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In Vitro Activity of U-57930E, a New Clindamycin Analog, Against Aerobic Gram-Positive Bacteria

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The in vitro activity of U-57930E, a new clindamycin analog, against aerobic gram-positive cocci was studied by microdilution broth susceptibility tests and compared with the activities of clindamycin, vancomycin, oxacillin, and ampicillin. U-57930E inhibited methicillin-susceptible *Staphylococcus aureus, Streptococcus pyogenes, Streptococcus agalactiae*, and *Streptococcus viridans* at concentrations of ≤1 μg/ml. This degree of activity was generally slightly less than that of the other antimicrobial agents tested. Methicillin-resistant *Staphylococcus aureus*, coagulase-negative staphylococci, penicillin-resistant *Streptococcus pneumoniae*, and enterococci were resistant to U-57930E. At the concentrations used, U-57930E exhibited bactericidal activity against most susceptible organisms, and a minimal effect of inoculum size was noted.

U-57930E, *cis*-4-ethyl-L-picecolic acid amide of 7-deoxy-7(*S*)-chloromethylthiolincosaminide hydrochloride hydrate (Fig. 1), is a new semisynthetic analog of clindamycin developed by The Upjohn Co., Kalamazoo, Mich. In an earlier study, the in vitro antibacterial activity of U-57930E was found to be similar to that of clindamycin and had a comparable to superior activity compared with clindamycin in experimentally infected mice (C. Lewis, K. F. Stein, and G. E. Zurenko, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 20th, New Orleans, Louisiana, abstr. no. 66, 1980). Preliminary investigation also suggests that U-57930E yields no biologically active metabolites and may thus have less of the side effects of clindamycin (The Upjohn Co.). U-57930E might therefore eventually replace clindamycin with the well-recognized gastrointestinal toxicity of clindamycin (1) being averted. To further elucidate the antimicrobial potentials of this new antibiotic, we studied its in vitro activity against gram-positive aerobic bacteria, using clindamycin, vancomycin, oxacillin, and ampicillin for comparison.

MATERIALS AND METHODS

Antibiotics. Standard susceptibility test powders were obtained from the following sources: U-57930E and clindamycin, The Upjohn Co.; oxacillin and ampicillin, Beecham Laboratories, Bristol, Tenn.; and vancomycin, Eli Lilly & Co., Indianapolis, Ind. Twofold serial dilutions of freshly prepared solutions were used in concentrations ranging from 64 to 0.01 μg/ml (from 16 μg/ml for most tests) and were delivered into microtiter wells with an automatic dispensor (MIC 2000, Dynatech Laboratories Inc., Alexandria, Va.).

Organisms. The organisms tested represented 179 strains isolated from patients at The Jewish Hospital and Medical Center of Brooklyn and State University Hospital in Brooklyn. Penicillin-resistant pneumococci were supplied by H. Bernheimer. Identification of these organisms was by the criteria of Lennette et al. (2).

Determination of MIC and MBC. Antibiotic susceptibility testing was by broth microdilution method with *Staphylococcus aureus* ATCC 25923 as control organism. Overnight cultures (4-h cultures for *Staphylococcus aureus*, enterococci and coagulase-negative staphylococci) in Trypticase soy broth supplemented with 10% sheep blood were diluted and inoculated into antibiotic-containing wells, using the MIC 2000 apparatus. Two final inocula of circa 10^5 and 10^7 colony-forming units per ml were used. The minimal inhibitory concentration (MIC) was taken as the lowest concentration of antibiotic which supported no visible growth after 24 and 48 h of incubation at 37°C.

Subcultures (0.15 ml) from the clear wells inoculated onto blood agar plates were examined after 24 and 48 h

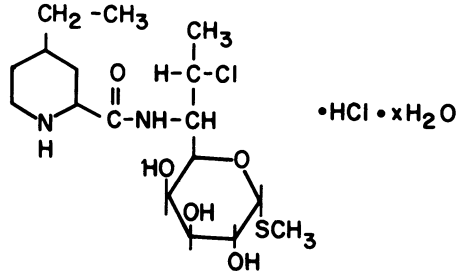

FIG. 1. Chemical structure of U-57930E.

TABLE 1. Comparative activities of antibiotics against aerobic gram-positive cocci

Bacteria	No. tested	Antibiotic[a]	MIC_{50}[b]	MIC_{90}	MIC range	MBC_{50}[c]	MBC_{90}	MBC range
Staphylococcus aureus (methicillin susceptible)	20	U	0.5	0.5	0.25–1	1	2	0.25–2
		CL	0.125	0.125	0.06–0.25	0.125	0.25	0.06–0.25
		VAN	0.5	0.5	0.5–1	0.5	1	0.5–1
		OX	0.5	2	0.125–4	0.5	2	0.125–4
		AMP	>16	>16	>16	>16	>16	>16
Staphylococcus aureus (methicillin resistant)	32	U	2	>16	1–>16	2	>16	1–>16
		CL	1	>16	0.5–>16	1	>16	0.5–>16
		VAN	0.5	1	0.5–1	0.5	1	0.5–1
		OX	>16	>16	>16	>16	>16	>16
		AMP	>16	>16	>16	>16	>16	>16
Staphylococcus spp. (coagulase negative)	30	U	1	>16	0.5–>16	1	>16	0.5–>16
		CL	0.25	>16	0.06–>16	0.25	>16	0.06–>16
		VAN	1	2	0.5–2	1	2	0.5–2
		OX	0.5	>16	0.06–>16	0.5	>16	0.06–>16
		AMP	2	>16	0.06–>16	2	>16	0.06–>16
Streptococcus pyogenes	11	U	0.25	0.5	0.25–0.5	0.25	0.5	0.25–0.5
		CL	0.03	0.06	0.03–0.06	0.06	0.125	0.03–0.125
		VAN	0.06	0.125	0.06–0.125	0.06	0.125	0.06–0.125
		OX	0.03	0.06	0.03–0.06	0.03	0.06	0.03–0.06
		AMP	0.06	0.125	0.03–0.125	0.03	0.03	0.03
Streptococcus agalactiae	8	U	0.5	1	0.5–1	0.5	1	0.5–1
		CL	0.06	0.5	0.03–0.5	0.125	0.125	0.03–0.5
		VAN	0.125	0.25	0.06–0.25	0.5	0.5	0.06–0.25
		OX	0.06	0.5	0.03–0.5	0.125	0.125	0.06–0.5
		AMP	0.03	0.03	0.03	0.03	0.03	0.03–0.125
Streptococcus pneumoniae (penicillin susceptible)	10	U	0.25	0.5	0.125–0.5	0.25	0.5	0.125–0.5
		CL	0.125	0.25	0.06–0.25	0.125	0.25	0.06–0.25
		VAN	0.5	1	0.25–1	0.5	1	0.25–1
		OX	0.125	0.125	0.03–0.125	0.125	0.125	0.03–0.125
		AMP	0.03	0.125	0.01–0.125	0.03	0.125	0.01–0.06
Streptococcus pneumoniae (penicillin resistant)	10	U	>16	>16	2–>16	>16	>16	2–>16
		CL	1	16	0.25–>16	1	16	0.25–>16
		VAN	1	1	0.5–1	0.06	0.125	0.06–0.125
		OX	8	8	4–8	1	1	0.5–1
		AMP	4	8	2–8	>16	>16	4–>16

Enterococcus spp.	29	U	≥16	>16	8->16	≥16	>16	8->16
		CL	≥16	>16	4->16	≥16	>16	4->16
		VAN	0.5	1	0.5–1	0.5	1	0.5–1
		OX	2	2	1–2	1	4	1–4
		AMP	1	1	0.5–1	1	1	0.5–1
Streptococcus viridans	17	U	0.5	0.5	0.25–0.5	0.5	0.5	0.25–0.5
		CL	0.06	0.06	≤0.01–0.06	0.06	0.06	≤0.01–0.06
		VAN	≤0.01	0.06	≤0.01–0.125	≤0.01	0.06	≤0.01–0.06
		OX	0.03	0.06	0.03–0.06	0.03	0.06	0.03–0.06
		AMP	≤0.01	0.03	≤0.01–0.125	≤0.01	0.125	≤0.01–0.125
Other *Streptococcus* spp. (β-hemolytic)	14	U	0.5	1	0.25–1	0.5	1	0.25–1
		CL	0.06	0.5	0.06–0.5	0.06	0.25	0.06–0.5
		VAN	0.125	0.125	0.06–0.125	0.06	0.125	0.03–0.125
		OX	0.03	0.06	0.03–0.06	0.03	0.06–	0.03–0.06
		AMP	0.06	0.125	0.03–0.125	0.06	0.125	0.03–0.25

[a] Abbreviations: U, U-57930E; CL, clindamycin; VAN, vancomycin; OX, oxacillin; and AMP, ampicillin.
[b] MIC values are expressed in micrograms per milliliter.
[c] MBC values are expressed in micrograms per milliliter.

of incubation at 37°C. The minimal bactericidal concentration (MBC) was defined as the lowest antibiotic concentration with at least 99.9% of the original inoculum killed.

Inoculum effect. The effect of inoculum was determined by performing the MIC and MBC at 10^5 and 10^7 colony-forming units for each organism.

RESULTS

Table 1 shows the MICs and MBCs of U-57930E compared with other antimicrobial agents. Its range of MICs and inhibitory activity against 50% (MIC_{50}) and 90% (MIC_{90}) of organisms were similar to MBC range, MBC_{50} and MBC_{90}, respectively, except against *Staphylococcus aureus* (methicillin susceptible). The MBCs against this species were seldom one or two dilutions higher than MICs. U-57930E thus demonstrated bactericidal activity against all but one of the species tested.

Inoculum effect. U-57930E MICs and MBCs were overall about 2.5-fold higher with an inoculum of 10^7 colony-forming units of *Staphylococcus aureus* than were the values obtained with an inoculum of 10^5 colony-forming units. This consistent inoculum effect was also demonstrated by clindamycin and oxacillin.

Effect of prolonged incubation. Although there was an occasional increase in MICs of U-57930E after 48 h of incubation compared with 24 h of incubation, the general pattern was one of similar values at the different incubation times.

DISCUSSION

The activity of U-57930E was judged fairly good for *Streptococcus pneumoniae* (penicillin susceptible) and *Staphylococcus aureus* (methicillin susceptible) with an MIC_{90} of 0.5 μg/ml or less for both species (Table 1). Low resistance to U-57930E was demonstrated by *Streptococcus viridans*, *Streptococcus agalactiae*, and other β-hemolytic streptococci as MIC_{90}, against these species was circa 1 μg/ml. *Enterococci*, *Streptococcus pneumoniae* (penicillin resistant), coagulase-negative *Staphylococcus*, and *Staphylococcus aureus* (methicillin resistant) were more resistant to U-57930E with MIC_{90} mostly >16 μg/ml. Methicillin-susceptible *Staphylococcus aureus* showed only slight resistance to U-57930E and clindamycin, the MIC_{50} values being 2 and 1 μg/ml, respectively. Clindamycin, however, showed overall much better activity than U-59730E except for *Enterococcus*, which showed a similar degree of resistance to both drugs. U-57930E had four- to eightfold-higher MIC_{90} values than did clindamycin for the rest of the bacteria tested. This contrasts with recent reports of better activity of U-57930E than of clindamycin against anaerobic bacteria (V. K. Dhawan, M. B. Bansal, and H. Thadepalli,

abstr. no. 430; M. R. Karim and S. M. H. Qadri, abstr. no. 429, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 21st, Chicago, Ill., 1981).

U-57930E was also far less active than vancomycin for all bacterial species tested, except for *Streptococcus pneumoniae* (penicillin susceptible). Organisms that were susceptible to oxacillin and ampicillin had lower MIC_{90} values than for U-57930E.

Based on our results, U-57930E appears to be slightly less active than clindamycin in vitro against aerobic bacteria. The clinical significance of this observation will await further studies on the drug, especially as Lewis et al. (20th ICAAC, abstr. no. 66) have reported a 2- to 20-times-higher protective activity than clindamycin in mice experimentally infected with *Staphylococcus aureus, Streptococcus pyogenes*, and *Streptococcus pneumoniae*.

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