In Vitro Activity of Decaplanin (M86-1410), a New Glycopeptide Antibiotic

MARThA L. SANcHEZ,1 RICHARD P. WEnZEL,2 AND RONALD N. JONES1

Department of Pathology1 and Division of General Medicine, Clinical Epidemiology and Health Services Research, Department of Internal Medicine,2 University of Iowa College of Medicine Iowa City, Iowa 52242

Received 6 December 1991/Accepted 31 January 1992

The in vitro activity of decaplanin (formerly M86-1410), a novel glycopeptide antimicrobial agent, was tested against 169 gram-positive bloodstream isolates from patients at the University of Iowa Hospitals and Clinics and 12 selected vancomycin-resistant strains. Enterococcus faecalis, E. faecium, Staphylococcus aureus, streptococci, bacilli, corynebacteria, and listeria were inhibited by decaplanin (MICs for 90% of the strains tested [MIC₉₀], 0.12 to 4 µg/ml). However, some rarely isolated and selected Enterococcus sp. populations had a MIC₉₀ of 16 µg/ml, and S. haemolyticus strains had a MIC₉₀ of 8 µg/ml. These in vitro results suggest that decaplanin may be useful against most gram-positive strains, even though some Enterococcus species and coagulase-negative staphylococci were potentially resistant (MICs ≥8 µg/ml).

Decaplanin (formerly M86-1410) is one of the newer glycopeptides developed as alternative antimicrobial agents for therapeutic use against a wide range of gram-positive bacteria (1, 4; Fig. 1). Vancomycin, a glycopeptide prototypic drug, has become a reliable drug for treatment of severe infections caused by some gram-positive pathogens (methicillin-resistant staphylococci) or as an alternative antimicrobial agent for patients with penicillin allergy or macrolide intolerance (13, 14). However, resistance to vancomycin among gram-positive organisms has been an emerging problem (5, 8–10, 12). Several studies have described specific types of resistance among isolates of clinical significance, such as Leuconostoc spp., Lactobacillus spp., and Pediococcus spp. (8). These organisms have dairy and food industry utility but have also been isolated as pathogens from blood cultures of compromised human hosts (8). Antimicrobial agent-resistant coagulase-negative staphylococci, usually associated with nosocomial infections, have also been noted (5, 6, 12, 13), as have, more recently, Enterococcus faecalis and E. faecium strains (5, 9–11). Vancomycin resistance in enterococci was initially described in Europe (5), and subsequently resistant organisms have been discovered worldwide (9, 10). The purpose of this study was to determine the in vitro activity of decaplanin compared with previously studied glycopeptides (teicoplanin and vancomycin), daptomycin, and ampicillin.

Antimicrobial agents. Laboratory standard drugs used in the study were obtained as follows. Decaplanin was from Beecham AG (Frankfurt, Germany), teicoplanin was from Marion Merrell Dow Pharmaceutical Inc. (Cincinnati, Ohio), daptomycin and vancomycin were from Eli Lilly & Co., (Indianapolis, Ind.), and ampicillin was from Wyeth Laboratories (West Chester, Pa.). Compounds were diluted and stored as recommended by the manufacturers, at −60°C or below until used.

Bacterial strains. One hundred sixty-nine gram-positive strains were used in this study, and the species and strains are listed in Table 1. All strains were recent blood culture isolates from patients at the University of Iowa Hospitals and Clinics (Iowa City). We also tested 12 reference vancomycin-resistant strains (Table 2), which were identified and classified by the criteria published by investigators at the Centers for Disease Control (2). Some of these isolates were kindly provided by Jana Swenson (2), David Preston (8, 9), Daniel Sahm (10), and Hana Canawati (11).

Susceptibility testing. MICs were determined by agar dilution and broth microdilution procedures as recommended by the National Committee for Clinical Laboratories Standards (7). Quality control strains (E. faecalis ATCC 29212 and Staphylococcus aureus ATCC 29213) were processed concurrently for technical and reagent quality assurance. The inocula were prepared from fresh broth cultures and adjusted to a concentration of 10⁴ CFU per spot for agar dilution tests or 5 × 10⁵ CFU/ml for broth microdilution tests. The plates were incubated at 35°C in ambient air for 15 to 18 h, and the MICs were interpreted as the lowest drug concentration that totally suppressed visible growth. Strains considered susceptible to decaplanin were those for which the MICs were ≤4 µg/ml, vancomycin susceptibility was defined as a MIC of ≤4 µg/ml, and teicoplanin susceptibility was defined as a MIC of ≤8 µg/ml (6; Table 1).

FIG. 1. Structure of decaplanin.

* Corresponding author.
Daptomycin MICs for resistant strains were >8 µg/ml, and ampicillin resistance was defined as a MIC of >2 µg/ml for *Streptococcus* spp. and >8 µg/ml for enterococci (7; Table 2).

There was a tendency for decaplanin to be less active than vancomycin (Table 1), a finding also made by Chin et al. (1). In turn, vancomycin was less active than teicoplanin, a result also supported by other investigators (8, 10). However, some *Staphylococcus haemolyticus* strains were resistant to teicoplanin and decaplanin while remaining susceptible to vancomycin. This observation was similar to those reported by others (6, 12). Also, the vancomycin MIC for 90% of the strains tested (MIC90) for *S. haemolyticus* (range, 0.5 to 4 µg/ml) approached the highest level of susceptibility (7). Some of these strains had potentially intermediate decaplanin MICs (8 µg/ml), if comparable levels of decaplanin could be achieved in vivo. We must maintain a high level of vigilance and concern for the increasing resistance among organisms of this species. Such concern is justified in light of our recent report showing the emergence of vancomycin resistance in a previously susceptible strain of *S. haemolyticus* during prolonged therapy with vancomycin (12).

A minority of the clinical *Enterococcus* sp. strains were potentially resistant to decaplanin (MICs, ≥16 µg/ml), but vancomycin had intermediate activity (MIC, 8 µg/ml). Of 15 species tested, 4 (*E. faecium, E. faecalis*, oxacillin resistant and susceptible *S. aureus*, and *S. epidermidis*) had very similar, lower decaplanin and vancomycin MICs. Decaplanin was less active (2- to 16-fold) than teicoplanin against all *Enterococcus* species, *S. aureus* (oxacillin resistant and susceptible), coagulase-negative staphylococci, *Bacillus cereus*, and *Listeria monocytogenes* strains. *Streptococcus pneumoniae* isolates resistant to penicillin were very susceptible to all three of the compounds tested (MIC90, 0.12 to ≤1 µg/ml).

Table 2 lists the results of the reference vancomycin-resistant strains that were tested against decaplanin, teicoplanin, ampicillin, and the lipopeptide daptomycin. Generally, the six *Enterococcus* species strains were resistant to decaplanin, daptomycin, ampicillin, and teicoplanin. Only *E. faecium* E001 (low level, nontransferable vancomycin resistance) was susceptible to teicoplanin (MIC, 0.25 µg/ml) agreeing with similar results reported by Sahm et al. (10) and Fantin et al. (3). *E. faecalis* E084 was susceptible to ampicillin, although it possesses a transferable factor that confers vancomycin resistance (3, 9, 10, 14). Glycopeptide-resistant enterococcus-caused infections appear to respond to high-dose glycopeptide regimens in combination with an aminoglycoside (3). Vancomycin- and decaplanin-resistant *Pediococcus* and *Leuconostoc* were uniformly susceptible to daptomycin and the older penicillins (8).
Decaplanin closely resembles vancomycin in its gram-positive spectrum, although its activity is slightly inferior. These findings confirm those reported by Chin et al. (1) and by the manufacturer (4). Emerging glycopeptide-resistant gram-positive species also had elevated decaplanin MICs. The role of decaplanin for human gram-positive infection therapy awaits the reports of toxicologic and pharmacokinetic studies.

We thank the staff at the Anti-Infectives Research Center, University of Iowa College of Medicine, for technical support. Word processing was provided by Linda Miller.

REFERENCES