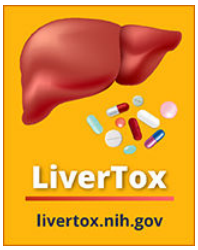
U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Quinupristin-Dalfopristin. [Updated 2018 May 21].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/



Quinupristin-Dalfopristin

Updated: May 21, 2018.

OVERVIEW

Introduction

Quinupristin and dalfopristin are intravenously administered, streptogramin antibiotics used in fixed combination to treat severe bacterial infections due to susceptible organisms including methicillin resistant Staphylococcus aureus (MRSA). The fixed combination of quinupristin and dalfopristin is associated with a low rate of serum enzyme elevations during therapy but has not been convincingly linked to instances of clinically apparent liver injury.

Background

Quinupristin (kwin" ue pris' tin) and dalfopristin (dal" foe pris' tin) are streptogramin antibiotics that were initially isolated from Streptomyces pristinaspiralis. Quinupristin, a derivative of pristamycin IA, and dalfopristin, a derivative of pristamycin IIA, are synergistic in activity and are used in a fixed dose combination in a ratio of 30:70 by weight. This combination binds and inhibits the activity of the 50S subunit of bacterial ribosomes, which yields potent bactericidal activity against many gram positive bacteria including methicillin resistant forms of Staphylococcus aureus (MRSA). Quinupristin and dalfopristin also have activity against some gram negative bacteria including Enterococcus species. The combination of quinupristin and dalfopristin under the brand same of Synercid was approved for use in the United States in 1999. Current indications include complicated skin and skin structure infections caused by susceptible strains of Staphylococcus aureus or Streptococcus pyogenes and severe infections due to susceptible vancomycin-resistant Enterococcus faecium. The combination of quinupristin and dalfopristin is available in solution in 10 mL vials of 500 mg (150 mg of quinupristin and 350 mg of dalfopristin) and the typical dose regimen is 7.5 mg/kg intravenously every 8 to 12 hours for 5 to 14 days. Side effects may include nausea, diarrhea, headache, skin rash, myalgia, arthralgia and injection site reactions (burning, irritation, pain). Rare, but potentially severe side effects include anaphylaxis and angioneurotic edema.

Hepatotoxicity

Elevations in serum aminotransferase levels occur in a proportion of patients receiving quinupristin and dalfopristin, but rates are minimally higher than with placebo or comparator drugs. The elevations are generally mild-to-moderate, asymptomatic and self-limited, frequently resolving without discontinuation or even interruption of therapy. Elevations above 5 times ULN occur in less than 1% of patients. Quinupristin-dalfopristin can also cause elevations in direct as well as total bilirubin, but these elevations are mild and not accompanied by elevations in serum enzymes or other evidence of liver injury. In the many clinical trials of quinupristin and dalfopristin there were no instances of clinically apparent liver injury that could be attributed

convincingly to their use. Patients who receive quinupristin and dalfopristin are often severely ill, septic and receiving multiple medications or parenteral nutrition, so that jaundice arising during therapy is often multifactorial and difficult to assign to a specific cause. Nevertheless, since the approval and more wide spread use of this antibiotic combination, there have been no published reports of hepatitis or jaundice linked specifically to it use. Thus, clinically apparent liver injury from quinupristin and dalfopristin may occur, but is quite rare.

Likelihood score: E* (unproven but suspected rare cause of clinically apparent liver injury).

Mechanism of Injury

The cause of the mild-to-moderate serum aminotransferase elevations that occur during quinupristin and dalfopristin therapy is unknown. Both are extensively metabolized in the liver, largely via the cytochrome P450 system (CYP 3A4) and the combination is susceptible to drug-drug interactions with agents that are substrates for 3A4.

Outcome and Management

The severity of the liver injury linked to quinupristin and dalfopristin therapy is usually mild and self-limited and dose modification or discontinuation is rarely necessary. No instances of acute liver failure, chronic hepatitis or vanishing bile duct syndrome have been attributed to quinupristin and dalfopristin therapy. Also, there is no information on cross sensitivity between quinupristin and dalfopristin and other antibiotics used for MRSA infections, but there is little reason to believe that such sensitivity exists.

Drug Class: Antiinfective Agents, Miscellaneous

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Quinupristin-Dalfopristin – Synercid®

DRUG CLASS

Antiinfective Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

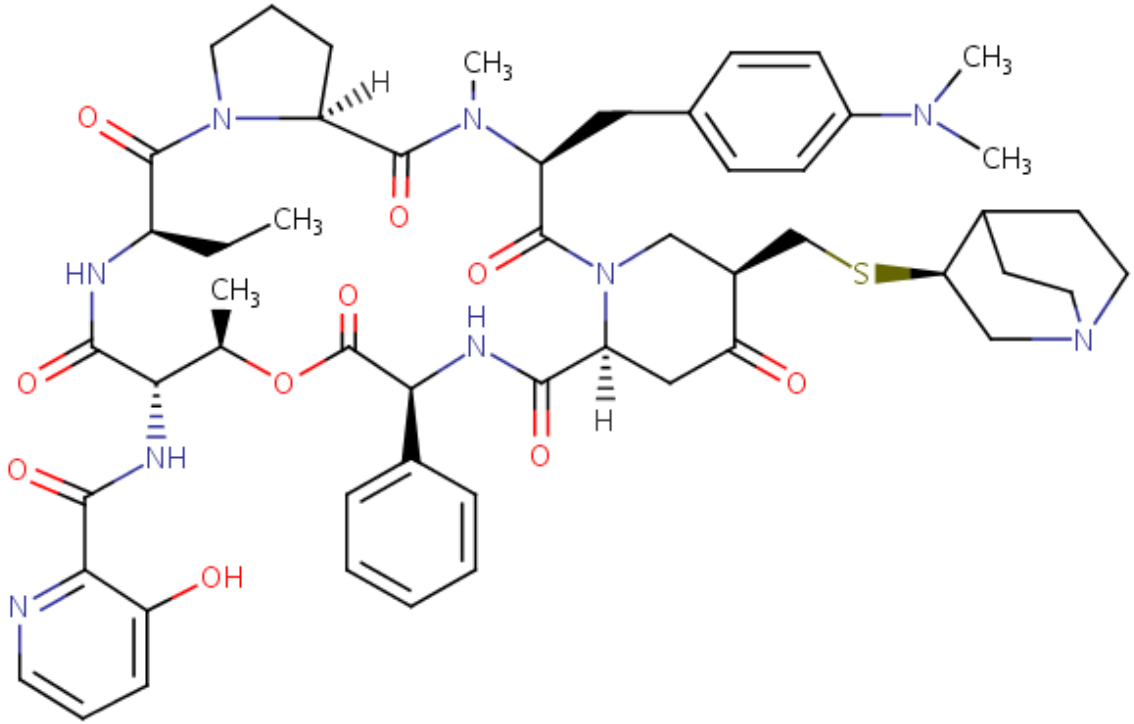
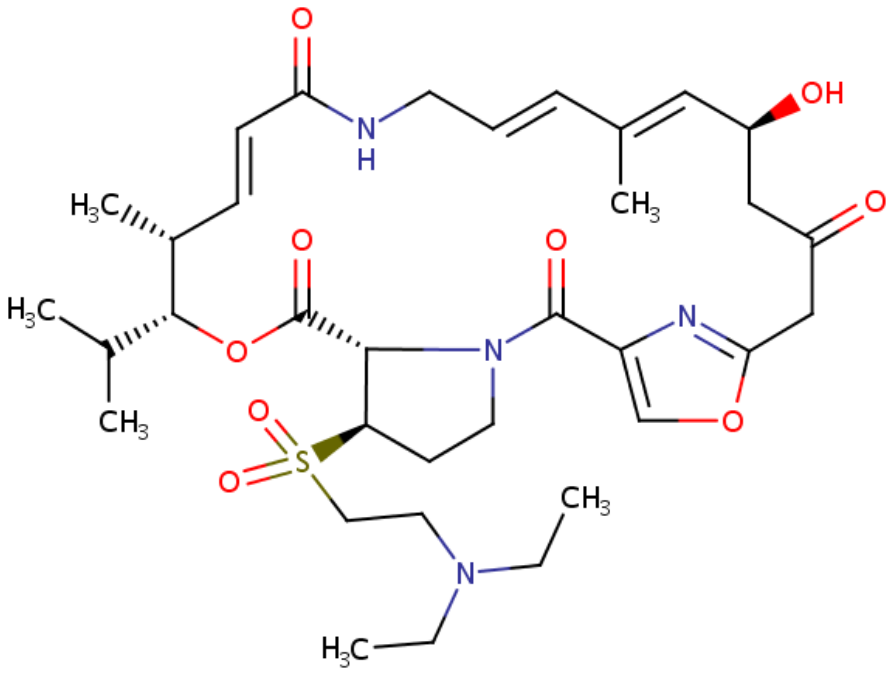
DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Quinupristin	120138-50-3	C53-H67-N9-O10-S	

Table continued from previous page.

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Dalfopristin	112362-50-2	C34-H50-N4-O9-S	

ANNOTATED BIBLIOGRAPHY

References updated: 21 May 2018

Zimmerman HJ. Hepatotoxic effects of oncotherapeutic and immnosuppressive agents. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999: pp. 673-708.

(Expert review of hepatotoxicity published in 1999; does not discuss quinupristin-dalfopristin).

Moseley RH. Hepatotoxicity of antimicrobial and antifungal agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd edition. Amsterdam: Elsevier, 2013. p. 463-81.

(Expert review of antibiotic induced liver injury; does not discuss quinupristin or dalfopristin).

Raad I, Bompart F, Hachem R. Prospective, randomized dose-ranging open phase II pilot study of quinupristin/dalfopristin versus vancomycin in the treatment of catheter-related staphylococcal bacteremia. Eur J Clin Microbiol Infect Dis 1999; 18: 199-202. PubMed PMID: 10357054.

(Among 39 patients with Staphylococcal bacteremia due to intravenous catheters treated with quinupristin-dalfopristin or vancomycin, response rates were similar and side effects included arm and chest pain, fever, arthritis and phlebitis; no mention of ALT elevations or hepatotoxicity).

Moellering RC, Linden PK, Reinhardt J, Blumberg EA, Bompart F, Talbot GH. The efficacy and safety of quinupristin/dalfopristin for the treatment of infections caused by vancomycin-resistant Enterococcus faecium. Synercid Emergency-Use Study Group. J Antimicrob Chemother 1999; 44: 251-61. PubMed PMID: 10473233.

(Among 396 patients with vancomycin resistant Enterococcus faecium infections treated with quinupristin-dalfopristin, the overall response rate was 74% and arthralgia and myalgia were the most frequent adverse events and led to discontinuation in 6% of patients; only one patient had ALT elevations that required early discontinuation).

Rubinstein E, Prokocimer P, Talbot GH. Safety and tolerability of quinupristin/dalfopristin: administration guidelines. J Antimicrob Chemother 1999; 44 Suppl A: 37-46. PubMed PMID: 10511396.

(Pooled analysis of 2298 patients enrolled in 8 prospective studies of quinupristin-dalfopristin found common adverse events were arthralgia, nausea, diarrhea, and rash; serum direct bilirubin levels became elevated in 5.5% and bilirubin above 5 mg/dL in 1.5% of patients, but without concurrent serum enzyme elevations which were rarely elevated [ALT in 1.9% vs 3.8%, Alk P in 1% vs 2.7% receiving comparator drugs]).

Quinupristin/dalfopristin. Med Lett Drugs Ther 1999; 41 (1066): 109-10. PubMed PMID: 10987009.

(Concise review of the antibacterial activity, pharmacokinetics, clinical efficacy, safety and costs of quinupristin-dalfopristin shortly after its approval in the US mentions side effects of infusion site reactions, thrombophlebitis, allergic reactions, myalgia and occasional increases in serum direct bilirubin).

Fagon J, Patrick H, Haas DW, Torres A, Gibert C, Cheadle WG, Falcone RE, et al. Treatment of gram-positive nosocomial pneumonia. Prospective randomized comparison of quinupristin/ dalfopristin versus vancomycin. Nosocomial Pneumonia Group. Am J Respir Crit Care Med 2000; 161 (3 Pt 1): 753-62. PubMed PMID: 10712318.

(Among 198 patients with nosocomial pneumonia caused by gram-positive bacteria treated with either quinupristin-dalfopristin or vancomycin, both clinical response and adverse event rates were similar in the two groups; no mention of ALT elevations or hepatotoxicity).

Winston DJ, Emmanouilides C, Kroeber A, Hindler J, Bruckner DA, Territo MC, Busuttil RW. Quinupristin/Dalfopristin therapy for infections due to vancomycin-resistant Enterococcus faecium. Clin Infect Dis 2000; 30: 790-7. PubMed PMID: 10817685.

(Among 24 patients with vancomycin resistance Enterococcus faecium infections treated with quinupristin and dalfopristin, the only adverse events attributed to the drug were arthralgia and myalgia [33%] without CPK or aldolase elevations; no mention of ALT elevations or hepatotoxicity).

Drew RH, Perfect JR, Srinath L, Kurkimilis E, Dowzicky M, Talbot GH. Treatment of methicillin-resistant staphylococcus aureus infections with quinupristin-dalfopristin in patients intolerant of or failing prior therapy. For the Synercid Emergency-Use Study Group. J Antimicrob Chemother 2000; 46: 775-84. PubMed PMID: 11062197.

(Among 90 patients with MRSA infections who had failed or were intolerant to other antibiotic therapies and who were treated with quinupristin-dalfopristin, the overall response rate was 71% and common side effects were local venous infusion reactions, arthralgia, myalgia and nausea; no mention of ALT elevations or hepatotoxicity).

Linden PK, Bompart F, Gray S, Talbot GH. Hyperbilirubinemia during quinupristin-dalfopristin therapy in liver transplant recipients: correlation with available liver biopsy results. Pharmacotherapy 2001; 21: 661-8. PubMed PMID: 11401179.

(Among 25 liver transplant patients who developed a vancomycin-resistant Enterococcus faecium infection and received quinupristin-dalfopristin for 6-13 days and underwent liver biopsy, cholestasis was often found, but was also present before the antibiotic was started in many patients).

Carver PL, Whang E, VandenBussche HL, Kauffman CA, Malani PN. Risk factors for arthralgias or myalgias associated with quinupristin-dalfopristin therapy. Pharmacotherapy 2003; 23: 159-64. PubMed PMID: 12587804.

(Among 50 patients treated with quinupristin-dalfopristin at a single referral center between 1996 and 2000, 25 developed arthralgia or myalgia and factors that were associated with these symptoms were female sex, chronic liver disease, liver transplant, elevated serum bilirubin before starting therapy, major surgery and receipt of mycophenolate or cyclosporine).

Raad I, Hachem R, Hanna H, Afif C, Escalante C, Kantarjian H, Rolston K. Prospective, randomized study comparing quinupristin-dalfopristin with linezolid in the treatment of vancomycin-resistant Enterococcus faecium infections. J Antimicrob Chemother 2004; 53: 646-9. PubMed PMID: 14998986.

(Among 40 patients with cancer and vancomycin-resistant Enterococcus faecium infection treated with quinupristin-dalfopristin or linezolid, response rates were similar; and while quinupristin-dalfopristin treated subjects were more like to have myalgia or arthralgia [33% vs 0%], they had lower rates of nausea, serum bilirubin elevations and thrombocytopenia; no mention of ALT elevations or hepatotoxicity).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 19132805.

(Among 300 cases of drug induced liver disease in the US collected from 2004 to 2008, none were attributed to quinupristin-dalfopristin).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013; 144: 1419-25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, but none were attributed to quinupristin-dalfopristin).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America. An analysis of published reports. Ann Hepatol 2014; 13: 231-9. PubMed PMID: 24552865.

(Systematic review of literature of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases, but none were attributed to quinupristin-dalfopristin).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury in the US collected between 2004 and 2012, 323 cases were attributed to antibiotics, but none to quinupristin-dalfopristin).