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Pharmacodynamics of Ceftazidime Administered as Continuous Infusion or Intermittent Bolus Alone and in Combination with Single Daily-Dose Amikacin against *Pseudomonas aeruginosa* in an In Vitro Infection Model

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We compared the pharmacodynamics and killing activity of ceftazidime, administered by continuous infusion and intermittent bolus, against *Pseudomonas aeruginosa* ATCC 27853 and ceftazidime-resistant *P. aeruginosa* 27853CR with and without a single daily dose of amikacin in an in vitro infection model over a 48-h period. Resistance to ceftazidime was selected for by serial passage of *P. aeruginosa* onto agar containing increasing concentrations of ceftazidime. Human pharmacokinetics and dosages were simulated as follows: half-life, 2 h; intermittent-bolus ceftazidime, 2 g every 8 h (q8h) and q12h; continuous infusion, 2-g loading dose and maintenance infusions of 5, 10, and 20 μg/ml; amikacin, 15 mg/kg q24h. There was no significant difference in time to 99.9% killing between any of the monotherapy regimens or between any combination regimen against ceftazidime-susceptible *P. aeruginosa*. Continuous infusions of 10 and 20 μg/ml killed as effectively as an intermittent bolus of 2 g q12h and q8h, respectively. Continuous infusion of 20 μg/ml and an intermittent bolus of 2 g q8h were the only regimens which prevented organism regrowth at 48 h, while a continuous infusion of 5 μg/ml resulted in the most regrowth. All of the combination regimens exhibited a synergistic response, with rapid killing of ceftazidime-susceptible *P. aeruginosa* and no regrowth. Against ceftazidime-resistant *P. aeruginosa*, none of the ceftazidime monotherapy regimens achieved 99.9% killing. The combination regimens exhibited the same rapid killing of the resistant strain as occurred with the susceptible strain; however, regrowth occurred with all regimens. The combination regimens of continuous infusion of 20 μg/ml plus amikacin and intermittent bolus q8h or q12h plus amikacin continued to be synergistic. Overall, continuous infusion monotherapy with ceftazidime at concentrations 4 to 5 and 10 to 15 times the MIC was as effective as an intermittent bolus of 2 g q12h (10 to 15 times the MIC) and q8h (25 to 35 times the MIC), respectively, against ceftazidime-susceptible *P. aeruginosa*. Combination therapy with amikacin plus ceftazidime, either intermittently q8h or by continuous infusion of 20 μg/ml, appeared to be effective and exhibited synergism against ceftazidime-resistant *P. aeruginosa*.

Continuous infusion of β-lactams has been advocated for years as an alternative method of administration on the basis of their pharmacodynamics. β-Lactams demonstrate concentration-independent killing and do not possess an appreciable postantibiotic effect against gram-negative bacilli (4). Duration of an antibiotic concentration above the MIC, and not the magnitude of the concentration, appears to be the parameter which best predicts successful treatment. Intermittent bolus administration results in high peak and low trough concentrations in serum (potentially below the MIC for the organism). Continuous infusion administration of β-lactams should optimize the time above the MIC for the infecting organism and potentially allow higher concentrations of a drug to be achieved in infected tissues. Animal and in vitro studies have indicated that there is little benefit to raising the concentrations much above four to eight times the MIC (1, 3–5, 15). Time-kill curve experiments by Craig and Ebert utilizing ticarcillin resulted in only about a 0.5-log difference in CFU per milliliter between antibiotic concentrations 4 and 16 times the MIC against *Pseudomonas aeruginosa* ATCC 27853 (4). Studies with both normal and neutropenic animals have shown continuous infusion of β-lactams to be as effective as, and sometimes more effective than, intermittent administration (12, 15, 18, 19). Isolated case reports of treatment failure with 2 g of ceftazidime given every 8 h (q8h) and treatment success when the patients were switched to continuous infusion of ceftazidime have been reported (6, 7). In one of the cases, the patient was switched to continuous infusion with the same total daily dose. There was a more rapid clinical improvement with continuous infusion, and ceftazidime concentrations were sustained longer in the skin lesions with continuous infusion than with intermittent administration (6). There are only two previously reported randomized clinical trials with humans comparing intermittent administration and continuous infusion of β-lactams. Both studies enrolled primarily neutropenic patients, and both demonstrated that continuous infusion of β-lactams was as efficacious as intermittent administration (2, 11). The objective of this study was to determine if the method of ceftazidime administration (by continuous infusion or intermittent bolus) affects bactericidal activity against both ceftazidime-susceptible and -resistant *P. aeruginosa* strains with and without amikacin.

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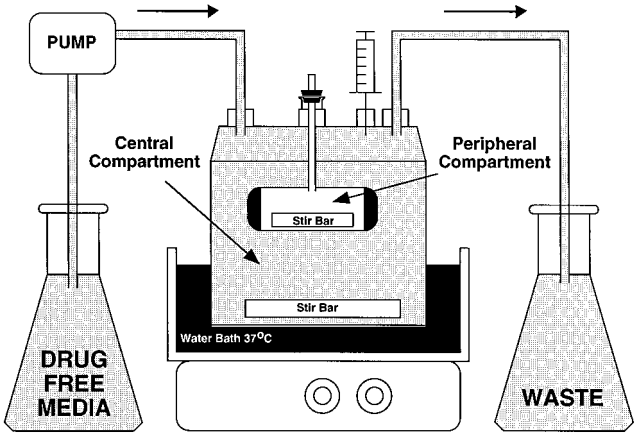

FIG. 1. Schematic illustration of the in vitro model used in this study.

MATERIALS AND METHODS

Organisms. The following *P. aeruginosa* strains were studied: ceftazidime-susceptible strain ATCC 27853 (Difco Bactrol Disk) and ceftazidime-resistant strain 27853CR. Resistant strain 27853CR was made in vitro by serial passage of strain ATCC 27853 through increasing concentrations of ceftazidime in solid medium (10). The MIC and MBC of each drug were determined by broth microdilution by following guidelines set forth by the National Committee for Clinical Laboratory Standards (17). MICs and MBCs were also determined with an inoculum of 10^7 CFU/ml. Fractional inhibitory indices were determined by the checkerboard microtiter technique with indices defined as follows: synergism, <0.5; addition, >0.5 to 1; indifference, >1 to 4; antagonism, >4 (13).

Antibiotics. Analytical ceftazidime pentahydrate (lot 130632) and ceftazidime for injection (L-arginine formulation; lot Z90043EY), supplied by Glaxo, and amikacin for injection (lot A2J14A) and amikacin analytical powder (lot 20040), supplied by Bristol Myers Squibb, were used. Analytical powders were used for all susceptibility testing, and drugs for injection were used in the model experiments.

Medium. Mueller-Hinton broth (Difco, Detroit, Mich.) supplemented with calcium (25 mg/liter) and magnesium (12.5 mg/liter) (SMHB) was used for all susceptibility and model experiments. Tryptic soy agar (Difco) was used for colony counting.

In vitro model. The in vitro infection model shown in Fig. 1 is a two-compartment model used to simulate human pharmacokinetics in the presence of bacteria. The central compartment is represented by a 250-ml specially made glass container filled with SMHB. The 10-ml peripheral compartment (which represents a small infected fluid space) is represented by a hollow glass T tube fitted on the ends with an inert 0.2-μm-pore-size polycarbonate membrane. Broth and antibiotic flow through the membrane and into the T tube and to interact with the bacteria and prevents the bacteria from leaving the peripheral compartment. The entire model apparatus was placed in a 37°C water bath. Magnetic stirring bars were placed in both the central and peripheral compartments to ensure equal distribution of the drug(s). All model experiments were carried out in duplicate for 48 h. Targeted peak concentrations of ceftazidime and amikacin in the central compartment were 160 and 80 μg/ml, respectively. Dosage regimens were simulated as follows: intermittent bolus, 2 g of ceftazidime q8h and q12h; continuous infusion, 2-g loading dose and maintenance infusions of 5, 10, and 20 μg/ml; amikacin, 15 mg/kg q24h. Each of these regimens was tested as monotherapy, and all ceftazidime regimens were combined with amikacin. For the bolus administration models, Mueller-Hinton broth containing an antibiotic was displaced from the central compartment at the same rate that antibiotic-free growth medium was pumped into the central compartment by a peristaltic pump. The clearance of ceftazidime and amikacin from the central compartment (pump rate) was set at a rate equal to the serum half-life of the two antibiotics of approximately 2 h. Continuous infusion of ceftazidime was achieved by pumping antibiotic-containing medium into the central compartment to achieve ceftazidime concentrations of 5, 10, and 20 μg/ml while maintaining a half-life in serum of 2 h. During the first 60 min, antibiotic free medium was pumped into the central compartment to allow the organism and system to equilibrate prior to exposure to the antibiotics. A 2-g bolus was delivered prior to the start of all constant-infusion regimens. The initial inoculum was prepared by inoculating three to five colonies of bacteria into 5 ml of SMHB and incubating it at 37°C for 18 to 24 h. The overnight stock organism was diluted to 10^7 CFU/ml, and 1 ml of this was added to the peripheral compartment, resulting in an initial inoculum of 10^6 CFU/ml.

Pharmacodynamic and pharmacokinetic analysis. Samples (0.1 ml) were taken from the central and peripheral compartments at the following times for assessment of pharmacokinetics the killing activity of each regimen: 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 26, 28, 30, 32, 36, and 48 h. Suitable dilutions of the samples were made in 0.9% sodium chloride, and 20 μl was plated in triplicate on tryptic soy agar. The plates were incubated at 37°C for 18 to 24 h, and colonies were counted. The limit of detection by this method was previously determined in our laboratory to be 100 CFU/ml (14). Time-kill curves were constructed by plotting $\log_{10}$ CFU per milliliter against time over a 48-h period. Time to 99.9% killing was calculated by using linear regression over the first 8 h. The correlation coefficients were all greater than 0.9 for all model experiments. Antibiotic carryover experiments using simulated peak drug concentrations from the peripheral compartment were performed with an inoculum of 10^6 CFU/ml. The area under the concentration-time curve (AUC) was calculated for the central and peripheral compartments from 0 to 24 and 24 to 48 h by the trapezoid method utilizing the LAGRAN program, version 2.1, for the ceftazidime monotherapy regimens only. The AUC/MIC ratios for the same time intervals were calculated for both of the organisms (8). Ceftazidime concentrations were determined by a modified high-pressure liquid chromatography assay. The standards, controls, and model samples were all prepared the same way and contained cefuroxime as an internal standard. The assay sensitivity was 0.2 μg/ml, and the intra- and interday coefficients of variation were both less than 6% at concentrations of 5, 15, and 25 μg/ml. The standard curve prepared over a concentration range of 0 to 50 μg/ml resulted in an r^2 value of 1.000. Amikacin concentrations were determined by fluorescence polarization immunoassay (Abbott-TDx; Abbott Laboratories, Irving, Tex.). The assay sensitivity with the model medium was 2 μg/ml, and the intra- and interrun coefficients of variation were less than 10% in the concentration range of 2 to 8 μg/ml. Samples were stored at −80°C until tested.

Antibiotic resistance. To detect emergence of resistance, 0.1-ml samples obtained from the peripheral compartment at 0, 24, and 48 h were serially diluted and plated on freshly prepared antibiotic-containing agar. The antibiotic concentrations in the agar were 2, 8, and 16 times the MICs of both ceftazidime and amikacin. If resistance was detected, the MIC and MBC were determined and the percent change in the subpopulation over time was evaluated.

Statistics. Time-kill curves (numbers of CFU per milliliter at 48 h) and time to 99.9% reduction of the inoculum from 0 to 12 h were compared by using a two-way analysis of variance and Tukey's test for multiple comparisons of significance. A P value of 0.05 was considered significant.

RESULTS

Susceptibility results. The MICs and MBCs of ceftazidime and amikacin for *P. aeruginosa* ATCC 27853 were 1.56 and 3.13 and 3.13 and 6.25 μg/ml, respectively. For *P. aeruginosa* 27853CR, the corresponding results were 50 and 100 and 1.56 and 6.25 μg/ml. The fractional inhibitory indices for *P. aeruginosa* ATCC 27853 and 27853CR were 1.25 and 1, respectively. At an inoculum of 10^7 CFU/ml, the MIC and MBC of ceftazidime for *P. aeruginosa* ATCC 27853 were 100 and 100 μg/ml, demonstrating a significant inoculum effect. There was no change in the amikacin MIC or MBC with the larger inoculum.

Pharmacokinetics. Central- and peripheral-compartment pharmacokinetics of both ceftazidime and amikacin are presented in Table 1. The elimination half-lives of ceftazidime and amikacin, respectively, were 1.7 and 2.5 h. In general, peak concentrations of ceftazidime in the central compartment were 22 to 40 μg/ml above the target level of 160 μg/ml while peak concentrations of amikacin were closer to the target of 80 μg/ml. Peripheral-compartment ceftazidime concentrations for all regimens were similar (range, 52 to 76 μg/ml) at 4 h. However, 48-h concentrations were much more variable and reflected the dose and route of administration. Ceftazidime concentrations in the peripheral compartment in the last 24 h were above the MIC for *P. aeruginosa* ATCC 27853 for all regimens except constant infusion of 5 μg/ml. By contrast, the only regimen to achieve a concentration equal to the MIC for *P. aeruginosa* 27853CR was 2 g q8h. The AUCs and AUC/MIC ratios of the ceftazidime monotherapy regimens are listed in Table 2. The AUCs and AUC/MIC ratios of the q8h and q12h regimens for the peripheral compartment were not calculated. This was due to insufficient sampling for calculation of the AUC and the fact that equilibration between the central and peripheral compartments had not been obtained.

Antibiotic carryover. The ceftazidime and amikacin concentrations used were 110 and 55 μg/ml. These values were estimates of anticipated maximal peaks in the peripheral compartment and were well above the actual peak concentrations in

TABLE 1. Central- and peripheral-compartment pharmacokinetics of ceftazidime and amikacin

Regimen	Drug concn (μg/ml) in central compartment at:			$t_{1/2}$ (h)	Drug concn (μg/ml) in peripheral compartment at:		
	0.5 h	24 h	48 h		4 h	24 h	48 h
Ceftazidime (2 g q8h)	190.6 ± 17.4	9.8 ± 1.7	10.9 ± 1.7	1.6 ± 0.05	63.2 ± 2.8	54.7 ± 1	55.0 ± 2.1
Ceftazidime (2 g q12h)[a]	207.6	2.6	2.8	1.8 ± 0.09	57.6	22.3	34.7
Ceftazidime (CI[b] 20 μg/ml)[a]	172.5	30.8	27.3	ND[c]	76.2	32.6	28.2
Ceftazidime (CI, 10 μg/ml)	191.0 ± 14.3	11.9 ± 2.4	11.7 ± 2.1	ND	52.2 ± 1.8	15.6 ± 2.4	11.7 ± 2.0
Ceftazidime (CI, 5μg/ml)	189.2 ± 2.1	5.6 ± 3.1	5.9 ± 2.6	ND	56.7 ± 1.2	10.2 ± 1.7	5.5 ± 2.5
Daily amikacin	81.2 ± 0.9	<2	<2	2.35 ± 0.07	28.7 ± 0.4	<2	<2

[a] Insufficient sample volume for duplication of assay.
[b] CI, continuous infusion.
[c] ND, not done.

the peripheral compartment (76 and 28 μg/ml, respectively). The 10-fold serial dilutions performed effectively diluted the antibiotics, and detection of the 10^6-CFU/ml inoculum was not interfered with. When lower colony counts were anticipated, the samples were filtered with 10 ml of saline and the filters were plated and colonies were counted without interference from the antibiotics.

Time-kill studies. (i) *P. aeruginosa* ATCC 27853. The results of the time-kill studies are shown in Fig. 2. The calculated time to 99.9% killing was not significantly different for any of the ceftazidime monotherapy regimens. Apparent regrowth at 48 h occurred only with continuous infusion of 5 μg/ml, and incomplete killing occurred with continuous infusions of 10 and 20 μg/ml and a 2-g bolus q12h. Ceftazidime at 2 g q8h was the only monotherapy regimen to kill below the limit of detection; however, this was not statistically significantly different from any of the regimens that resulted in incomplete killing. Comparison of colony counts at 48 h showed statistically significance differences between continuous infusion of 5 μg/ml versus a 2-g bolus q8h and continuous infusion of 5 μg/ml versus continuous infusion of 20 μg/ml ($P = 0.027$ and $P = 0.037$). The time to 99.9% reduction in CFU per milliliter for the combination regimens and amikacin monotherapy was between 2 and 3.5 h. Similar to the results of the monotherapy regimens, statistically there was no significant difference. No regrowth was observed with any of the combination regimens; however, a significant difference in regrowth was observed for amikacin monotherapy compared with the combination regimens ($P = 0.002$).

(ii) *P. aeruginosa* 27853CR. The results of the time-kill studies are shown in Fig. 3. None of the ceftazidime monotherapy regimens achieved a 3-$\log_{10}$ reduction in CFU (time to 99.9% killing). Regrowth at 48 h occurred with all regimens. The time to 99.9% reduction in CFU per ml for the combination regimens and amikacin monotherapy was between 2 and 3.5 h. Regrowth occurred at 48 h for amikacin monotherapy and all combination regimens except the 2-g bolus q8h and continuous infusion of 20 μg/ml plus amikacin. The regrowth was statistically significantly different for amikacin monotherapy versus combination regimens of 2 g q12h or q8h and continuous infusion of 20 μg/ml plus amikacin ($P = 0.033$, $P = 0.006$, and $P = 0.007$, respectively).

Development of resistance. (i) *P. aeruginosa* ATCC 27853. Resistance to ceftazidime was not detected during administration of any regimen, monotherapy or combination. Resistance to amikacin developed only during monotherapy. The change in the subpopulations over time was most pronounced between 24 and 48 h, with 34% of the subpopulation growing on antibiotic plates containing amikacin at eight times the MIC (Fig. 4). The MIC increased from 3.13 μg/ml at time zero to 25 μg/ml at 48 h. After six passes to antibiotic-free agar, the MIC reverted back to the baseline.

(ii) *P. aeruginosa* 27853CR. Resistance to amikacin developed during monotherapy and continuous infusion of 10 μg of ceftazidime per ml plus amikacin. The change in the subpopulations over time, as with the susceptible isolate, was most pronounced between 24 and 48 h, with about 21% of the subpopulation growing on antibiotic plates containing amikacin at eight times the MIC (data not shown). The MICs increased from 1.56 μg/ml at time zero to 12.5 and 25 μg/ml, respectively, for the combination and monotherapy at 48 h. The resistance of this isolate, however, was stable; after 10 passes to antibiotic-free agar, the MICs remained increased to 12.5 and 25 μg/ml.

DISCUSSION

It has been proposed that to optimize the bactericidal killing of β-lactams, the time that the concentration is above the MIC should be maximized and the concentration should be maintained at about four to five times the MIC (1, 3–5, 15). This is supported and further delineated by the results of this study. The rates of killing were comparable over the first 12 h for all of the ceftazidime monotherapy regimens used because of the loading dose given prior to initiation of the constant infusions. Differentiation between the continuous infusions occurred af-

TABLE 2. Central- and peripheral-compartment AUCs and AUC/MIC ratios obtained with ceftazidime monotherapy[a]

Regimen	Central compartment			Peripheral compartment		
	$AUC_{24–48}$	$^{S}AUC/MIC_{24–48}$	$^{R}AUC/MIC_{24–48}$	$AUC_{24–48}$	$^{S}AUC/MIC_{24–48}$	$^{R}AUC/MIC_{24–48}$
2 g q8h	1,780.7	1,141.5	35.6	ND	ND	ND
2 g q12h	875.3	561.1	17.5	ND	ND	ND
CI, 20 μg/ml	677	434	13.5	689.9	442.2	13.8
CI, 10 μg/ml	284.9	182.6	5.7	279.2	179	5.6
CI, 5 μg/ml	137.1	87.88	2.7	135.6	86.9	2.7

[a] S, susceptible isolate; R, resistant isolate; ND, not done; CI, continuous infusion.

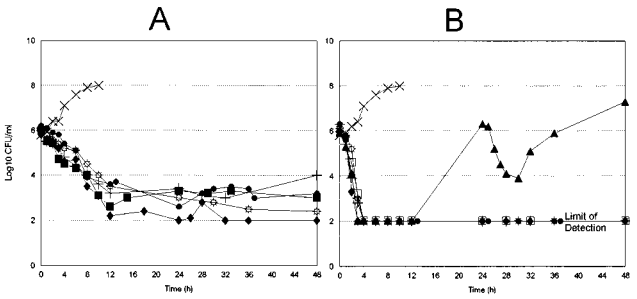

FIG. 2. Time-kill curves for *P. aeruginosa* ATCC 27853. (A) Ceftazidime monotherapy. Symbols: ×, growth control; ●, 2 g q12h; ◆, 2 g q8h; +, continuous infusion at 5 μg/ml; ■, continuous infusion at 10 μg/ml; ✲, continuous infusion of 20 μg/ml. (B) Amikacin with or without ceftazidime. Symbols: ×, growth control; ●, 2 g q12h plus amikacin; ◆, 2 g q8h plus amikacin; +, continuous infusion of 5 μg/ml plus amikacin; ■, continuous infusion of 10 μg/ml plus amikacin; ✲, continuous infusion of 20 μg/ml plus amikacin; ▲, amikacin monotherapy.

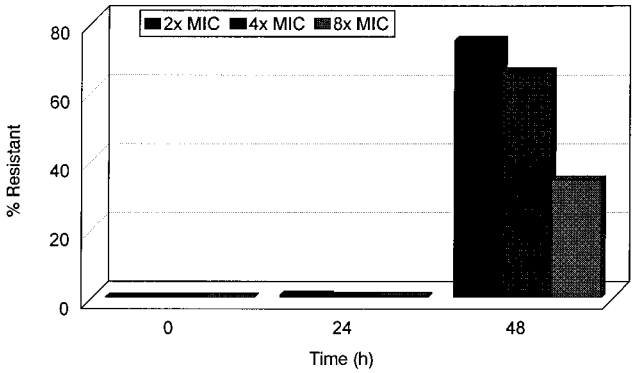

FIG. 4. *P. aeruginosa* ATCC 27853 subpopulation change during amikacin monotherapy.

ter 12 h in that the 20-μg/ml regimen continued to demonstrate bactericidal activity through 48 h while the other regimens (5 and 10 μg/ml) resulted in incomplete killing. The time and magnitude that the ceftazidime concentration was above the MIC for the organism at the site of infection was suboptimal during the second 24 h of the experiment for continuous infusion of 5 μg/ml. The range of concentrations was 1 to 3 times the MIC for the 5-μg/ml regimen, while those of the 10- and 20-μg/ml regimens were 4 to 5 and 10 to 15 times the MIC, respectively. Although the 20-μg/ml continuous-infusion regimen continued to kill over the 48-h interval and the 10-μg/ml regimen resulted in a plateau of approximately $\log_{10}$ 3 CFU/ml, there was no significant difference between these regimens. The peak concentrations of ceftazidime in the central compartment were higher than anticipated for the bolus doses, while the continuous-infusion concentrations were as expected. We have no satisfactory explanation for this; however, since ceftazidime exhibits concentration-independent killing, the overall effect on the results of the experiment should be minimal.

Continuous infusion of 20 μg/ml was found to be as effective in bactericidal activity as the simulated 2-g-q8h regimen. The concentration of ceftazidime at the site of the infection (peripheral compartment) for the 2-g-q8h regimen was 25 to 35 times the MIC for the organism, compared with 10 to 15 times the MIC for continuous infusion of 20 μg/ml, thus indicating little improvement in bactericidal activity with higher concentrations. Continuous infusion of 10 μg/ml was as effective as the 2-g-q12h, regimen; however, both regimens resulted in incomplete killing between 12 and 24 h, in contrast to the killing activity of the q8h bolus and 20-μg/ml constant-infusion regimens. These results are similar to the time-kill curve results obtained by Craig and Ebert utilizing ticarcillin, which indicated no significant increase in killing at concentrations between 4 and 16 times the MIC (4).

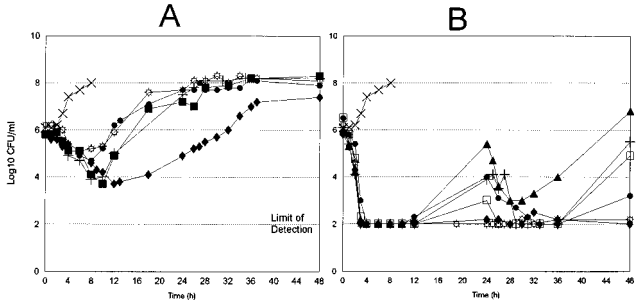

FIG. 3. Time-kill curves for *P. aeruginosa* 27853CR. (A) Ceftazidime monotherapy. Symbols: ×, growth control; ●, 2 g q12h; ◆, 2 g q8h; +, continuous infusion of 5 μg/ml; ■, continuous infusion of 10 μg/ml; ✲, continuous infusion of 20 μg/ml. (B) Amikacin with or without ceftazidime. Symbols: ×, growth control; ●, 2 g q12h plus amikacin; ◆, 2 g q8h plus amikacin; +, continuous infusion of 5 μg/ml plus amikacin; ■, continuous infusion of 10 μg/ml plus amikacin; ✲, continuous infusion of 20 μg/ml plus amikacin; ▲, amikacin monotherapy.

It is known that an inoculum effect can be demonstrated in vitro with β-lactam antibiotics. We observed this phenomenon in this study with susceptibility testing at 10^7 CFU/ml. A preliminary model experiment was performed with an inoculum of 10^7 CFU of the susceptible isolate per ml and 2 g of ceftazidime given q12h. The result was a 1-$\log_{10}$ reduction in the colony count over 48 h (data not shown). The inoculum effect was eliminated by reducing the initial concentration of the organism to 10^6 CFU/ml. Also, because of the inoculum effect, caution should be used in extrapolating the results obtained with the ceftazidime monotherapy regimens at 10^6 CFU/ml to larger-inoculum infections.

Use of the AUC/MIC ratio is an attempt to combine the MIC for an organism with the pharmacokinetics of an antibiotic to assess or predict the outcome of therapy. Schentag and colleagues used computer models and simulations to find an index value to compare the AUC/MIC ratios within and between antibiotic classes (20). They found that an AUC/MIC index of 125 indicates that 80% of the AUC is above the MIC for ciprofloxacin, cefmenoxime, and tobramycin against select gram-negative bacilli. In a retrospective study by Goss and colleagues, they compared the in vivo bactericidal rates of ciprofloxacin and cefmenoxime with the AUC/MIC ratios (8). The results indicated that an AUC/MIC ratio of 250 to 500 was the optimal target for the rate of bacterial killing of each antibiotic. It was hypothesized by the investigators that with cefmenoxime, an AUC/MIC ratio above the optimum does not result in increased killing activity. The results of our study also support the lack of increased killing activity with higher AUC/MIC ratios. For the 2-g-q8h and 20-μg/ml continuous-infusion regimens, the AUC/MIC indices for the susceptible isolate were 1,141 and 434, respectively, producing similar rates and extents of bactericidal activity. The only regimen not achieving an AUC/MIC index of at least 125 was 5-μg/ml continuous-infusion monotherapy, which had suboptimal killing activity against the susceptible isolate. All ceftazidime monotherapy regimens failed against the resistant isolate, as shown by both the AUC/MIC values (all were below 40) and the killing curves.

It is well established that β-lactams and aminoglycosides often exhibit synergism when combined. This is also evident in

the results of this study with the combinations of continuous infusion of ceftazidime at 5 and 10 μg/ml and an intermittent regimen of 2 g q12h with amikacin resulting in lower *P. aeruginosa* ATCC 27853 colony counts at 48 h than each monotherapy regimen. Against ceftazidime-resistant *P. aeruginosa* 27853CR, monotherapy was ineffective while combination treatment with amikacin plus 2 g of ceftazidime q12h or q8h or continuous infusion at 20 μg/ml was both effective and synergistic. In lieu of development of resistance to amikacin during continuous infusion of 10 μg/ml plus amikacin treatment, the colony count at 48 h was 1.5 $\log_{10}$ CFU/ml lower than that obtained with amikacin monotherapy. However, the colony counts for the two regimens were not significantly different and the regrowth was markedly greater than that obtained with the synergistic combination regimens. This regrowth phenomenon observed for many of the regimens may be due to suboptimal therapy or release of adherent bacteria from the walls of the peripheral chamber (9). Ceftazidime concentrations equal to one-fifth or one-tenth of the MIC (continuous infusions of 10 and 5 μg/ml, respectively) in combination with amikacin appear to be inferior therapies against this ceftazidime-resistant isolate of *P. aeruginosa*.

Resistance developed between 24 and 48 h during monotherapy with amikacin for both isolates and during the combination of continuous infusion of 10 μg/ml plus amikacin against *P. aeruginosa* 27853CR. The mechanism(s) of resistance to amikacin by these isolates was not characterized in this study, and extrapolation to a specific mechanism(s) is not possible. General mechanisms for the development of resistance to amikacin include mutation of the organism, a change in the outer membrane decreasing its permeability for a drug, and adaptive resistance.

A recent in vitro study by Mouton and den Hollander compared continuous infusion of 20 μg/ml with a simulation of 1 g of ceftazidime q8h against *P. aeruginosa* ATCC 27853. Those investigators found the continuous-infusion regimen to have more effective killing activity than intermittent administration over a 36-h period. Intermittent administration of 1 g resulted in suboptimal ceftazidime concentrations in the infection compartment, allowing the organism to regrow, whereas the continuous-infusion regimen maintained the antibiotic concentration at about 20 times the MIC for the organism (16). These results are consistent with our results, which showed continuous infusion of 20 μg/ml to be as effective as the 2-g-q8h regimen.

We have demonstrated that continuous infusion of ceftazidime at 20 μg/ml is equivalent in efficacy to intermittent administration of 2 g q8h. In addition, there appears to be an economical advantage to constant infusion. With standard pharmacokinetic characteristics of ceftazidime (volume of distribution of 16 liters, elimination half-life of about 2 h, and weight of 70 kg), the dose required to achieve a concentration of 20 μg/ml is approximately 2.5 g/day. This is nearly 2 to 4 g less than the 2-g-q12h and 2-g-q8h regimens traditionally used in clinical practice. Our data support the need for clinical investigation of administration of ceftazidime by continuous infusion to further define its impact on clinical efficacy and patient care.

Ceftazidime monotherapy administered as a continuous infusion at 20 and 10 μg/ml with a loading dose is as effective as administration of 2 g q8h or q12h in the treatment of *P. aeruginosa* infections. It appears that ceftazidime at the MIC for the organism is inadequate for treatment of infections, while optimal concentrations in this experiment were 10 to 20 times the MIC for the infecting organism. AUC/MIC ratios above the optimum do not correlate with increased bactericidal activity of ceftazidime. Synergism was observed for the combination of ceftazidime and amikacin against both ceftazidime-susceptible and -resistant isolates of *P. aeruginosa*.

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