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In Vitro Studies of BMY-28142, a New Broad-Spectrum Cephalosporin

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BMY-28142 was compared with other broad-spectrum antibiotics against gram-positive cocci and gram-negative bacilli. BMY-28142 was highly active against all gram-negative bacilli and especially against *Enterobacter cloacae*, *Serratia marcescens*, and *Morganella morganii*. Its in vitro activity suggests that BMY-28142 should prove to be useful for the treatment of gram-negative bacillary infections.

During the past decade many new antibiotics have been discovered. Among these are a variety of new β-lactams, including broad-spectrum penicillins and cephalosporins, thienamycins, and monobactams. Several of the new cephalosporins which have been synthesized have a broad spectrum of activity against *Enterobacteriaceae*, and some have antipseudomonal activity as well. However, the molecular modifications which have extended the gram-negative spectrum have resulted in decreased gram-positive activity, especially against *Staphylococcus aureus*. BMY-28142 is a new broad-spectrum cephalosporin which we have evaluated in vitro against clinical isolates collected from infected cancer patients (Fig. 1).

Bacterial isolates. A total of 130 clinical isolates of gram-positive cocci and 387 clinical isolates of gram-negative bacilli were tested. All but eight of the isolates of gram-negative bacilli were cultured from blood specimens obtained from cancer patients at this institution during the past 10 years. Isolates of gram-positive cocci were obtained from cultures taken from various body sites of hospitalized patients, some of whom did not have cancer. All isolates were maintained in stock by lyophilization or ultrafreezing methods. Organisms were tested in duplicate simultaneously. *S. aureus* isolates were considered to be methicillin resistant on the basis of an MIC of ≥12.5 μg/ml, methicillin susceptible on the basis of an MIC of ≤1.56 μg/ml, and penicillin G susceptible on the basis of an MIC of <0.1 μg/ml. An additional group of 25 gram-negative bacilli were selected that were known to be resistant to at least 50 μg of aztreonam, moxalactam, ceftazidime, or cefoperazone per ml (2).

Organisms were inoculated into broth cultures and incubated at 37°C for 18 h. Appropriate dilutions were made so that the final concentration of organisms was 10^5 CFU/ml.

Antibiotics. BMY-28142 and amikacin were supplied by Bristol Laboratories, Syracuse, N.Y.; imipenem by Merck Sharp & Dohme Research Laboratories, Rahway, N.J.; cefotaxime by Hoechst-Roussel Pharmaceuticals Inc., Somerville, N.J.; aztreonam by E. R. Squibb & Sons, Inc., Princeton, N.J.; ceftazidime by Glaxo Research Ltd., Research Triangle Park, N.C.; cefoperazone by Pfizer Inc., New York; and piperacillin by Lederle Laboratories, Pearl River, N.Y. Antibiotic concentrations were prepared manually in Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.) or tryptose-phosphate broth (Difco) and dispensed automatically by use of an MIC 2000 dispenser (Dynatech Laboratories, Inc., Alexandria, Va.). Serial twofold dilutions were prepared at concentrations ranging from 100 to 0.0125 μg/ml.

Susceptibility testing. All isolates were tested in Mueller-Hinton broth, with the exception of *Streptococcus pyogenes* isolates, which were tested in tryptose-phosphate broth. *Streptococcus pneumoniae* was tested with the addition of Mg^{2+} (25 mg/liter), Ca^{2+} (50 mg/liter), and 5% lysed defibrinated horse blood (6). Amikacin was also prepared in the medium containing the magnesium and calcium ions. For the comparative studies of the eight antibiotics, the plates were inoculated automatically. *S. aureus* ATCC 25923, *Escherichia coli* ATCC 25922, and *Pseudomonas aeruginosa* ATCC 27853 were included as controls during each procedure.

The effect of inoculum size was determined with concentrations of 10^3, 10^4, 10^5, 10^6, and 10^7 CFU/ml. The same 10 strains each of *E. coli*, *Klebsiella* spp., and *P. aeruginosa* were also used for studies of different media and pH. Studies of the effect of pH on the activity of BMY-28142 were conducted in Mueller-Hinton broth, and the pH was adjusted with phosphate buffer.

Definitions. The MIC was defined as the lowest concentration of drug which suppressed visible growth after incubation at 37°C for 18 h for gram-negative bacilli and isolates of *S. aureus* and after incubation at 37°C in a CO_2 incubator for 24 h for isolates of *S. pyogenes* and *S. pneumoniae*.

The activity of BMY-28142 against gram-positive cocci and gram-negative bacilli compared with those of other antibiotics is shown in Table 1. All of the antibiotics were active against *S. pneumoniae* and *S. pyogenes*. Imipenem was the most active and ceftazidime was the least active

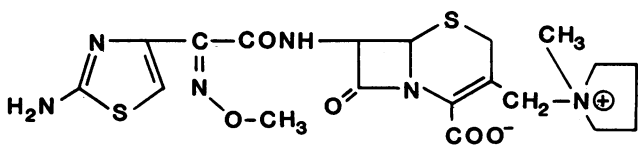

FIG. 1. Chemical structure of BMY-28142.

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TABLE 1. In vitro susceptibilities of organisms to various antibiotics

Organism (no.)	Antibiotic	MIC (μg/ml)[a]		
		50%	90%	Range
Streptococcus pneumoniae (10)	BMY-28142	0.25	0.5	0.025–0.20
	Imipenem	≤0.0125	0.025	≤0.0125–0.025
	Cefotaxime	≤0.0125	0.025	≤0.0125–0.20
	Ceftazidime	0.39	0.39	0.20–6.25
	Cefoperazone	0.05	0.20	0.025–0.39
	Piperacillin	0.025	0.05	≤0.0125–0.10
Streptococcus pyogenes (25)	BMY-28142	≤0.0125	0.10	≤0.0125–12.5
	Imipenem	≤0.0125	0.025	≤0.0125–0.78
	Cefotaxime	≤0.0125	0.05	≤0.0125–1.56
	Ceftazidime	0.10	0.78	0.025–50
	Cefoperazone	0.05	0.20	≤0.0125–25
	Piperacillin	0.025	0.20	0.0125–1.56
Enterococci (25)	BMY-28142	50	>100	6.25–>100
	Imipenem	0.78	12.5	0.39–50
	Cefotaxime	>100	>100	3.12–>100
	Ceftazidime	>100	>100	100–>100
	Cefoperazone	25	>100	6.25–>100
	Piperacillin	3.12	50	1.56–50
Staphylococcus epidermidis (25)	BMY-28142	0.78	3.12	0.10–50
	Imipenem	0.10	0.78	≤0.0125–50
	Cefotaxime	1.56	6.25	0.10–>100
	Ceftazidime	12.5	50	3.12–100
	Cefoperazone	1.56	3.12	0.39–12.5
	Amikacin	3.12	6.25	0.20–12.5
	Piperacillin	3.12	12.5	0.39–100
Staphylococcus aureus Penicillin G susceptible (20)	BMY-28142	1.56	1.56	0.39–1.56
	Imipenem	≤0.0125	0.025	≤0.0125–0.025
	Cefotaxime	1.56	1.56	0.39–3.12
	Ceftazidime	6.25	12.5	6.25–12.5
	Cefoperazone	1.56	1.56	0.39–3.12
	Amikacin	3.12	6.25	0.78–6.25
	Piperacillin	0.78	0.78	0.20–1.56
Methicillin susceptible (14)	BMY-28142	1.56	1.56	0.78–1.56
	Imipenem	≤0.0125	0.025	≤0.0125–0.25
	Cefotaxime	1.56	1.56	0.78–1.56
	Ceftazidime	6.25	6.25	6.25
	Cefoperazone	1.56	1.56	0.78–3.12
	Amikacin	0.78	1.56	0.10–1.56
	Piperacillin	0.78	0.78	0.39–1.56
Methicillin resistant (11)	BMY-28142	25	100	3.12–>100
	Imipenem	3.12	50	0.0125–50
	Cefotaxime	25	>100	6.25–>100
	Ceftazidime	100	>100	12.5–>100
	Cefoperazone	>100	>100	6.25–>100
	Amikacin	12.5	12.5	1.56–12.5
	Piperacillin	>100	>100	6.25–>100
Escherichia coli (50)	BMY-28142	0.05	0.20	≤0.0125–1.56
	Imipenem	0.10	0.20	0.05–0.20
	Cefotaxime	0.05	0.20	0.025–25
	Aztreonam	0.10	0.20	0.025–100
	Ceftazidime	0.20	0.39	0.05–>100
	Cefoperazone	0.20	6.25	0.05–25
	Amikacin	1.56	3.12	0.39–6.25
	Piperacillin	1.56	>100	0.39–>100
Citrobacter freundii (25)	BMY-28142	0.05	0.78	0.0125–1.56
	Imipenem	0.39	0.78	0.20–0.78
	Cefotaxime	0.39	50	0.05–100
	Aztreonam	0.39	50	0.05–100
	Ceftazidime	3.12	100	0.10–>100
	Cefoperazone	6.25	50	0.10–100

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TABLE 1—*Continued*

Organism (no.)	Antibiotic	MIC (μg/ml)[a]		
		50%	90%	Range
	Amikacin	0.78	1.56	0.39–3.12
	Piperacillin	12.5	>100	0.39–>100
Citrobacter diversus (25)	BMY-28142	0.025	0.10	0.0125–0.20
	Imipenem	0.20	0.39	0.10–0.39
	Cefotaxime	0.10	0.39	0.05–25
	Aztreonam	0.05	1.56	0.025–25
	Ceftazidime	0.20	0.39	0.10–25
	Cefoperazone	0.20	3.12	0.10–25
	Amikacin	0.78	1.56	0.39–3.12
	Piperacillin	3.12	12.5	0.78–25
Klebsiella pneumoniae (50)	BMY-28142	0.10	0.78	0.25–1.56
	Imipenem	0.20	0.39	0.05–0.78
	Cefotaxime	0.05	0.78	0.025–3.12
	Aztreonam	0.05	0.20	0.025–0.39
	Ceftazidime	0.20	0.78	0.10–1.56
	Cefoperazone	0.39	6.25	0.10–100
	Amikacin	0.78	3.12	0.78–6.25
	Piperacillin	6.25	>100	1.56–>100
Enterobacter cloacae (50)	BMY-28142	0.10	0.78	0.0125–3.12
	Imipenem	0.39	0.39	0.20–0.78
	Cefotaxime	50	100	0.05–100
	Aztreonam	0.78	50	0.05–100
	Ceftazidime	3.12	100	0.10–>100
	Cefoperazone	3.12	100	0.10–>100
	Amikacin	1.56	3.12	0.78–>25
	Piperacillin	6.25	100	0.39–>100
Serratia marcescens (25)	BMY-28142	0.10	0.20	0.05–0.20
	Imipenem	0.39	0.78	0.20–0.78
	Cefotaxime	0.39	12.5	0.10–50
	Aztreonam	0.10	0.20	0.05–0.78
	Ceftazidime	0.20	0.39	0.10–0.78
	Cefoperazone	1.56	3.12	0.39–6.25
	Amikacin	1.56	6.25	1.56–12.5
	Piperacillin	0.78	6.25	0.39–50
Proteus mirabilis (50)	BMY-28142	0.05	0.05	0.025–0.10
	Imipenem	1.56	3.12	0.10–6.25
	Cefotaxime	0.025	0.025	0.0125–0.39
	Aztreonam	0.0125	0.0125	≤0.0125–0.025
	Ceftazidime	0.10	0.10	0.05–0.39
	Cefoperazone	0.39	0.78	0.20–1.56
	Amikacin	1.56	6.25	0.78–25
	Piperacillin	0.20	0.78	0.20–6.25
Morganella morganii (10)	BMY-28142	0.025	0.05	0.0125–0.20
	Imipenem	1.56	3.12	0.78–6.25
	Cefotaxime	0.10	6.25	0.0125–6.25
	Aztreonam	0.10	0.78	≤0.0125–6.25
	Ceftazidime	0.20	12.5	0.05–12.5
	Cefoperazone	3.12	25	0.39–25
	Amikacin	0.78	3.12	0.78–3.12
	Piperacillin	1.56	50	0.20–>100
Pseudomonas aeruginosa (52)	BMY-28142	1.56	6.25	0.20–25
	Imipenem	1.56	3.12	0.39–>100
	Cefotaxime	>100	>100	12.5–>100
	Aztreonam	6.25	50	3.12–100
	Ceftazidime	1.56	25	0.78–>100
	Cefoperazone	6.25	100	3.12–>100
	Amikacin	6.25	12.5	3.12–>100
	Piperacillin	6.25	100	3.12–>100

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TABLE 1—*Continued*

Organism (no.)	Antibiotic	MIC (μg/ml)[a]		
		50%	90%	Range
Acinetobacter anitratus (25)	BMY-28142	1.56	6.25	0.39–25
	Imipenem	0.20	0.20	0.05–0.39
	Cefotaxime	12.5	12.5	1.56–100
	Aztreonam	25	100	3.12–>100
	Ceftazidime	6.25	12.5	0.78–25
	Cefoperazone	50	100	3.12–100
	Amikacin	1.56	6.25	0.10–12.5
	Piperacillin	12.5	25	3.12–100
Acinetobacter lwoffii (25)	BMY-28142	0.78	6.25	0.10–25
	Imipenem	0.10	0.39	≤0.0125–0.78
	Cefotaxime	3.12	25	0.39–50
	Aztreonam	12.5	>100	1.56–>100
	Ceftazidime	3.12	12.5	0.39–>100
	Cefoperazone	50	>100	0.78–>100
	Amikacin	0.78	100	0.20–>100
	Piperacillin	6.25	50	0.39–>100

[a] 50% and 90%, MIC of antibiotic that inhibited 50 and 90%, respectively, of the isolates.

antibiotic against these organisms. Only imipenem and piperacillin had substantial activity against enterococci. Imipenem was the most active antibiotic against *Staphylococcus epidermidis*, but BMY-28142 and several of the other cephalosporins had substantial activity. Imipenem was also the most active antibiotic against the various groups of *S. aureus*. BMY-28142 had substantial activity against penicillin G-susceptible and methicillin-susceptible *S. aureus* but not against methicillin-resistant *S. aureus*. The antistaphylococcal activity of BMY-28142 was comparable to those of cefotaxime and cefoperazone, although the drug was more active than cefoperazone against some isolates of methicillin-resistant *S. aureus*.

All of the cephalosporins and imipenem were more active against *E. coli* than amikacin and piperacillin. BMY-28142 was highly active against all strains of *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter* spp. tested. It was the most active agent against *Citrobacter* and *Enterobacter* spp. and *Morganella morganii*. Only imipenem was more active than BMY-28142 against *Acinetobacter* spp. and *P. aeruginosa*.

Table 2 shows the activity of the antibiotics against resistant, gram-negative bacilli. Only BMY-28142, imipenem, and amikacin were active against *Enterobacter cloacae* and *Klebsiella* spp. BMY-28142 was the most active antibiotic against the 10 resistant isolates of *Pseudomonas* spp., and all were inhibited by ≤25 μg/ml.

The effect of pH on the activity of BMY-28142 was determined against 10 isolates each of *E. coli*, *Klebsiella pneumoniae*, and *P. aeruginosa*. The activity of BMY-28142 was the same at pHs of 6.4, 7.2, and 8.0. The activity of BMY-28142 against the same organisms was determined in Mueller-Hinton broth, brain heart infusion broth, tryptose-soy broth, and nutrient broth. The MIC for 90% of the isolates was the same or varied by one tube for all three organisms when the four different media were used. The addition of 50% human serum to Mueller-Hinton broth did not alter the activity of BMY-28142 against these isolates. The effect of inoculum size was determined for the same 30 isolates (Table 3). Generally, the MIC for 100% of the isolates increased 2-fold as the inoculum size increased by 10-fold. However, when the inoculum size was increased from 10^6 to 10^7 CFU/ml, the MIC for 100% of the isolates increased to >50 μg/ml for *E. coli* and *P. aeruginosa* but to only 12.5 μg/ml for *K. pneumoniae*.

TABLE 2. In vitro activity of various antibiotics against resistant, gram-negative bacilli

Organism (no.)	Antibiotic	MIC (μg/ml)[a]		
		50%	90%	Range
E. cloacae (10)	BMY-28142	0.39	0.78	0.20–3.12
	Imipenem	0.39	1.56	0.20–3.12
	Cefotaxime	50	100	0.39–>100
	Aztreonam	25	50	0.20–>100
	Ceftazidime	100	>100	1.56–>100
	Cefoperazone	50	100	25–>100
	Amikacin	1.56	3.12	0.78–25
	Piperacillin	100	>100	50–>100
Pseudomonas spp. (10)	BMY-28142	3.12	12.5	0.78–25
	Imipenem	1.56	>100	0.78–>100
	Cefotaxime	>100	>100	12.5–>100
	Aztreonam	25	>100	6.25–>100
	Ceftazidime	3.12	100	1.56–100
	Cefoperazone	6.25	>100	3.12–>100
	Amikacin	12.5	>100	3.12–>100
	Piperacillin	12.5	>100	3.12–>100
Klebsiella spp. (5)	BMY-28142			0.025–12.5
	Imipenem			0.20–12.5
	Cefotaxime			≤0.05–>100
	Aztreonam			≤0.05–>100
	Ceftazidime			≤0.10–>100
	Cefoperazone			3.12–>100
	Amikacin			0.78–>1.56
	Piperacillin			12.5–>100

[a] 50% and 90%, MIC of antibiotic that inhibited 50 and 90%, respectively, of the isolates.

TABLE 3. Effect of inoculum size on activity of BMY-28142

Organism (no.)	MIC (μg/ml) at inoculum (CFU/ml) of:				
	10^3	10^4	10^5	10^6	10^7
E. coli (10)	0.39	0.78	1.56	3.12	>50
K. pneumoniae (10)	0.05	0.10	0.20	0.20	12.5
P. aeruginosa (10)	6.25	6.25	6.25	50	>50

BMY-28142 is an interesting new cephalosporin that has a broad spectrum of activity against gram-negative bacilli. A major advantage of this antibiotic is its high level of inhibitory and killing activity against *Enterobacter* spp., *Serratia marcescens*, and *M. morganii*. It was the most active cephalosporin tested against *Acinetobacter* spp., although it was not as active as imipenem. Ceftizidime has been the most active broad-spectrum cephalosporin against *P. aeruginosa*, but BMY-28142 is as active as ceftazidime in vitro (1). Furthermore, some isolates that were resistant to ceftazidime were susceptible to BMY-28142. Unlike some other broad-spectrum cephalosporins, BMY-28142 has activity against methicillin-resistant and penicillin G-resistant *S. aureus* (5).

The broad-spectrum cephalosporins have become established as important antibiotics for the therapy of serious gram-negative bacillary infections. Several have been found to be effective in the treatment of gram-negative bacillary meningitis (3). They have been successfully substituted for aminoglycosides in antibiotic combinations for the treatment of fever in neutropenic patients (4). The encouraging in vitro results with BMY-28142 indicate that, depending upon its pharmacokinetic and toxicological properties, it should prove to be a useful new broad-spectrum cephalosporin.

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