ANTIBACTERIAL ACTIVITY OF BMY-28142, A NOVEL BROAD-SPECTRUM CEPHALOSPORIN

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BMY-28142, 7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-methylpyrrolidinio)methyl-3-cephem-4-carboxylate, exhibited a well-balanced, extended-spectrum of antibacterial activity both *in vitro* and *in vivo*. Against Staphylococci and Streptococci, BMY-28142 was about four to ten times more active than ceftazidime and comparable to cefotaxime. Most Enterobacteriaceae were more susceptible to BMY-28142 than to ceftazidime, though strains of *Pseudomonas aeruginosa* were slightly more sensitive to ceftazidime. BMY-28142 showed potent activity against Gram-negative bacteria resistant to ceftazidime and/or cefotaxime. Bactericidal activity of BMY-28142 against 10 strains of *P. aeruginosa* was superior to that of ceftazidime. In bacterial infection models in mice, BMY-28142 was more effective than ceftazidime against three Gram-positive and three Gram-negative pathogens. The anti-pseudomonal *in vivo* activity of BMY-28142 was nearly comparable to that of ceftazidime. The blood levels and urinary excretion rates of BMY-28142 in mice were similar to those of ceftazidime.

In recent years, a number of β-lactamase-stable, extended-spectrum cephalosporins have been developed for clinical use. These are commonly referred to as "third generation cephalosporins". These compounds are characterized by their very potent activity against a wide range of Enterobacteriaceae, while only a few exhibit substantial activity against *Pseudomonas* species. Attempts at chemical modification to increase the anti-pseudomonal activity has often resulted in a decrease in the intrinsic Gram-positive activity.

BMY-28142 is a new member of the aminothiazolyl-α-methoxyiminocephalosporins having a quaternized *N*-methylpyrrolidine group at the 3-position (Fig. 1) and was synthesized by the Organic Chemistry Department of Bristol-Myers Research Institute in Tokyo[1]. It shows a broad-spectrum of activity against Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa*.

This paper reports the *in vitro* activity of BMY-28142 against a total of 263 strains of aerobic and anaerobic bacteria in comparison with ceftazidime and cefotaxime. The *in vivo* therapeutic efficacy and pharmacokinetic properties in mice are also described.

Materials and Methods

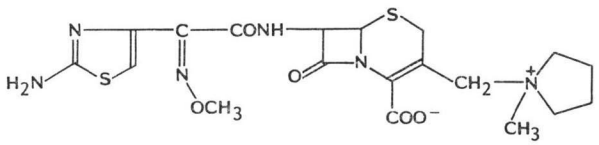
Antibiotics

BMY-28142 was synthesized at Bristol-Myers Research Institute, Tokyo, Japan. Ceftazidime was kindly supplied by Glaxo Inc. and cefotaxime was obtained commercially.

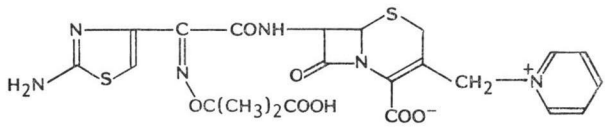
Test Strains

Fifty-four clinical isolates of Gram-positive cocci and 209 isolates of Gram-negative bacilli were used for the microbiological evaluation. The bacterial strains known to produce β-lactamases were kindly supplied by Dr. S. MITSUHASHI of Gunma University, Dr. T. SAWAI of Chiba University and

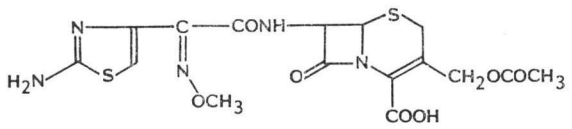
Fig. 1. Chemical structures of BMY-28142, ceftazidime and cefotaxime.



BMY-28142



Ceftazidime



Cefotaxime

by the Microbiological Research Department of Bristol-Myers Company.

Susceptibility Tests

Minimum inhibitory concentrations (MICs) of the cephalosporins were determined by the standard two-fold agar dilution method[2]. Mueller-Hinton agar (Eiken) was generally used for aerobic bacteria, GC medium (Eiken) for fastidious organisms such as *Neisseria* species, and GAM agar medium (Nissui) for anaerobic bacteria. The inoculum used for MIC determination was approximatory 10^6 cfu/ml. The broth dilution method was used for determination of bacteriostatic and bactericidal activities against *P. aeruginosa*, the inoculum size being standardized to 10^5 and 10^6 cfu/ml in Mueller-Hinton broth. The lowest concentration inhibiting the visible growth after 20 hours incubation at 37°C was expressed as the minimum bacteriostatic concentration (MIC). Immediately following the MIC determination, 0.1 ml each of the contents of the turbidity-free tube was spread on an agar plate. The lowest concentration of antibiotics that reduced the initial cell count by 99.9% after overnight incubation at 37°C was designated as the minimum bactericidal concentration (MBC).

Blood Levels and Urinary Recovery

Blood levels were determined in male *dd*Y mice following intramuscular administration of the cephalosporins. Blood samples were collected from orbital sinuses and were assayed by the paper disc-agar diffusion method using *Escherichia coli* Ess-22-31 as the test organism. In general, 10 to 15 mice were used for each dose level. In the urinary recovery test, two groups of 5 mice were kept in metabolic cages to collect urine after intramuscular administration of the compounds. Urine samples were assayed by the same method as used for the blood level determination.

In Vivo Therapeutic Test

The *in vivo* efficacy of the cephalosporins was assessed in experimental infections of mice caused by 9 starins of Gram-positive and Gram-negative bacteria. Mice were challenged intraperitoneally with a multiple of the median lethal dose of the pathogen in a 5% suspension of hog gastric mucin (American Laboratory, Omaha, Neb.). Cephalosporins were administered intramuscularly just before the bacterial challenge to groups of 5 mice for each dose level. The 50% protective dose was expressed in terms of ED_{50} determined at 96 hours after antibiotic administration according to the method of LITCHFIELD and WILCOXON[3].

Table 1. *In vitro* activity of BMY-28142, ceftazidime and cefotaxime against aerobic and anaerobic bacteria.

Organism (No. of strains)	Antibiotic	MIC (μg/ml)	
		Range	Geometric mean
Streptococcus pyogenes (6)	BMY-28142	0.013	0.013
	Ceftazidime	0.1	0.10
	Cefotaxime	<0.0063	<0.0063
S. pneumoniae (6)	BMY-28142	<0.0063~0.013	0.0094
	Ceftazidime	0.1~0.2	0.14
	Cefotaxime	<0.0063	<0.0063
Enterococcus faecalis	BMY-28142	6.3~50	40
(15)	Ceftazidime	>100	>100
	Cefotaxime	25~>100	>100
E. faecium (5)	BMY-28142	>100	>100
	Ceftazidime	>100	>100
	Cefotaxime	>100	>100
Staphylococcus aureus	BMY-28142	0.4~1.6	0.92
PCase$^-$ (5)	Ceftazidime	3.1~6.3	4.7
(Ampicillin-sensitive)	Cefotaxime	0.4~1.6	1.1
S. aureus PCase$^+$ (8)	BMY-28142	3.1~6.3	3.4
(Ampicillin-resistant)	Ceftazidime	12.5~25	14
	Cefotaxime	1.6~6.3	2.4
S. aureus PCase$^+$ (9)	BMY-28142	25~50	40
(Methicillin-resistant)	Ceftazidime	25~100	54
	Cefotaxime	25~50	40
Escherichia coli CSase$^-$ (8)	BMY-28142	<0.0063~0.025	0.0068
(Cephalothin-sensitive)	Ceftazidime	0.013~0.2	0.059
	Cefotaxime	<0.0063~0.1	0.011
E. coli CSase$^+$ (9)	BMY-28142	<0.0063~0.2	0.037
(Cephalothin-resistant)	Ceftazidime	0.1~25	0.58
	Cefotaxime	0.025~0.8	0.093
Klebsiella pneumoniae (10)	BMY-28142	0.025~0.4	0.050
	Ceftazidime	0.025~0.8	0.14
	Cefotaxime	0.013~0.2	0.031
Proteus mirabilis (10)	BMY-28142	0.025~0.05	0.033
	Ceftazidime	0.05~0.1	0.057
	Cefotaxime	0.013~0.05	0.023
P. vulgaris (10)	BMY-28142	0.025~1.6	0.062
	Ceftazidime	0.05~0.8	0.087
	Cefotaxime	0.013~12.5	0.076
Providencia rettgeri (10)	BMY-28142	0.013~0.025	0.020
	Ceftazidime	0.025~0.1	0.050
	Cefotaxime	0.013~0.05	0.019
Morganella morganii (10)	BMY-28142	0.025~0.05	0.031
	Ceftazidime	0.025~6.3	0.11
	Cefotaxime	0.013~6.3	0.11
Enterobacter cloacae (7)	BMY-28142	0.013~0.2	0.050
	Ceftazidime	0.2~12.5	1.2
	Cefotaxime	0.025~25	0.80
Serratia marcescens (9)	BMY-28142	0.025~1.6	0.22
	Ceftazidime	0.05~6.3	0.23
	Cefotaxime	0.1~25	0.79
Pseudomonas aeruginosa	BMY-28142	<0.05~>100	2.7
(64)	Ceftazidime	<0.05~25	2.0
	Cefotaxime	3.1~>100	19

Table 1. (Continued)

Organism (No. of strains)	Antibiotic	MIC (μg/ml)	
		Range	Geometric mean
Pseudomonas cepacia (13)	BMY-28142	1.6~12.5	6.6
	Ceftazidime	1.6~12.5	2.8
	Cefotaxime	6.3~100	13
Xanthomonas maltophilia (11)	BMY-28142	25~>100	57
	Ceftazidime	3.1~>100	25
	Cefotaxime	50~>100	>100
Acinetobacter sp. (10)	BMY-28142	0.2~12.5	2.5
	Ceftazidime	1.6~3.1	1.7
	Cefotaxime	3.1~12.5	3.8
Neisseria gonorrhoeae (5)	BMY-28142	0.013	0.013
	Ceftazidime	0.025~0.05	0.038
	Cefotaxime	0.05	0.050
N. meningitidis (5)	BMY-28142	0.013	0.013
	Ceftazidime	0.025~0.05	0.040
	Cefotaxime	0.025~0.05	0.040
Haemophilus influenzae (10)	BMY-28142	0.013	0.013
	Ceftazidime	0.025~0.05	0.041
	Cefotaxime	0.013	0.013
Bacteroides fragilis CSase$^-$ (4)	BMY-28142	12.5~25	18
	Ceftazidime	6.3~12.5	8.9
	Cefotaxime	12.5~25	18
B. fragilis CSase$^+$ (4)	BMY-28142	>100	>100
	Ceftazidime	50~>100	>100
	Cefotaxime	50~>100	>100

PCase; Penicillinase.
CSase; Cephalosporinase.

Results

In Vitro Activity against Aerobic and Anaerobic Bacteria

Table 1 shows the *in vitro* activity of BMY-28142 against 263 clinical isolates in comparison with ceftazidime and cefotaxime. BMY-28142 was about 10 times more active than ceftazidime against *Streptococcus pyogenes* and *Streptococcus pneumoniae*. BMY-28142 showed an appreciable level of activity against *Enterococcus faecalis*, though species of Enterococci are generally resistant to cephalosporins. Against staphylococcal strains, BMY-28142 was about 4 times as active as ceftazidime and comparable to cefotaxime. No cephalosporin tested showed any significant activity against methicillin-resistant strains of *Staphylococcus aureus*. BMY-28142 and cefotaxime were more potent than ceftazidime against both cephalosporinase-producing and nonproducing strains of *E. coli*. Most Enterobacteriaceae were also highly susceptible to BMY-28142, and the MIC values of BMY-28142 against *Klebsiella pneumoniae*, *Providencia rettgeri*, *Morganella morganii* and *Enterobacter cloacae* were below 0.5 μg/ml. There were some ceftazidime-resistant strains among these bacteria, against which BMY-28142 showed higher activity than cefotaxime. The mean MIC value of BMY-28142 against *P. aeruginosa* was similar to that of ceftazidime and about 7 times lower than that of cefotaxime. *Neisseria* species and *Haemophilus influenzae* strains were highly susceptible to BMY-28142 which was, for these organisms about 3-fold more potent than ceftazidime. The cephalosporinase-producing strains of *Bacteroides fragilis* were resistant to all the cephalosporins tested, while the β-

Table 2. *In vitro* activity of BMY-28142, ceftazidime and cefotaxime against β-lactamase-producing organisms.

Test organism	MIC (μg/ml)		
	BMY-28142	Ceftazidime	Cefotaxime
Penicillinase			
Escherichia coli W3630/Rms 212 Type I	0.05	0.4	0.2
E. coli W3630/Rms 213 Type II	0.025	0.2	0.05
E. coli W3630/Rte 16 Type III	0.025	0.2	0.05
E. coli ML1410/Rms 149 Type IV	0.013	0.2	0.1
Pseudomonas aeruginosa M1/Rms 139 Type IV	6.3	1.6	>100
Cephalosporinase			
Escherichia coli GN5842	0.025	1.6	1.6
E. coli A20343	0.1	12.5	3.1
Enterobacter aerogenes A21046	0.2	50	50
E. aerogenes A21160	0.2	50	12.5
E. cloacae GN7471	0.2	25	50
E. cloacae A20495	0.8	100	100
E. cloacae A25049	0.2	50	50
Morganella morganii A9553	0.025	6.3	6.3
M. morganii A9636	0.05	25	12.5
Providencia rettgeri GN4430	0.013	0.1	0.025
Serratia marcescens GN10857	3.1	3.1	25
S. marcescens AKH-4	0.4	100	100
Citrobacter freundii GN7391	3.1	>100	>100
C. freundii GN346	0.4	25	25
Pseudomonas aeruginosa GN10367	3.1	3.1	25
P. aeruginosa GN10364	1.6	1.6	12.5
Cefuroximase			
Pseudomonas cepacia GN11164	3.1	0.8	1.6
Xanthomonas maltophilia GN12873	50	100	>100
Proteus vulgaris GN7919	3.1	3.1	50

lactamase-nonproducing strains were moderately susceptible.

Activity against β-Lactamase-producing and Ceftazidime/Cefotaxime-resistant Strains

The antibacterial activities of BMY-28142, ceftazidime and cefotaxime against strains which produce various types of β-lactamase are shown in Table 2. BMY-28142 inhibits all but one strain at concentrations up to 6.3 μg/ml. Whereas many of the cephalosporinase-producing strains examined, were resistant to ceftazidime and cefotaxime. A strain of *Xanthomonas maltophilia* which produced a "cefuroximase" was highly resistant to BMY-28142 and two reference cephalosporins.

Bacteriostatic and Bactericidal Activities against *Pseudomonas aeruginosa*

Bacteriostatic and bactericidal activities of BMY-28142 against 10 strains of *P. aeruginosa* were determined using 2 levels of inoculum size (10^4 and 10^5 cfu/ml) and the results are shown in Table 3. The bactericidal activity of BMY-28142 was at least as good as that of ceftazidime, and the activity of BMY-28142 was a little affected by the inoculum size. The MBC values were not more than 2-fold higher than the corresponding MIC values for BMY-28142.

Blood Levels and Urinary Excretion in Mice

BMY-28142 and ceftazidime showed similar pharmacokinetic properties with respect to peak blood level (C_{max}), half-life ($T_{1/2}$) and area under the curve (AUC) after intramuscular administra-

Table 3. Bacteriostatic and bactericidal activities of BMY-28142, ceftazidime and cefotaxime against *Pseudomonas aeruginosa* (10 strains).

Compound	Bacteriostatic activity (μg/ml)			
	8.1×10^{4}*		8.1×10^{5}*	
	Range	Geometric mean	Range	Geometric mean
BMY-28142	0.8~6.3	2.8	1.6~12.5	3.9
Ceftazidime	1.6~12.5	4.1	1.6~25	4.8
Cefotaxime	6.3~50	27	6.3~200	50

Compound	Bactericidal activity (μg/ml)			
	8.1×10^{4}*		8.1×10^{5}*	
	Range	Geometric mean	Range	Geometric mean
BMY-28142	1.6~12.5	4.1	1.6~12.5	5.8
Ceftazidime	1.6~12.5	5.1	1.6~50	10
Cefotaxime	25~200	93	50~400	190

* Inoculum size (cfu/ml).

Table 4. Blood levels of BMY-28142, ceftazidime and cefotaxime in mice after intramuscular administration.

Compound	Dose (mg/kg)	C_{max} (μg/ml)	$T_{1/2}$ (minutes)	AUC (μg·hours/ml)
BMY-28142	40	31	23	19
	20	20	18	11
	10	8.0	17	5.3
Ceftazidime	40	29	20	18
	20	16	16	9.8
	10	7.4	15	5.0
Cefotaxime	20	27	18	16

Table 5. Urinary recovery of BMY-28142, ceftazidime and cefotaxime in mice after intramuscular administration of 20 mg/kg.

Compound	Percent urinary recovery				
	0~2 hour(s)	2~4 hours	4~6 hours	6~24 hours	Total
BMY-28142	62	7.5	1.7	0.7	72
Ceftazidime	62	4.6	1.5	0.5	69
Cefotaxime	60	0.6	0.3	1.8	63

tions at 40, 20 and 10 mg/kg (Table 4). The urinary recovery of BMY-28142 was comparable to that of ceftazidime, and slightly higher than that of cefotaxime (Table 5).

In Vivo Efficacy in Mouse Infection Models

Table 6 shows the *in vivo* therapeutic efficacy of BMY-28142 against three Gram-positive and six Gram-negative bacterial infections in mice. BMY-28142 was several times more potent than ceftazidime against infections of *S. aureus*, *S. pyogenes*, *E. coli* and *K. pneumoniae*, and comparable to the latter against *Proteus vulgaris*. In the infections caused by three pseudomonal strains, BMY-28142

Table 6. *In vivo* therapeutic efficacy of BMY-28142, ceftazidime and cefotaxime in experimental infections in mice.

Pathogen	Inoculum ($\times LD_{50}$)	BMY-28142		Ceftazidime		Cefotaxime	
		ED_{50}[a]	MIC[b]	ED_{50}	MIC	ED_{50}	MIC
Staphylococcus aureus Smith	122	1.7	1.6	13	6.3	1.8	1.6
S. aureus BX-1633[c]	18	3.1	3.1	16	12.5	3.1	1.6
Streptococcus pyogenes A20201	22	0.034	0.013	0.52	0.1		
Escherichia coli Juhl	122	0.012	0.025	0.11	0.2	0.040	0.013
Klebsiella pneumoniae D-11	300	0.020	0.013	0.12	0.05		
Proteus vulgaris A9436	83	0.016	0.025	0.025	0.05		
Pseudomonas aeruginosa A9843A	56	6.2	1.6	6.8	1.6	80	12.5
P. aeruginosa A21509	200	7.6	3.1	6.3	3.1	>50	25
P. aeruginosa A20599	122	7.6	3.1	5.6	3.1	>50	25

[a] Median effective dose in mg/kg, im.
[b] Minimum inhibitory concentration in μg/ml.
[c] Penicillinase-producing strain.

was almost equivalent to ceftazidime. Cefotaxime showed *in vivo* anti-staphylococcal activity similar to that of BMY-28142, but was almost inactive against pseudomonal infections.

Discussion

A number of broad-spectrum cephalosporins have been developed which display high activity against Enterobacteriaceae while only a few exhibit substantial activity against *Pseudomonas* species. Cefotaxime[4,5] is the first representative of this class of cephalosporins. It shows excellent activity against Enterobacteriaceae, good activity against Staphylococci but poor activity against *P. aeruginosa*. Ceftazidime[6,7] has potent anti-pseudomonal activity, comparable to that of aminoglycoside antibiotics, but unfortunately it is not sufficiently active against staphylococcal strains.

In the present study, we showed BMY-28142 to have an extended-spectrum of antibacterial activity against Staphylococci, Enterobacteriaceae and pseudomonal strains, confirming the findings reported by KHAN *et al.*[8], BODEY *et al.*[9], KESSLER *et al.*[10], TSUJI *et al.*[11], VUYE and PIJCK[12], FUCHS *et al.*[13] and STEELE *et al.*[14]. A considerable number of ceftazidime/cefotaxime-resistant Gram-negative bacteria were found to be inhibited by BMY-28142. This may be explained, in part, by the finding of PHELPS *et al.*[15] that BMY-28142 has low binding affinity for β-lactamases combined with high resistance to hydrolysis. The anti-pseudomonal bactericidal activity of BMY-28142 was similar to that of ceftazidime.

BMY-28142 and ceftazidime showed similar pharmacokinetic profile in mice. BMY-28142 was highly active *in vivo* in a number of experimental infections in mice, being 5~10 times more effective than ceftazidime against infections by *S. aureus*, *S. pyogenes*, *E. coli* and *K. pneumoniae*, and only marginally less active than ceftazidime against infections due to three pseudomonal strains.

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