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In Vitro Evaluation of DuP 105 and DuP 721, Two New Oxazolidinone Antimicrobial Agents

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DuP 105 and DuP 721 are two members of the oxazolidinones, a new class of synthetic antimicrobial agents with activity against gram-positive bacteria. In vitro tests compared the two new drugs with five other antimicrobial agents against 216 gram-positive isolates representing 4 genera and 10 species. DuP 721 MICs for 50% of the strains tested (MIC_{50}s) ranged from 2.0 to 8.0 μg/ml, DuP 105 MIC_{50}s ranged from 4.0 to 16 μg/ml, and vancomycin MIC_{50}s ranged from 0.25 to 1.0 μg/ml. Methicillin-resistant and -susceptible staphylococci were susceptible to ciprofloxacin, vancomycin, and DuP 721.

DuP 105 and DuP 721 are two new antimicrobial agents belonging to the oxazolidinone series, a new class of synthetic antibacterial agents which has been developed by scientists at E. I. du Pont de Nemours & Co. (A. M. Slee, M. A. Wuonola, R. J. McRipley, I. Zajac, M. J. Zawada, P. T. Bartholomew, W. A. Gregory, and M. Forbes, Program Abstr. 27th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 244, 1987; D. C. Eustice and A. M. Slee, 27th ICAAC, abstr. no. 246, 1987). Both drugs are structurally unrelated to any other class of antimicrobial agents currently available. Figure 1 displays the structures of DuP 105 and DuP 721. DuP 721 may be administered orally, whereas DuP 105 may have both oral and parenteral formulations. Preliminary pharmacokinetic studies in experimental animals suggest that peak levels in blood of at least 16 μg/ml might be anticipated for both drugs (I. Zajac, G. N. Lam, H. E. Hoffman, and A. M. Slee, 27th ICAAC, abstr. no. 247, 1987).

This report describes in vitro studies which compare the activity of DuP 105 and DuP 721 with that of vancomycin, ciprofloxacin, erythromycin, cefaclor, and ampicillin. Broth microdilution tests were performed with 216 bacterial isolates; the species that were represented are identified in Table 1. The testing procedure followed the procedures outlined by the National Committee for Clinical Laboratory Standards (1). Cation-supplemented Mueller-Hinton broth was used. The inocula were approximately 5×10^5 CFU/ml, and MICs were recorded after 16 to 18 h at 35°C in ambient air. When testing nonenterococcal streptococci, 3 to 5% lysed horse blood was added. Fifty isolates of *Haemophilus influenzae* were also tested with 3 to 5% lysed horse blood and NAD (25 μg/ml) added to the broth.

Table 1 identifies the gram-positive species that were studied and summarizes the results of the studies. Against most gram-positive microorganisms, DuP 721 was approximately twice as potent as DuP 105. On a weight-to-weight basis, vancomycin and ciprofloxacin were more potent than the two oxazolidinones. Methicillin-resistant staphylococci were just as susceptible as methicillin-susceptible staphylococci to DuP 721, DuP 105, vancomycin, and ciprofloxacin. Compared with nonenterococcal streptococci, the enterococci were less susceptible to all seven study drugs. The 50 *H. influenzae* isolates were resistant; all DuP 105 MICs were 64 μg/ml, and all DuP 721 MICs were 32 μg/ml (data not shown). β-Lactamase-producing strains of *Staphylococcus* spp. were less susceptible to cefaclor and to ampicillin than were β-lactamase-negative strains. The antistaphylococcal potency of ciprofloxacin was greater than that of vancomycin and of the oxazolidinones. Ampicillin was more potent than the other study drugs against *Streptococcus* spp., *Enterococcus* spp., *Listeria monocytogenes*, and β-lactamase-negative strains of *Staphylococcus* spp. The two oxazolidinone antimicrobial agents have been found to be bacteriostatic by time-kill studies (J. S. Daly, G. M. Eliopoulos, E. Reiszner, and R. C. Moellering, Jr., 27th ICAAC, abstr. no. 245, 1987).

Human pharmacokinetic studies have not yet been performed. Consequently, MIC breakpoints for defining the susceptible and resistant categories cannot be firmly established. However, on the basis of preliminary studies with

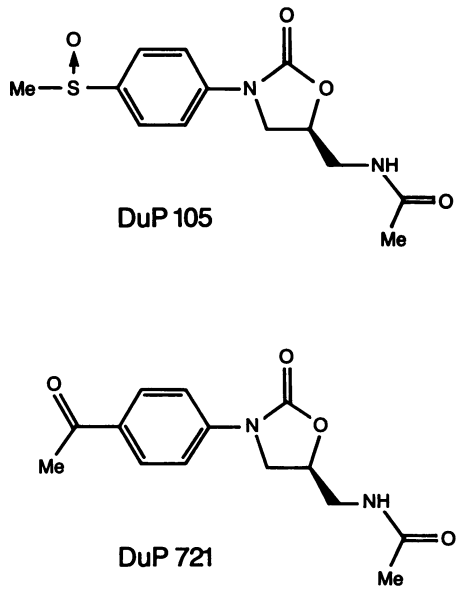

FIG. 1. Chemical structures of two synthetic antimicrobial agents belonging to the oxazolidinone group.

TABLE 1. In vitro activity of two oxazolidinone antimicrobial agents (DuP 105 and DuP 721) compared with that of five other agents

Microorganism (no. tested)	Antimicrobial agent	MIC (μg/ml)[a]		
		Range	50%	90%
Staphylococcus spp.[b]				
Penicillin susceptible (35)	DuP 105	2.0–8.0	4.0	8.0
	DuP 721	1.0–4.0	2.0	4.0
	Vancomycin	0.5–2.0	0.5	1.0
	Ciprofloxacin	0.06–0.5	0.12	0.25
	Erythromycin	≤0.06–>32	0.25	0.5
	Cefaclor	≤0.06–2.0	0.5	1.0
	Ampicillin	≤0.12–0.5	≤0.12	≤0.12
Penicillin resistant (35)	DuP 105	2.0–16	8.0	8.0
	DuP 721	1.0–4.0	4.0	4.0
	Vancomycin	0.5–2.0	1.0	1.0
	Ciprofloxacin	0.06–0.5	0.12	0.25
	Erythromycin	0.25–>32	0.25	>32
	Cefaclor	0.5–8.0	2.0	4.0
	Ampicillin	≤0.12–>16	2.0	>16
Methicillin resistant (30)	DuP 105	2.0–16	8.0	16
	DuP 721	1.0–4.0	4.0	4.0
	Vancomycin	0.5–2.0	1.0	1.0
	Ciprofloxacin	0.06–0.25	0.12	0.25
	Erythromycin	≤0.06–>32	>32	>32
	Cefaclor	4.0–>32	>32	>32
	Ampicillin	4.0–>16	16	>16
L. monocytogenes (16)	DuP 105	4.0–16	16	16
	DuP 721	1.0–8.0	4.0	4.0
	Vancomycin	0.25–2.0	0.5	0.5
	Ciprofloxacin	≤0.03–4.0	0.5	1.0
	Erythromycin	0.12–2.0	0.25	1.0
	Cefaclor	0.5–16	4.0	16
	Ampicillin	≤0.12–0.5	0.25	0.5
Streptococcus spp.[c] (65)	DuP 105	2.0–8.0	4.0	4.0
	DuP 721	1.0–4.0	2.0	4.0
	Vancomycin	≤0.12–0.5	0.25	0.25
	Ciprofloxacin	0.25–4.0	0.5	1.0
	Erythromycin	≤0.06–>32	0.12	32
	Cefaclor	≤0.06–8.0	0.25	0.5
	Ampicillin	≤0.12–2.0	≤0.12	≤0.12
Enterococcus spp.[d] (35)	DuP 105	2.0–32	16	16
	DuP 721	2.0–8.0	8.0	8.0
	Vancomycin	0.5–8.0	1.0	4.0
	Ciprofloxacin	0.25–>8.0	1.0	8.0
	Erythromycin	≤0.06–>32	2.0	>32
	Cefaclor	8.0–>32	32	>32
	Ampicillin	≤0.12–8.0	0.5	4.0

[a] 50% and 90%, MIC for 50 and 90% of isolates tested, respectively.
[b] Includes 30 coagulase-negative species (10 penicillin-susceptible, 10 penicillin-resistant, and 10 methicillin-resistant strains).
[c] Includes 20 *S. agalactiae*, 20 *S. pyogenes*, 20 *S. pneumoniae*, and 5 *S. bovis*.
[d] Includes 20 *E. faecalis*, 12 *E. faecium*, and 3 *E. durans*.

both drugs in animals, we tentatively selected MICs of ≤4.0 μg/ml for susceptible and ≥16 μg/ml for resistant (M. Forbes, personal communication). The same breakpoints are currently being applied to tests with vancomycin. All but one of our gram-positive isolates were susceptible to vancomycin (MIC, ≤4.0 μg/ml). For all of these isolates, DuP 721 MICs were ≤8.0 μg/ml, and for 87%, MICs were ≤4.0 μg/ml (27 of 35 enterococci were intermediate in susceptibility). The proposed MIC breakpoints separated distinct populations of species susceptible to DuP 721, but that was not the case with DuP 105. Among the gram-positive isolates that we tested, 19% were resistant to DuP 105 (MIC, ≥16 μg/ml) and 29% were intermediate in susceptibility (MIC, 8.0 μg/ml). Only 52% of our isolates would be considered susceptible to DuP 105 (MIC, ≤4.0 μg/ml). The spectrum of activity of DuP 105 would be markedly improved if the dosage schedules could be adjusted to achieve levels in blood or tissue great enough to justify a susceptible MIC breakpoint of ≤8.0 μg/ml. If that could be accomplished, 81.5% of our gram-positive isolates would be susceptible and 18.5% would be intermediate in susceptibility (19 of 35 enterococci and 14 of 16 *L. monocytogenes* isolates required 16 μg/ml for inhibition).

In summary, DuP 105 and DuP 721 are two members of a new class of synthetic antimicrobial agents with in vitro activity against gram-positive microorganisms, including activity against methicillin-resistant *Staphylococcus* spp. Al-

though the new drugs are not as potent as some of the established antibiotics, their prospects for clinical utility will depend on the levels that might be achieved in blood or tissue. DuP 721 is particularly interesting, especially if peak blood levels in excess of 16 μg/ml can be achieved consistently in different human subjects.

LITERATURE CITED

1. **National Committee for Clinical Laboratory Standards.** 1985. Standard methods for dilution susceptibility tests for bacteria that grow aerobically. Approved Standard M7-A. National Committee for Clinical Laboratory Standards, Villanova, Pa.