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BMY 28100, a New Oral Cephalosporin

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BMY 28100, a new oral cephalosporin with a (Z)-propenyl side chain at the 3 position and a *p*-hydroxyphenylglycyl substituent at the 7 position, was evaluated in comparison with cefaclor and cephalexin and, when appropriate, ampicillin and vancomycin. In vitro, BMY 28100 was more active than the reference cephalosporins against streptococci, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Listeria monocytogenes*, *Haemophilus influenzae*, *Propionibacterium acnes*, *Clostridium perfrigens*, and *Clostridium difficile*. BMY 28100 was comparable to cefaclor and more active than cephalexin against *Staphylococcus saprophyticus* and ampicillin-susceptible strains of *Branhamella cattarhalis*; but against ampicillin-resistant strains of *B. cattarhalis*, BMY 28100 was comparable to cephalexin and more active than cefaclor. Against *Neisseria gonorrhoeae*, BMY 28100 was comparable to cephalexin, but less active than cefaclor. Members of the family *Enterobacteriaceae* overall were equally susceptible to BMY 28100 and cefaclor but were less susceptible to cephalexin. In human serum, BMY 28100 was 45% protein bound. After an oral dose to mice, 82% of the drug was recovered in urine. The oral therapeutic efficacy of BMY 28100 in systemically infected mice reflected its activity in vitro.

Whereas parenteral cephalosporins have been prepared with an array of side chains at the 3 and 7 positions, structural requirements for good gastrointestinal absorption have limited the choice of side chains for oral cephalosporins. The number of distinct substituents at the 3 position on oral cephalosporins currently in clinical use is small, and all substituents at the 7 position are of a single design: a native or modified phenylglycyl radical. Recent attempts to deviate from this pattern have yielded compounds with a broader spectrum of activity against gram-negative organisms but reduced gastrointestinal absorption and little antistaphylococcal activity (4, 9, 13; T. Suematsu, H. Sakamoto, and K. Takai, Proc. 14th Int. Congr. Chemother., p. 1147–1148, 1985; T. Takaya, T. Kamimuro, Y. Yokota, Y. Mine, H. Kikuchi, S. Goto, and S. Kuwahara, Proc. 14th Int. Congr. Chemother., p. 1143–1144, 1985; W. Tosch, I. Csendes, O. Zak, and R. Scartazzini, Program Abstr. 25th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 595, 1985).

BMY 28100 is a new oral cephalosporin of conventional design. It has a (*Z*)-propenyl side chain at the 3 position and a *p*-hydroxyphenylglycyl substituent at position 7 (Fig. 1). In this report we compare the biological and physicochemical properties of BMY 28100 with those of the two most widely used oral cephalosporins, cephalexin and cefaclor. When appropriate, ampicillin and vancomycin were also included as reference compounds.

(This study was presented in part at the 14th International Congress of Chemotherapy, Kyoto, Japan [F. Leitner, R. E. Buck, T. A. Pursiano, M. Misiek, R. E. Kessler, and K. E. Price, Proc. 14th Int. Congr. Chemother., p. 1153–1154, 1985; Y. H. Tsai, D. R. Chisolm, and F. Leitner, Proc. 14th Int. Congr. Chemother., p. 1155–1156, 1985].)

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MATERIALS AND METHODS

Antibiotics. BMY 28100, 7-[(*R*)-2-amino-2-(4-hydroxyphenyl)acetamido]-3-[(*Z*)-propenyl]-3-cephem-4-carboxylic acid monohydrate, was first prepared by Bristol-Myers Research Institute, Tokyo, Japan (T. Naito, H. Hoshi, Y. Abe, S. Abukari, J. Okumura, and H. Kawaguchi, Proc. 14th Int. Congr. Chemother., p. 1149–1150, 1985; K. Tomatsu, T. Hoshiya, S. Ando, and T. Miyaki, Proc. 14th Int. Congr. Chemother., p. 1151–1152, 1985). Later lots were supplied by Bristol-Myers Co., Industrial Division. Cephalexin monohydrate, cefaclor monohydrate, and vancomycin hydrochloride were from Eli Lilly & Co., Indianapolis, Ind. The sodium salt of ampicillin was a product of Bristol Laboratories, Syracuse, N.Y.

Bacteria. The organisms were obtained from numerous clinical sources of broad geographical distribution. Organisms were stored as follows: streptococci other than enterococci, *Listeria monocytogenes*, *Haemophilus influenzae*, *Branhamella catarrhalis*, *Neisseria gonorrhoeae*, *Acinetobacter calcoaceticus*, and obligate anaerobes in tryptic soy broth (GIBCO Laboratories, Lawrence, Mass.) with 15% glycerol at −70°C. All other organisms were stored as a dry film on porcelain insulator beads (Honeywell, Inc., Fort Washington, Pa.).

Antimicrobial spectrum. Growth inhibitory activity was determined on solid medium by the antibiotic dilution technique. Mueller-Hinton agar (BBL Microbiology Systems, Cockeysville, Md.) was used for enterococci, staphylococci, members of the family *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *A. calcoaceticus*; the same medium was supplemented with 4% defibrinated sheep blood for streptococci other than enterococci and *L. monocytogenes*. The antibiotic susceptibility of *H. influenzae*, *B. catarrhalis*, and *N. gonorrhoeae* was determined on GC medium base (BBL) supplemented with 1% hemoglobin (BBL) and 1% IsoVitaleX (BBL). Activity against obligate anaerobes was

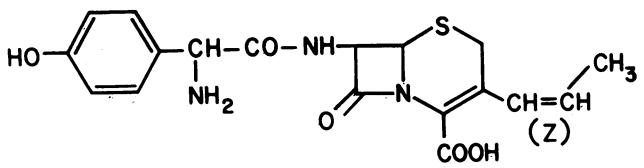

FIG. 1. Structure of BMY 28100.

assayed on brucella agar (BBL) supplemented with 10 μg of vitamin K per ml and 5% laked sheep blood. Inoculum size, assessed by plating, ranged from 3×10^5 to 8×10^6 CFU; *Clostridium* spp., with an inoculum size of 5×10^4 CFU, were exceptions. Otherwise, assay conditions were as described previously (10, 12).

Bactericidal activity. Kinetic bactericidal experiments were done in appropriate concentrations of antibiotic in Mueller-Hinton broth containing 1% Tween 80 with cells from the exponential phase of growth at a starting culture density of approximately 10^6 CFU/ml. The Tween 80 was used to minimize adhesion of viable cells to test tube walls as previously described (8, 10). For *H. influenzae*, the medium was enriched with supplement C (Difco Laboratories, Detroit, Mich.). Samples were removed at 0, 1.5, 3, 4.5, 6, 7.5, and 24 h for viable count determination. Serial dilutions of cultures gave proportional cell counts indicating no significant carry-over of drug.

Binding to serum proteins. The extent to which BMY 28100 and cephalexin are bound to human serum proteins was determined by an ultrafiltration procedure described previously (10), except that the cephalosporin concentration in 95% human serum was 10 μg/ml and the mixture was incubated for 15 min before filtration. The assay organism was *Micrococcus luteus* ATCC 9341.

Stability in solution. Cephalosporins were incubated at 37°C in 0.004 M citric acid-hydrochloride buffer (pH 2.0), 0.05 M phosphate buffer (pH 7.4), or 95% human serum. The initial antibiotic concentration was 50 μg/ml. Residual antibiotic activity was determined periodically over a 24-h period by an antibiotic diffusion technique on antibiotic assay medium (Difco) and with *M. luteus* ATCC 9341 as the assay organism. Acid samples were neutralized, and serum samples were precipitated with acetone and centrifuged prior to assay.

Pharmacokinetics in mice. The antibiotic concentration in the blood of male Swiss-Webster mice (weight, 20 ± 2 g), dosed by gavage with 50 mg/kg, was determined as described previously (11), except that blood samples were obtained 0.25, 0.5, 1, 1.5, 2, and 2.5 h after administration. Bioassay was performed with *M. luteus* ATCC 9341 or *Bacillus subtilis* ATCC 6633. Drug concentrations beyond the peak value were fitted to a regression line by the method of least mean squares. The half-life was determined by dividing ln 2 by the slope of the line. The area under the drug concentration-time curve was obtained by successive trapezoidal approximation from time zero to 2.5 h.

Urine was collected in three fractions (0 to 3, 3 to 6, and 6 to 24 h), and drug recovery was determined as described previously (10).

Therapeutic efficacy in systemically infected mice. Male Swiss-Webster mice (weight, 20 ± 2 g) were challenged intraperitoneally with 0.5 ml of a bacterial suspension containing a sufficient number of organisms to kill untreated controls within 72 h. Streptococci were suspended in brain heart infusion broth (Difco), penicillinase-producing staphylococci were suspended in broth containing 2% hog gastric mucin (American Laboratories, Inc., Omaha, Nebr.), and the other organisms were suspended in broth containing 4% mucin. Animals were treated by gavage. Experimental conditions were as described previously (11). The Spearman-Karber method (7) was used to calculate 95% confidence limits.

RESULTS

Antimicrobial spectrum. BMY 28100 was 2 to 8 times more active than cefaclor and 8 to 32 times more active than cephalexin against streptococci other than enterococci (Table 1). *Streptococcus faecalis* was inhibited by 8 to 16 μg of BMY 28100 per ml, and *Streptococcus faecium* was inhibited by 8 to 32 μg of BMY 28100 per ml. Cefaclor was 2 to 4 times less active and cephalexin was more than 10 times less active than BMY 28100. All penicillinase-producing strains of *Staphylococcus aureus* were inhibited by 4 μg or less of BMY 28100 per ml compared with 32 μg/ml for cefaclor and cephalexin. Against *Staphylococcus aureus* lacking penicillinase and *Staphylococcus epidermidis*, BMY 28100 was two- to fourfold more active than cefaclor and about eightfold more active than cephalexin; against *Staphylococcus saprophyticus*, BMY 28100 was twofold more active than cefaclor and four to eight times more active than cephalexin. *L. monocytogenes* was susceptible to BMY 28100, moderately susceptible to cefaclor, and resistant to cephalexin.

Against *H. influenzae*, with half of the strains being β-lactamase producers, BMY 28100 had a twofold advantage over cefaclor and cephalexin. Although all three compounds were approximately equally active against *B. catarrhalis*, BMY 28100 and cephalexin tended to be more active than cefaclor or ampicillin against those strains with higher MICs for ampicillin. Twenty-five strains of *N. gonorrhoeae* were ampicillin susceptible and eight were ampicillin resistant. MICs of the cephalosporins for the ampicillin-resistant strains clustered near the upper end of the MIC range of the ampicillin-susceptible strains. BMY 28100 activity was comparable to that of cephalexin but lower than that of cefaclor.

Against *Proteus mirabilis*, BMY 28100 and cefaclor had similar ranges of growth-inhibitory activities but BMY 28100 was two- to fourfold more active than cefaclor. The two cephalosporins were 16- to 32-fold more active than cephalexin against 80% of the strains but had a lesser or no advantage against the remaining strains. Against *Escherichia coli*, the MIC_{50} (MIC for 50% of strains tested) of BMY 28100 was fourfold lower than that of cefaclor or cephalexin; the MIC_{90}s (MICs for 90% of strains tested) of all three were >125 μg/ml. Against *Shigella* spp., *Salmonella* spp., and *Citrobacter diversus*, BMY 28100 activity overall was comparable to that of cefaclor, and for the majority of strains BMY 28100 was more active than cephalexin. About one-quarter of the strains, however, were either more susceptible to cephalexin or similarly susceptible to BMY 28100 and cephalexin. Against *Klebsiella pneumoniae* and *Klebsiella oxytoca*, BMY 28100 and cefaclor were comparably active. The more susceptible strains were inhibited to a greater extent by BMY 28100; the more resistant strains were inhibited to a greater extent by cephalexin.

Propionibacterium acnes was more susceptible to BMY 28100 than to cefaclor or cephalexin. Against *Clostridium perfringens*, BMY 28100 had a 2- to 4-fold advantage over vancomycin and cefaclor and a 12-fold advantage over cephalexin. BMY 28100 displayed remarkable activity against *Clostridium difficile*. The compound was one-fifth as active as vancomycin but 8- and 16- to 32-fold more active

TABLE 1. Antibacterial spectrum of BMY 28100 and reference compounds

Organism (no. of strains)	Compound	MIC (μg/ml)[a]		
		Range	50%	90%
Streptococcus pyogenes (31)	BMY 28100	0.008–0.016	0.016	0.016
	Cefaclor	0.032–0.125	0.063	0.063
	Cephalexin	0.125–0.25	0.125	0.125
Streptococcus agalactiae (38)	BMY 28100	0.032–0.125	0.063	0.125
	Cefaclor	0.25–1	0.5	1
	Cephalexin	0.5–4	2	4
Viridans group streptococci (20)	BMY 28100	0.063–0.5	0.125	0.5
	Cefaclor	0.25–2	0.5	1
	Cephalexin	1–8	2	8
Streptococcus pneumoniae (24)	BMY 28100	0.032–0.5	0.125	0.25
	Cefaclor	0.125–1	0.5	0.5
	Cephalexin	0.5–2	2	2
Streptococcus faecalis (22)	BMY 28100	8–16	8	16
	Cefaclor	32–63	32	63
	Cephalexin	63–>125	125	>125
Streptococcus faecium (18)	BMY 28100	8–32	16	32
	Cefaclor	16–63	32	63
	Cephalexin	32–>125	125	>125
Staphylococcus aureus, strains lacking penicillinase (20)	BMY 28100	0.25–1	0.5	0.5
	Cefaclor	0.5–2	1	2
	Cephalexin	2.0–8	2	4
Staphylococcus aureus, penicillinase producers (42)	BMY 28100	0.5–4	2	4
	Cefaclor	2–32	8	32
	Cephalexin	4–32	8	32
Staphylococcus epidermidis (24)	BMY 28100	0.125–1	0.25	1
	Cefaclor	0.25–4	1	2
	Cephalexin	1–8	2	4
Staphylococcus saprophyticus (28)	BMY 28100	1	1	1
	Cefaclor	1–2	2	2
	Cephalexin	4–8	4	8
Listeria monocytogenes (21)	BMY 28100	2–4	4	4
	Cefaclor	8–16	16	16
	Cephalexin	32–125	63	63
Haemophilus influenzae, strains lacking β-lactamase (19)	BMY 28100	4–16	8	16
	Cefaclor	8–32	16	32
	Cephalexin	8–63	16	32
	Ampicillin	0.25–0.5	0.25	0.5
Haemophilus influenzae, β-lactamase producers (21)	BMY 28100	4–32	8	32
	Cefaclor	8–63	32	63
	Cephalexin	8–63	16	32
	Ampicillin	32–>125	>125	>125
Branhamella catarrhalis (16)	BMY 28100	1–8	4	8
	Cefaclor	2–32	8	16
	Cephalexin	2–8	4	8
	Ampicillin[b]	0.016	0.016	0.016
	Ampicillin[c]	1–63	2	16
Neisseria gonorrhoeae (33)	BMY 28100	0.063–8	2	4
	Cefaclor	0.016–1	0.25	1
	Cephalexin	0.125–8	4	4
	Ampicillin[d]	0.016–1	0.125	0.5
	Ampicillin[e]	63–>125	>125	>125

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TABLE 1—*Continued*

Organism (no. of strains)	Compound	MIC (μg/ml)[a]		
		Range	50%	90%
Proteus mirabilis (49)	BMY 28100	0.5–>125	1	8
	Cefaclor	0.5–>125	2	63
	Cephalexin	8–>125	32	63
Escherichia coli (55)	BMY 28100	0.5–>125	4	>125
	Cefaclor	0.5–>125	16	>125
	Cephalexin	0.8–>125	16	>125
Shigella spp. (21)	BMY 28100	0.5–63	2	8
	Cefaclor	0.25–32	2	16
	Cephalexin	4–16	8	16
Salmonella spp. (37)	BMY 28100	0.25–>125	0.5	>125
	Cefaclor	0.25–>125	1	125
	Cephalexin	2–63	4	16
Citrobacter diversus (22)	BMY 28100	0.5–>125	1	63
	Cefaclor	0.5–>125	2	32
	Cephalexin	8–125	8	63
Klebsiella pneumoniae (70)	BMY 28100	0.5–>125	8	>125
	Cefaclor	0.5–>125	8	>125
	Cephalexin	4–>125	8	63
Klebsiella oxytoca (20)	BMY 28100	0.5–>125	32	>125
	Cefaclor	0.5–>125	16	>125
	Cephalexin	4–>125	8	>125
Propionibacterium acnes (13)	BMY 28100	0.063–0.25	0.125	0.25
	Cefaclor	0.25–1	0.25	0.5
	Cephalexin	0.25–2	0.5	2
Clostridium perfringens (15)	BMY 28100	0.032–2	0.25	0.5
	Cefaclor	0.125–4	0.5	2
	Cephalexin	1–8	2	8
	Vancomycin	0.5–1	0.5	1
Clostridium difficile (15)	BMY 28100	2–4	4	4
	Cefaclor	8–63	32	32
	Cephalexin	32–125	63	125
	Vancomycin	0.5–1	0.5	1

[a] 50% and 90%, MIC for 50 and 90% of strains, respectively.
[b] Five strains susceptible to ampicillin.
[c] Eleven strains moderately susceptible or resistant to ampicillin.
[d] Twenty-five strains susceptible to ampicillin.
[e] Eight strains resistant to ampicillin.

than cefaclor and cephalexin, respectively. None of the cephalosporins had useful activity against methicillin-resistant staphylococci, *Proteus vulgaris*, *Morganella morganii*, *Providencia rettgeri*, *Providencia stuartii*, *Citrobacter freundii*, *Enterobacter cloacae*, *Enterobacter aerogenes*, *Serratia marcescens*, *Pseudomonas aeruginosa*, *Acinetobacter calcoaceticus*, *Bacteroides fragilis*, and those *Bacteroides* spp. previously classified as subspecies of *B. fragilis*.

Bactericidal kinetics were determined for one strain each of *Staphylococcus aureus*, *H. influenzae*, and *E. coli*. Time-kill curves followed apparent first-order kinetics for at least 4 h; at times a lag preceded the loss of viability. Maximum bactericidal activity was assessed in terms of the time required to reduce the number of CFU by 90% ($t_{1/10}$). Results with *Staphylococcus aureus* 5, a penicillinase-producing strain, are illustrated in Fig. 2. At the maximum rate of kill, measured at drug concentrations of 64 μg/ml, the $t_{1/10}$ value was about 2.5 h with all three cephalosporins. The lowest concentrations at which viability continued to decline after 8 h of incubation were as follows: BMY 28100, 4 μg/ml; cefaclor, 16 μg/ml; cephalexin, 64 μg/ml. For *H. influenzae* (lacking β-lactamase) and *E. coli* (β-lactamase producer), the maximum cidal rate of the cephalosporins corresponded to a $t_{1/10}$ of approximately 1.25 h. The lowest cephalosporin concentrations that prevented regrowth of *H. influenzae* between 8 and 24 h were as follows: BMY 28100, 1 μg/ml; cefaclor, 2 μg/ml; cephalexin, 4 μg/ml. The corresponding values for *E. coli* were 4, 8, and 16 μg/ml.

Binding to serum proteins. In 95% human serum, BMY 28100 was 45% protein bound and cephalexin was 17% protein bound. Under similar experimental conditions cefaclor was 47% protein bound (14).

Stability in solution at 37°C. BMY 28100, cefaclor, and cephalexin had a half-life of more than 24 h in citrate buffer (pH 2.0). In phosphate buffer (pH 7.4) and in 95% human serum, the half-life of BMY 28100, 4.8 and 5.5 h, respectively, was twice that of cefaclor (2.3 and 2.7 h, respectively). In either medium the activity of cephalexin declined with a half-life of >24 h.

Pharmacokinetics in mice. After an oral dose of 50 mg/kg to mice, the pharmacokinetic parameters of BMY 28100 overall

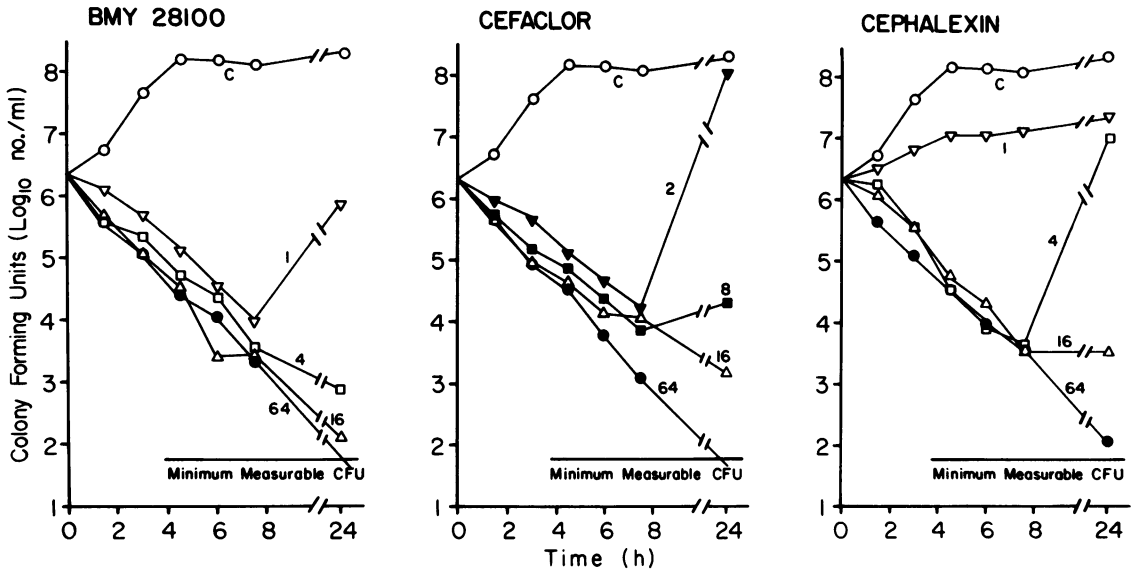

FIG. 2. Bactericidal activity of BMY 28100, cefaclor, and cephalexin against *Staphylococcus aureus* 5 in Mueller-Hinton broth. MICs were as follows: BMY 28100, 1 μg/ml; cefaclor, 8 μg/ml; and cephalexin, 16 μg/ml. C, Control culture; numbers represent drug concentration in micrograms per milliliter.

were comparable to those of cephalexin and more favorable than those of cefaclor (Table 2). About 95% of the dose recovered in urine was excreted during the first 3 h after administration.

Therapeutic efficacy in systemically infected mice. BMY 28100 was more effective than the two reference compounds against infections caused by streptococci and penicillinase-producing *Staphylococcus aureus* strains (Table 3). A penicillinase-negative strain of *Staphylococcus aureus* was equally susceptible to treatment by any one of the cephalosporins. The inefficacy of cefaclor in treating staphylococcal infections caused by penicillinase-producing strains no doubt reflects its relative lability to the enzyme. Against infections with gram-negative organisms *H. influenzae*, *Proteus mirabilis*, *E. coli*, and *K. pneumoniae*, BMY 28100 was comparable to cefaclor and more effective than cephalexin.

DISCUSSION

BMY 28100 is a new oral cephalosporin of traditional structural design. In vitro the compound was more active than cefaclor and cephalexin against streptococci, including enterococci, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, *L. monocytogenes*, and *H. influenzae*. The larger differential in activity between BMY 28100 and cefaclor against penicillinase-producing *Staphylococcus aureus* isolates compared with that of nonproducers suggest that BMY 28100 is hydrolyzed more slowly than cefaclor. The relative rate of hydrolysis by purified enzyme is 10-fold less for BMY 28100 compared with that for cefaclor (unpublished results). BMY 28100 activity was comparable to that of cefaclor and higher than that of cephalexin against ampicillin-susceptible strains of *B. catarrhalis*, but against ampicillin-resistant strains of this organism BMY 28100 activity was comparable to that of cephalexin and higher than that of cefaclor. Against *N. gonorrhoeae*, BMY 28100 activity was comparable to that of cephalexin but lower than that of cefaclor. Members of the family *Enterobacteriaceae* overall were equally susceptible to BMY 28100 and cefaclor and less susceptible to cephalexin. However, the MIC_{50} of BMY 28100 for *E. coli* was fourfold lower than for both cefaclor and cephalexin, suggesting a small advantage for this species alone. With many species, susceptibility to BMY 28100 and cefaclor was bimodal, and, thus, cephalexin often had an advantage against the more resistant strains, particularly at the higher inoculum.

BMY 28100 displayed unexpectedly good activity against *C. difficile*, which is the causative agent of antibiotic-associated pseudomembranous colitis. The disease is thought to be caused by an imbalance in the colonic flora, which is generated by the administration of antibiotic and which permits proliferation of toxigenic *C. difficile* isolates either during or after cessation of treatment. Parenteral and oral cephalosporins are among the antibiotics that have been implicated in the disease (1, 3). There are reports of cases in which an antibiotic has been effective in vitro against the offending strain (5). Hence, the clinical relevance of activity in vitro is not clear. An investigation of the relative liabilities

TABLE 2. Pharmacokinetic parameters of BMY 28100 and reference compounds in mice after an oral dose of 50 mg/kg[a]

Compound[b]	Parameters for compounds in blood[c]			Percentage of dose recovered in 24 h in urine
	C_{max} (μg/ml)	$t_{1/2}$ (min)	$AUC_{0-2.5}$ (μg · h/ml)	
BMY 28100	35.2 ± 6.5	38.2 ± 5.3	36.6 ± 1.2	81.6 ± 6.8
Cefaclor	27.8 ± 5.9	28.0 ± 2.6	25.6 ± 4.4	68.6 ± 8.0
Cephalexin	34.2 ± 2.7	29.5 ± 3.5	35.7 ± 3.2	83.6 ± 8.2

[a] Values are mean ± standard deviation.

[b] For all compounds the time to maximum concentration of drug in serum was 15 min.

[c] By Student's *t* test, values for BMY 28100 differ significantly from those of cefaclor ($P < 0.01$ for the maximum concentration of drug in serum [C_{max}]; $P < 0.001$ for the other parameters). The half-life ($t_{1/2}$) of BMY 28100 was significantly longer than that of cephalexin ($P < 0.001$). $AUC_{0-2.5}$, Area under the concentration-time curve from 0 to 2.5 h after drug administration.

TABLE 3. Oral therapeutic efficacy of BMY 28100 and reference compounds in systemically infected mice[a]

Organism	Challenge dose (CFU)	PD_{50}/treatment (mg/kg)[b]		
		BMY 28100	Cefaclor	Cephalexin
Streptococcus pyogenes	9×10^3	0.08 (0.05–0.10)	1.4 (1.1–1.9)	3.9 (2.6–5.9)
Streptococcus pneumoniae	6×10^3	1.0 (0.7–1.5)	5.4 (3.5–8.6)	21 (16–29)
Staphylococcus aureus				
Strain lacking β-lactamase	5×10^6	0.04 (0.03–0.06)	0.07 (0.04–0.10)	0.07 (0.05–0.11)
Penicillinase producer	1×10^9	18 (13–23)	>400	28 (24–33)
Penicillinase producer	1×10^9	19 (14–26)	>400	50 (36–69)
Haemophilus influenzae (penicillinase producer)	4×10^7	3.1 (1.6–6.0)	6.2 (2.9–14)	14 (6.9–30)
Proteus mirabilis	4×10^6	1.5 (1.1–2.0)	1.5 (1.2–1.9)	14 (11–19)
Escherichia coli	7×10^6	2.0 (1.6–2.5)	1.8 (1.3–2.3)	11 (7.8–16)
Klebsiella pneumoniae	8×10^6	2.8 (1.9–4.2)	2.1 (1.6–2.7)	15 (12–20)

[a] Animals were treated twice. Those infected with streptococci and *Staphylococcus aureus* (strain lacking β-lactamase) were treated at 1 and 3.5 h following infection; all other animals were treated at 0 and 2 h following infection.

[b] PD_{50}, 50% protective dose; values in parentheses are 95% confidence limits.

of BMY 28100, cefaclor, and cephalexin in a hamster model of pseudomembranous colitis (2, 6) is in progress.

The oral therapeutic efficacy of BMY 28100 in systemically infected mice was congruent with its activity in vitro. BMY 28100 is currently in clinical trial.

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