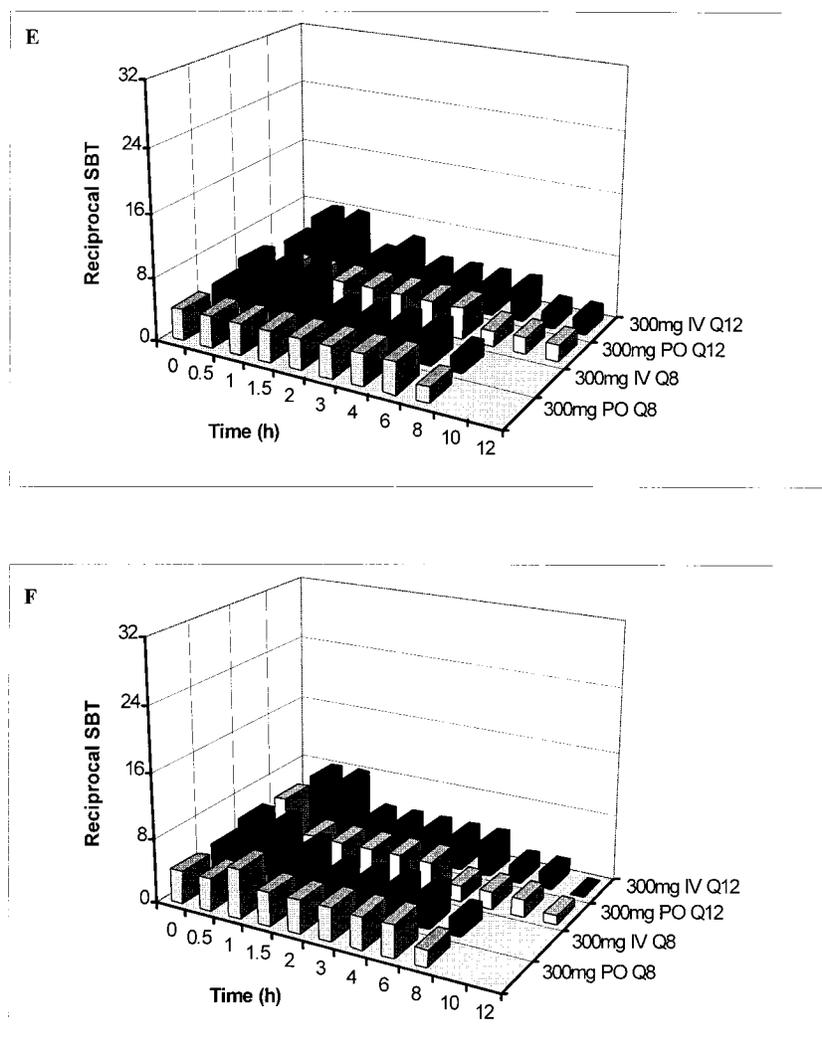


FIG. 1—Continued.

For this study we compared the duration of measured bactericidal activity (SBT) with a predicted assessment of the duration of activity (time which one-half of the mean serum drug concentration remained above the MIC). The observed and predictive values obtained were similar for the isolates of *S. aureus* and *S. pneumoniae*; however, against *B. fragilis*, the predicted duration of activity was 50 to 75% less than the measured duration of activity. In this case, by using only population pharmacokinetics and isolate MICs, the activity of clindamycin would have been significantly underestimated.

Recently, Xue and colleagues proposed similar low-dose regimens for clindamycin (14). In their investigation, the authors formulated a dosing regimen for clindamycin against *S. aureus* utilizing postantibiotic-effect data and published healthy-subject pharmacokinetic values. The authors concluded that a 300-mg q8h p.o. dosing regimen or a q6h i.v. regimen of clindamycin should provide adequate coverage against *S. aureus*. These findings correlate with the results of our study, in which we found that a 300-mg dose of clindamycin administered either i.v. or p.o. q8h provided an excellent duration of antimicrobial activity.

One of the most commonly vocalized concerns from clini-

cians regarding the use of clindamycin is the fear of *Clostridium difficile* superinfection. Superinfection occurs as the result of a disruption of the patient's normal gastrointestinal flora with subsequent overgrowth of an opportunistic pathogen, such as *C. difficile*. By utilizing low-daily-dose clindamycin regimens, such as those described above, the risk of such complications theoretically may be lessened by minimizing the patient's exposure to clindamycin.

In summary, we found that low-dose extended-interval dosing regimens of clindamycin provide excellent bactericidal coverage against a variety of commonly encountered pathogens. A dosing regimen of 300 mg of clindamycin i.v. or p.o. q12h provides adequate coverage against *S. pneumoniae* and *B. fragilis*. However, dosing interval adjustment to q8h may be required for the treatment of infections secondary to *S. aureus*. Lastly, this was not a clinical trial; therefore, the limitations of the data should be recognized and the results should be confirmed by closely monitored clinical evaluation.

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