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Quinupristin–Dalfopristin

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1. DESCRIPTION

Streptogramins belong to the macrolide–lincosamide–streptogramin group of antibiotics. They constitute a family of compounds including pristinamycins, oestreomycins, and mikamycins, all isolated from *Streptomyces pristinaespiralis,* and virginiamycins, isolated from *Streptomyces virginae* (Vasquez, 1967). Streptogramins are divided into two groups (group A and group B) based on their molecular structure. Quinupristin (derived from pristinamycin IA) is a group B streptogramin, whereas dalfopristin (derived from pristinamycin IIA) is a semisynthetic derivative of a group A streptogramin. These two water-soluble streptogramins have been combined in the first parenteral streptogramin preparation commercially available at a 30:70 weight-to-weight ratio (Synercid, Aventis Pharmaceutical Products Inc., Parsippany, NJ). Quinupristin is a combination of three peptide macrolactones. Its main component (> 88%) has an empirical formula of $C_{53}H_{67}N_9O_{10}S$ and a molecular weight of 1022.24 g/mol and its structural formula is shown in Figure 77.1. Dalfopristin has an empirical formula of $C_{34}H_{50}N_4O_9S$, a molecular weight of 690.85 g/mol (Figure 77.1).

Quinupristin–dalfopristin is active against a range of Gram-positive bacteria that are usually resistant to other agents including penicillin-resistant *Streptococcus pneumoniae,* methicillin-resistant *Staphylococcus aureus,* glycopeptides-intermediate *S. aureus,* and vancomycin-resistant *Enterococcus faecium* (Aventis, 1999; NCCLS, 2002; Barrett and Jones, 1996).

The commercially available formulation for intravenous injection (Synercid 500 mg) is a sterile lyophilized formulation of quinupristin mesylate (150 mg), dalfopristin mesylate (350 mg), and two excipients (methane sulfonic acid and sodium hydroxide) (Aventis, 1999).

2. ANTIMICROBIAL ACTIVITY

2a. Routine susceptibility

The Clinical Laboratory Standards Institute (CLSI) has determined the minimum inhibitory concentration (MIC) susceptibility breakpoints for quinupristin–dalfopristin against the Gram-positive organisms *E. faecium*, *Staphylococcus* spp. and *Streptococcus* spp. as follows: ≤ 1 mg/l, susceptible; 2 mg/l, intermediate susceptible; ≥ 4 mg/l, resistant (NCCLS, 2002). However, the effectiveness of quinupristin and dalfopristin in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials.

GRAM-POSITIVE BACTERIA

Quinupristin–dalfopristin's spectrum of activity extends to many multidrug-resistant Gram-positive aerobic bacteria (Barrett and Jones, 1996). Quinupristin–dalfopristin is commonly active on aerobic and anaerobic Gram-positive bacteria including *S. aureus* (methicillin-susceptible and methicillin-resistant strains), coagulase-negative staphylococci (including methicillin-resistant strains), *S. pneumoniae* (whatever the susceptibility to beta-lactams or macrolides), streptococcal species other than *S. pneumoniae*, *Clostridium* species, and *Corynebacterium jeikeium* (Table 77.1). Quinupristin–dalfopristin is almost always inactive against *Enterococcus faecalis,* whereas most strains of *E. faecium* are susceptible, including strains that are resistant to erythromycin, gentamicin, and vancomycin. An efflux pump conferring resistance to dalfopristin appears to be intrinsic in these species (Nadler *et al.,* 1999). In contrast, most isolates of *E. faecium* (including vancomycin-resistant strains) are susceptible to this agent. Differentiation of enterococcal species is thus important. Other organisms that commonly cause upper respiratory tract infections against which quinupristin–dalfopristin has demonstrated *in vitro* activity include *Haemophilus influenzae*, *Legionella* spp., *Mycoplasma* spp., and *Chlamydophila pneumoniae* (Nadler *et al.,* 1999; Yu *et al.,* 2014; Maraki *et al.,* 2014; Kullar *et al.,* 2015; Jones *et al.,* 1998; Mathai *et al.,* 2001; Sambatakou *et al.,* 1998; Mouton *et al.,* 1997).

GRAM-NEGATIVE BACTERIA

Aerobic Gram-negative enteric bacilli and nonfermenting Gram-negative bacteria such as *Pseudomonas aeruginosa* and