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Comparative In Vitro Activity of Moxalactam, Cefotaxime, Cefoperazone, Piperacillin, and Aminoglycosides Against Gram-Negative Bacilli

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The in vitro activities of four new beta-lactam antimicrobial agents (moxalactam, cefotaxime, cefoperazone, and piperacillin) and the aminoglycosides against 744 recent clinical isolates of facultative gram-negative bacilli were compared simultaneously by the agar dilution method. The major in vitro difference of these newer beta-lactam compounds appeared to be their antipseudomonal activity; cefoperazone was the most active, whereas cefotaxime had the least potency. The aminoglycosides, however, had the most effective in vitro activity on a weight basis against *Pseudomonas aeruginosa*.

Moxalactam, cefotaxime, cefoperazone, and piperacillin are four new beta-lactam antibiotics developed in the past few years with a wide spectrum of activity against gram-negative bacilli. Preliminary testing has suggested that these new beta-lactam antibiotics possess a broad spectrum of in vitro activity against most clinically important gram-negative bacteria, including *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Enterobacter* species, and *Bacteroides fragilis*. Indeed, the potential clinical usefulness of these new beta-lactam antibiotics appears to be related to a wider spectrum of activity than other beta-lactam antibiotics and lower toxicity than the aminoglycoside drugs. Several previous in vitro studies (1, 5, 8, 10, 11, 14) have compared each of these newly developed compounds individually with the older beta-lactam antibiotics, but there is relatively little information on the comparative in vitro activity of all four drugs tested simultaneously against recent clinical isolates of gram-negative bacilli (2, 6, 9, 15). For these reasons, we conducted in vitro susceptibility tests on 744 recent clinical isolates of gram-negative bacilli to moxalactam, cefotaxime, cefoperazone, piperacillin, and the aminoglycosides (gentamicin, tobramycin, and amikacin).

All organisms used in this study were recently cultured from clinical material at the Clinical Microbiology Laboratories of the University of California at Los Angeles Center for the Health Sciences and identified by standard criteria (4, 7, 12). The standard reference strains of *Escherichia coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 (Boston strain) were used as internal controls. Standard powders of the antimicrobial agents were provided as follows: moxalactam (lot no. S1-1139G; potency, 1,000 μg/mg) and tobramycin (lot no. S1-368T; potency, 1,000 μg/mg), Eli Lilly & Co., Indianapolis, Ind.; cefotaxime (lot no. RP1672; potency, 1,000 μg/mg), Hoechst-Roussel Pharmaceuticals, Inc., Somerville, N.J.; cefoperazone (lot no. I114; potency, 936 μg/mg), Pfizer Pharmaceuticals, New York, N.Y.; gentamicin (lot no. GMC-5-M6123; potency, 568 μg/mg), Schering Corp., Bloomfield, N.J.; and amikacin (lot no. F8653; potency, 862 μg/mg), Bristol Laboratories, Syracuse, N.Y. Antimicrobial susceptibility testing was performed by the International Collaborative Study-World Health Organization agar dilution method (3, 13). Mueller-Hinton agar containing twofold increments of each antimicrobial agent was used. The following ranges of drug concentrations (in micrograms per milliliter) were tested: moxalactam, 0.5 to 32; cefotaxime, 0.5 to 32; cefoperazone, 0.5 to 32; piperacillin, 8.0 to 256; gentamicin, 0.25 to 8; tobramycin, 0.25 to 8; and amikacin, 2.0 to 32. An inoculum of approximately 10^4 organisms diluted from broth cultures in the logarithmic phase of growth was used.

The minimum inhibitory concentrations (MICs) of moxalactam, cefotaxime, cefoperazone, piperacillin, and the aminoglycosides against facultative gram-negative bacilli are shown in Table 1. Cefoperazone was the most active of the four new beta-lactam antibiotics against *P. aeruginosa*. Of the *P. aeruginosa* isolates, 88 and 93% were inhibited by 16 and 32 μg of cefoperazone per ml, respectively, whereas only 70 and 81% of the *P. aeruginosa* strains were inhibited by 16 and 32 μg of mox-

TABLE 1. *Comparative MICs of seven antibiotics for aerobic gram-negative bacilli*

Organism[a]	Antibiotic	MIC (μg/ml) at % inhibition:	
		50	90
P. aeruginosa (150)	Moxalactam	16	>32
	Cefotaxime	>32	>32
	Cefoperazone	8.0	32
	Piperacillin	8.0	64.0
	Gentamicin	4.0	4.0
	Tobramycin	1.0	1.0
	Amikacin	2.0	8.0
E. coli (356)	Moxalactam	0.5	0.5
	Cefotaxime	0.5	0.5
	Cefoperazone	0.5	2.0
	Piperacillin	8.0	256
	Gentamicin	1.0	4.0
	Tobramycin	1.0	4.0
	Amikacin	2.0	4.0
K. pneumoniae (99)	Moxalactam	0.5	0.5
	Cefotaxime	0.5	0.5
	Cefoperazone	0.5	8.0
	Piperacillin	8.0	64.0
	Gentamicin	1.0	1.0
	Tobramycin	1.0	1.0
	Amikacin	2.0	2.0
E. cloacae (31)	Moxalactam	0.5	0.5
	Cefotaxime	2.0	16.0
	Cefoperazone	0.5	2.0
	Piperacillin	8.0	8.0
	Gentamicin	1.0	1.0
	Tobramycin	1.0	1.0
	Amikacin	2.0	4.0
E. aerogenes (18)	Moxalactam	0.5	8.0
	Cefotaxime	0.5	>32
	Cefoperazone	0.5	16
	Piperacillin	8.0	8.0
	Gentamicin	1.0	1.0
	Tobramycin	1.0	1.0
	Amikacin	2.0	4.0
S. marcescens (15)	Moxalactam	0.5	8.0
	Cefotaxime	0.5	2.0
	Cefoperazone	2.0	8.0
	Piperacillin	8.0	8.0
	Gentamicin	1.0	4.0
	Tobramycin	4.0	4.0
	Amikacin	4.0	16.0
Proteus mirabilis (35)	Moxalactam	0.5	0.5
	Cefotaxime	0.5	0.5
	Cefoperazone	0.5	0.5
	Piperacillin	8.0	8.0
	Gentamicin	1.0	4.0
	Tobramycin	1.0	4.0
	Amikacin	2.0	8.0
Indole-positive *Proteus* spp. (18)	Moxalactam	0.5	0.5
	Cefotaxime	0.5	8.0
	Cefoperazone	2.0	8.0
	Piperacillin	8.0	8.0
	Gentamicin	1.0	1.0

TABLE 1—*Continued*

Organism[a]	Antibiotic	MIC (μg/ml) at % inhibition:	
		50	90
	Tobramycin	1.0	4.0
	Amikacin	2.0	4.0
C. freundii (12)	Moxalactam	0.5	0.5
	Cefotaxime	0.5	2.0
	Cefoperazone	0.5	2.0
	Piperacillin	8.0	8.0
	Gentamicin	0.25	0.25
	Tobramycin	1.0	4.0
	Amikacin	2.0	4.0
A. calcoaceticus (10)	Moxalactam	32	>32
	Cefotaxime	>32	>32
	Cefoperazone	32	>32
	Piperacillin	8.0	64
	Gentamicin	1.0	>8
	Tobramycin	1.0	>8
	Amikacin	2.0	32

[a] Number of isolates tested is shown within parentheses.

alactam per ml, respectively. Somewhat surprisingly, cefotaxime had very little activity against the *P. aeruginosa* isolates tested in this study (only 5% were inhibited by 32 μg of cefotaxime per ml). Piperacillin inhibited 79 and 98% of the *P. aeruginosa* isolates at concentrations of 8 and 64 μg/ml, respectively. The three aminoglycosides were generally four- to eightfold more active on a weight basis against *P. aeruginosa* than the beta-lactam compounds. Most *Enterobacteriaceae* were susceptible to all four beta-lactam drugs, although piperacillin had the poorest activity against *E. coli* and *K. pneumoniae*, and cefotaxime was the least-active agent for *Enterobacter cloacae* and *Enterobacter aerogenes*. Overall, moxalactam was the most active of the beta-lactam antibiotics against the *Enterobacteriaceae* and was as active as the aminoglycosides against these same organisms. Similarly, moxalactam was somewhat more active against indole-positive *Proteus* spp. and *Citrobacter freundii* than cefotaxime, cefoperazone, and piperacillin. Piperacillin and amikacin were the most active antimicrobial agents tested against *Acinetobacter calcoaceticus*.

This study demonstrates that moxalactam, cefotaxime, cefoperazone, and piperacillin are highly active against most clinically important bacterial strains isolated from patients at a large university hospital. Moxalactam, cefotaxime, and cefoperazone inhibited 90% or more of the strains of *E. coli*, *K. pneumoniae*, *Enterobacter* species, *S. marcescens*, *Proteus* species, and *C. freundii* at 16 μg/ml, and most were inhibited by 8 μg/ml. Except for *E. coli*, piperacillin inhibited 90% of these same organisms at 64 μg/ml. Moxalactam was the most active of the beta-lactam antibiotics against the *Enterobacteriaceae* and inhibited most strains at 0.5 μg/ml. In general, except for *P. aeruginosa*, moxalactam's in vitro activity was comparable to that of the aminoglycosides.

P. aeruginosa isolates were less susceptible to the beta-lactam antibiotics. Indeed, cefotaxime had relatively little antipseudomonal activity and inhibited only 5% of the *P. aeruginosa* isolates at 32 μg/ml. These results are somewhat surprising in view of cefotaxime's favorable antipseudomonal activity reported by others (2, 6, 10, 15). Regional variations in the susceptibility patterns of bacterial isolates as well as the recovery of many of our *P. aeruginosa* isolates from a large population of immunocompromised patients commonly infected with more resistant organisms may account for some of these differences. Cefoperazone, a cephalosporin analog of piperacillin, was twofold more active than moxalactam or piperacillin for *P. aeruginosa* and was the most active beta-lactam agent for *P. aeruginosa*. Similar results favoring cefoperazone over moxalactam, cefotaxime, and piperacillin for *P. aeruginosa* have been reported by Neu et al. (10) and Hall et al. (6). However, the aminoglycosides were still 4- to 8-fold more active than cefoperazone for the *P. aeruginosa* isolates in our study.

We did not perform comparative susceptibility tests with gram-positive organisms and anaerobes in this study, but other investigators (6, 8, 10) have shown that *Staphylococcus aureus* and facultative streptococci usually require MICs of 2 to 8 μg of moxalactam, cefotaxime,

and cefoperazone per ml, and that *Streptococcus faecalis* isolates are invariably resistant to these antimicrobial agents (MIC > 32 μg/ml). In contrast, piperacillin usually inhibits most *S. faecalis* strains but lacks activity against *Staphylococcus aureus* (14). Previous comparative anaerobic susceptibility tests suggest that moxalactam's activity against *B. fragilis* is superior to that of cefotaxime, cefoperazone, cefoxitin, and other cephalosporins (2).

In summary, our results show that cefoperazone was the most active of the beta-lactam antibiotics against *P. aeruginosa*. Moxalactam had the greatest activity on a weight basis against the *Enterobacteriaceae* and was comparable to the aminoglycosides against these same organisms. The significance of these relative differences of in vitro activity, however, must await carefully conducted comparative clinical trials.

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