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Comparative Antibacterial Activity of the New Oral Cephalosporin BMY-28100

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The in vitro activity of BMY-28100 was compared with that of four other oral cephalosporins against gram-positive cocci, *Branhamella catarrhalis* and *Haemophilus influenzae*. BMY-28100 showed 5–20 times better activity against staphylococci and streptococci. Methicillin-resistant staphylococci and enterococci were resistant to the drug. *Branhamella catarrhalis* and *Haemophilus influenzae* strains were moderately susceptible. Time-kill curve studies showed BMY-28100 to be equally as active as benzylpenicillin, amoxycillin, flucloxacillin and cefaclor. By virtue of its in vitro spectrum, BMY-28100 can be considered a potentially useful agent for treatment of respiratory tract infections.

BMY-28100 is a new semisynthetic cephalosporin structurally similar to other orally absorbed cephalosporins which have a 7-phenylglycyl side-chain. This new cephalosporin has exhibited an excellent safety profile in animals and in single dose human studies (Investigator's Brochure, Bristol Myers, Belgium). We compared the activity of this new drug with other oral cephalosporins, cephalothin, amoxycillin, benzylpenicillin and erythromycin against gram-positive cocci, *Haemophilus influenzae* and *Branhamella catarrhalis*. MICs were determined by a standard serial two-fold agar dilution technique (1). MICs for non-fastidious organisms were determined on Mueller-Hinton (MH) agar (BBL, USA). MICs for streptococci and *Branhamella catarrhalis* were determined on MH agar supplemented with 5 % defibrinated sheep blood. The antibiotic susceptibility of *Haemophilus influenzae* was evaluated on MH agar supplemented with 1 % hemoglobin (BBL) and 1 % isovitaleX (BBL). All culture plates were incubated at 35 °C for 18 h. Data were expressed as the geometric mean MICs and the concentrations necessary to inhibit 50 % and 90 % of the strains respectively. The bactericidal activity of BMY-28100 and the reference compounds was determined by exposing organisms to four-fold concentrations of the antibiotics in MH broth for staphylococci, Todd-Hewitt broth for streptococci and MH broth supplemented with 2 % Fildes extract for *Haemophilus influenzae* using the NCCLS broth macro-dilution procedure (1). Approximately 10^6 organisms/ml were inoculated into 20 ml broth containing four times the MIC of the respective drug. Cultures were incubated and shaken in Erlenmeyer flasks at 37 °C. At appropriate time intervals samples were withdrawn and the number of viable cells was determined by plate count.

BMY-28100 was active against penicillinase-negative and -positive staphylococci in concentrations eight times lower than those of the other oral cephalosporins. No activity against methicillin-resistant strains was recorded. Against streptococci of groups A, B, C and G, the viridans streptococci and *Streptococcus pneumoniae*, BMY-28100 was generally ten times more active than the other cephalosporins. Pneumococcal strains were collected in 1985/86 during a study on the antibiotic resistance and capsular serotypes of this organism in Switzerland. Resistance to benzylpenicillin (MIC $\geqslant$ 2 mg/l) was not observed, but occasionally strains with intermediate susceptibility to penicillin (MICs 0.12–1 mg/l) were found (unpublished observation). Only moderate activity of BMY-28100 against these latter strains was observed. All enterococci were resistant to BMY-28100. The drug showed moderate activity against *Branhamella catarrhalis* and *Haemophilus influenzae*, and was four times less active against penicillinase-producing *Haemophilus influenzae* strains than against pencillinase-negative strains. The killing curves showed BMY-28100 to be equally as active as the other antibiotics tested.

This study showed that the activity of BMY-28100 compares favorably with that of other oral cephalosporins against many bacteria causing infections of the respiratory tract. The drug showed excellent activity against staphylococci and streptococci, with the exception of enterococci. Against *Branhamella catarrhalis* and *Haemophilus influenzae*, BMY-28100 exhibited moderate activity, as was observed with the older oral cephalosporins. Pharmacokinetic investiga-

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Table 1: Comparative activity of BMY-28100 and other antibiotics against gram-positive cocci, *Haemophilus influenzae* and *Branhamella catarrhalis*.

Organism (n)	Antibiotic	MIC (mg/l)			
		Mean	Range	MIC50	MIC90
Methicillin-susceptible *Staphylococcus aureus* (10)	BMY-28100	0.50	0.25–1	0.25	1
	cefaclor	2.83	1 –16	2	8
	cephalexin	4	1 –16	4	8
	cefadroxil	5.28	1 –16	4	16
	RO 19-5247	3.73	2 –8	2	8
	cephalothin	0.15	0.06–0.25	0.12	0.25
	amoxycillin	0.33	0.06–2	0.25	1
	erythromycin	59.7	0.5 – > 256	256	> 256
Methicillin-resistant *Staphylococcus aureus* (10)	BMY-28100	64	32 –256	64	64
	cefaclor	55.7	16 –128	32	128
	cephalexin	128	64 –256	128	256
	cefadroxil	104	32 –256	64	128
	RO 19-5247	147	8 – > 256	64	256
	cephalothin	1.32	0.25–16	1	4
	amoxycillin	11.3	0.25–32	16	32
	erythromycin	73.5	0.5 – > 256	2	> 256
Methicillin-susceptible coagulase-negative staphylococci (10)	BMY-28100	0.46	0.12–2	0.5	1
	cefaclor	1.67	0.12–8	2	4
	cephalexin	3.27	0.5 –32	2	16
	cefadroxil	1.83	0.5 –8	2	4
	RO 19-5247	2.24	0.03–16	2	8
	cephalothin	0.16	0.03–0.5	0.12	0.25
	amoxycillin	1.6	0.25–8	2	4
	erythromycin	0.27	⩽ 0.01 – > 256	0.03	256
Methicillin-resistant coagulase-negative staphylococci (13)	BMY-28100	4.95	1 –128	2	32
	cefaclor	14.3	4 –64	8	16
	cephalexin	24.5	16 –128	16	64
	cefadroxil	13.6	4 –256	8	128
	RO 19-5247	14.3	4 – > 256	8	128
	cephalothin	0.77	0.25–64	0.5	1
	amoxycillin	19.8	4 –128	8	64
	erythromycin	0.65	0.01 – > 256	0.06	> 256
Group A streptococci (10)	BMY-28100	0.03	0.01–0.06	0.01	0.03
	cefaclor	0.33	0.12–0.5	0.25	0.5
	cephalexin	0.93	0.5 –4	0.5	1
	cefadroxil	0.93	0.5 –4	0.5	1
	RO 19-5247	0.01	⩽ 0.01–0.03	⩽ 0.01	0.01
	amoxycillin	0.01	⩽ 0.01–0.01	⩽ 0.01	0.01
	erythromycin	0.01	⩽ 0.01–0.06	⩽ 0.01	0.03
Group B streptococci (10)	BMY-28100	0.16	0.12–0.25	0.12	0.25
	cefaclor	2.64	0.5 –4	2	4
	cephalexin	6.5	4 –8	4	8
	cefadroxil	6.9	4 –8	4	8
	RO 19-5247	0.06	0.06	0.06	0.06
	amoxycillin	0.01	⩽ 0.01–0.25	⩽ 0.01	0.12
	erythromycin	0.01	⩽ 0.01–0.06	⩽ 0.01	0.03
Group C streptococci (7)	BMY-28100	0.03	0.01–0.06	0.03	0.03
	cefaclor	0.37	0.12–1	0.25	0.5
	cephalexin	0.45	0.25–1	0.25	8
	cefadroxil	0.34	0.06–0.5	0.25	0.5
	RO 19-5247	0.01	⩽ 0.01–0.01	⩽ 0.01	0.01
	amoxycillin	⩽ 0.01	⩽ 0.01	⩽ 0.01	⩽ 0.01
	erythromycin	0.01	⩽ 0.01–0.01	⩽ 0.01	0.01

Table 1 (continued)

Organism (n)	Antibiotic	MIC (mg/l)			
		Mean	Range	MIC50	MIC90
Group G streptococci (10)	BMY-28100	0.03	0.03–0.06	0.03	0.06
	cefaclor	0.93	0.5 –1	0.5	1
	cephalexin	1	1	1	1
	cefadroxil	0.87	0.25–1	0.25	1
	RO 19-5247	0.01	⩽0.01–0.01	⩽0.01	0.01
	amoxycillin	0.01	⩽0.01–0.25	⩽0.01	0.06
	erythromycin	0.02	⩽0.01–0.06	0.01	0.03
Streptococcus faecalis (10)	BMY-28100	17.2	8 –32	16	32
	cefaclor	68.5	32 –128	64	128
	cephalexin	128	128	128	128
	cefadroxil	64	64	64	64
	RO 19-5247	39.4	2 –256	64	256
	amoxycillin	0.76	1 –0.5	0.5	1
	erythromycin	0.62	0.25–2	0.51	1
Streptococcus pneumoniae MIC of penicillin ⩽0.06 mg/l (131)	BMY-28100	0.12	4 –0.06	0.06	0.12
	cefaclor	0.69	4 –0.12	0.5	1
	RO 19-5247	0.01	0.25– ⩽0.01	⩽0.01	0.03
	Penicillin G	0.01	0.06– ⩽0.01	⩽0.01	0.01
	amoxycillin	0.01	0.12– ⩽0.01	⩽0.01	0.01
	erythromycin	0.03	256 – ⩽0.01	0.01	0.06
	cephalexin[a]	2.16	2 –4	2	4
	cefadroxil[a]	5.88	2 –8	4	8
Streptococcus pneumoniae MIC of penicillin ⩾0.12 mg/l (14)	BMY-28100	0.53	4 –0.06	0.5	4
	cefaclor	4.20	32 –0.5	4	32
	RO 19-5247	0.20	2 – ⩽0.01	0.25	2
	penicillin G	0.43	1 –0.12	0.5	1
	amoxycillin	0.12	1 –0.03	0.06	0.5
	erythromycin	0.03	0.06– ⩽0.01	0.03	0.06
Viridans streptococci (8)	BMY-28100	0.39	0.25–0.5	0.25	1
	cefaclor	5.19	2 –16	4	16
	cephalexin	9.51	4 –16	8	16
	cefadroxil	16	8 –32	16	32
	RO 19-5247	0.06	⩽0.01–0.12	0.06	0.12
	amoxycillin	⩽0.01	⩽0.01	⩽0.01	⩽0.01
	erythromycin	0.01	⩽0.01–0.01	⩽0.01	0.01
Branhamella catarrhalis (14)	BMY-28100	2.21	0.25–32	2	8
	cefaclor	1.4	0.25–16	1	4
	cephalexin	4.2	1 –32	2	16
	cefadroxil	9.28	2 –128	8	64
	RO 19-5247	0.3	0.01–8	0.25	4
	amoxycillin	0.37	⩽0.01–16	0.25	8
	erythromycin	0.09	⩽0.01–1	0.06	0.5
Nitrocefin negative *Haemophilus influenzae* (23)	BMY-28100	1.31	0.12–4	1	2
	cefaclor	7.53	4 –32	8	8
	cephalexin	17.5	2 –64	16	64
	cefadroxil	51.8	8 –256	32	128
	RO 19-5247	0.02	⩽0.01–0.5	0.01	0.06
	amoxycillin	0.7	0.25–1	0.5	1
	erythromycin	2.87	1 –8	2	4
Nitrocefin positive *Haemophilus influenzae* (10)	BMY-28100	5.66	2 –16	4	8
	cefaclor	3.48	2 –8	2	4
	cephalexin	17.2	4 –64	16	32
	cefadroxil	24.25	4 –128	16	64
	RO 19-5247	0.01	⩽0.01–0.03	⩽0.01	0.03
	amoxycillin	22.6	16 –32	16	32
	erythromycin	3.25	1 –8	2	8

[a] Results for 9 strains only.

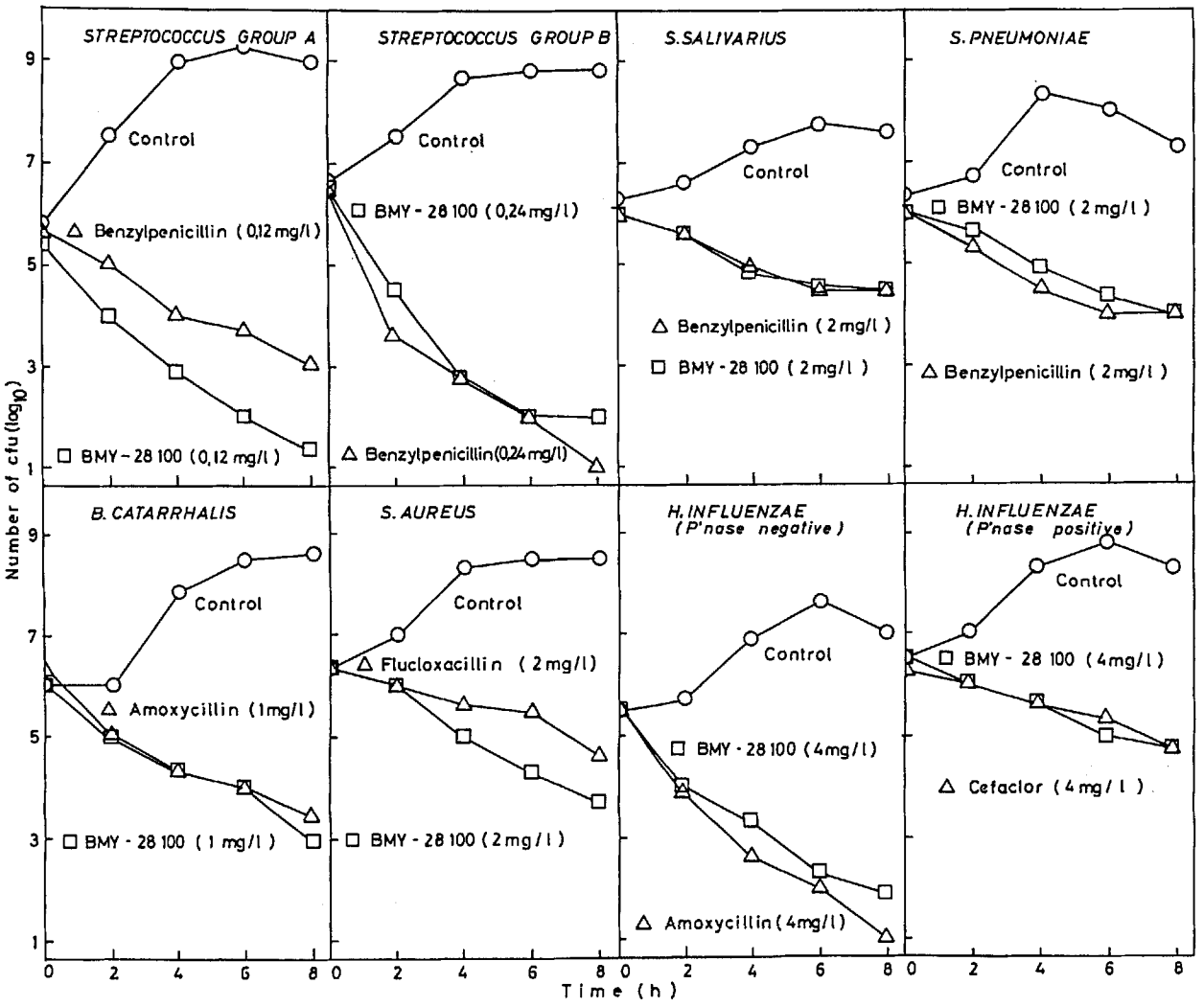

Figure 1: Rates of killing of bacteria by BMY-28100 and comparative standard compounds.

tions with BMY-28100 have shown mean peak concentrations after doses of 250, 500 and 1000 mg of 6.2 ± 0.6, 9.3 ± 1.1 and 17.7 ± 2.2 mg/l respectively (Investigator's Brochure, Bristol Myers). Other investigators have demonstrated excellent activity of BMY-28100 against many gram-negative enterobacteria (26th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, 1986, Abstracts No. 646-660). Thus BMY-28100 has a broad spectrum of antibacterial activity which warrants clinical trials.

References

1. **National Committee for Clinical Laboratory Standards:** Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard M7-A. Villanova, PA, 1985.