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In Vitro Comparison of Third-Generation Cephalosporins, Piperacillin, Dibekacin, and Other Aminoglycosides Against Aerobic Bacteria

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The in vitro activities of four new beta-lactam antibiotics and dibekacin against aerobic bacteria were compared. The new cephalosporins were more broadly active against gram-negative bacteria than were presently available cephalosporins, but were less active against staphylococci.

Recently, a number of "third-generation" cephalosporins and new semisynthetic penicillins have become available for clinical testing. This study compares the in vitro activity of some of the new oxycephalosporins and piperacillin with existing beta-lactam antibiotics, gentamicin, and amikacin. In addition, the aminoglycoside dibekacin, a dideoxykanamycin B which has been used extensively in Japan and will be shortly undergoing clinical trials in the United States, was included in the comparison.

A total of 134 clinical isolates were tested. All strains were recently isolated from patients at San Francisco General Hospital Medical Center. Isolates were cultured and maintained on nutrient agar slants at 2°C. Antibiotic powders were kindly provided by the following manufacturers: moxalactam (LY127935) from Eli Lilly & Co., cefotaxime (HR756) from Hoechst-Roussel Pharmaceuticals, cefoperazone (T1551) from Pfizer Pharmaceuticals, piperacillin from Lederle Laboratories, and dibekacin and gentamicin from USV Pharmaceutical Corporation. The remaining drugs were purchased from the manufacturers.

Minimum inhibitory concentrations (MICs) were determined by the microtiter technique (1), using the Dynatech MIC-2000 system (Dynatech Laboratories, Inc., Alexandria, Va.). An inoculum of 5×10^5 colony-forming units per ml was used. Dilutions were prepared in Mueller-Hinton broth (BBL Microbiology Systems, Cockeysville, Md.). The aminoglycoside dilution mixture was supplemented with 50 mg of calcium per liter and 20 mg of magnesium per liter. Plates were incubated at 35°C for 18 h.

The results are shown in Tables 1 and 2. Against *Staphylococcus aureus*, cephalothin, cefamandole, and the aminoglycosides were the most active drugs. Cefoxitin and the third-generation cephalosporins had high MICs for staphylococci, and these differences were magnified

TABLE 1. *In vitro comparison of antimicrobial agents*[a]

Organism	No. of isolates	Moxalactam			Cefoperazone			Cefotaxime
		Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range
S. aureus	11	8–128	16	128	2–>256	2	32	2–>128
S. aureus (methicillin resistant)	14	32–>256	64	>256	32–>256	32	>256	4–>128
S. faecalis	13	0.06–>256	>256	>256	0.5–16	16	16	0.06–>128
E. coli	13	≤0.06–0.5	≤0.06	0. 5	≤0.06–16	0.25	8	≤0.06–0.12
Proteus mirabilis	12	≤0.06–0.25	≤0.06	0.25	0.25–2	0.5	1	≤0.06
Proteus spp. (indole positive)	6	≤0.06–25	0.125	0.125	0.125–2	0.5	1	≤0.06
Enterobacter spp.	14	≤0.06–64	0.25	64	<0.06–8	0.25	8	≤0.06–8
K. pneumoniae	14	≤0.06–0.25	0.12	0.25	0.12–4	0.25	1	≤0.06
S. marcescens	10	0.25–8	1	4	0.5–>256	>256	>256	0.25–4
Citrobacter sp.	7	≤0.06–0.5	≤0.06	0.5	0.12–1	0.25	0.5	≤0.06–0.12
P. aeruginosa	15	0.12–128	32	64	0.12–32	4	16	≤0.06–64
Pseudomonas spp./ *Acinetobacter* spp.	5	32–64	64	64	8–>256	64	>256	0.12–16

[a] MICs given in micrograms per milliliter; MIC_{50}, MIC for 50% of strains tested; MIC_{90}, MIC for 90% of strains tested.

with methicillin-resistant *S. aureus*, such that many of the MICs, determined at 24 and 48 h, were well above expected serum levels. Against *Streptococcus faecalis*, piperacillin had significant activity, whereas cefoperazone was the most effective cephalosporin tested (2).

Against *Escherichia coli* and *Klebsiella pneumoniae*, moxalactam and cefotaxime were the most active agents. All drugs were satisfactory, except carbenicillin. As expected, *Enterobacter* spp. showed a significant degree of resistance to first- and second-generation cephalosporins (cephalothin, cefamandole, and cefoxitin). All of the other agents tested showed good activity, in contrast to the results of some investigators who have shown cefoperazone to be only moderately active against *Enterobacter* spp. (3). The lowest MICs against these organisms were achieved by the aminoglycosides, but all of the beta-lactam drugs had MICs which were substantially below the achievable peak serum concentrations. *Serratia marcescens* isolates were frequently resistant to the agents tested. Moxalactam and cefotaxime were active against most gram-negative strains. Both indole-positive *Proteus* spp. and *Proteus mirabilis* were only marginally susceptible to cephalothin, cefamandole, and cefoxitin, but all of the other agents tested were effective. Again, moxalactam and cefotaxime were the most active overall against these organisms. Against *Pseudomonas aeruginosa*, piperacillin, dibekacin, and amikacin had the lowest MICs, but since the serum levels of piperacillin that can be achieved are substantially higher than the aminoglycosides, the therapeutic ratio here is likely to favor piperacillin. Moxalactam and cefotaxime were significantly active against all *Enterobacteriaceae* tested. As has been reported previously, cephalothin, cefoxitin, and cefamandole were not significantly active against *P. aeruginosa* (4).

Dibekacin was two to four times more active against *Pseudomonas* spp. than was gentamicin or amikacin, but was two to four times less active against *Enterobacteriaceae* than was gentamicin (4, 5). In this respect, its in vitro activity is quite similar to that of tobramycin; however, in contrast to tobramycin, dibekacin had excellent activity against our strains of methicillin-resistant *S. aureus* which by Kirby Bauer disk agar diffusion had no zone of inhibition around the disk containing 10 μg of tobramycin.

Piperacillin was clearly more active than carbenicillin, based on in vitro testing. Nonetheless, there are many piperacillin-resistant strains of *S. marcescens*, and this drug is not effective against staphylococci because of its susceptibility to staphylococcal penicillinase. Of the cephalosporins tested, cefoperazone was the most active against *P. aeruginosa* and *S. faecalis* and, in addition, had significant activity against all other aerobic gram-negative rods, except for *S. marcescens*. Moxalactam and cefotaxime had the lowest overall MICs for all aerobic gram-negative rods, although their activity against *P. aeruginosa* and *S. faecalis* was less than that of piperacillin or cefoperazone.

In conclusion, moxalactam, cefotaxime, cefoperazone, and piperacillin have a broader spectrum than presently available beta-lactam antibiotics based on in vitro testing (4, 6, 7), and if this advantage holds up on clinical testing, these drugs will have important advantages over available agents. Dibekacin appears to be similar in its in vitro activity to gentamicin and amikacin and would not appear to offer any therapeutic advantage unless it is less toxic than other aminoglycosides tested.

Cefotaxime		Cefamandole			Cefoxitin			Cephalothin		
MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}
2	32	0.5–16	0.5	8	4–32	4	32	0.5–32	0.5	2
16	32	2–6	8	16	16–128	32	>128	1–64	4	8
>128	>128	0.06–32	32	32	2–>128	>128	>128	4–32	16	32
≤0.06	0.12	0.25–32	1	16	2–8	4	8	4–32	8	32
≤0.06	0.06	0.25–16	0.5	16	1–8	4	4	2–>256	2	>256
≤0.06	≤0.06	≤0.06–>256	16	128	2–8	4	8	8–>256	>256	>256
0.25	8	0.5–>256	8	>256	16–>128	128	128	64–>256	128	>256
≤0.06	≤0.06	0.5–4	1	2	2–8	4	4	1–4	2	2
0.5	2	16–>256	128	>256	8–128	32	64	>256	>256	>256
0.12	0.12	0.5–1	0.5	1	2–64	16	16	2–32	16	32
16	32	4–>256	>256	>256	4–>128	>128	>128	>256	>256	>256
8	16	≤0.06–128	64	128	0.5–>128	64	128	1–>256	>256	>256

TABLE 2. *In vitro comparison of antimicrobial agents*[a]

Organism	No. of isolates	Piperacillin			Carbenicillin			Dibekacin			Gentamicin			Amikacin		
		Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}
S. aureus	11	0.5->256	8	>256	1->256	16	>256	0.06–2	0.12	1	0.06–0.12	0.12	0.12	0.5–4	0.5	4
S. aureus (methicillin resistant)	14	32->256	>256	>256	32->256	>256	>256	1–4	2	2	0.06–0.12	0.12	0.12	4	4	4
S. faecalis	13	≤0.25–4	4	4	2–64	64	64	1–16	8	8	0.5–16	4	8	1->64	>64	>64
E. coli	13	0.5–8	2	8	2->256	16	>256	0.5–16	1	4	0.25–16	0.5	2	0.5–16	1	4
P. mirabilis	12	<0.25–4	0.5	1	0.5->256	2	2	0.25–1	1	1	0.25–1	0.5	1	0.5–4	1	1
Proteus spp. (indole positive)	6	≤0.25–0.5	≤0.25	0.5	1–32	1	4	0.25–4	1	1	0.25–1	0.5	0.5	0.5–1	0.5	1
Enterobacter spp.	14	1–16	2	16	2–64	8	32	0.25–1	0.5	1	0.12–1	0.25	0.5	0.5–4	1	4
K. pneumoniae	14	1–16	4	8	>256	>256	>256	0.12–4	1	1	0.12–1	0.25	0.5	0.25–2	1	2
S. marcescens	10	1->256	32	>256	4->256	>256	>256	0.5->64	>64	>64	0.25->64	>64	>64	1–32	2	16
Citrobacter sp.	7	1–4	2	2	2->256	4	>256	0.12–1	0.5	1	0.12–0.25	0.25	0.25	0.5–1	1	1
P. aeruginosa	15	1–8	4	8	4->256	64	>256	0.5->64	2	8	0.25->64	4	16	0.5–32	4	8
Pseudomonas spp./ *Acinetobacter* spp.	5	2–6	16	16	2–32	32	32	0.5–2	1	2	0.5–2	1	2	1–8	2	8

[a] See footnote *a* of Table 1.

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