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NOTES

Comparative In Vitro Antibacterial Activity of Sch 34343, a Novel Penem Antibiotic

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Using agar and broth dilutions, Sch 34343 was found to be highly active against gram-positive and gram-negative aerobic, facultatively anaerobic, and anaerobic bacteria, with the exceptions of enterococci, methicillin-resistant staphylococci, and *Pseudomonas* spp., which were resistant. Comparisons were made with imipenem, cefuroxime, cefotaxime, gentamicin, clindamycin, and metronidazole.

The first penem antibiotic to be extensively evaluated was Sch 29482, which chemically is 5R:6S:8R-6 (1-hydroxyethyl) 2-ethylthio-penem-3-carboxylic acid (2; Fig. 1). The antibacterial activity of Sch 29482 was characterized by stability to hydrolysis by bacterial β-lactamases and high activity against gram-negative and gram-positive bacteria, including *Serratia* spp., *Acinetobacter* spp., *Staphylococcus aureus*, and *Bacteroides fragilis*, but not *Pseudomonas aeruginosa* and enterococci (1, 4, 5). A clear drawback with Sch 29482 is an extensive metabolism in humans, resulting in only 2% or less urinary recovery of the dose administered (3). The antibiotic therefore has not undergone extensive clinical studies. In this report, the comparative in vitro activity of a new penem derivative, Sch 34343, SR:6S:8R-2-carbamoyloxy-ethylthio-6-(1-hydroxyethyl)-penem-3-carboxylic acid (Fig. 1) is described.

(This study was presented at the 24th Interscience Conference on Antimicrobial Agents and Chemotherapy, 8 to 10 October 1984, Washington, D.C.)

Sch 34343 and gentamicin were obtained from Schering Corp., Bloomfield, N.J. Other comparative agents used were cefotaxime (Hoechst, Frankfurt, West Germany), cefuroxime (Glaxo, Greenford, Middlesex, England), clindamycin (The Upjohn, Co., Kalamazoo, Mich.), imipenem (Merck, Sharp & Dohme, Rahway, N.J.) and metronidazole (Leo-Rhodia, Helsingborg, Sweden). All antibiotics were provided with known potency.

When aerobic test conditions were used, the medium was Mueller-Hinton agar or broth (Merck, Darmstadt, West Germany). Five percent lysed citrated horse blood was added when gram-positive cocci were tested. For *Haemophilus influenzae*, McLeod Gc agar base (Difco Laboratories, Detroit, Mich.), 36 g/1,000 mg, and Bacto agar (Difco), 1 g/1,000 ml supplemented with 1% hemoglobin powder (Oxoid) and 1% IsoVitaleX (BBL Microbiology Systems, Cockeysville, Md.), were used. For anaerobic bacteria, brain heart infusion agar (Oxoid) was used and supplemented with 0.5% yeast extract (Oxoid), 0.05% cysteine-hydrochloride (Merck), 4% horse blood, vitamin K (Menadion; Merck), and hemin (Kebo-Grave, Stockholm, Sweden). All media were prepared within 2 days before use.

All strains studied were clinical isolates. Some of them were obtained directly from patient samples; others had been stored lyophilized. In no case had a strain been passaged more than three times in the laboratory.

Agar dilution MICs were determined by incorporating the antibiotics in twofold dilutions into the agar at final concentrations ranging from 64 to 0.0625 μg/ml. Overnight cultures of the test strains were applied onto agar plates with a diameter of 8.5 cm, using a modified Steers replicator giving 0.010 ml per spot. The inocula used were 10^4 to 7×10^5 and 10^6 to 7×10^7 CFU per application and are referred to below as low and high inocula, respectively. Aerobes were incu-

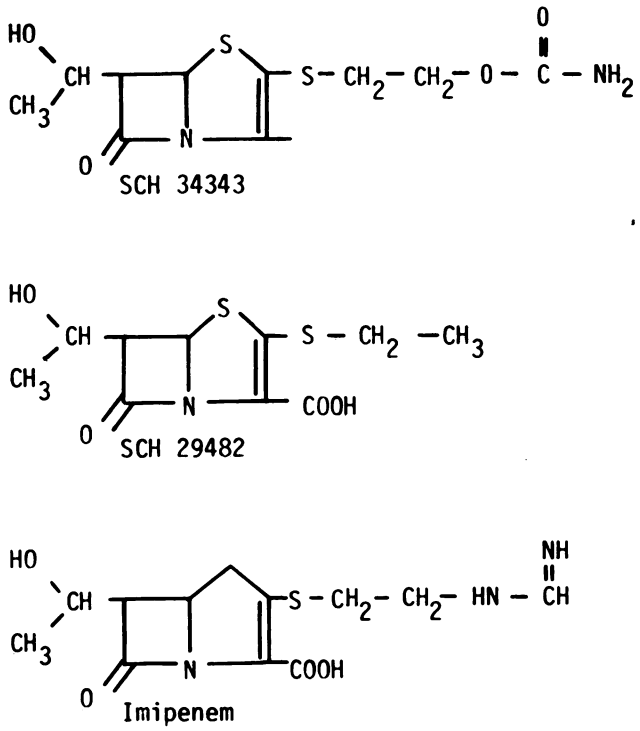

FIG. 1. Chemical structures of Sch 34343, Sch 29482, and imipenem.

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TABLE 1. Agar dilution MICs of Sch 34343 and comparative agents

Species (no. of strains)	Antibiotic	MIC (μg/ml) against high or low inoculum[a]					
		MIC range		MIC_{50}		MIC_{90}	
		Low	High	Low	High	Low	High
Escherichia coli (40)	Sch 34343	0.13–0.5	0.5–16	0.5	4	0.5	8
	Cefotaxime	≤0.06–0.13	0.5–16	≤0.06	8	0.13	16
	Cefuroxime	1–16	2–32	4	8	8	16
	Imipenem	0.25–0.5	0.25–16	0.25	4	0.25	16
	Gentamicin	0.25–16	0.5–64	0.5	2	1	4
Klebsiella pneumoniae (39)	Sch 34343	0.25–4	0.5–32	0.5	1	1	8
	Cefotaxime	<0.06–1	≤0.06–64	≤0.06	1	0.5	16
	Cefuroxime	0.5–≥64	1–64	4	8	32	>64
	Imipenem	0.25–2	0.5–8	0.5	2	1	4
	Gentamicin	0.125–0.5	0.25–2	0.25	1	0.5	1
Proteus mirabilis (31)	Sch 34343	4–≥64	0.5–2	1	64	2	>64
	Cefotaxime	≤0.06–0.125	2–≥64	≤0.06	32	≤0.06	>64
	Cefuroxime	1–16	4–64	2	64	4	>64
	Imipenem	1–8	64–≥64	8	≥64	8	>64
	Gentamicin	0.25–8	1–64	0.5	2	1	2
Proteus vulgaris (15)	Sch 34343	1–2	8–≥64	1	16	1	>64
	Cefotaxime	≤0.06	2–32	≤0.06	16	≤0.06	>64
	Cefuroxime	1–8	8–64	2	64	4	>64
	Imipenem	2–8	64–	8	>64	8	>64
	Gentamicin	0.5–8	2–64	1	2	2	4
Providencia rettgeri (7)	Sch 34343	1–≥64	8–≥64	2	16	2	>64
	Cefotaxime	≤0.06–32	32–≥64	≤0.06	>64	16	>64
	Cefuroxime	2–≥64	64–≥64	>64	>64	>64	>64
	Imipenem	2–≥64	16–≥64	4	64	8	>64
	Gentamicin	0.5–64	2–≥64	1	2	32	64
Morganella morganii (5)	Sch 34343	0.5–8	0.5–≥64	0.5	32	8	>64
	Cefotaxime	≤0.06–≥64	≥64	≤0.06	64	>64	>64
	Cefuroxime	2–≥64	>64	32	>64	>64	>64
	Imipenem	0.5–8	1≥64	4	64	8	>64
	Gentamicin	0.25–2	0.5–4	0.5	2	2	4
Acinetobacter spp. (3)	Sch 34343	4–8	4–32	8	32	8	32
	Cefotaxime	16–>64	16–>64	16	>64	>64	>64
	Cefuroxime	32–>64	64	64	>64	>64	>64
	Imipenem	0.5–4	0.5–2	0.5	2	4	2
	Gentamicin	0.5–4	0.5–4	2	2	4	4
Serratia spp. (13)	Sch 34343	1–8	2–16	2	8	8	16
	Cefotaxime	0.13–16	64–>64	0.5	>64	16	>64
	Cefuroxime	64–>64	>64	>64	>64	>64	>64
	Imipenem	1–32	16–32	1	16	2	32
	Gentamicin	0.5–4	0.5–4	1	1	1	4
Pseudomonas aeruginosa (21)	Sch 34343	>64	>64	>64	>64	>64	>64
	Cefotaxime	8–>64	16–>64	>64	>64	>64	>64
	Cefuroxime	>64	>64	>64	>64	>64	>64
	Imipenem	1–16	1–32	4	8	8	16
	Gentamicin	0.25–4	0.5–4	0.5	2	1	4
Haemophilus influenzae (10)	Sch 34343	0.25–1	0.5–8	1	1	1	8
	Cefotaxime	0.06–2	0.06–4	0.06	0.06	0.06	0.06
	Cefuroxime	0.25–2	0.5–4	0.5	1	1	1
	Imipenem	NT[b]	NT	NT	NT	NT	NT
	Gentamicin	1–64	1–>64	2	2	2	2
Staphylococcus aureus (penicillinase negative) (14)	Sch 34343	0.13–0.25	0.13–0.25	0.13	0.13	0.13	0.25
	Cefotaxime	2–4	2–4	2	2	4	4
	Cefuroxime	1–2	1–2	1	2	2	2
	Imipenem	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
	Gentamicin	0.13–0.5	0.13–8	0.25	1	0.5	2

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TABLE 1—*Continued*

Species (no. of strains)	Antibiotic	MIC (μg/ml) against high or low inoculum[a]					
		MIC range		MIC_{50}		MIC_{90}	
		Low	High	Low	High	Low	High
Staphylococcus aureus (penicillinase producing) (21)	Sch 34343	0.13	0.13–0.25	0.13	0.13	0.13	0.25
	Cefotaxime	1–2	2–4	2	2	2	4
	Cefuroxime	1–2	1–2	2	2	2	2
	Imipenem	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
	Gentamicin	0.13–0.5	0.5–1	0.13	0.5	0.25	0.5
Staphylococcus epidermidis (methicillin sensitive) (16)	Sch 34343	≤0.06–0.25	0.13–0.5	0.25	0.25	0.25	0.5
	Cefotaxime	0.25–4	0.5–4	1	2	4	4
	Cefuroxime	0.25–2	0.25–4	1	1	2	2
	Imipenem	≤0.06	≤0.06–0.5	≤0.06	≤0.06	≤0.06	0.13
	Gentamicin	≤0.06–2	≤0.06–16	0.13	0.25	1	1
Staphylococcus epidermidis (methicillin resistant) (6)	Sch 34343	0.25–>64	4–>64	1	>64	>64	>64
	Cefotaxime	0.5–>64	4–>64	>64	>64	>64	>64
	Cefuroxime	1–>64	1–>64	>64	>64	>64	>64
	Imipenem	0.13–64	1–>64	0.25	16	32	>64
	Gentamicin	0.06–32	0.13–32	0.13	0.13	32	32
β-*Streptococci, group A* (17)	Sch 34343	≤0.06–32	≤0.06–1	≤0.06	1	0.13	1
	Cefotaxime	≤0.06–0.25	≤0.06–0.5	≤0.06	≤0.06	≤0.06	0.25
	Cefuroxime	≤0.06–0.25	≤0.06–0.5	≤0.06	≤0.06	0.13	0.13
	Imipenem	≤0.06	≤0.06–0.25	≤0.06	0.13	≤0.06	0.25
	Gentamicin	4–8	4–8	8	8	8	8
α-*Streptococci* (11)	Sch 34343	≤0.06–4	≤0.06–16	≤0.06	0.5	4	8
	Cefotaxime	≤0.06–2	≤0.06–8	≤0.06	0.13	2	4
	Cefuroxime	≤0.06–8	≤0.06–16	0.25	1	2	16
	Imipenem	≤0.06–4	≤0.06–8	0.06	0.25	2	2
	Gentamicin	0.13–16	0.25–16	1	8	8	16
Enterococci (19)	Sch 34343	≤0.06–32	≤0.06–64	8	8	8	16
	Cefotaxime	≤0.06–>64	0.25–>64	>64	>64	>64	>64
	Cefuroxime	0.25–>64	0.5–>64	>64	>64	>64	>64
	Imipenem	≤0.06–8	0.13–8	2	2	4	4
	Gentamicin	4–32	4–16	8	8	16	16
Bacteroides fragilis (20)	Sch 34343	≤0.06–1	0.25–1	≤0.06	0.5	0.13	0.5
	Imipenem	≤0.06–2	≤0.06–4	0.5	2	1	4
	Clindamycin	≤0.06–2	≤0.06–1	0.25	0.5	1	1
	Metronidazole	0.25–1	0.25–2	0.5	0.5	1	2
Clostridium spp. (24)	Sch 34343	0.18–8	0.25–16	0.25	1	1	2
	Imipenem	0.13–4	0.5–8	0.5	2	1	4
	Clindamycin	>0.06–2	≤0.06–2	0.13	1	2	2
	Metronidazole	0.13–4	0.5–16	0.25	1	0.5	16
Peptostreptococcus spp. (6)	Sch 34343	0.13–0.5	0.13–2	0.13	0.13	0.5	2
	Imipenem	0.13–0.5	0.25–8	0.13	0.25	0.5	8
	Metronidazole	>0.06–>64	>0.06–>64	0.5	0.5	>64	>64

[a] Low inoculum 10^4 to 7×10^5 = CFU application; high inoculum, 10^6 to 7×10^7 = CFU application.
[b] NT, Not tested.

bated for 24 h, and anaerobes for 48 h, at 37°C. MICs were the lowest concentrations that completely inhibited growth. For selected strains, broth dilution MICs were performed. One milliliter of broth was used for each test, and antibiotics were added in twofold dilution to give final concentrations ranging from 256 to 0.0625 μg/ml. The inocula used varied from 10^4 to 7×10^5 and from 10^6 to 7×10^7 CFU/ml. MICs were the lowest antibiotic concentrations inhibiting visible growth after 24 h of incubation at 37°C.

Table 1 shows the agar dilution MICs of Sch 34343 and comparative agents against low and high inocula. At the low inoculum, 1 μg/ml or less was required to inhibit 90% of tested strains of *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, or *H. influenzae*. Using the same inoculum, 90% of strains of *Proteus mirabilis* and *Providencia rettgeri* were inhibited by 2 μg/ml. With *Morganella morganii*, *Acinetobacter spp.*, and *Serratia spp.*, 8 μg/ml was required for inhibition of 90% of the strains. *Pseudomonas aeruginosa* was resistant to Sch 34343. At the high inoculum, MICs of Sch 34343 increased 2 to ≥64 times. In comparison with the two cephalosporins tested, Sch 34343 was generally more active than cefuroxime at all inocula, whereas cefotaxime was more active at the low inoculum and less active at the high. In fact, the cefotaxime MICs

TABLE 2. Agar dilution versus broth dilution MICs of Sch 34343

Species (no. of strains)	No. of strains with the following MIC ratio (broth dilution/agar dilution)											
	Low inoculum[a]						High inoculum[b]					
	1	2	4	8	16	32	1	2	4	8	16	32
Escherichia coli (10)			3	4	3		3	1	3		1	2
Klebsiella pneumoniae (10)	1	2	2	2	2	1	5		3		2	
Proteus mirabilis (10)				1		9	Not evaluated					
Proteus vulgaris (5)						5	Not evaluated					
Providencia rettgeri (5)			3			2	Not evaluated					
Morganella morganii (3)			1	1		1	Not evaluated					
Acinetobacter spp. (3)	3						3					
Serratia spp. (5)	5						5					
Staphylococcus aureus (12)	7	3	1	1			11	1				
Staphylococcus epidermidis (methicillin susceptible) (5)	3	2					5					
Enterococci (10)	10						Not evaluated					

[a] Low inoculum: 10^4 to 7×10^5 CFU per application (agar dilution) or per ml (broth dilution).

[b] High inoculum: 10^6 to 7×10^7 CFU per application (agar dilution) or per ml (broth dilution).

differed only marginally from those of cefuroxime at the high inoculum. Against these species, Sch 34343 seemed slightly more effective than imipenem at both the low and the high inoculum. Imipenem, however, was considerably more active against *Pseudomonas aeruginosa*. Gentamicin was as active as Sch 34343 against *E. coli* and *K. pneumoniae* and slightly more active against the other gram-negative aerobic bacilli, especially at the high inoculum. An exception was *Providencia rettgeri*, which was more susceptible to Sch 34343 than to gentamicin.

Sch 34343 and imipenem were the two agents most active against the tested strains of gram-positive aerobic cocci. With the exception of methicillin-resistant *Staphylococcus epidermidis*, all strains were inhibited by 0.25 μg/ml or less, also at the high inoculum. Imipenem was slightly more active than Sch 34343 against these species as well as against the streptococcal species tested. The inoculum dependence was less pronounced for gram-positive than for gram-negative organisms when Sch 34343 was considered.

Sch 34343 was equally or more active than imipenem, clindamycin, and metronidazole against *B. fragilis*, *Clostridium* spp. (mainly *C. perfringens*), and peptostreptococci, a few of the latter being resistant to metronidazole. The MICs of Sch 34343 for *H. influenzae* and anaerobes may have been higher than the true ones since, after these studies were completed, it came to our attention that Sch 34343 is unstable in the presence of cysteine (G. Miller, Schering Corp., personal communication), which was used to supplement the media for these species in our study.

Table 2 shows the differences observed when agar and broth dilution MICs were compared for Sch 34343. Broth dilution MICs were 8.5 times (mean) higher than agar dilution ones.

In summary, this study, in which very high bacterial inocula were used, showed that Sch 34343 had an antibacterial activity superior to that of the newer cephalosporins with regard to gram-positive pathogens and anaerobes, and similar to that of cefotaxime against gram-negative aerobic and facultatively anaerobic bacteria. In comparison with imipenem, it was more active against anaerobes and had similar activity against other species, with the exceptions of enterococci and *Pseudomonas* spp., which were more susceptible to imipenem. For both imipenem and Sch 34343, a slightly lower activity against *Proteus* spp. than against other gram-negative organisms was noted. Sch 34343 seems to have a spectrum very similar to that of Sch 29482 (1, 4, 5). From a clinical point of view, Sch 34343 is an interesting candidate for clinical trials, especially in mixed infections involving both aerobes and anaerobes and in which *Pseudomonas* is not a suspected pathogen.

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