In Vitro Activity of the New Oxazolidinone AZD2563 against Enterococci

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The activity of a new oxazolidinone antimicrobial, AZD2563, was assessed against >500 clinical isolates of enterococci representing six species. All isolates, including those resistant to other antibiotic classes, were inhibited by AZD2563 at concentrations ≤2 μg/ml, except for four strains resistant to linezolid. In most cases, AZD2563 was twofold more active than linezolid against enterococci.

Infections due to enterococci resistant to multiple antimicrobial agents represent an important clinical problem. In particular, vancomycin (VAN)-resistant strains of Enterococcus faecium are usually resistant to a broad variety of available antibiotics (4). The introduction of quinupristin-dalfopristin (Q-D) provided an alternative for treatment of infections due to E. faecium (3), but this agent has certain limitations of spectrum and ease of use. The approval of an oxazolidinone, linezolid (LZD), expanded therapeutic options to include other enterococcal species and permitted use of oral therapy (1).

AZD2563 is a new oxazolidinone in development (M. B. Gravestock, M. J. Betts, E. Chawner, L. Dawson, A. McGregor, S. D. Mills, R. C. Wilson, L. Woods, and A. Wookey, Abstr. 41st Intersci. Conf. Antimicrob. Agents Chemother., abstr. 1023, 2001) (Fig. 1). Preliminary reports indicate that this agent would have activity against gram-positive bacteria of medical importance (P. J. Turner, A. Wookey, J. M. Greenhalgh, J. Clarke, and M. Eastwood, Abstr. 41st Intersci. Conf. Antimicrob. Agents Chemother., abstr. 1024, 2001). It is believed that the pharmacodynamic characteristics of this agent may favor once-daily dosing (W. A. Craig and D. R. Andes, Abstr. 41st Intersci. Conf. Antimicrob. Agents Chemother., abstr. 1037, 2001). In the present study, we examined the in vitro activity of AZD2563 against a large collection of clinical isolates of enterococci and compared the activity of this antimicrobial with those of linezolid (LZD) and several other agents.

(This study was presented in part at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Ill., 16 to 19 December 2001 [G. Eliopoulos et al., Abstr. 41st Intersci. Conf. Antimicrob. Agents Chemother., abstr. 1034, 2001].)

The bacterial strains used were 521 clinical isolates selected from our collection to represent various species and resistance profiles, but without reference to oxazolidinone susceptibility. Most of the VAN-resistant isolates were collected in the United States in the late 1990s, but strains collected into 2000 are represented. Four isolates with reduced susceptibility to LZD recovered from four patients hospitalized in Massachusetts in 2001 were also examined. Antimicrobial susceptibility was determined by the NCCLS broth microdilution method (5). Frozen panels containing antimicrobials were provided by Trek Diagnostic Systems, Inc. (Westlake, Ohio). These contained AZD2563, LZD, Q-D, ampicillin (AMP), VAN, teicoplanin (TEC), erythromycin (ERY), and levofloxacin (LVX). The plates also contained wells for screening for high-level resistance (HLR) to streptomycin (STR) or gentamicin (GEN). Enterococcus faecalis ATCC 29212, E. faecalis ATCC 51219, and Staphylococcus aureus ATCC 29213 were used as quality control strains.

Inocula were prepared by the direct colony suspension method. Initial suspensions were in water, adjusted to a 0.5 McFarland standard, and subsequently diluted 1:100 in cation-adjusted Mueller-Hinton broth (Binax/Nel, Waterville, Maine). Aliquots of 50 μl were dispensed into the 96-well plates with a Sensititre AutoInoculator (Sensititre Microbiology Systems, Ltd., East Grinstead, England), leading to a final inoculum of approximately 5 × 10⁵ CFU/ml. The plates were incubated in room air at 35°C, and MICs were determined, using a mirror, at 16 to 20 h unless otherwise required by NCCLS protocols for determination of VAN MICs and HLR to GEN (24 h) and HLR to STR (24 and 48 h) (5).

The activities of AZD2563 and the comparator antimicrobials are shown in Table 1. All of the 521 isolates included in this collection without reference to oxazolidinone susceptibility were inhibited by AZD2563 at concentrations ≤2 μg/ml. LZD inhibited all of these strains at concentrations ≤4 μg/ml. MICs for 4 μg/ml (intermediate susceptible) for 511 strains and 4 μg/ml (susceptible range) for 511 strains (1.9%). For each of the strains inhibited by LZD at 4 μg/ml, the MIC of

FIG. 1. Structure of the oxazolidinone AZD2563

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AZD2563 was 1 dilution lower at 2 μg/ml. Four isolates of LZD-resistant enterococci (MICs, 8 and 32 μg/ml for two strains each) were referred to our laboratory. The corresponding MICs of AZD2563 for these four isolates were also increased to 4 and 32 μg/ml, respectively.

The following information serves further to characterize the original population of 521 organisms studied. Of the E. faecium isolates, 90.6% were susceptible to Q-D, while 7.0% were intermediate and 2.4% were resistant (MIC ≥ 4 μg/ml). Only 12 isolates of E. faecium (3.2%) were susceptible to AMP (MIC ≤ 8 μg/ml). ERY susceptibility was encountered uncommonly among the E. faecalis (6.4%) isolates tested and rarely
among the E. faecium (0.26%) isolates tested. HLR to STR and HLR to GEN were frequent among the E. faecalis and E. faecium isolates tested. HLR to the aminoglycosides STR and GEN occurred among the organisms at the following rates: E. faecalis, VAN susceptible, 36 and 40%, respectively; E. faecalis VanA phenotype, 30 and 20%, respectively; E. faecalis VanB phenotype, 76 and 100%, respectively; E. faecium, VAN susceptible, 69 and 48%, respectively; E. faecium VanA, 89 and 78%, respectively; and E. faecium VanB, 73 and 61%, respectively.

As previously shown for LZD (2), the MICs of AZD2563 for enterococci clustered tightly within a narrow range of concentrations. All strains except the LZD-resistant isolates were inhibited by AZD2563 in a 3-dilution range at concentrations between 0.5 and 2 μg/ml. This activity against enterococci appears to be generally similar to that reported against coagulase-negative and coagulase-positive staphylococci, 90% of which were inhibited by AZD2563 at concentrations of 1 and 2 μg/ml, respectively (R. N. Jones, T. R. Anderegg, D. J. Biedenbach, and M. A. Pfaller, Abstr. 41st Intersci. Conf. Antimicrob. Agents Chemother., abstr. 1029, 2001). The new oxazolidinone was at least as active as LZD against enterococci and, based on comparison of the MICs at which 90% of isolates are inhibited (MIC90), was often twofold more active against the various organism groups. This somewhat greater potency may be an advantage against strains that are intermediate to LZD or resistant to the latter just at the breakpoint concentration. Unfortunately, for enterococci resistant to LZD (MICs = 32 μg/ml), there appears to be complete cross-resistance to AZD2563.

In summary, with the exception of LZD-resistant strains, AZD2563 demonstrated consistent in vitro activity against a representative collection of enterococci, including isolates resistant to other classes.

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REFERENCES