Comparative in vitro activity of alexomycin (U-82127) tested against *Escherichia coli*, *Salmonella* spp., and enterococci of animal and human origin

*Clin Microbiol Infect* 1998; 4: 601–603

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Accepted 24 April 1998

The spread of glycopeptide-resistant enterococcal infections across the continental USA has been well documented in the current decade [1,2]. This expansion has been attributed to the selective pressures associated with extensive use of broad-spectrum antimicrobials (cephalosporins, fluoroquinolones) and vancomycin [1-3]. Recent reports of vancomycin-resistant enterococci isolated from the feces of poultry or swine and from the carcasses of food animals has intensified the debate concerning the likelihood of these species being a reservoir for pathogens causing both nosocomial and community-acquired infection in humans [4-8]. The use of glycopeptides and other drugs in western Europe as growth promoters in food animals had been common practice [7,9]. Earlier studies had demonstrated cross-resistance between veterinary-use glycopeptides (avoparcin) and vancomycin or teicoplanin among enterococci of animal and human origin [5,10].

Alexomycin (U-82,127) is an antimicrobial complex that belongs to the cyclic peptide class [11]. It is a thiopptide related to the sulfomycins and is produced by *Streptomyces arginensis*. The reported spectrum of alexomycin includes Gram-positive pathogens, and the compound has been utilized to promote growth in weanling swine [12] with acceptable results at doses ranging from 3.3 to 55 mg/kg. The most recent investigation determined the most efficacious alexomycin dose range to be between 2.3 and 6.2 mg/kg [10]. This peptide appears to be a promising candidate to complement or replace other compounds used in animal growth promotion [7,10], especially those glycopeptides that may select resistant strains thus complicating both animal and human antimicrobial chemotherapy [4-6,8,11,12]. In this report we summarize the in vitro characterization of alexomycin compared to two glycopeptides, a lipopeptide, selected β-lactams, macrolides, clindamycin, streptogramins, chloramphenicol, fluoroquinolones, and a tetracycline tested against three bacterial groups.

The antimicrobial agents were obtained from the following manufacturers: alexomycin, cefiofur and clindamycin from Pharmacia & Upjohn Pharmaceuticals (Kalamazoo, MI, USA), avoparcin from Hoffmann-LaRoche (Basel, Switzerland), teicoplanin from Hoechst Marion-Roussel (Kansas City, MO, USA), vancomycin from Eli Lilly and Co. (Indianapolis, IN, USA), quinupristin/dalfopristin from Rhone-Poulenc Rorer (Collegeville, PA, USA), ciprofloxacin from Bayer (West Haven, CT, USA), and the remaining antimicrobial agents (ampicillin, erythromycin A, chloramphenicol, doxycycline) from Sigma Chemical Co. (St Louis, MO, USA).

Minimum inhibitory concentrations (MICs) were determined by the broth microdilution method [14], and the interpretive criteria for susceptibility were those published by the National Committee for Clinical Laboratory Standards (NCCLS) [13]. Mueller–Hinton broth microdilution trays were manufactured by Prepared Media Laboratories (Wilsonville, OR, USA) and stored at −70°C until used. Quality control strains recommended by the NCCLS (*Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Pseudomonas aeruginosa* ATCC 27853, *Escherichia coli* ATCC 25922) were processed concurrently during in vitro susceptibility testing. The alexomycin activity against these strains revealed susceptibility among staphylococci (MICs, 0.12-0.5 mg/L), but resistance in Gram-negative bacilli (MIC, >32 mg/L).

Table 1 illustrates the potent activity of alexomycin (MIC range, 0.06–0.5 mg/L) against a selected collection of 42 enterococcal strains. The majority of strains (24) had vanA-, vanB-, vanC1- or vanC2- mediated glycopeptide resistances, but remained
Table 1  Alexomyxin (U-82,127) in vitro activity compared to 11 other antimicrobial agents, tested against enterococci with various glycopeptide resistance patterns

<table>
<thead>
<tr>
<th>Antimicrobial agents</th>
<th>MICs (mg/L)</th>
<th>50%</th>
<th>90%</th>
<th>Range</th>
<th>50%</th>
<th>90%</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vancomycin susceptible (18 strains)</td>
<td></td>
<td></td>
<td></td>
<td>Vancomycin resistant (24 strains)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alexomycin</td>
<td>0.12</td>
<td>0.25</td>
<td>0.12-0.5</td>
<td>0.12</td>
<td>0.25</td>
<td>0.06-0.5</td>
<td></td>
</tr>
<tr>
<td>Avoparcin</td>
<td>1</td>
<td>1</td>
<td>0.3-2</td>
<td>4</td>
<td>1</td>
<td>1 to &gt;32</td>
<td></td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>0.12</td>
<td>0.5</td>
<td>0.015-1</td>
<td>0.5</td>
<td>32</td>
<td>0.06 to &gt;32</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1</td>
<td>2</td>
<td>0.5-2</td>
<td>&gt;16</td>
<td>&gt;16</td>
<td>4 to &gt;16</td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>≤2</td>
<td>&gt;16</td>
<td>≤2 to &gt;16</td>
<td>≤2</td>
<td>&gt;16</td>
<td>≤2 to &gt;16</td>
<td></td>
</tr>
<tr>
<td>Ceftiofur</td>
<td>&gt;16</td>
<td>&gt;16</td>
<td>&gt;16</td>
<td>&gt;16</td>
<td>&gt;16</td>
<td>8 to &gt;16</td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>4</td>
<td>&gt;32</td>
<td>0.1-32</td>
<td>&gt;32</td>
<td>&gt;32</td>
<td>0.12 to &gt;32</td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>32</td>
<td>&gt;32</td>
<td>≤1 to &gt;32</td>
<td>&gt;32</td>
<td>&gt;32</td>
<td>0.12 to &gt;32</td>
<td></td>
</tr>
<tr>
<td>Quinupristin/dalfopristin</td>
<td>2</td>
<td>4</td>
<td>0.5-8</td>
<td>1</td>
<td>16</td>
<td>0.25-16</td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>8</td>
<td>16</td>
<td>4-16</td>
<td>8</td>
<td>16</td>
<td>2-64</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1</td>
<td>&gt;8</td>
<td>0.25 to &gt;8</td>
<td>4</td>
<td>&gt;8</td>
<td>0.25 to &gt;8</td>
<td></td>
</tr>
<tr>
<td>Doxycycline</td>
<td>16</td>
<td>0.06-16</td>
<td>0.12</td>
<td>8</td>
<td>0.06-8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Vancomycin-susceptible strains had negative PCR tests for vanA, vanB, vanC1, or vanC2-3 and MICs of ≤4 mg/L [13]. These isolates included: Enterococcus faecalis (seven strains), Enterococcus faecium (eight strains), Enterococcus durans (two strains), and Enterococcus avium (one strain). Eight of these strains (four Enterococcus faecalis, three Enterococcus faecium, one Enterococcus durans) were isolated from animals.
- Vancomycin resistance was determined by the presence of a vanA, vanB, vanC1, or vanC2-3 gene as determined by the PCR test. These strains included: Enterococcus faecalis vanA (two strains) and vanB (three strains), Enterococcus faecium vanA (five strains) and vanB (five strains), Enterococcus gallinarum vanC1 (seven strains), and Enterococcus casseliflavus vanC2-3 (two strains). None of these strains was from animal sources.

Table 2  The antimicrobial activity of alexomycin (U-82,127) and 12 comparison compounds tested against 40 strains of Escherichia coli and 40 strains of Salmonella spp.

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>E. coli (40)</th>
<th>Salmonella spp. (40)</th>
<th>MIC (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50%</td>
<td>90%</td>
<td>Range</td>
</tr>
<tr>
<td>Alexomycin</td>
<td>&gt;32</td>
<td>&gt;32</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Avoparcin</td>
<td>&gt;32</td>
<td>&gt;32</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>&gt;32</td>
<td>&gt;32</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>&gt;16</td>
<td>&gt;16</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>4</td>
<td>&gt;16</td>
<td>≤2 to &gt;16</td>
</tr>
<tr>
<td>Penicillin</td>
<td>&gt;1</td>
<td>&gt;1</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>&gt;32</td>
<td>&gt;32</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>&gt;32</td>
<td>&gt;32</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Quinupristin/dalfopristin</td>
<td>&gt;32</td>
<td>&gt;32</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>8</td>
<td>8</td>
<td>2 to &gt;64</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.008</td>
<td>0.008</td>
<td>≤0.004-0.03</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>2</td>
<td>32</td>
<td>0.5 to &gt;32</td>
</tr>
<tr>
<td>Salt (mg/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Includes 20 strains from animals and 20 strains from human infections.
- Includes 20 Salmonella enteritidis strains isolated from humans and 20 strains of other Salmonella spp. isolated from animals (Salmonella cholerae-suis, five strains; Salmonella typhimurium, eight strains; Salmonella dublin, four strains; Salmonella mbandaka, three strains).
- Susceptibility as defined by the NCCLS [14].
- No interpretive criteria have been established, but high MIC results indicate poor potential utility against these Gram-negative species.
susceptible to ≤0.5 mg/L of alexomycin. The most active comparison drugs tested were quinupristin/dalfopristin (MIC50, 1 or 2 mg/L), chloramphenicol (MIC50, 8 mg/L), and doxycycline (MIC50, 0.12–4 mg/L). Quinupristin/dalfopristin was only effective against Enterococcus faecium strains (all MICs, ≤2 mg/L). Avoparcin was less active than teicoplanin, but was generally more potent than vancomycin, against these enterococci.

Enteritis-associated pathogens, Escherichia coli and Salmonella spp., were also tested, many strains originating from cultures of humans and various animal species. As expected, the following compounds demonstrated little inhibitory action: alexomycin, avoparcin, teicoplanin, vancomycin, penicillin G, erythromycin A, clindamycin, and the streptogramin combination. Variable activity was noted for other drugs (53–100% susceptible) with cephalothin, chloramphenicol and ciprofloxacin inhibiting >90% of the 80 tested Enterobacteriaceae strains (Table 2).

The search for antimicrobial agents that have activity against Gram-positive pathogens has led to structural modifications of existing classes as well as the study of sometimes older compounds with unique characteristics, e.g. everninomycin (SCH 27899), glycylcyclines, novobiocin, oxazolidinones, and alexomycin. The potency of alexomycin against vancomycin-resistant enterococci was excellent, and cross-resistance with other antimicrobials was not demonstrated among clinical isolates of enterococci. Also, its spectrum does not include common enteric pathogens from the Enterobacteriaceae. Where glycopeptide-resistant enterococci may have already emerged in the flora of animal species, alexomycin appears to remain a viable alternative as a growth promoter [11,12], and no similar agent has been applied to therapy of human infections. This latter fact should limit the potential for interspecies transfer of resistance or the strains having developed genetic factors compromising chemotherapy of important clinical infections.

References