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NOTES

Serum Bactericidal Activity of Moxalactam and Cefotaxime With and Without Tobramycin Against *Pseudomonas aeruginosa* and *Staphylococcus aureus*

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Serum bactericidal activity was determined against 10 strains each of *Pseudomonas aeruginosa* and *Staphylococcus aureus* in serum from volunteers 1 and 6 h after intravenous infusion of cefotaxime, tobramycin, and the combination; or of moxalactam, tobramycin, and the combination. High serum bactericidal activity against *P. aeruginosa* was found significantly more frequently with moxalactam plus tobramycin than with cefotaxime, moxalactam, and tobramycin alone or with cefotaxime plus tobramycin.

Moxalactam (1-oxa-β-lactam) and cefotaxime are new antibiotics with increased activity against *Enterobacteriaceae* relative to older penicillins and cephalosporins (2, 9, 12-15). In addition, both drugs have in vitro activity against *Pseudomonas aeruginosa* (2, 9, 12, 13, 15). Both of these agents have in vitro activity against *Staphylococcus aureus*, but this activity may not be as great as that of older antibiotics of similar composition (2, 9, 12, 15). Cephalosporins and penicillins are used frequently in combination with aminoglycoside antibiotics in the treatment of gram-negative rod bacteremia (4), and the synergistic activity obtained with these combinations has been related to improved outcome in severely neutropenic bacteremic patients (6). Also, in vitro studies have demonstrated synergism between cefotaxime and aminoglycosides against aminoglycoside-resistant strains of *P. aeruginosa* (8). Since *P. aeruginosa* and *S. aureus* are frequently cultured from infected neutropenic patients, this study was designed to evaluate the serum bactericidal activity (SBA) of cefotaxime and moxalactam with or without tobramycin against 10 strains each of *P. aeruginosa* and *S. aureus* isolated from patients at Institut Jules Bordet, Brussels.

Minimal inhibitory concentrations (MICs) were determined in Mueller-Hinton broth (MHB) supplemented with calcium chloride (50 mg/liter) and magnesium sulfate (20 mg/liter), using a twofold dilution technique in microtiter plates. A final concentration of 5×10^4 organisms per ml for *P. aeruginosa* and 5×10^5 viable organisms per ml for *S. aureus* was included in each well. The MIC was defined as the lowest concentration at which no visible growth occurred after 18 h of incubation at 37°C. Minimal bactericidal concentrations (MBCs) were performed by replicate inoculation onto antibiotic-free media. The MBC was defined as the lowest concentration of drug yielding a 99.9% reduction in the original inoculum.

Bactericidal activity was determined in serum from two groups of six volunteers. Each group of volunteers received on separate days either cefotaxime (15 mg/kg), tobramycin (1.5 mg/kg), or the combination; or moxalactam (15 mg/kg), tobramycin, or the combination. These antibiotics were diluted in 50 ml of 5% dextrose in water and infused over 15 min. The sequence of administration of the studied drugs within each group of six volunteers was assigned randomly by using a Latin square design. These volunteers included healthy young adults and patients hospitalized for noninfectious causes. All volunteers gave informed consent to participate in the study, and all had normal renal and hepatic function. Serum samples were obtained from each subject 1 and 6 h after the infusion.

The concentrations of cefotaxime and moxalactam were measured in these serum samples by the agar diffusion method of Bennett et al. (1). *Escherichia coli* ATCC 10536 and *E. coli* V

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6310-65 were used for the determination of moxalactam and cefotaxime, respectively, on nutrient agar (Biomerieux) at pH 6.8 supplemented with sodium polyanethol sulfonate when tobramycin was present in the serum sample. This supplementation is necessary to selectively inhibit the aminoglycoside activity (3). All serum samples were assayed for tobramycin using a radioimmunoassay kit and standard (Rianen Assay System; New England Nuclear Corp.).

SBA on the serum samples was measured in microtiter plates as described previously (5). Serum dilutions were made with a 1:1 mixture of pooled human serum in MHB supplemented as above with calcium and magnesium (13). Each serum sample was tested against each of the 10 strains of *P. aeruginosa* (at 5×10^4 organisms per ml) and against each of the 10 strains of *S. aureus* (at 5×10^5 organisms per ml).

Median MICs and MBCs were similar for both cefotaxime and moxalactam against *P. aeruginosa* (MIC, 3 μg/ml; MBC, 6 μg/ml for each antibiotic). The MIC and MBC of tobramycin for *P. aeruginosa* were 0.2 μg/ml and 0.3 μg/ml, respectively. Against *S. aureus*, MICs and MBCs were lower for cefotaxime than for moxalactam (cefotaxime MIC = 1.5 μg/ml, MBC = 3 μg/ml; moxalactam MIC = 6 μg/ml, MBC = 12 μg/ml). The MIC and MBC of tobramycin for *S. aureus* were 0.03 μg/ml and 0.07 μg/ml, respectively.

Serum levels of moxalactam and cefotaxime were similar when the drug was administered alone or in combination with tobramycin. Cefotaxime levels at 1 h were 7.77 ± 1.2 μg/ml alone and 8.97 ± 1.5 μg/ml in combination. At 6 h these levels were 0.2 ± 0.07 μg/ml, 0.17 ± 0.05 μg/ml, respectively. Moxalactam serum levels at 1 h were 25.7 ± 4.6 μg/ml when the drug was administered alone and 22.58 ± 3.0 μg/ml when the drug was administered in combination. At 6 h these values were 5.38 ± 1.65 μg/ml and 4.22 ± 0.78 μg/ml, respectively.

The results of SBA determinations are presented in Table 1. For the 10 strains of *P. aeruginosa* the median SBA for cefotaxime was less than 1:2, whereas that for moxalactam was 1:8. The greatest number of serum specimens with SBA ≥1:8 was obtained with moxalactam plus tobramycin (87%). Sera with SBA ≥1:8 were found significantly more frequently with moxalactam plus tobramycin than with moxalactam alone, tobramycin alone, or cefotaxime plus tobramycin. Cefotaxime plus tobramycin produced SBA ≥1:8 in 50% of the tested sera compared to 20% of sera containing cefotaxime alone, $P < 0.02$. At 6 h after infusion, moxalactam plus tobramycin was also more active than cefotaxime plus tobramycin and tobramycin alone. For *S. aureus* at 1 h after infusion, tobramycin, cefotaxime plus tobramycin, and moxalactam plus tobramycin produced similar SBA. Each of these regimens was significantly more active than cefotaxime or moxalactam alone. Most of this activity appeared to be due to that of tobramycin. At 6 h after infusion, little detectable activity was found with any regimen.

The increased SBA against *Pseudomonas* observed for moxalactam compared with cefotaxime may be due to the higher serum levels obtained with the oxa-β-lactam compound. The higher serum levels with moxalactam may be the result of its longer half-life relative to that of cefotaxime (10, 11). The serum half-life of tobra-

TABLE 1. *Median SBA and percentage of sera with SBA ≥1:8*

Antibiotic	SBA against *P. aeruginosa* at:				SBA against *S. aureus* at:			
	1 h		6 h		1 h		6 h	
	Median SBA	No. (%) sera with SBA ≥1:8	Median SBA	No. (%) sera with SBA ≥1:8	Median SBA	No. (%) sera with SBA ≥1:8	Median SBA	No. (%) sera with SBA ≥1:8
Cefotaxime	$<\frac{1}{2}$	$\frac{16}{60}$ (27)	$<\frac{1}{2}$	$\frac{13}{60}$ (22)	$\frac{1}{2}$	$\frac{1}{60}$ (2)	$<\frac{1}{2}$	$\frac{0}{60}$ (0)
Moxalactam	$\frac{1}{8}$	$\frac{36}{60}$ (60)	$\frac{1}{2}$	$\frac{18}{60}$ 30	$\frac{1}{2}$	$\frac{5}{60}$ (8)	$<\frac{1}{2}$	$\frac{0}{60}$ (0)
Tobramycin	$\frac{1}{4}$	$\frac{58}{120}$ (48)	$<\frac{1}{2}$	$\frac{26}{120}$ (22)	$\frac{1}{8}$	$\frac{85}{120}$ (71)	$<\frac{1}{2}$	$\frac{8}{120}$ (7)
Cefotaxime + tobramycin	$\frac{1}{8}$	$\frac{30}{60}$ (50)	$<\frac{1}{2}$	$\frac{10}{60}$ (17)	$\frac{1}{8}$	$\frac{45}{60}$ (75)	$<\frac{1}{2}$	$\frac{4}{60}$ (7)
Moxalactam + tobramycin	$\frac{1}{16}$	$\frac{52}{60}$ (87)	$\frac{1}{4}$	$\frac{27}{60}$ (45)	$\frac{1}{8}$	$\frac{43}{60}$ (72)	$<\frac{1}{2}$	$\frac{7}{60}$ (12)

[a] $P < 0.001$ by chi-square test.
[b] $P < 0.02$.

mycin (7) is closer to that of moxalactam than to that of cefotaxime, and this may account for the persistence of a similar proportion of these two drugs in serum after intravenous administration of the drugs in combination. Since this situation might be favorable for the maintenance of antibiotic synergism, this possibly could explain the higher SBA for moxalactam plus tobramycin compared with cefotaxime plus tobramycin both at 1 and 6 h after infusion, although it is also possible that this is due to the more potent interaction of the former antibiotics. The SBA of moxalactam against *Pseudomonas* obtained in this series was reasonable in that 60% of specimens were ≥1:8 (5). This might be expected to increase at higher dosage levels. These results suggest that moxalactam might be useful in the treatment of gram-negative rod bacteremia, including those due to *P. aeruginosa*.

The antistaphylococcal activity of cefotaxime and moxalactam was less than anticipated despite reasonable in vitro susceptibility. Most of the antistaphylococcal activity of these drugs in combination with tobramycin was due to tobramycin. From these data it would be unlikely that moxalactam or cefotaxime used alone would be adequate empirical therapy in immunocompromised patients at high risk of staphylococcal infection. The addition of another antibiotic to moxalactam, such as an aminoglycoside, also might prevent the emergence of resistant strains during therapy (A. de Maria, S. Alvarez, and W. R. McCabe, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 20th, New Orleans, La., abstr. no. 723, 1980).

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