Quinupristin-Dalfopristin:
A New Antibiotic for Severe Gram-Positive Infections

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The steady increase in resistant organisms is related to the widespread use of antibiotics in community and hospital settings. New therapeutic options are needed, including treatments for infections caused by antibiotic-resistant gram-positive organisms. Quinupristin-dalfopristin, the first formulation of a distinct class of antibiotics known as the streptogramins, has activity against a range of gram-positive bacteria that are usually resistant to other agents, including vancomycin-resistant *Enterococcus faecium*. The pharmacodynamic (postantibiotic effect) and pharmacokinetic characteristics of quinupristin-dalfopristin allow dosing at eight- to 12-hour intervals. The safety profile of the formulation is generally favorable, with no demonstrable ototoxicity, nephrotoxicity, bone marrow suppression, or cardiovascular adverse effects. Reversible arthralgias, myalgias, and peripheral venous irritation are the formulation's major side effects. A potential for drug interactions exists because quinupristin-dalfopristin significantly inhibits the cytochrome P450-3A4 enzyme system. Quinupristin-dalfopristin has been shown to be effective in the management of documented severe infections caused by vancomycin-resistant *E. faecium*, nosocomial pneumonia, and infections related to the use of intravascular catheters. (Am Fam Physician 2001;64:1863-6. Copyright© 2001 American Academy of Family Physicians.)

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Antimicrobial resistance among gram-positive organisms has been increasing steadily during the past several decades. According to data from the National Nosocomial Infection Surveillance System (1989 to 1993),[1] the percentage of nosocomial enterococcal isolates that are resistant to vancomycin (Vancocin) has increased from 0.3 percent to 8 percent. Even more strikingly, the percentage of vancomycin-resistant enterococcal isolates in intensive care units has increased from 0.4 percent to almost 14 percent.[1] Unfortunately, extensive use of antibiotics provides selective pressure for the emergence of resistant organisms, which, in turn, limits therapeutic options.

In September 1999, the U.S. Food and Drug Administration labeled quinupristin-dalfopristin (Synercid) for use in the treatment of serious or life-threatening infections associated with vancomycin-resistant *Enterococcus faecium* bacteremia and complicated skin and skin structure infections caused by methicillin-susceptible *Staphylococcus aureus* and *Streptococcus pyogenes* (group A streptococcus).

Quinupristin-dalfopristin has been shown to be effective in the management of nosocomial pneumonia and infections related to the use of intravascular catheters.

Quinupristin-dalfopristin is a streptogramin. This class of antibiotics is an important addition to the options available for the treatment of severe infections caused by gram-positive organisms, including nosocomial pneumonia and infections related to the use of intravascular catheters.

Chemistry and Mechanism of Action

The streptogramins are macromolecular antibiotics produced by *Streptomyces pristinaepiralis*.[2] They belong to the macrolide-lincosamide-streptogramin group of antibiotics. Quinupristin-dalfopristin is made up of chemically modified, water-soluble, injectable derivatives of type B streptogramin (quinupristin) and type A streptogramin (dalfopristin) in a 30:70 ratio.

The combination of quinupristin and dalfopristin is synergistic, and is generally bactericidal compared with either agent used alone or compared with similar antibiotics in the macrolide group. The main target is the bac-

TABLE 1
Selected Drugs Predicted to Have Increased Plasma Levels After Quinupristin-Dalfopristin Administration*

Drug class	*Examples*
Anti-HIV drugs	Delavirdine (Rescriptor), indinavir (Crixivan), nevirapine (Viramune), ritonavir (Norvir)
Antineoplastic drugs	Docetaxel (Taxotere), paclitaxel (Taxol), vinca alkaloids
Benzodiazepines	Diazepam (Valium), midazolam (Versed)
Calcium channel blockers	Diltiazem (Cardizem), nifedipine (Procardia), verapamil (Calan)
HMG-CoA reductase inhibitors (statins)	Lovastatin (Mevacor)
Immunosuppressive drugs	Cyclosporine (Sandimmune), tacrolimus (Prograf)
Corticosteroids	Methylprednisolone
Others	Carbamazepine (Tegretol), disopyramide (Norpace), lidocaine (Xylocaine), quinidine

HIV = human immunodeficiency virus; HMG CoA = 3-hydroxy-3-methyglutaryl coenzyme A.

**—The list of drugs in this table is not all-inclusive. Only representative drugs from each class are given.*

Adapted with permission from Synercid [annotated package insert]. Parsippany, N.J.: Aventis Pharmaceuticals, 1999.

terial 50S ribosome, with the formulation acting to inhibit protein synthesis.[3] Dalfopristin blocks an early step in protein synthesis by forming a bond with a ribosome to prevent elongation of the peptide chain. Quinupristin blocks a later step by preventing the extension of peptide chains and causing incomplete chains to be released.

Although resistance to quinupristin-dalfopristin can develop through one of several mechanisms (i.e., modification of the target binding site, enzymatic inactivation, or active efflux), it is not common.[3] When resistance has emerged during the treatment of vancomycin-resistant *E. faecium* infections, it has been to both components of the formulation.

Pharmacokinetics

Quinupristin and dalfopristin are the main active components circulating in plasma. Both are converted to several active metabolites that contribute to the antimicrobial activity of the formulation.[2] The half-life of quinupristin and its metabolites is approximately three hours, whereas the half-life of dalfopristin and its metabolites is approximately one hour.

Hepatic clearance and fecal (biliary) elimination are the major elimination routes for quinupristin, dalfopristin, and their metabolites (approximately 75 percent of the given dose). Urinary excretion accounts for 15 percent of the quinupristin dose and 19 percent of the dalfopristin dose.

The peak plasma level of quinupristin-dalfopristin after a single 7.5 mg per kg intravenously administered dose is 2.3 μg per L for quinupristin and 6.5 μg per L for dalfopristin. Both components penetrate well into interstitial fluid. Finally, quinupristin-dalfopristin demonstrates a prolonged postantibiotic effect, which is the phenomenon of continued suppression of bacterial growth after serum levels have fallen below the minimum inhibitory concentration (MIC).[4] The duration of this effect may be up to 10 hours for *S. aureus* and nine hours for *Streptococcus pneumoniae*.

Drug Interactions

In vitro drug interaction studies have shown that quinupristin-dalfopristin significantly inhibits the cytochrome P450-3A4 enzyme system. Selected drugs whose plasma concentrations are predicted to increase following quinupristin-dalfopristin administration are listed in *Table 1*.[5] In particular, cyclosporine (Sandimmune) levels should be monitored when this drug is used concomitantly with quinupristin-dalfopristin.

Adverse Reactions

The safety profile of quinupristin-dalfopristin has been evaluated in more than 2,000 patients. Pain and inflammation at the infusion site are common but require discontinuation of treatment in fewer than 10 percent of patients.[5]

The most common side effects of quinupristin-dalfopristin have been arthralgias (9 percent) and myalgias (6 percent), which have led to the discontinuation of quinupristin-dalfopristin in one third to one half of affected patients. Other common systemic adverse events have been nausea (4.6 percent of patients), diarrhea (2.7 percent), vomiting (2.7 percent), rash (2.5 percent), headache (1.6 percent), pruritus (1.5 percent), and pain (1.5 percent).[6]

Liver function abnormalities have occurred in approximately 1 percent of patients who received quinupristin-dalfopristin. However, these effects have generally been mild and transient. No significant effects on renal function have been reported, and bone marrow toxicity has been rare.[6]

In Vitro Antimicrobial Activity

One study[3] used multiple standardized susceptibility tests to evaluate the antimicrobial activity of quinupristin-dalfopristin against more than 28,000 clinical isolates from

200 centers across the United States and Canada. Quinupristin-dalfopristin demonstrated activity in vitro with an MIC of less than or equal to 1 μg per mL in 90 percent of strains of a wide variety of multidrug-resistant gram-positive organisms, including *E. faecium*, methicillin-susceptible *S. aureus*, methicillin-resistant *S. aureus,* and *Staphylococcus epidermidis*.

The study[3] found that strains of *Enterococcus faecalis* are generally resistant to quinupristin-dalfopristin. Therefore, this antibiotic formulation should not be used to treat *E. faecalis* infections.

Of the more than 4,000 isolates of *S. pneumoniae* that were tested, 98 percent were susceptible to quinupristin-dalfopristin, irrespective of resistance to beta-lactam or macrolide antibiotics. Similarly, 97 percent of streptococcal species other than *S. pneumoniae* were susceptible to quinupristin-dalfopristin.[3]

Other organisms against which quinupristin-dalfopristin demonstrated in vitro activity included *Haemophilus influenzae*, Legionella species, Mycoplasma species, Clostridium species and *Chlamydia pneumoniae*. Aerobic gram-negative enteric bacilli were not susceptible to quinupristin-dalfopristin.[3]

Clinical Studies

Two simultaneously conducted prospective studies[6] assessed the clinical efficacy and safety of quinupristin-dalfopristin in the treatment of vancomycin-resistant *E. faecium* infection. The first study enrolled only patients with vancomycin-resistant *E. faecium* infection. The second study included patients with infections caused by other gram-positive bacterial pathogens in addition to vancomycin-resistant *E. faecium*.

Patients were included in the studies if they had signs and symptoms of active infection caused by a pathogen presumed to be susceptible to quinupristin-dalfopristin, with no appropriate antibacterial alternative.[6] In addition, patients were required to have documented intolerance to other agents or treatment failure with other agents. Patients were not excluded because of severity of illness, infection site or pending death. A total of 396 patients with vancomycin-resistant *E. faecium* infection were enrolled. The treatment regimen was quinupristin-dalfopristin in a dosage of 7.5 mg per kg administered intravenously every eight hours for a duration judged appropriate by the investigator.

The most frequent indications for treatment were bacteremia of unknown origin, bone and joint infection, catheter-related bacteremia, intra-abdominal infection, skin structure infection, and urinary tract infection. The mean duration of treatment was 14.5 ± 10.7 days (range: one to 108 days). The clinical success rate was 74 percent (95 percent confidence interval [CI]: 67 to 80 percent). The bacteriologic success rate was 71 percent (95 percent CI: 65 to 78 percent). The overall clinical and bacteriologic success rate was 66 percent. The worst outcomes occurred in patients who had vancomycin-resistant *E. faecium* bacteremia at entry into the study, who were on mechanical ventilation, or who had undergone laparotomy.[6]

In the two studies,[6] arthralgias and myalgias were the most common adverse events related to treatment. Local peripheral vein inflammation was common but rarely led to the discontinuation of therapy. Superinfection by gram-positive organisms was documented in 22 percent of patients, and resistance to quinupristin-dalfopristin developed in six of 156 bacteriologically evaluable patients (4 percent).

Another group of investigators[7] compared quinupristin-dalfopristin with cefazolin, oxacillin, and vancomycin in two randomized, open-label clinical trials involving hospitalized patients with complicated gram-positive skin and skin structure infections. A total of 893 patients were enrolled in the studies, with 450 patients randomized to the quinupristin-dalfopristin group and 443 patients randomized to the comparison group. The majority of patients had erysipelas, traumatic wound infection, or clean surgical wound infection. *S. aureus* was the most frequently isolated pathogen.

The two trials[7] found comparable clinical success rates in the quinupristin-dalfopristin group (68 percent) and the comparison group (71 percent). The incidence of drug-related venous adverse events was higher in patients treated with quinupristin-dalfopristin (66 percent) than in those who received the comparison drugs (28 percent). The authors concluded that, in hospitalized patients, quinupristin-dalfopristin is an effective alternative for the treatment of complicated skin and skin structure infections caused by gram-positive organisms that are susceptible to the formulation.

Yet another investigative team[8] found quinupristin-dalfopristin to be effective in the treatment of catheter-related bacteremia caused by *S. aureus* or coagulase-negative staphylococci. In this small study (39 patients), quinupristin-dalfopristin was compared with vancomycin. The

outcomes for the two treatment groups were the same (50 percent clinical and bacteriologic responses), and the safety profiles were comparable.

A phase III prospective, randomized study[9] conducted in several countries compared quinupristin-dalfopristin (with or without aztreonam [Azactam]), and vancomycin in the treatment of nosocomial pneumonia. Demographic and prognostic risk factors were similar in the two treatment groups. In the bacteriologically evaluable patients, therapy was clinically successful (i.e., cure or improvement) in 49 of the 87 patients (56 percent) who received quinupristin-dalfopristin and 49 of the 84 patients (58 percent) who were given vancomycin. Equivalent clinical success was also observed in the all-treated population (N = 298).

In this study,[9] patients with *S. aureus* pneumonia and, specifically, patients with pneumonia caused by methicillin-resistant *S. aureus* had comparable clinical response rates. However, the number of patients with methicillin-resistant *S. aureus* pneumonia was relatively small (20 in the quinupristin-dalfopristin group and 18 in the vancomycin group).

Dosage

The recommended dosage of quinupristin-dalfopristin for the treatment of vancomycin-resistant *E. faecium* infections in adults is 7.5 mg per kg administered intravenously every eight hours. The recommended dosage for complicated skin and skin structure infections is 7.5 mg per kg given intravenously every 12 hours. In vancomycin-resistant *E. faecium* infections, the duration of treatment should be based on the site and severity of the infection. The recommended minimum duration of treatment for complicated skin and skin structure infections is seven days.[5]

The dosage of quinupristin-dalfopristin does not have to be adjusted in elderly patients or patients with renal impairment. Limited clinical data are available on the use of quinupristin-dalfopristin in patients with hepatic disease, but a dosage reduction may be required in patients with cirrhosis. The safety and efficacy of quinupristin-dalfopristin have not been well studied in children.[5]

Quinupristin-dalfopristin is available in a single 500-mg vial. The recommended infusion volume and duration is 250 mL given over 60 minutes. A 500-mg vial of quinupristin-dalfopristin costs approximately $107.

The author indicates that he does not have any conflicts of interest. Sources of funding: none reported.

The author thanks Melissa Portner for technical assistance in the preparation of this manuscript.

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