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Comparative In Vitro Activities of Cefpiramide and Apalcillin Individually and in Combination

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The in vitro activities of cefpiramide and apalcillin were compared with those of other third-generation cephalosporins and extended-spectrum penicillins against over 1,000 clinical bacterial isolates. The activity of cefpiramide against *Pseudomonas aeruginosa* was comparable to those of piperacillin and cefoperazone, inhibiting 90% of strains at concentrations ≤16.0 μg/ml. This drug was also active against a broad range of gram-negative organisms but was generally less active than many of the other cephalosporins tested against members of the family *Enterobacteriaceae*. The activity of cefpiramide against gram-positive organisms was comparable to that of cefoperazone. Apalcillin, along with ceftazidime, was the most active agent tested against *P. aeruginosa* and *Acinetobacter calcoaceticus* subsp. *anitratus*, inhibiting 90% of these strains at concentrations ≤8 μg/ml. Against other gram-negative and gram-positive organisms, its activity was similar to that of piperacillin. The activities of both cefpiramide and apalcillin were significantly reduced by the presence of several plasmid-mediated β-lactamases in a series of otherwise isogenic strains of *P. aeruginosa* in comparison with their activities against a parent strain which lacks these enzymes. Many strains of *Enterobacter cloacae* were synergistically inhibited by the combination of gentamicin with either cefpiramide (5 of 10 strains) or apalcillin (6 of 10 strains). Most strains of *P. aeruginosa* were synergistically inhibited by the combination of gentamicin with either cefpiramide (8 of 10 strains) or apalcillin (10 of 10 strains). However, cefoxitin antagonized the activity of both cefpiramide and apalcillin against most of these same strains.

Cefpiramide (SM-1652, WY-44,635) is a new semisynthetic cephalosporin that is structurally related to cefoperazone. A number of recent studies have documented its broad spectrum of activity against both gram-negative and gram-positive organisms. Compared with other cephalosporins, it is particularly active against *Pseudomonas aeruginosa* (6, 8, 14). In addition, cefpiramide has a half-life of approximately 4.5 h in humans, which is significantly longer than those of other third-generation cephalosporins, such as ceftazidime and cefoperazone, but shorter than that of ceftriaxone (10).

Apalcillin (PC-904) is a naphthyridine derivative of ampicillin. Its spectrum of activity is similar to that of piperacillin, although it exhibits greater activity against *P. aeruginosa* than does piperacillin (1, 5, 12, 13). Apalcillin also differs from piperacillin in having a slightly longer half-life and in being largely eliminated by hepatobiliary mechanisms (9).

In the present study, we examined the in vitro activity of both cefpiramide and apalcillin against more than 1,000 routine clinical isolates of gram-positive and gram-negative bacteria as well as organisms selected for resistance to multiple antibiotics. The activity of these two agents was also tested in combination with other β-lactams and gentamicin.

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MATERIALS AND METHODS

Bacterial strains. Gram-negative bacteria used in this study were routine clinical isolates recently collected (1983 to 1984) from the New England Deaconess Hospital and the Massachusetts General Hospital, Boston. The organisms collected were isolated from multiple body sites including urine, sputum, blood, feces, wounds, and cerebrospinal fluid. Duplicate isolates from individual patients were excluded, but otherwise isolates were unselected. β-Lactamase-producing strains of *Neisseria gonorrhoeae* were kindly provided by Clyde Thornsberry (Centers for Disease Control, Atlanta, Ga.).

Routine gram-positive isolates had been collected earlier at the Massachusetts General Hospital. Penicillin-resistant pneumococci and viridans group streptococci were obtained as previously reported (3, 4). In certain specified studies, multiply resistant gram-negative bacilli were used from our collection established over the past 5 to 10 years. The following MIC criteria were used for defining resistance: amikacin, ≥32 μg/ml; gentamicin, ≥8 μg/ml; carbenicillin, ≥32 μg/ml (≥250 μg/ml for *P. aeruginosa*); cephalothin, ≥32 μg/ml; cefamandole, ≥32 μg/ml; and cefoxitin, ≥32 μg/ml (11). *P. aeruginosa* transconjugants containing various defined plasmid-mediated β-lactamases were provided by George Jacoby (Massachusetts General Hospital) and have been described previously (2).

Antimicrobial agents. Standard antimicrobial reference powders were obtained from the following sources: apalcillin and cefpiramide, Wyeth Laboratories, Inc., Philadelphia, Pa.; piperacillin, Lederle Laboratories, Pearl River, N.Y.; moxalactam, cefamandole, and cephalothin, Eli Lilly & Co., Indianapolis, Ind.; imipenem and cefoxitin, Merck Sharp & Dohme, Rahway, N.J.; aztreonam, E. R. Squibb & Sons,

TABLE 1. Comparative in vitro activities of cefpiramide and apalcillin

Organism (no. of isolates)	Antibiotic	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
Pseudomonas aeruginosa (90)	Cefpiramide	0.25–>128	4	16
	Apalcillin	≤0.06–>128	2	8
	Piperacillin	0.5–>128	8	16
	Azlocillin	1.0–>128	16	32
	Aztreonam	0.25–128	8	32
	Cefoperazone	2.0–>128	8	32
	Ceftriaxone	8.0–>128	64	>128
	Ceftazidime	1.0–>128	2	8
	Cefsulodin	1.0–128	8	32
	Gentamicin	0.5–>128	4	8
Pseudomonas cepacia (10)	Cefpiramide	1.0–>128	65	>128
	Apalcillin	1.0–>128	16	>128
	Piperacillin	0.5–>128	32	>128
	Aztreonam	2.0–>128	64	>128
	Cefoperazone	8.0–>128	128	>128
	Ceftriaxone	0.5–32	0.5	16
	Ceftazidime	0.5–16	2	16
	Gentamicin	1.0–>128	32	>128
Pseudomonas fluorescens/putida (10)	Cefpiramide	8.0–32	16	16
	Apalcillin	2.0–8	4	4
	Piperacillin	2.0–32	8	16
	Aztreonam	32.0–128	64	>128
	Cefoperazone	8.0–64	8	16
	Ceftriaxone	16.0–128	16	128
	Ceftazidime	1.0–16	2	16
	Gentamicin	≤0.06–>128	0.25	1
Pseudomonas maltophilia (20)	Cefpiramide	2.0–128	32	64
	Apalcillin	2.0–>128	32	128
	Piperacillin	32.0–>128	128	>128
	Aztreonam	8.0–>128	128	>128
	Cefoperazone	8.0–>128	32	64
	Ceftriaxone	32.0–>128	>128	>128
	Ceftazidime	2.0–>128	8	128
	Gentamicin	1.0–>128	32	>128
Acinetobacter calcoaceticus subsp. *antiratus* (30)	Cefpiramide	4.0–128	32	64
	Apalcillin	4.0–16	8	8
	Piperacillin	2.0–>128	16	32
	Aztreonam	8.0–>128	32	64
	Cefoperazone	16.0–>128	64	>128
	Ceftriaxone	2.0–64	16	16
	Ceftazidime	4.0–32	4	8
	Gentamicin	0.25–64	1	2
Aeromonas hydrophila (10)	Cefpiramide	1.0–32	2	8
	Apalcillin	2.0–128	4	8
	Piperacillin	1.0–128	2	4
	Aztreonam	≤0.06–0.25	≤0.06	≤0.06
	Cefoperazone	0.25–8	0.5	2
	Ceftriaxone	≤0.06–4	0.5	4
	Ceftazidime	0.125–2	0.25	1
	Gentamicin	0.25–2	0.25	1
Haemophilus influenzae (β-lactamase negative) (20)	Cefpiramide	≤0.06–0.5	0.125	0.250
	Apalcillin	≤0.06–2	0.25	0.5
	Piperacillin	≤0.06–0.5	≤0.06	0.125
	Aztreonam	≤0.06–0.25	≤0.06	≤0.06
	Cefoperazone	≤0.06–0.125	≤0.06	≤0.06
	Ceftriaxone	≤0.06	≤0.06	≤0.06
	Ceftazidime	≤0.06–0.5	0.125	0.125
	Gentamicin	0.25–8	2	4
Haemophilus influenzae (β-lactamase positive) (10)	Cefpiramide	1.0–4	2	2
	Apalcillin	128.0–>128	>128	>128
	Piperacillin	32.0–>128	128	>128

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TABLE 1—*Continued*

Organism (no. of isolates)	Antibiotic	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
	Aztreonam	≤0.06	≤0.06	≤0.06
	Cefoperazone	0.125–0.5	0.125	0.5
	Ceftriaxone	≤0.06	≤0.06	≤0.06
	Ceftazidime	≤0.06–0.125	0.125	0.125
	Gentamicin	2.0–4	2	4
Neisseria gonorrhoeae (β-lactamase negative) (10)	Cefpiramide	≤0.06–0.25	≤0.06	0.125
	Apalcillin	≤0.06–0.5	≤0.06	0.25
	Piperacillin	≤0.06–0.5	≤0.06	≤0.06
	Aztreonam	≤0.06–0.125	≤0.06	≤0.06
	Cefoperazone	≤0.06–0.25	≤0.06	≤0.06
	Ceftriaxone	≤0.06	≤0.06	≤0.06
	Ceftazidime	≤0.06–0.25	≤0.06	≤0.06
	Penicillin	≤0.06–0.125	≤0.06	≤0.06
Neisseria gonorrhoeae (β-lactamase positive) (8)	Cefpiramide	≤0.06–0.5	0.25	0.5
	Apalcillin	1.0–32	2	16
	Piperacillin	0.5–32	1	8
	Aztreonam	≤0.06–0.125	≤0.06	≤0.06
	Cefoperazone	≤0.06–0.25	0.125	0.25
	Ceftriaxone	≤0.06	≤0.06	≤0.06
	Ceftazidime	≤0.06	≤0.06	≤0.06
	Penicillin	1.0–64	8	64
Pasteurella multocida (10)	Cefpiramide	≤0.06–0.125	≤0.06	0.125
	Apalcillin	≤0.06	≤0.06	≤0.06
	Piperacillin	≤0.06–0.125	≤0.06	0.125
	Aztreonam	≤0.06	≤0.06	≤0.06
	Cefoperazone	≤0.06	≤0.06	0.125
	Ceftriaxone	≤0.06	≤0.06	≤0.06
	Ceftazidime	≤0.06–0.25	0.125	0.25
	Gentamicin	0.125–1	1	1
Citrobacter diversus (10)	Cefpiramide	0.125–2	0.5	2
	Apalcillin	1.0–8	4	8
	Piperacillin	1.0–8	4	8
	Aztreonam	≤0.06	≤0.06	≤0.06
	Cefoperazone	≤0.06–0.25	≤0.06	0.125
	Ceftriaxone	≤0.06–0.25	≤0.06	≤0.06
	Ceftazidime	≤0.06–0.125	≤0.06	≤0.06
	Gentamicin	≤0.06–1.0	0.25	0.5
Citrobacter freundii (40)	Cefpiramide	1.0–>128	4	>128
	Apalcillin	1.0–>128	2	>128
	Piperacillin	1.0–>128	4	128
	Aztreonam	≤0.06–64	0.125	32
	Cefoperazone	0.125–>128	0.5	128
	Ceftriaxone	≤0.06–128	0.125	64
	Ceftazidime	0.125–>128	0.5	128
	Gentamicin	0.25–64	0.5	1
Escherichia coli (90)	Cefpiramide	0.125–>128	1	32
	Apalcillin	0.5–>128	1	128
	Piperacillin	0.5–>128	2	128
	Aztreonam	≤0.06–0.25	≤0.06	0.125
	Cefoperazone	≤0.06–32	0.25	4
	Ceftriaxone	≤0.06	≤0.06	≤0.06
	Ceftazidime	≤0.06–0.5	0.125	0.25
	Gentamicin	0.25–2	0.5	1
Enterobacter spp. (90)	Cefpiramide	0.25–>128	4	128
	Apalcillin	0.5–>128	4	64
	Piperacillin	0.25–>128	4	32
	Aztreonam	≤0.06–64	≤0.06	16
	Cefoperazone	≤0.06–>128	0.5	16
	Ceftriaxone	≤0.06–>128	0.125	16
	Ceftazidime	≤0.06–128	0.25	32
	Gentamicin	0.25–1	0.5	0.5

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TABLE 1—*Continued*

Organism (no. of isolates)	Antibiotic	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
Klebsiella oxytoca (30)	Cefpiramide	1.0–>128	8	32
	Apalcillin	4.0–>128	8	16
	Piperacillin	1.0–>128	8	32
	Aztreonam	≤0.06–2	≤0.06	0.5
	Cefoperazone	0.125–>128	2	4
	Ceftriaxone	≤0.06–0.5	≤0.06	0.125
	Ceftazidime	≤0.06–0.5	0.125	0.125
	Gentamicin	0.25–1	0.5	0.5
Klebsiella pneumoniae (60)	Cefpiramide	0.125–64	2	16
	Apalcillin	0.5–64	8	16
	Piperacillin	1.0–64	4	32
	Aztreonam	≤0.06–0.5	≤0.06	≤0.06
	Cefoperazone	≤0.06–8	0.25	1
	Ceftriaxone	≤0.06–0.5	≤0.06	0.125
	Ceftazidime	≤0.06–4	0.25	4
	Gentamicin	0.25–8	0.5	1
Morganella morganii (30)	Cefpiramide	8.0–≤128	16	32
	Apalcillin	2.0–≤128	2	32
	Piperacillin	0.5–64	1	8
	Aztreonam	≤0.06–1	≤0.06	≤0.06
	Cefoperazone	0.5–32	1	4
	Ceftriaxone	≤0.06–1	≤0.06	0.125
	Ceftazidime	≤0.06–16	≤0.06	0.5
	Gentamicin	0.25–1	0.25	0.5
Proteus mirabilis (70)	Cefpiramide	1.0–128	8	8
	Apalcillin	0.25–>128	2	2
	Piperacillin	0.25–>128	0.5	1
	Aztreonam	≤0.06–0.125	≤0.06	≤0.06
	Cefoperazone	0.25–8	1	2
	Ceftriaxone	≤0.06–0.25	≤0.06	≤0.06
	Ceftazidime	≤0.06–2	≤0.06	≤0.06
	Gentamicin	0.125–8	1	2
Proteus vulgaris (20)	Cefpiramide	4.0–32	8	32
	Apalcillin	1.0–8	4	4
	Piperacillin	0.5–8	2	4
	Aztreonam	≤0.06	≤0.06	≤0.06
	Cefoperazone	0.5–8	2	4
	Ceftriaxone	≤0.06–1	0.25	0.5
	Ceftazidime	≤0.06–0.25	≤0.06	0.125
	Gentamicin	0.25–8	1	4
Providencia spp. (16)	Cefpiramide	4.0–128	4	128
	Apalcillin	1.0–>128	2	>128
	Piperacillin	0.5–>128	1	>128
	Aztreonam	≤0.06	≤0.06	≤0.06
	Cefoperazone	0.25–32	1	16
	Ceftriaxone	≤0.06–0.125	≤0.06	≤0.06
	Ceftazidime	≤0.06–2	0.125	1
	Gentamicin	0.125–32	0.5	16
Serratia marcescens (60)	Cefpiramide	8.0–>128	64	>128
	Apalcillin	1.0–>128	32	128
	Piperacillin	1.0–>128	8	64
	Aztreonam	≤0.06–>128	0.25	1
	Cefoperazone	1.0–>128	4	32
	Ceftriaxone	≤0.06–>128	0.5	8
	Ceftazidime	0.125–>128	0.25	2
	Gentamicin	0.5–64	1	32
Salmonella enteritidis (10)	Cefpiramide	4.0–>128	4	8
	Apalcillin	2.0–>128	2	8
	Piperacillin	2.0–>128	2	8
	Aztreonam	≤0.06–0.25	≤0.06	0.125
	Cefoperazone	0.5–32	0.5	2

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TABLE 1—*Continued*

Organism (no. of isolates)	Antibiotic	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
	Ceftriaxone	≤0.06–0.25	≤0.06	0.125
	Ceftazidime	0.25–1	0.5	0.5
	Gentamicin	0.25–1	0.5	1
Staphylococcus aureus (methicillin susceptible) (30)	Cefpiramide	2.0–4	2	4
	Apalcillin	2.0–128	8	64
	Piperacillin	1.0–128	16	128
	Aztreonam	>128	>128	>128
	Cefoperazone	2.0–8	4	8
	Ceftriaxone	2.0–4	4	4
	Ceftazidime	8.0–32	16	16
	Gentamicin	0.25–32	0.5	0.05
Staphylococcus aureus (methicillin resistant) (20)	Cefpiramide	16–128	64	128
	Apalcillin	64–>128	128	>128
	Piperacillin	128–>128	>128	>128
	Aztreonam	>128	>128	>128
	Cefoperazone	32–>128	128	>128
	Ceftriaxone	32–>128	>128	>128
	Ceftazidime	128–>128	>128	>128
	Gentamicin	0.25–128	64	64
Staphylococcus epidermidis (30)	Cefpiramide	0.25–8	2	8
	Apalcillin	≤0.06–64	2	32
	Piperacillin	≤0.06–64	2	64
	Aztreonam	128–>128	>128	>128
	Cefoperazone	0.5–8	2	8
	Ceftriaxone	0.5–>128	4	64
	Ceftazidime	2.0–64	8	64
	Gentamicin	≤0.06–128	0.125	32
Streptococcus faecalis (30)	Cefpiramide	8.0–32	16	32
	Apalcillin	2.0–8	4	4
	Piperacillin	2.0–8	4	4
	Aztreonam	>128	>128	>128
	Cefoperazone	16–64	32	64
	Ceftriaxone	128–>128	>128	>128
	Ceftazidime	>128	>128	>128
	Gentamicin	8.0–>128	16	32
Streptococcus pyogenes (10)	Cefpiramide	≤0.06–0.125	0.125	0.125
	Apalcillin	≤0.06–0.125	0.125	0.125
	Piperacillin	≤0.06–0.25	0.125	0.125
	Aztreonam	8.0–16	16	16
	Cefoperazone	0.125–0.25	0.125	0.25
	Ceftriaxone	≤0.06	≤0.06	≤0.06
	Ceftazidime	≤0.06–0.25	0.125	0.125
	Gentamicin	1.0–8	4	8
Streptococcus agalactiae (10)	Cefpiramide	0.25–2	0.5	0.5
	Apalcillin	0.25–2	0.5	0.5
	Piperacillin	0.25–2	0.25	0.5
	Aztreonam	128–>128	>128	>128
	Cefoperazone	0.125–2	0.25	0.25
	Ceftriaxone	≤0.06–0.25	≤0.06	≤0.06
	Ceftazidime	0.5–2	0.5	0.5
	Gentamicin	16–64	16	32
Streptococcus pneumoniae (penicillin resistant) (9)	Cefpiramide	0.25–8	1	8
	Apalcillin	0.125–8	2	8
	Piperacillin	0.25–16	4	16
	Aztreonam	64–>128	>128	>128
	Cefoperazone	0.5–8	2	8
	Ceftriaxone	0.125–4	1	4
	Ceftazidime	1.0–128	16	128
	Gentamicin	2.0–32	16	32

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TABLE 1—*Continued*

Organism (no. of isolates)	Antibiotic	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
Viridans group streptococci (penicillin susceptible) (10)	Cefpiramide	0.25–2	0.5	2
	Apalcillin	≤0.06–0.5	0.25	0.25
	Piperacillin	≤0.06–0.5	0.25	0.5
	Aztreonam	128–>128	>128	>128
	Cefoperazone	0.125–1	0.5	1
	Ceftriaxone	≤0.06–0.5	0.125	0.5
	Ceftazidime	≤0.06–32	2	16
	Gentamicin	0.25–4	0.5	2
Viridans group streptococci (penicillin resistant) (10)	Cefpiramide	8.0–32	8	32
	Apalcillin	2.0–8	4	8
	Piperacillin	4.0–32	16	16
	Aztreonam	>128	>128	>128
	Cefoperazone	4.0–16	8	16
	Ceftriaxone	1.0–4	2	4
	Ceftazidime	16–64	16	32
	Gentamicin	2.0–16	8	16
Group G streptococci (10)	Cefpiramide	0.125–0.25	0.125	0.25
	Apalcillin	0.125	0.125	0.125
	Piperacillin	0.125	0.125	0.125
	Aztreonam	64	64	64
	Cefoperazone	0.25	0.25	0.25
	Ceftriaxone	≤0.06	≤0.06	≤0.06
	Ceftazidime	0.25	0.25	0.25
	Gentamicin	8.0	8	8
Listeria monocytogenes (20)	Cefpiramide	0.5–8	4	8
	Apalcillin	≤0.06–2	2	2
	Piperacillin	0.5–4	2	4
	Aztreonam	64–>128	>128	>128
	Cefoperazone	1.0–64	32	32
	Ceftriaxone	1.0–>128	128	>128
	Ceftazidime	8.0–>128	>128	>128
	Gentamicin	0.125–0.5	0.5	0.5

Princeton, N.J.; ceftriaxone, Hoffmann-La Roche Inc., Nutley, N.J.; cefoperazone, Pfizer Inc., Groton, Conn.; carbenicillin, Beecham Laboratories, Bristol, Tenn.; ceftazidime, Glaxo Laboratories, Fort Lauderdale, Fla.; cefsulodin, Abbott Laboratories, North Chicago, Ill.; and gentamicin, Schering Corp., Kenilworth, N.J. Antibiotic solutions were prepared daily as needed, and antibiotic-containing plates were inoculated within 18 h of preparation.

Susceptibility studies. MICs were determined by an agar dilution technique (16) with Mueller-Hinton agar (BBL Microbiology Systems, Cockeysville, Md.). The concentration of agar was increased to 4% with Bacto-Agar (Difco Laboratories, Detroit, Mich.) when testing *Proteus* sp. to prevent swarming. When streptococci were tested, Mueller-Hinton agar was supplemented with 5% sheep blood. *Campylobacter jejuni* was tested with brucella agar (BBL) supplemented with 10% sheep blood. For *Haemophilus influenzae* and *N. gonorrhoeae*, chocolate agar supplemented with 1% IsoVitaleX (BBL) was used. Overnight cultures of test organisms in Mueller-Hinton broth (BBL), Todd-Hewitt broth (for streptococci; BBL), or thioglycolate medium (for *C. jejuni*; GIBCO Diagnostics, Madison, Wis.) were diluted in fresh broth to approximately 10^7 CFU/ml. For *H. influenzae* and *N. gonorrhoeae*, fresh colonies from chocolate agar plates were dispersed in broth to the same density of organisms. For *Streptococcus pneumoniae*, fresh colonies from brucella agar plates were dispersed in broth to the same density. Inocula of approximately 10^4 CFU were applied with a 32-prong replicating device. Plates were examined for growth after 18 h of incubation at 37°C. A single colony or faint haze was ignored when determining endpoints. *C. jejuni* strains were incubated in a microaerophilic atmosphere (Campy

TABLE 2. Number of strains showing synergy, indifference, and antagonism for combinations of agents tested against gram-negative bacilli

Antibiotic combination	No. of strains showing synergy/indifference/antagonism[a]		
	K. pneumoniae	*E. cloacae*	*P. aeruginosa*
Cefpiramide and gentamicin	6/4/0	5/5/0	8/2/0
Apalcillin and gentamicin	0/10/0	6/4/0	10/0/0
Cefpiramide and cefoxitin	0/10/0	0/0/10	0/2/8
Apalcillin and cefoxitin	0/10/0	0/2/8	0/1/9
Piperacillin and cefoxitin	0/10/0	0/2/8	0/0/10
Cefpiramide and piperacillin	0/10/0	0/10/0	1/9/0
Apalcillin and piperacillin	0/10/0	3/7/0	2/8/0

[a] Numerals separated by shills represent the number of strains showing synergy, indifference, and antagonism, respectively.

TABLE 3. Comparative in vitro activities of antibiotics against resistant organisms

Bacteria (no. of isolates)	Antibiotic	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
Escherichia coli resistant to gentamicin, tobramycin, and amikacin (15)	Cefpiramide	0.5–>128	4	32
	Apalcillin	0.5–>128	2	128
	Carbenicillin	2.0–>256	32	>256
	Piperacillin	1.0–>128	4	128
	Cefoperazone	≤0.06–32	0.25	32
	Moxalactam	≤0.06–128	0.25	0.5
	Aztreonam	≤0.06–>128	0.125	2
	Ceftriaxone	≤0.06–>128	≤0.06	1
	Ceftazidime	≤0.06–>128	0.25	8
Pseudomonas aeruginosa resistant to gentamicin, tobramycin, and amikacin (15)	Cefpiramide	2.0–>128	8	>128
	Apalcillin	2.0–>128	4	128
	Carbenicillin	32–>256	128	>256
	Piperacillin	4.0–>128	16	>128
	Cefoperazone	4.0–>128	16	>128
	Moxalactam	0.25–>128	32	>128
	Aztreonam	4.0–>128	8	>128
	Ceftriaxone	2.0–>128	128	>128
	Ceftazidime	0.25–>128	2	64
Serratia marcescens resistant to first- and second-generation cephalosporins (10)	Cefpiramide	32–>128	64	>128
	Apalcillin	8.0–>128	32	64
	Carbenicillin	16–>256	64	256
	Piperacillin	4.0–>128	4	16
	Cefoperazone	2.0–>128	4	32
	Moxalactam	0.25–64	1	8
	Aztreonam	0.125–8	0.25	2
	Ceftriaxone	0.25–64	0.5	4
	Ceftazidime	0.25–16	0.5	2
	Imipenem	0.5–2	1	2
	Gentamicin	1.0–32	1	16
Escherichia coli resistant to ampicillin, carbenicillin, and cephalothin (8)	Cefpiramide	8.0–128	64	128
	Apalcillin	16–>128	>128	>128
	Piperacillin	16–>128	>128	>128
	Cefamandole	4.0–32	8	32
	Cefoxitin	4.0–32	4	8
	Cefoperazone	1.0–32	8	16
	Moxalactam	0.125–0.5	0.125	0.25
	Aztreonam	≤0.06–4	0.125	0.125
	Ceftriaxone	≤0.06–1	≤0.06	≤0.06
	Ceftazidime	0.125–8	0.25	0.25
	Imipenem	0.25–0.5	0.25	0.25
	Gentamicin	0.25–2	1	2
Klebsiella pneumonia resistant to carbenicillin and cephalothin (9)	Cefpiramide	16.0–>128	32	>128
	Apalcillin	4.0–>128	16	>128
	Piperacillin	4.0–>128	32	>128
	Cefamandole	1.0–128	16	128
	Cefoxitin	4.0–>128	16	64
	Cefoperazone	0.25–32	4	32
	Moxalactam	0.125–8	0.125	1
	Aztreonam	≤0.06–0.5	0.25	0.25
	Ceftriaxone	≤0.06–0.5	0.125	0.25
	Ceftazidime	0.125–4	1	2
	Imipenem	0.125–1	0.25	0.5
	Gentamicin	0.5–32	2	32
Enterobacter cloacae resistant to carbenicillin and cefamandole (9)	Cefpiramide	16–>128	>128	>128
	Apalcillin	4.0–>128	64	>128
	Piperacillin	4.0–>128	64	>128
	Cefoperazone	2.0–>128	32	128
	Moxalactam	0.125–32	16	16
	Aztreonam	0.25–64	16	32
	Ceftriaxone	0.25–128	32	128
	Ceftazidime	1.0–128	32	128
	Imipenem	0.5–2	0.5	1
	Gentamicin	0.5–1	0.5	1

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TABLE 3—*Continued*

Bacteria (no. of isolates)	Antibiotic	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
Pseudomonas aeruginosa resistant to carbenicillin (8)	Cefpiramide	4.0->128	16	64
	Apalcillin	4.0->128	16	64
	Piperacillin	16.0->128	32	128
	Cefoperazone	16.0->128	32	128
	Moxalactam	8.0->128	64	128
	Aztreonam	8.0->128	16	>128
	Ceftriaxone	8.0->128	64	>128
	Ceftazidime	2.0->128	4	16
	Imipenem	4.0->128	4	>128
	Gentamicin	4.0->128	4	128

Pak II; BBL), and *N. gonorrhoeae* strains were incubated in 5% CO_2. All other strains were incubated in room air.

Antibiotic combinations were tested in a checkerboard agar dilution matrix. Synergism was said to be present when the MIC of each drug tested in combination was fourfold or more lower than the MIC of each drug tested individually. Antagonism of drug A by drug B was said to be present when the MIC of drug A was fourfold or more higher in the presence of B than in its absence. Indifference was said to be present when the criteria for neither synergism nor antagonism were met.

RESULTS

Susceptibility studies. Results of agar dilution susceptibility studies are shown in Table 1. Except for ceftazidime, cefpiramide was the most active cephalosporin tested against *P. aeruginosa*. Against other nonfermenters, its activity was generally comparable to that of cefoperazone. However, against most members of the *Enterobacteriaceae*, cefpiramide was less active than the other cephalosporins tested. Against gram-positive organisms, the pattern of activity of cefpiramide was very similar to that of cefoperazone, and against *Listeria monocytogenes* it was the most active cephalosporin tested (MIC for 90% of the strains tested [MIC_{90}] = 8 μg/ml). *C. jejuni* strains were resistant to cefpiramide, with MICs of ≥128 μg/ml for all of the 24 strains tested. When cefpiramide was tested against three strains of *Yersinia enterocolitica*, the MICs obtained ranged from 8.0 to 32.0 μg/ml, higher than those obtained for any other antibiotic in this study.

Apalcillin was the most active penicillin tested against *P. aeruginosa*, with activity equal to that of ceftazidime against these isolates (MIC_{90} = 8 μg/ml). Against other nonfermenters, the activity of apalcillin either equaled or exceeded those of both piperacillin and mezlocillin (data for mezlocillin not shown). Strains of *H. influenzae* that produced β-lactamase were resistant to all three penicillins; against β-lactamase-negative strains, apalcillin was slightly less active than either piperacillin or mezlocillin. The activity of apalcillin against members of the *Enterobacteriaceae* was comparable to those of the other penicillins. Although it was the most active of the three penicillins tested against *L. monocytogenes* (MIC_{90} = 2.0 μg/ml), against other gram-positive organisms, apalcillin was comparable to piperacillin and only slightly less active than mezlocillin (data not shown). Apalcillin exhibited poor activity against 24 strains of *C. jejuni*, with an MIC_{50} of 32 μg/ml and an MIC_{90} of 128 μg/ml (MIC range, 1.0 to 128.0 μg/ml). Against three strains of *Y. enterocolitica*, the range of MICs obtained for apalcillin was 8 to 16 μg/ml, higher than those obtained for any other antibiotic in this study with the exception of cefpiramide.

Antibiotic combinations. The results of testing these antibiotics in combination with other agents are presented in Table 2. The combination of cefpiramide and gentamicin synergistically inhibited 80% of *P. aeruginosa* strains, 50% of *Enterobacter cloacae* strains, and 60% of *Klebsiella pneumoniae* strains tested. Similarly, the combination of apalcillin and gentamicin synergistically inhibited 100% of *P. aeruginosa* and 60% of *E. cloacae* strains tested but none of the *K. pneumoniae* strains tested. However, cefoxitin antagonized the activity of cefpiramide against 100% of *E. cloacae* and 80% of *P. aeruginosa* strains. Similarly, cefoxitin antagonized the activity of apalcillin against 80% of *E. cloacae* and 90% of *P. aeruginosa* strains tested. Neither cefpiramide nor apalcillin antagonized the activity of any other

TABLE 4. Antimicrobial susceptibility of plasmid-containing strains of *P. aeruginosa* PU21

β-Lactamase type	MIC (μg/ml) of:					
	Cefpiramide	Apalcillin	Piperacillin	Cefoperazone	Ceftazidime	Imipenem
None	4	2	16	16	2	4
TEM-1	64	>128	>128	128	4	4
TEM-2	128	>128	>128	128	2	4
OXA-1	32	128	>128	16	2	4
OXA-2	64	>128	>128	64	8	4
OXA-3	>128	>128	>128	>128	16	4
PSE-1	32	128	>128	64	2	4
PSE-2	128	128	>128	>128	2	4
PSE-3	8	64	128	32	2	4
PSE-4	32	>128	>128	128	2	4

drug with which it was combined against any of these strains (Table 2).

Activity against resistant isolates. The results of susceptibility testing against selected strains of gram-negative bacilli resistant to multiple antibiotics are presented in Table 3. When tested against members of the *Enterobacteriaceae* resistant to other β-lactam agents, apalcillin and cefpiramide were significantly less active than moxalactam, ceftazidime, ceftriaxone, aztreonam, and imipenem. However, against carbenicillin-resistant strains of *P. aeruginosa*, both apalcillin and cefpiramide were slightly more active than the other agents tested, with the exception of ceftazidime.

In otherwise isogenic strains of *P. aeruginosa*, the presence of any one of nine plasmid-mediated β-lactamases adversely affected the activities of both cefpiramide and apalcillin (Table 4).

DISCUSSION

This study demonstrated the marked activity of both cefpiramide and apalcillin against *P. aeruginosa*. The activities of these two agents in this regard are comparable to those of the most active of the currently available β-lactams. Against a broad range of other gram-negative and gram-positive organisms, the activities of cefpiramide and apalcillin were sufficient to be clinically useful. However, against members of the *Enterobacteriaceae*, cefpiramide was the least active cephalosporin tested. The in vitro susceptibility results obtained in this study for both agents are in general agreement with those obtained by other investigators (5, 6, 8, 12–14).

Against strains selected for multiple resistance, neither cefpiramide nor apalcillin appeared to offer a significant advantage over other currently available agents. Similarly, when tested against a series of otherwise isogenic strains of *P. aeruginosa*, the activities of both cefpiramide and apalcillin were markedly reduced in the presence of each of nine different plasmid-mediated β-lactamases, although the activity of cefpiramide was less affected than that of apalcillin. This is consistent with previous work demonstrating susceptibility of both apalcillin and cefpiramide to hydrolysis by a number of β-lactamases (8, 12).

Cefoxitin antagonized the activities of both cefpiramide and apalcillin against most strains of *E. cloacae* and *P. aeruginosa*. This suggests that induction of the chromosomal β-lactamase that nearly all strains of *E. cloacae*, *P. aeruginosa*, and many other species of gram-negative bacilli possess adversely affects the activities of cefpiramide and apalcillin (7, 15). In light of this, it might be anticipated that resistance to both of these antibiotics may emerge while patients are undergoing antibiotic therapy, particularly when *P. aeruginosa* or *E. cloacae* is the infecting species. This is a potential problem that cefpiramide and apalcillin share with many other β-lactam antibiotics (15).

Based on these in vitro results, a major potential application of these two new drugs would be in the treatment of infections due to *P. aeruginosa*. In addition, both agents have potential pharmacokinetic advantages. Cefpiramide has the longest half-life of any of the β-lactams tested (10) with the exception of ceftriaxone, a drug which was much less active against *P. aeruginosa* in this study. Apalcillin differs from the other extended-spectrum penicillins in that it is primarily excreted via hepatobiliary mechanisms (9). In certain settings, this may be an important consideration.

Given these characteristics, clinical evaluation of both of these agents would appear warranted to determine whether their in vitro activities, particularly against *P. aeruginosa*, and their pharmacokinetic properties can be translated into effective therapy for specific infections.

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