ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 1996, p. 61–64 Vol. 40, No. 1
0066-4804/96/$04.00+0

Serum Bactericidal Activity of Ceftazidime: Continuous Infusion versus Intermittent Injections

DAVID P. NICOLAU,[1,2,3]* CHARLES H. NIGHTINGALE,[3,4] MARY ANNE BANEVICIUS,[1] QIANG FU,[1] AND RICHARD QUINTILIANI[2,5]

Department of Pharmacy,[1] Office for Research,[4] Division of Infectious Diseases,[2] Hartford Hospital, Hartford, Connecticut 06102; School of Pharmacy, University of Connecticut, Storrs, Connecticut 06268[3]; and School of Medicine, University of Connecticut, Farmington, Connecticut 06032[5]

Received 28 December 1994/Returned for modification 18 June 1995/Accepted 15 October 1995

Since β-lactam antibiotics have concentration-independent killing, bacterial eradication is a function of the time the serum drug concentration remains above the drug's MIC ($T >$ MIC). We compared the serum bactericidal titers (SBTs) of ceftazidime given by continuous infusion (CI) or by intermittent bolus dosing (BD) against two clinical isolates each of *Pseudomonas aeruginosa* and *Escherichia coli* to determine if CI would allow lower daily dosing while still providing equal bactericidal activity compared with BD. This was an open-labeled, randomized, steady-state, four-way crossover study with 12 healthy volunteers. The ceftazidime regimens were 1 g every 8 h (q8h) BD, 1 g q12h BD, 3 g over 24 h CI, and 2 g over 24 h CI. The areas under the bactericidal curves were calculated by the trapezoidal rule using the reciprocal of the SBT. For all organisms the areas under the bactericidal curves for intermittent versus the CI regimens were the same for equal doses ($P > 0.05$). For both strains of *E. coli* all four regimens provided SBTs of ≥1:2 over the dosing interval and 100% $T >$ MIC. The 1-g q8h BD and q12h BD regimens provided $T >$ MIC of 82 and 52%, respectively, for both *P. aeruginosa* isolates (MICs, 4 μg/ml). In comparison, the 2- and 3-g CI regimens always maintained SBTs of ≥1:2 and $T >$ MIC over the 24-h period as serum drug concentrations were 12.8 ± 3.0 and 18.2 ± 4.5 μg/ml, respectively. CI optimizes the pharmacodynamic and pharmacoeconomic profile of ceftazidime by providing adequate antibacterial activity over the 24-h dosing period with a reduction in the total daily dose of the antimicrobial agent.

Only recently have sufficient pharmacodynamic data become available to aid in the development of the most appropriate method of antimicrobial administration to promote the maximal bactericidal effect. To optimize the bactericidal effect, the method of antimicrobial administration should be tailored to the drug class. For instance, since the bacterial killing of the aminoglycosides is concentration dependent, bactericidal activity is maximized by increasing the peak serum drug concentration-to-MIC ratio (16). On the other hand, the β-lactams are concentration independent, and, as a result, the rate and extent of bactericidal activity are not significantly increased when the concentration is increased by multiples of the MIC (6). Thus, it appears that the important determinant of β-lactam efficacy is the time the serum drug concentration is above the MIC ($T >$ MIC) for the pathogen during the dosing interval. One method to maximize the time that the β-lactam antibiotic remains above its MIC for a pathogen would be to administer the agent by continuous infusion. In addition to promoting maximal bactericidal activity, the continuous infusion method allows a reduction in both the amount of the antibiotic used per day and the preparation time required to prepare a daily intravenous regimen of the β-lactam antibiotic (5, 17).

The objective of this study was to compare the concentration-time profiles and serum bactericidal activities of four ceftazidime regimens administered by either intermittent bolus dosing or continuous infusion.

(This work was presented in part at the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy, Orlando, Fla., 6 October 1994 [14a]).

* Corresponding author. Mailing address: Division of Infectious Diseases, Hartford Hospital, 80 Seymour St., Hartford, CT 06102. Phone: (203) 545-3941. Fax: (203) 545-5112.

MATERIALS AND METHODS

Volunteers. Twelve healthy volunteers (eight men and four women) were enrolled in this study. The mean age and weight were 26.3 years (range, 22 to 40 years) and 71.2 kg (range, 53.0 to 89.5 kg). Prior to entering the study, each volunteer underwent a complete medical examination and a medical history was taken to rule out renal, hepatic, cardiovascular, endocrine, neurologic, or other disease, as well as any known allergies. Blood chemistries, hematology, and urinalysis were also performed for each subject prior to enrollment and at the conclusion of the study. Female volunteers were screened for pregnancy by a direct latex agglutination test. All medications, except for oral contraceptives and vitamins, were discontinued at least 72 h prior to the study, and subjects were told to refrain from consuming any alcohol-containing beverages. This study was approved by the Institutional Review Board at our institution, and all volunteers gave written informed consent prior to study initiation.

Study design. This was an open-labeled, randomized, steady-state, four-way crossover study to compare the concentration-time profiles and the serum bactericidal activities of the following intravenous ceftazidime drug regimens: 1 g every 8 h (q8h) BD, 1 g q12h BD, 3 g given by continuous infusion over 24 h, and 2 g given by continuous infusion over 24 h. Steady-state ceftazidime concentrations were achieved in the two bolus regimens by administering ceftazidime in each of the two regimens for 24 h prior to the sampling period. Steady-state ceftazidime concentrations were achieved in the two continuous infusion regimens by administering ceftazidime for 12 h prior to the sampling period. The study was conducted over a 4-week period with a 1-week washout period between regimens. The pharmacokinetic and pharmacodynamic analysis was performed following the last dose of the bolus regimens and after steady-state was achieved in the continuous infusion regimens.

Antimicrobial administration. The arginine formulation of ceftazidime (Ceptaz; Glaxo Pharmaceuticals, Research Triangle Park, N.C.) was used in this study. Subjects received the four regimens in a random crossover manner. The drug was reconstituted according to the manufacturer's guidelines and then further diluted in 100 ml of 5% dextrose in water prior to intravenous administration. All intravenous bolus infusions were given over a period of 30 min by using Sidekick (SoloPak Pharmaceuticals, Boca Raton, Fla.), an ambulatory drug delivery system for rapid intravenous administration. All continuous infusions were administered via Paragon (SoloPak Pharmaceuticals), a drug delivery sys-

tem consisting of a mechanical infuser and specially designed administration sets. During the second, third, and fourth weeks of this study the subjects were crossed over to receive each of the remaining regimens.

Blood sampling. Blood samples (10 ml) were obtained for q8h and q12h BD regimens prior to the start of dosing, at time zero (prior to the third dose), and 0.5, 1, 1.5, 2, 4, 6, 8, and 12 h (q12h only) after the start of the infusion. Blood samples (10 ml) were obtained for continuous-infusion regimens prior to the start of the infusion, at time zero (12 h after the start of the infusion, steady state), and 0.5, 1, 1.5, 2, 4, 6, 8, and 12 h later. All blood samples were drawn from a forearm vein via an intravenous catheter contralateral to the one used for drug administration. Blood samples were allowed to clot at room temperature for 15 min. Following centrifugation (1,000 × *g* for 15 min), the serum was aliquoted into three portions: one for drug concentration determinations and the other two for bactericidal activity testing. All serum samples were stored at −70°C until the time of analysis.

Test organisms. The test organisms chosen for serum bactericidal determinations were two clinical isolates each of *Pseudomonas aeruginosa* and *Escherichia coli*. The MIC and MBC of ceftazidime for each isolate were determined by the microdilution technique (14).

Serum bactericidal activity. Serum bactericidal titers (SBTs) were determined by the method of Reller and Stratton (13, 20). Drug-free, heat-inactivated pooled human serum was used as the diluent in all tests. Prior to the initiation of SBT testing, each subject's drug-free serum (obtained before ceftazidime administration) was evaluated for antibacterial activity against the test isolates. All isolates were found to grow adequately in each subject's drug-free serum, suggesting that the serum possessed no inherent antibacterial activity against the isolates selected for study. Serum samples were tested in duplicate for each subject at each time point for each antibiotic regimen. All SBT results were combined and used in the final analysis for comparison. The percentage of the dosing interval in which a regimen maintained an SBT of ≥1:2 was calculated on the basis of the SBT results for each organism. The area under the bactericidal concentration-time curve (AUBC) was calculated by the linear trapezoidal rule using the reciprocal of the SBT from time zero to the last sampling time (1). The AUBCs for all sampling periods were then multiplied to calculate the AUBC for each regimen over a 24-h period.

Analytical methods. Serum ceftazidime concentrations were determined by high-pressure liquid chromatography methods. Instruments and materials included a M510 pump (Waters Associates, Milford, Mass.), Waters autoinjector WISP 717, Waters data module, an SM4000 variable UV wavelength detector (LDC Analytical, Riviera Beach, Fla.), and a C_{18} Resolve column (5 μm, 3.9 by 150 mm). The mobile phase consisted of phosphate buffer and acetonitrile in a 92:8 ratio (vol/vol) at a flow rate of 1.2 ml/min. Cefpirome was used as the internal standard. Pooled human serum was used to prepare standards, check samples, and dilute serum samples as required. The assay was linear over the range of 0.5 to 30 μg/ml. Intraday coefficients of variation were 1.6 and 2.3%, and interday coefficients of variation were 4.4 and 1.6% for the low (2-μg/ml) and high (25-μg/ml) check samples, respectively.

Pharmacokinetic and statistical analysis. The disposition of ceftazidime was characterized by using standard noncompartmental methods (7). Serum ceftazidime concentrations were plotted versus time on a semilogarithmic scale, and the maximum concentration was read from the observed concentration-time data for each subject. The area under the serum drug concentration-time curve was obtained by using the linear trapezoidal rule up to the final measured concentration. The elimination half-life was determined from linear regression analysis of the postdistributive terminal portion (last four datum points) of the serum drug concentration-time curve. Total body clearance (Cl) was calculated as dose/area under the concentration-time curve.

A repeated-measures analysis of variance was employed for comparison of the AUBCs and the pharmacokinetic parameters for each regimen. Significance was defined as $P \leq 0.05$. When statistical differences were detected by the analysis of variance, this test was followed by the Scheffe's *F* test for multiple comparisons.

RESULTS

Ceftazidime susceptibilities. The MIC and MBC of ceftazidime for each of the four isolates were determined prior to, during, and at the conclusion of SBT testing. Throughout the study the MICs for the two *E. coli* isolates ranged from 0.25 to 0.5 μg/ml, while the MICs for both *P. aeruginosa* isolates were 4 μg/ml over the same period. The MICs and MBCs were the same for all test organisms.

Pharmacodynamic parameters. For all organisms the AUBCs for intermittent versus the continuous infusion regimens were the same for equal doses ($P > 0.05$). The AUBCs of ceftazidime after both intermittent dosing and continuous infusion dosing for *E. coli* are presented in Table 1. No statistically significant differences ($P > 0.05$) in AUBC between ceftazidime administration techniques were found for any isolate. As a result of the low MICs of ceftazidime, the concentration in serum always remained above the MIC and resulted in SBTs ≥ 1:2 throughout the dosing interval for all regimens. The pharmacodynamic parameters for both *P. aeruginosa* isolates are presented in Table 2. Despite similar MIC results for the two isolates (4 μg/ml), the AUBCs and SBTs were consistently higher for *P. aeruginosa* 25. Comparison of the AUBCs for *P. aeruginosa* 25 revealed that significant differences ($P < 0.05$) exist between the following regimens: 1-g-q8h and 1-g-q12h bolus dosing, 1-g-q8h bolus dosing and 2-g continuous infusion, 1-g-q12h bolus dosing and 3-g continuous infusion, and 2- and 3-g continuous infusion regimens. Comparison of the AUBCs for *P. aeruginosa* 28 revealed a significant difference ($P < 0.05$) only between the 1-g-q12h bolus dosing and 3-g continuous infusion ceftazidime regimens. The $T >$ MIC for *P. aeruginosa* with an MIC of 4 or 8 μg/ml (ceftazidime breakpoint concentration) ranged from 52 to 82% and from 37 to 61%, respectively, for the intermittent dosing regimens, whereas both continuous infusion regimens produce concentrations consistently exceeding these MICs. In addition, at 8 h after the intermittent dosing of 1 g, SBTs of ≥1:2 for *P. aeruginosa* 25 constituted 88 to 92%, while only 0 to 4% of the SBTs were ≥1:2 for *P. aeruginosa* 28. All activity was lost by 12 h for

TABLE 1. AUBC of ceftazidime after intermittent administration and continuous-infusion administration against *E. coli*[a]

Schedule	AUBC[b] for isolate:	
	27	28
1 g q12h	1,897	1,162
1 g q8h	2,703	1,578
2 g CI[c]/24 h	2,154	1,297
3 g CI/24 h	2,822	1,521

[a] MIC, 0.25 to 0.5 μg/ml. Percentage of time *T* was >MIC for a 24-h dosing period, 100% for all regimens. Percentage of time SBT was ≥1:2 at the end of the dosing interval, 100% for all regimens.
[b] Geometric mean for a 24-h dosing period.
[c] CI, continuous infusion.

TABLE 2. Pharmacodynamic parameters of ceftazidime after intermittent administration and continuous-infusion administration against *P. aeruginosa*[a]

Schedule and isolate	AUBC[b]	% $T >$ MIC[c]	% SBT ≥ 1:2[d]
1 g q12h			
25	150	52 (37)	100 (88)
28	67	52 (37)	42 (0)
1 g q8h			
25	232	82 (61)	100 (92)
28	95	82 (61)	42 (4)
2 g CI/24 h			
25	168	100 (100)	100
28	75	100 (100)	100
3 g CI/24 h			
25	227	100 (100)	100
28	108	100 (100)	100

[a] MIC, 4 μg/ml. CI, continuous infusion.
[b] Geometric mean for a 24-h dosing period.
[c] Percentage of time for a 24-h dosing period. The data for MIC = 8 μg/ml are given in parentheses.
[d] Percentage of time at 6 h (8 h for values in parentheses) for intermittent injection and 24 h for continuous infusion.

TABLE 3. Pharmacokinetic parameters of ceftazidime after intermittent administration and continuous-infusion administration[a]

Schedule	$t_{1/2}$ (h)	AUC (μg · h/ml)	C_{max} (μg/ml)	C_{mean} (μg/ml)	CL (ml/min)
1 g q12h	1.74 ± 0.07	305.1 ± 70.9	85.78 ± 29.48		115.2 ± 28.0
1 g q8h	1.67 ± 0.13	476.4 ± 138.5	82.05 ± 22.91		112.1 ± 27.8
2 g CI/24 h		298.9 ± 70.4		12.77 ± 2.95	113.9 ± 24.7
3 g CI/24 h		419.9 ± 108.7		18.15 ± 4.51	121.4 ± 29.2

[a] $t_{1/2}$, half-life; AUC, area under concentration-time curve for a 24-h dosing period. C_{max} and C_{min}, maximum and mean concentrations of ceftazidime in serum, respectively; CL, total body clearance; CI, continuous infusion.

both isolates. In comparison, both continuous infusion regimens always maintained SBTs of ≥1:2 over the 24-h period as concentrations in serum were 12.8 ± 3.0 and 18.2 ± 4.5 μg/ml for the 2- and 3-g continuous infusion regimens, respectively.

Pharmacokinetic parameters. The pertinent pharmacokinetic parameters of ceftazidime for each of the dosing regimens are given in Table 3. No significant differences were observed between the half-lives and maximum concentrations for the intermittent regimens. In addition, no differences were found between the areas under the concentration-time curves of similar doses (grams per day) or the total body clearances of ceftazidime for any regimens. The concentration-time profiles of the intermittent and continuous-infusion regimens are displayed in Fig. 1.

Safety and tolerance of the study drug. No significant adverse effects were observed during any of the four treatment arms of the study. Evaluation of poststudy laboratories confirmed that no chemical or hematologic adverse events resulted from the administration of ceftazidime. Additionally, all patients tolerated the continuous infusions with no infusion-related adverse effects (e.g., phlebitis).

DISCUSSION

Over the last decade significant advances that lend insight into the most appropriate administration techniques to optimize antimicrobial activity have been made. For the β-lactams it is generally accepted that the time the concentration in serum remains above the MIC ($T > MIC$) for a pathogen is the most important determinant of clinical outcome (5, 17, 18, 22). Although there are several methods to maximize the $T > MIC$ for β-lactam antimicrobial agents, the use of continuous infusion appears to be a particularly attractive pharmacoeconomic option for parenterally administered agents (15). In an animal model for extravascular penetration, continuous infusion produces higher concentrations than those achieved with intermittent dosing (19). Moreover, in several animal protection studies, continuous infusion β-lactam was superior to intermittent dosing in that the dose (in milligrams per kilogram of body weight per day) required to protect the animal was lower with continuous infusion (9, 10, 21). More recently, an in vitro simulation of human pharmacokinetics showed that the continuous administration of ceftazidime proved more efficacious than intermittent dosing (11). Although there appears to be a wealth of in vitro and in vivo animal work to support the use of continuous infusion, very few clinical data exist for humans (2, 4, 23). The pharmacokinetic data derived from this study are in accordance with those previously published for ceftazidime administration by both routes and indicate further that continuous infusion is the optimal administration technique to maximize bactericidal activity of the β-lactams (3, 12, 18). From these data it appears that a continuous infusion of 2 g/24-h period would provide both adequate concentrations in serum ($T > MIC$) and bactericidal activity for both *P. aeruginosa* and *E. coli*. Although we did not give our volunteers bolus doses prior to the initiation of the continuous infusion regimen, a 250- to 500-mg bolus dose would be required to achieve rapid steady-state concentrations in patients started on continuous infusion regimens. Furthermore, the continuous infusion approach requires lower daily doses to provide bactericidal activity equal to that observed with intermittent bolus dosing.

In addition to the potential for lower antimicrobial doses and improved outcomes, institutional cost savings may also be realized via a reduction in the number of antimicrobial-agent doses prepared by the pharmacy. At our 850-bed community-

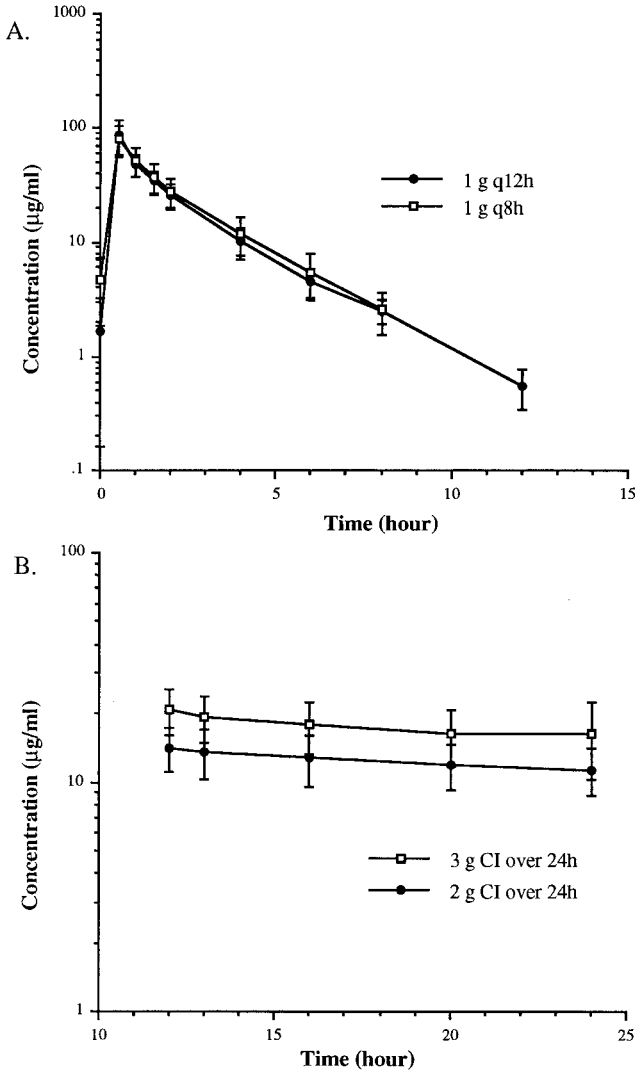

FIG. 1. Serum ceftazidime concentrations (means with standard deviations) following intermittent dosing (A) and continuous infusion (CI) (B).

teaching hospital approximately 167,000 doses of cephalosporin and penicillin antimicrobial products were prepared in 1993. Therefore, with a reduction in the amount of the drug required and reduced preparation and administration expenditures, considerable cost avoidance may be incurred with hospital-wide use of ceftazidime administered by continuous infusion. In addition, to the institutional benefits this methodology may also allow a more efficient and easy method of administration for those patients requiring home intravenous antimicrobial therapy. Although the use of home infusion devices was once thought of as very cumbersome, improvements in the quality of home care services and innovations in drug delivery systems now make it quite easy to use a continuous infusion device to provide a safe and cost-effective means of drug delivery outside the hospital setting.

At present, a variety of new in vitro and in vivo data continue to appear in the literature in support of this method of antimicrobial administration. Although additional trials are required to definitively prove the clinical utility of the continuous infusion administration, this approach appears to optimize the pharmacodynamic profile of ceftazidime and, potentially, other β-lactams, thus maximizing the potential for improved clinical outcomes.

ACKNOWLEDGMENTS

This study was sponsored by grants from Glaxo Pharmaceuticals, the I-Flow Corporation, and Fujisawa Pharmaceuticals.

REFERENCES

1. **Barriere, S. L., E. Ely, J. E. Kapusnik, and J. G. Gambertoglio.** 1985. Analysis of a new method for assessing activity of combinations of antimicrobials: area under the bactericidal activity curve. J. Antimicrob. Chemother. **16:**49–59.
2. **Bodey, G. P., S. J. Ketchel, and V. Rodriquez.** 1979. A randomized study of carbenicillin plus cefamandole or tobramycin in the treatment of febrile episodes in cancer patients. Am. J. Med. **67:**608–611.
3. **Castela, N., A. M. Taburet, J. Carlet, G. Nitenberg, M. Wolff, J. P. Sollet, J. J. Lefevre, and E. Singlas.** 1994. Pharmacokinetics of ceftazidime during continuous infusion in intensive care patients, abstr. A11. *In* Abstract of the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.
4. **Coppa, G. F., J. J. Hoballah, G. J. Jonas, and L. A. Sudarsky.** 1992. Pharmacokinetics of continuous-infusion intravenous antibiotics during operations for abdominal trauma. Infect. Med. **11:**48–52.
5. **Craig, W. A., and S. C. Ebert.** 1992. Continuous infusion of β-lactam antibiotics. Antimicrob. Agents Chemother. **36:**2577–2583.
6. **Ebert, S. C., and W. A. Craig.** 1990. Pharmacodynamic properties of antibiotics: application to drug monitoring and dosage regimen design. Infect. Control Hosp. Epidemiol. **11:**319–326.
7. **Gibaldi, M., and D. Perrier.** 1982. Noncompartmental analysis based on statistical moment theory, p. 409–417. *In* J. Swarbrick (ed.), Pharmacokinetics, 2nd ed., Marcel Dekker, Inc., New York.
8. **Kalman, D., S. L. Barriere, and B. L. Johnson, Jr.** 1992. Pharmacokinetic disposition and bactericidal activities of cefepime, ceftazidime, and cefperazone in serum and blister fluid. Antimicrob. Agents Chemother. **36:**453–457.
9. **Livingston, D. H., and M. T. Wang.** 1993. Continuous infusion of cefazolin is superior to intermittent dosing in decreasing infection after hemorrhagic shock. Am. J. Surg. **165:**203–207.
10. **Mordenti, J. J., R. Qunitiliani, and C. H. Nightingale.** 1985. Combination antibiotic therapy: comparison of constant infusion and intermittent bolus dosing in an experimental animal model. J. Antimicrob. Chemother. **15:**313–321.
11. **Mouton, J. W., and J. G. den Hollander.** 1994. Killing of *Pseudomonas aeruginosa* during continuous and intermittent infusion of ceftazidime in an in vitro pharmacokinetic model. Antimicrob. Agents Chemother. **38:**931–936.
12. **Mouton, J. W., A. M. Horrevorts, P. G. H. Mulder, E. P. Prens, and M. F. Michel.** 1990. Pharmacokinetics of ceftazidime in serum and suction blister fluid during continuous and intermittent infusions in healthy volunteers. Antimicrob. Agents Chemother. **34:**2307–2311.
13. **National Committee for Clinical Laboratory Standards.** 1987. Methodology for the serum bactericidal test. Proposed guideline M21-P. National Committee for Clinical Laboratory Standards, Villanova, Pa.
14. **National Committee for Clinical Laboratory Standards.** 1990. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 2nd ed. Approved standard M7-A2. National Committee for Clinical Laboratory Standards, Villanova, Pa.

14a. **Nicolau, D. P., C. H. Nightingale, M. A. Banevicius, Q. Fu, and R. Quintiliani.** 1994. Ceftazidime serum bactericidal activity: continuous infusion versus intermittent injections, abstr. A90, p. 118. *In* Abstracts of the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.

15. **Nicolau, D. P., and R. Quintiliani.** 1994. Choosing among the new cephalosporin antibiotics: a pharmacodynamic approach. PharmacoEconomics **5**(Suppl. 2)**:**34–39.
16. **Nicolau, D. P., R. Quintiliani, and C. H. Nightingale.** 1992. Once-daily aminoglycosides. Conn. Med. **56:**561–563.
17. **Nightingale, C. H., R. Quintiliani, and D. P. Nicolau.** 1994. Intelligent dosing of antimicrobials, p. 252–265. *In* J. S. Remington, M. N. Swartz (ed.), Current clinical topics in infectious diseases, vol. 14. Blackwell Scientific, Cambridge.
18. **Onyeji, C. O., D. P. Nicolau, C. H. Nightingale, and R. Quintiliani.** 1994. Optimal duration of time above the minimum inhibitory concentrations of ceftibuten and cefaclor in experimental intra-abdominal infections. Antimicrob. Agents Chemother. **38:**1112–1117.
19. **Peterson, L. R., D. N. Gerding, and C. E. Fasching.** 1981. Effects of method of antibiotic administration on extravascular penetration: cross-over study of cefazolin given by intermittent injection or constant infusion. J. Antimicrob. Chemother. **7:**71–79.
20. **Reller, L. B., and C. W. Stratton.** 1977. Serum dilution test for bactericidal activity. II. Standardization and correlation with antimicrobial assays and susceptibility tests. J. Infect. Dis. **136:**196–204.
21. **Roosendaal, R., I. A. J. M. Bakker-Woudenburg, J. C. van den Berg, and M. F. Michel.** 1985. Therapeutic efficacy of continuous versus intermittent administration of ceftazidime in an experimental *Klebseilla pneumoniae* pneumonia in rats. J. Infect. Dis. **152:**373–378.
22. **Vogelman, B., S. Gundmundsson, J. Legget, J. Turnidge, S. Ebert, and W. A. Craig.** 1988. Correlation of antimicrobial pharmacokinetic parameters with efficacy in an animal model. J. Infect. Dis. **158:**831–847.
23. **Zeisler, J. A., J. D. McCarthy, W. A. Richelieu, and M. B. Nichol.** 1992. Cefuroxime by continuous infusion: a new standard of care? Infect. Med. **11:**54–60.