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NOTES

In Vitro Activities of Aztreonam, Piperacillin, and Ticarcillin Combined with Amikacin Against Amikacin-Resistant *Pseudomonas aeruginosa* and *P. cepacia* Isolates from Children with Cystic Fibrosis

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Amikacin, combined with aztreonam, piperacillin, or ticarcillin, synergistically inhibited amikacin-resistant sputum isolates of *Pseudomonas aeruginosa* and *P. cepacia* from children with cystic fibrosis. Ticarcillin-amikacin was the least active combination. Aminoglycoside resistance should not preclude the use of β-lactam–aminoglycoside combinations in the treatment of pulmonary infections in cystic fibrosis.

Aztreonam is a new monobactam antibiotic with a spectrum of activity directed primarily against aerobic gram-negative bacilli. In particular, this agent is effective against species of *Pseudomonas*, an organism often responsible for pulmonary exacerbations of cystic fibrosis (2–5, 7). In vitro studies have demonstrated that several new β-lactam agents alone and in combination with aminoglycosides are bactericidal against pulmonary isolates of *Pseudomonas aeruginosa* from children with cystic fibrosis (6). The purpose of this study was to compare the in vitro inhibitory activity of aztreonam, piperacillin, and ticarcillin alone and combined with amikacin against amikacin-resistant sputum isolates of *P. aeruginosa* and *P. cepacia* from children with cystic fibrosis.

Twenty-two strains of *P. cepacia* and 22 strains of *P. aeruginosa* that were not inhibited by 64 μg of amikacin per ml were isolated from children with cystic fibrosis. The test organisms were incubated overnight in Mueller-Hinton broth. Separate Mueller-Hinton agar plates contained 0.5 to 64 μg of each β-lactam antibiotic per ml alone and combined with 16 or 32 μg of amikacin per ml. The overnight cultures were diluted to a McFarland 0.5 standard, and the plates were inoculated with a Steers replicator, yielding 10^4 CFU per spot. The plates were incubated at 37°C for 24 h before interpretation. Synergy was defined as a fourfold or greater decrease in the MIC of the β-lactam combined with amikacin when compared with the MIC of the β-lactam antibiotic alone.

Ninety percent of the *P. cepacia* isolates were inhibited by 32 or 64 μg of piperacillin or aztreonam per ml, respectively. All three drugs at 64 μg/ml did not inhibit the growth of 90% of the *P. aeruginosa* strains. Of all *Pseudomonas* isolates tested, 81.8% were inhibited by 16 μg or less of aztreonam per ml when combined with 32 μg of amikacin per ml (Table 1). Of the *P. aeruginosa* strains, 13.6% were susceptible to piperacillin alone and 50% were susceptible to the piperacillin-amikacin combination. Synergy between amikacin and aztreonam or piperacillin was noted in slightly fewer than half of all the *Pseudomonas* isolates tested. Amikacin was synergistic with ticarcillin against 13 and 41% of the strains of *P. cepacia* and *P. aeruginosa*. An increased percentage of *P. aeruginosa* isolates was inhibited synergistically by the higher concentration of amikacin combined with either aztreonam or ticarcillin. No antagonism was observed.

Amikacin interacted synergistically with aztreonam, piperacillin, and ticarcillin against amikacin-resistant pulmonary isolates of *P. aeruginosa* and *P. cepacia*. The described method for determining antimicrobial synergy was a modification of the method outlined by Berenbaum (1). Instead of using two agents with intrinsic antimicrobial activity against the test organisms, we selected isolates for resistance to one

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TABLE 1. In vitro activity of aztreonam, piperacillin, and ticarcillin alone and combined with amikacin against 44 *Pseudomonas* isolates

Antibiotic	*P. cepacia* (*n* = 22)				*P. aeruginosa* (*n* = 22)			
	% Susceptible[a]		% Synergy at amikacin concn (μg/ml) of:		% Susceptible[a]		% Synergy at amikacin concn (μg/ml) of:	
	β-Lactam	Combination	16	32	β-Lactam	Combination	16	32
Aztreonam	22.7	81.8	41	41	50	81.8	9	45
Piperacillin	86.3	100	45	45	13.6	50	50	50
Ticarcillin	0	4.5	13	13	4.5	40.9	26	41

[a] Inhibited by 16 μg or less of aztreonam, piperacillin, or ticarcillin per ml.

of the drugs studied, amikacin. Four-fold suppression of the MIC by the drug combination as compared with the MIC for the β-lactam alone strongly suggested synergism between aztreonam, piperacillin, or ticarcillin and amikacin against *P. cepacia* and *P. aeruginosa*. Using the microbroth checkerboard method and 60 amikacin-susceptible isolates of *P. aeruginosa* from children with cystic fibrosis, Scribner and his associates noted synergy between amikacin and piperacillin or ticarcillin for 53.3 and 46.7% of the strains tested (6). This observation is similar to the results reported here, supporting the use of the method described in this study. Although it is unrealistic to extrapolate these data to achievable pulmonary concentrations of the drugs tested, it is suggested that the use of aztreonam, piperacillin, or ticarcillin in combination with amikacin may be useful in treating children with pulmonary exacerbations of cystic fibrosis.

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