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Bactericidal Activity of Ceftazidime in Serum Compared with That of Ticarcillin Combined with Amikacin

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We compared the bactericidal activity of serum attained 1 and 6 h after the termination of infusions of either ceftazidime (2 g) or ticarcillin plus amikacin (5 g and 7.5 mg/kg, respectively) in 6 volunteers against a panel of the most common pathogens found in the blood of febrile granulocytopenic cancer patients. Ceftazidime consistently produced significantly higher serum bactericidal titers at both 1 and 6 h against all species of gram-negative bacilli. Its performance against *Pseudomonas aeruginosa* was especially impressive. The geometric mean titer against this organism was 1:41 at 1 h, contrasted with 1:12 for ticarcillin plus amikacin ($P = 0.025$). However, for *Staphylococcus aureus*, the geometric mean serum bactericidal titer of ceftazidime was 1:3.6 at 1 h and undetectable at 6 h. Ceftazidime shows promise as single-agent therapy for serious gram-negative bacillary infections. Whether this promise is fulfilled and whether the observed antistaphylococcal activity is adequate for empiric therapy in infected granulocytopenic patients need further investigation.

Ticarcillin plus amikacin is a standard therapy for the treatment of infected granulocytopenic cancer patients. It has been compared with other antibiotic combinations for the empiric therapy of suspected sepsis in this patient group and has withstood the test of time (2, 10). However, because aminoglycoside therapy has been associated with high rates of both nephro- and ototoxicity, a single, relatively nontoxic agent would be preferred (1; W. Pickard, D. Durack, and H. Gallis, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 22nd, Miami Beach, Fla., abstr. no. 5, 1982).

Ceftazidime is a new aminothiazolyl cephalosporin with a microbiological spectrum that encompasses *Staphylococcus aureus* plus members of the family *Enterobacteriaceae*. This compound also has been found to be highly microbiologically active against *Pseudomonas aeruginosa* (9), a major addition over currently available expanded-spectrum cephalosporins. Consequently, we decided to evaluate ceftazidime in comparison with ticarcillin plus amikacin with regard to the serum bactericidal activity produced in volunteers against *P. aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *S. aureus*, the most common pathogens recovered from the blood of granulocytopenic cancer patients.

MATERIALS AND METHODS

Volunteer studies. Normal male volunteers (age, 18 to 35 years; weight, 59 to 86.4 kg), fully informed before the study, received both ceftazidime and the combination of ticarcillin plus amikacin in a crossover manner, with at least 6 days elapsing between each administration. Ceftazidime (2 g) or ticarcillin (5 g) plus amikacin (7.5 mg/kg) were each diluted to 23 ml with 5% glucose in water and infused via a Harvard pump (Harvard Apparatus, Inc.) for 30 min. When ticarcillin plus amikacin was administered, the aminoglycoside was always infused first. Blood was obtained for serum bactericidal assay 1 and 6 h after the termination of the infusions.

Microbiological methods. A total of 31 strains of *P. aeruginosa* and 7 strains each of *E. coli*, *K. pneumoniae*, and *S. aureus* were chosen at random from a collection derived from the clinical services of the University of Maryland Cancer Center. The MICs of the test antimicrobial agents were determined concurrently for each organism. The determinations were performed by a microtiter dilution method, using Mueller-Hinton broth supplemented with calcium and magnesium as the growth medium and diluent. An overnight broth culture was adjusted to visually equal the density of a 0.5 McFarland standard (~10^8 CFU/ml). A further 1:200 dilution was made of this adjusted culture. The test wells contained 0.05 ml of antibiotic plus 0.05 ml of this dilution, producing an inoculum of ca. 10^5 to 10^6 CFU/ml. The MIC was defined as the lowest concentration that prevented grossly detectable growth after 18 h of incubation at 37°C.

Serum bactericidal activity. The bactericidal activity of serum samples was determined by a microtiter dilution method, utilizing equal quantities of pooled human serum and cation-supplemented Mueller-Hinton broth as the diluent (7). All samples were serially diluted from 1:2 to 1:256. The inoculum was 10^5 to 10^6 bacteria per ml. The endpoint for the serum inhibitory activity was the last well in which there was no turbidity. The endpoint for the serum bactericidal activity was determined as the greatest dilution which allowed no growth after subculturing 0.0015 ml of each nonturbid well onto agar plates (ca. 99.9% kill).

Statistical analysis. The geometric mean serum bactericidal activity calculated for each species of microorganism was tested by Student's t test to determine significant differences. The cumulative percentage of the serum bactericidal activity at each level of dilution was calculated for each species of microorganism for each drug.

RESULTS

Microbiological activity. The MICs of the test antimicrobial agents for inhibition of the organisms are displayed in Table 1. Ceftazidime was clearly the most active single agent against *P. aeruginosa*, with 30 of 31 strains susceptible to 8 μg/ml. Amikacin was also highly active, with 27 of 31 strains susceptible to 8 μg/ml. Ticarcillin displayed a different order

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TABLE 1. MICs of the test antibiotics for inhibition of the organisms

Test organism (no. of strains)	Test antibiotics	MIC (μg/ml)	
		Median	Range
P. aeruginosa (31)	Ceftazidime	2	0.5–16
	Ticarcillin	16	4–≥512
	Amikacin	4	1–16
E. coli (7)	Ceftazidime	0.125	0.06–0.5
	Ticarcillin	2.0	1–8
	Amikacin	2.0	2–4
K. pneumoniae (7)	Ceftazidime	0.25	0.06–0.5
	Ticarcillin	256	64–≥512
	Amikacin	2	1–4
S. aureus[a] (7)*	Ceftazidime	4	4–≥512
	Ticarcillin	4	2–≥512
	Amikacin	1	1–16

[a] Includes two methicillin-resistant strains.

of activity, with 25 of 31 strains susceptible to 32 μg/ml. All the test antimicrobial agents were highly active against *E. coli*. Ceftazidime was again highly active against *K. pneumoniae*, with 7 of 7 strains susceptible to 0.5 μg/ml, whereas 7 of 7 strains were susceptible to 4 μg of amikacin per ml. Ticarcillin, as expected, was not very active against *K. pneumoniae*. Two of the randomly selected strains of *S. aureus* were later found to be methicillin resistant. Consequently, all three test antimicrobial agents showed rather poorly against *S. aureus*. Nevertheless, the five methicillin-susceptible strains were susceptible to 8 μg/ml or less of both ceftazidime and ticarcillin with the standard inoculum. Amikacin was also active, with 5 of 5 methicillin-susceptible strains susceptible to 2 μg/ml and the methicillin-resistant strains susceptible to 16 μg/ml.

Serum bactericidal activity. The geometric mean serum bactericidal titers for both regimens at both 1 and 6 h are displayed in Table 2. The geometric mean bactericidal titers of ceftazidime were significantly better than those obtained with ticarcillin plus amikacin at both 1 and 6 h for each species of gram-negative bacilli. Against the 31 strains of *P. aeruginosa*, ceftazidime produced a geometric mean bactericidal titer of 1:40.7 after 1 h of antibiotic administration, which was over three times that generated by the combination of ticarcillin plus amikacin (1:12.2). At 6 h, the bactericidal titer of ceftazidime was still greater than twice that generated by the combination. Against *E. coli* and *K. pneumoniae*, ceftazidime showed uniformly good serum bactericidal activity at both 1 and 6 h, the lowest mean titer being 1:97 at 6 h against *K. pneumoniae*. Ticarcillin plus amikacin also performed quite well against these organisms. A geometric mean bactericidal titer of 1:125 at 1 h and 1:8 at 6 h was obtained against *E. coli*, and for *K. pneumoniae* a geometric mean titer of 1:86 was obtained at 1 h, declining to 1:8 at 6 h. Against *S. aureus*, ceftazidime performed poorly, with a geometric mean of 1:3.6 at 1 h, and failed to produce measurable bactericidal activity at 6 h. However, when the methicillin-resistant strains are removed from consideration, the geometric mean bactericidal titer at 1 h was 1:5.5 for ceftazidime, but no bactericidal activity was produced at 6 h. Ticarcillin plus amikacin was significantly better against this bacterium, with a mean titer of 1:24 at 1 h, declining to 1:3 at 6 h.

The cumulative percentage of determinations bactericidal at the different dilutions for the test strains are displayed in Fig. 1 and 2. Against *P. aeruginosa*, 95% of the determinations were bactericidal at 1:8 or greater for ceftazidime for the 1-h time point. By 6 h, 32% of the determinations were 1:8 or greater, and all determinations were bactericidal at 1:2. For ticarcillin and amikacin, 85% of the determinations were bactericidal at 1:8 or greater at the 1-h time point. By 6 h, only 2% of the determinations were cidal at 1:8, but 79% of the determinations were still bactericidal at 1:2. Against *E. coli* and *K. pneumoniae*, ceftazidime had 100% of the determinations bactericidal at 1:8 for both 1 and 6 h. For ticarcillin plus amikacin, 100% of the determinations were ≥1:8 for both *E. coli* and *K. pneumoniae* at the 1-h time point. For *E. coli*, ticarcillin plus amikacin was bactericidal at 1:8 against 60% of the determinations at 6 h, and 100% of these determinations were bactericidal at 1:2. For *K. pneumoniae*, 63% were bactericidal at 6 h at 1:8 or greater, and 100% were bactericidal at 1:2. Against *S. aureus* at the 1-h time point, ceftazidime had 29% of determinations at 1:8 or greater, contrasted with 71% of determinations with the combination of ticarcillin plus amikacin. If the methicillin-resistant strains are removed from consideration, the percentage greater than or equal to 1:8 rises to 40% for ceftazidime and 100% for the combination regimen.

DISCUSSION

Adequate single-agent therapy with a beta-lactam antibiotic has long been sought for the empiric therapy of suspected sepsis in granulocytopenic cancer patients because of the nephro- and ototoxicity associated with aminoglycoside-containing regimens (3, 6). A drug filling this role, however, should generate good bactericidal activities against the pathogens most commonly isolated from the blood of this patient group. Furthermore, current data suggest a serum bactericidal activity of 1:8 or greater 1 h after the termination of infusion is associated with a significantly better outcome for septic cancer patients (4). Whether this degree of bactericidal activity is an end in itself or whether it is important to generate this degree of bactericidal activity as a result of two drugs, each having a different mechanism of action, is a question which is unresolved (8). However, a minimal attainment for any purported single agent should be the reliable production of serum bactericidal activity at a 1:8 or greater dilution against *P. aeruginosa*, *E. coli*, *K. pneumoniae*, and *S. aureus*, the four most common bacteremic pathogens for these patients.

Ceftazidime performs extremely well against the gram-negative pathogens. It is particularly notable that it produces very good activity against *P. aeruginosa*, an organism that causes significant problems with currently available single-agent regimens. With ticarcillin plus amikacin as a standard, ceftazidime clearly outperforms the combination with regard

TABLE 2. Reciprocal geometric mean bactericidal titers generated at 1 and 6 h by each regimen

Test organism (no. of strains)	Titer obtained with:			
	Ceftazidime		Ticarcillin-amikacin	
	1 h	6 h	1 h	6 h
P. aeruginosa (31)	40.7	4.7	12.2	2.1
S. aureus (7)	3.6	NA	24.3	3.0
E. coli (7)	256.0	128.0	125.5	8.2
K. pneumoniae (7)	236.5	97.0	86.1	8.0

[a] NA, No activity assayable.

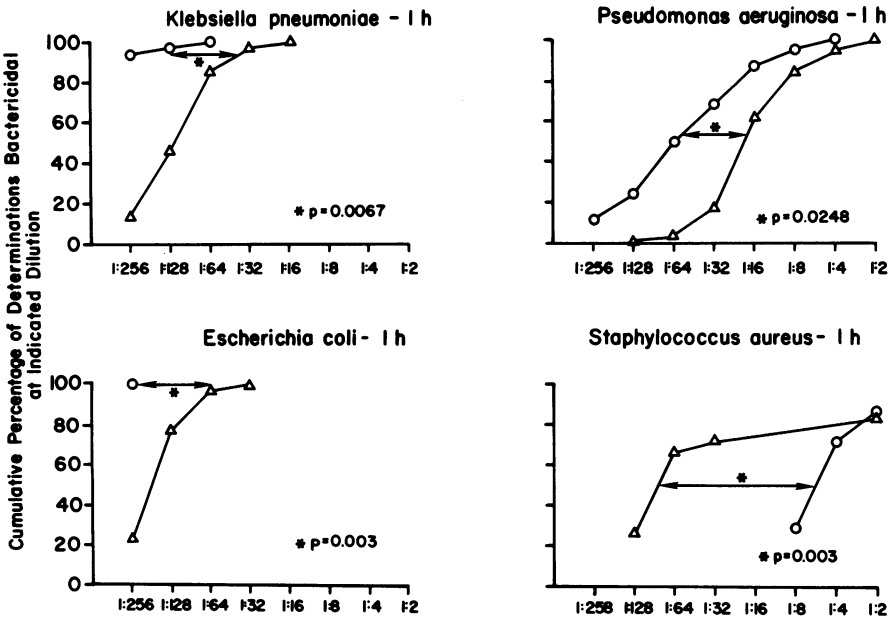

FIG. 1. Cumulative percentage of determinations bactericidal against pathogens commonly bacteremic in neutropenic cancer patients. Serum was obtained from volunteers 1 h after the end of the infusion. The *P* value represents the level of significance between geometric mean bactericidal titers produced by the two regimens. Symbols: ○, ceftazidime; △, ticarcillin plus amikacin.

to serum bactericidal activity. Whether this impressive in vitro activity carries over into the clinical situation needs to be evaluated in controlled clinical trials.

Against *E. coli* and *K. pneumoniae*, both regimens performed extremely well with ticarcillin plus amikacin, generating higher bactericidal titers against *K. pneumoniae* than would be expected on the basis of the microbiological activity of the agents involved. This is probably due to a synergistic interaction between the beta-lactam and the aminoglycoside for this organism.

Ladisch and Pizzo (5) and Wade et al. (11), among others, have reported an increasing incidence of gram-positive infections in granulocytopenic patients. Consequently, it is of interest to note that ceftazidime performed relatively poorly against the staphylococci in our study. When the two methicillin-resistant strains are removed from consideration, the geometric mean titer 1 h after the end of the infusion still remained at only 1:5.5. Even more concerning is that in no instance was there any serum bactericidal activity detected at 6 h. Whether this profile of antistaphylococcal activity is

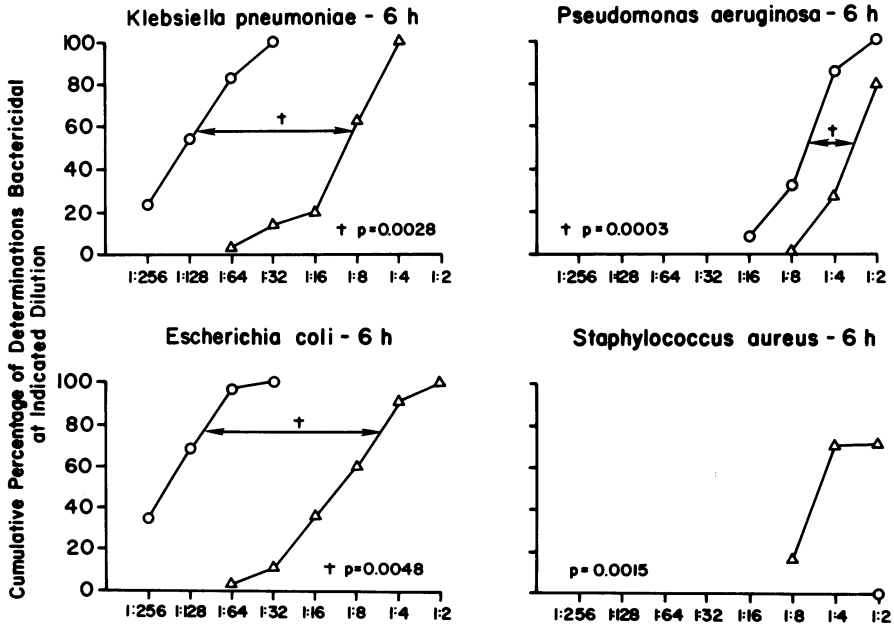

FIG. 2. Cumulative percentage of determinations bactericidal against pathogens commonly bacteremic in neutropenic cancer patients. Serum was obtained from volunteers 6 h after the end of the infusion. The *P* value represents the level of significance between geometric mean bactericidal titers produced by the two regimens. Symbols: ○, ceftazidime; △, ticarcillin plus amikacin.

adequate until the organism is identified and more specific therapy can be initiated cannot be answered from the available information and will have to be addressed in clinical trials. The antistaphylococcal activity seen with the combination of ticarcillin plus amikacin is somewhat greater than would be expected. Although this activity may be influenced by inoculum size, it is important to note that clinical trial experience has shown that ticarcillin plus an aminoglycoside provides very effective antimicrobial therapy in the empiric treatment situation for the staphylococcus (3).

In summary, ceftazidime is a new aminothiazolyl cephalosporin which appears to be a very active single agent for *P. aeruginosa*. It couples this antipseudomonal activity with excellent killing power against members of the family *Enterobacteriaceae*. Against *S. aureus*, however, the activity of ceftazidime is somewhat more suspect, and the serum bactericidal activity achieved is of an order which raises doubts as to its protective ability for neutropenic cancer patients in the empiric therapy situation. The prediction of efficacy for gram-negative infections and the question of adequacy of ceftazidime for staphylococcal infections clearly need resolution in well-controlled, comparative clinical trials.

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