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Dronedarone

Updated: January 5, 2018.

OVERVIEW

Introduction

Dronedarone is an antiarrhythmic and a synthetic derivative of amiodarone that is used for maintaining sinus rhythm for patients with atrial fibrillation or flutter. Dronedarone is associated with a variable rate of serum enzyme elevations during therapy and to rare instances of clinically apparent liver injury, which can be severe and have resulted in deaths and need for liver transplantation.

Background

Dronedarone (droe ne' da rone) is a synthetic derivative of amiodarone, a benzofuran derivative that is a structural analogue of thyroid hormone. However, unlike amiodarone and thyroxine, dronedarone is not iodinated and was specifically designed to avoid some of the end-organ adverse effects associated with amiodarone use. Dronedarone, like amiodarone, has a multitude of electrophysiologic properties, including inhibition of several potassium currents as well as sodium and slow L-type calcium channels. In clinical trials, dronedarone improved maintenance of sinus rhythm in patients with atrial fibrillation or flutter. Dronedarone was approved for use in the United States in 2009 and its current indications are for oral treatment of paroxysmal or persistent atrial fibrillation or flutter. Dronedarone is available in tablets of 400 mg under the brand name Multaq and the recommended maintenance dose in adults in 400 mg twice daily (an initial loading dose of twice that amount if usually recommended). Side effects of dronedarone include gastrointestinal upset, nausea, diarrhea, headache and mild elevations in serum creatinine. Recent large, long term trials of dronedarone have suggested that its use is associated with an increased risk in cardiovascular events, heart failure, stokes and deaths in certain populations.

Hepatotoxicity

Chronic therapy with dronedarone has been associated with mild serum enzyme elevations in up to 12% of patients, but similar rates were found in comparator arms and even in placebo recipients. The serum aminotransferase elevations that occur during chronic dronedarone therapy are generally mild-to-moderate in severity and asymptomatic, rarely requiring discontinuation or dose modification. In preapproval clinical trials, clinically apparent liver injury was not described. Since its approval and more wide scale use, however, dronedarone has been linked to several cases of clinically apparent liver injury with jaundice, some of which have been severe. The onset of injury ranged from 2 to 11 months and the clinical presentation was similar to acute viral hepatitis, with symptoms of fatigue and abdominal discomfort followed by jaundice and a hepatocellular pattern of serum enzyme elevations. Several instances have resulted in acute liver failure requiring emergency liver transplantation. However, specific clinical features of cases of clinically apparent liver injury

from dronedarone have not been well defined and the relationship of dronedarone to the described liver injury has not always been well documented.

Likelihood score: C (probable cause of clinically apparent liver injury).

Mechanism of Injury

The cause of dronedarone hepatotoxicity is not clear. The clinical presentation of injury is somewhat different than that described commonly associated with amiodarone which shares clinical features with alcoholic liver injury marked by insidious onset, minimal serum enzyme elevations, and liver histology showing steatosis and ballooning degeneration with fibrosis and Mallory bodies. Dronedarone is extensively metabolized by the cytochrome P450 system (predominantly CYP 3A) and the liver injury may be due to a toxic metabolite.

Outcome and Management

The liver injury attributed to dronedarone can be severe and lead to liver failure and death. There are no known specific therapies for reversing dronedarone effects. There is also no information about cross sensitivity with hepatic injury from amiodarone, but other approaches to atrial arrhythmia control are probably advisable.

Drug Class: Antiarrhythmic Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Dronedarone – Multaq®

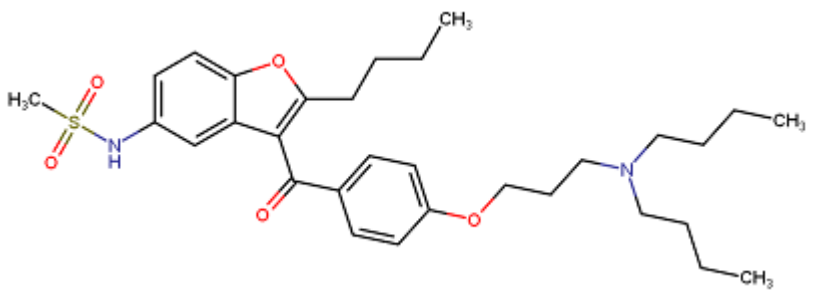
DRUG CLASS

Antiarrhythmic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Dronedarone	141626-36-0	C31-H44-N2-O5-S	

ANNOTATED BIBLIOGRAPHY

References updated: 05 January 2018

Zimmerman HJ. Hepatotoxic effects of oncotherapeutic and immunosuppressive agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 648-52.

(Expert review of hepatotoxicity published in 1999; patterns of liver injury associated with amiodarone include frequent minor serum enzyme elevations [14-83%] and, less commonly, chronic liver disease resembling alcoholic hepatitis and cirrhosis, acute hepatitis with jaundice, phospholipidosis, Reye syndrome and cholestasis; dronedarone is not discussed).

De Marzio DH, Navarro VJ. Antiarrhythmics. Hepatotoxicity of cardiovascular and antidiabetic drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 520-22.

(Review of hepatotoxicity of cardiovascular drugs mentions that two cases of acute liver failure attributed to dronedarone that were reported after its approval in 2009, which led to an FDA warning and recommendation for routine periodic monitoring of liver tests, the effectiveness of which has not been shown).

Roden DM. Antiarrhythmic drugs. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 899-932.

(Textbook of pharmacology and therapeutics).

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: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, 2 were attributed to amiodarone, but none to dronedarone, which however was not approved until after 2008).

Singh BN, Connolly SJ, Crijns HJ, Roy D, Kowey PR, Capucci A, Radzik D, et al; EURIDIS and ADONIS Investigators. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. N Engl J Med 2007; 357: 987-99. PubMed PMID: 17804843.

(Prospective study of dronedarone, a benzofuran derivative of amiodarone, versus placebo in 828 patients with atrial fibrillation or flutter for up to one year: abnormalities in liver tests occurred in 12.2% of dronedarone vs 13.6% of placebo recipients; no mention of clinically apparent liver injury).

Davy JM, Herold M, Hoglund C, Timmermans A, Alings A, Radzik D, Van Kempen L; ERATO Study Investigators. Dronedarone for the control of ventricular rate in permanent atrial fibrillation: the Efficacy and safety of dronedarone for the control of ventricular rate during atrial fibrillation (ERATO) study. Am Heart J 2008; 156: 527. PubMed PMID: 18760136.

(Controlled trial of dronedarone vs placebo for 6 months in 174 patients with permanent atrial fibrillation; no specific mention of ALT elevations or hepatotoxicity but authors conclude: "dronedarone was well tolerated with no evidence of organ toxicities").

Køber L, Torp-Pedersen C, McMurray JJ, Gøtzsche O, Lévy S, Crijns H, Amlie J, et al; Dronedarone Study Group. Increased mortality after dronedarone therapy for severe heart failure. N Engl J Med 2008; 358: 2678-87. PubMed PMID: 18565860.

(Controlled trial of dronedarone vs placebo in 627 patients with symptomatic heart failure was terminated early because of excess mortality in dronedarone [8.1%] compared to placebo treated subjects [3.8%], largely due to worsening of heart failure; no mention of hepatotoxicity).

Dronedarone (Multaq) for atrial fibrillation. Med Lett Drugs Ther 2009; 51 (1322): 78-80. PubMed PMID: 19798011.

(Concise review of the mechanism of action, clinical efficacy and safety of dronedarone shortly after its approval in the US).

Patel C, Yan GX, Kowey PR. Dronedarone. Circulation 2009; 120: 636-44. PubMed PMID: 19687370.

(Review of the chemical structure, mechanism of action, pharmacokinetics, clinical efficacy and safety of dronedarone; in the 4640-patient ATHENA trial, liver test abnormalities occurred no more frequently in dronedarone than in placebo treated subjects [0.5% vs 0.6%]).

Le Heuzey JY, De Ferrari GM, Radzik D, Santini M, Zhu J, Davy JM. A short-term, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of dronedarone versus amiodarone in patients with persistent atrial fibrillation: the DIONYSOS study. J Cardiovasc Electrophysiol 2010; 21: 597-605. PubMed PMID: 20384650.

(Controlled trial of dronedarone vs amiodarone in 504 patients with persistent atrial fibrillation found higher rate of recurrence with dronedarone, whereas thyroid, neurologic, skin and ocular adverse events were less; ALT or AST elevations [2 times ULN] occurred at similar rates [12% vs 10.6%]).

Christiansen CB, Torp-Pedersen C, Køber L. Efficacy and safety of dronedarone: a review of randomized trials. Expert Opin Drug Saf 2010; 9: 189-99. PubMed PMID: 20001756.

(Review of efficacy and safety of dronedarone based on results of 7 controlled trials; no mention of ALT elevations or hepatotoxicity).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, but none were attributed to amiodarone, dronedarone or other antiarrhythmic agents).

Connolly SJ, Camm AJ, Halperin JL, Joyner C, Alings M, Amerena J, Atar D, et al; PALLAS Investigators. Dronedarone in high-risk permanent atrial fibrillation. N Engl J Med 2011; 365: 2268-76. PubMed PMID: 22082198.

(Among 3236 elderly adults with persistent atrial fibrillation treated with dronedarone or placebo, there was an increased rate of primary outcomes including death in the dronedarone treated group, and the study was terminated early; ALT elevations above 3 times ULN occurred in 1.5% on dronedarone versus 0.6% on placebo).

In brief: FDA warning on dronedarone (Multaq). Med Lett Drugs Ther 2011; 53 (1359): 17. PubMed PMID: 21383666.

(Warning from FDA of several cases of severe liver injury and liver failure, two requiring transplantation, during dronedarone therapy [after 4.5 and 6 months]).

Safety of dronedarone (Multaq). Med Lett Drugs Ther 2011; 53 (1379-1380): 103-4. PubMed PMID: 22173456.

(Discussion of safety of dronedarone mentioning studies showing that its use is associated with an increased risk of stroke, heart failure and cardiovascular death).

Joghetaei N, Weirich G, Huber W, Büchler P, Estner H. Acute liver failure associated with dronedarone. Circ Arrhythm Electrophysiol 2011; 4: 592-3. PubMed PMID: 21846890.

(70 year old woman developed jaundice 6 months after starting dronedarone for atrial fibrillation [peak bilirubin 30.3 mg/dL, ALT and Alk P not provided], with progressive hepatic failure leading to emergency liver transplantation 20 days after presentation).

Del Pozo Ruiz JJ, Martín Sanz A, Alvarez Vicente G, Arenas Monzo C. [Dronedarone-associated hepatotoxicity. A propos of a case]. Farm Hosp 2012; 36: 545-7. Spanish. PubMed PMID: 23461450.

(75 year old man developed abdominal pain, nausea and liver test abnormalities a week after starting dronedarone [bilirubin 1.9 mg/dL, ALT 478 U/L, Alk P normal], symptoms resolving rapidly and all values falling into the normal range within 3 weeks of stopping).

De Ferrari GM, Dusi V. Drug safety evaluation of dronedarone in atrial fibrillation. Expert Opin Drug Saf 2012; 11: 1023-45. PubMed PMID: 22971242.

(Extensive review of structure, mechanism of action, pharmacokinetics, clinical efficacy and safety of dronedarone in comparison to amiodarone).

Jahn S, Zollner G, Lackner C, Stauber RE. Severe toxic hepatitis associated with dronedarone. Curr Drug Saf 2013; 8: 201-2. PubMed PMID: 23789833.

(69 year old woman developed jaundice 11 months after starting dronedarone and 4 months after starting phenprocoumon [bilirubin 4.9 rising to 33.5 mg/dL, ALT 1314 U/L, Alk P 244 U/L, ANA 1:160, peak INR 1.4], subsequently worsening, but ultimately recovering fully within 6 months of onset).

Friberg L. Safety of Dronedarone in Routine Clinical Care. J Am Coll Cardiol 2014; 63: 2376-84. PubMed PMID: 24727250.

(Among 174,995 patients with atrial fibrillation in a Swedish Patient Registry, there was a lower rate of mortality among the 4856 who received dronedarone [1.3% annually] than among those who did not [14%] and no excess in clinically apparent liver disease [0.2% vs 0.6% annually]).

Gao S, Dai W, Zhang L, Juhaeri J, Wang Y, Caubel P. Risk of cardiovascular events, stroke, congestive heart failure, interstitial lung disease, and acute liver injury: dronedarone versus amiodarone and other antiarrhythmics. J Atr Fibrillation 2013; 6: 890. PubMed PMID: 28496906.

(Analysis of health care database of 10,455 adults with atrial fibrillation or flutter seen between 2009 and 2010 for serious outcomes including myocardial infarction, stroke, congestive heart failure, interstitial lung diseaes and acute liver injury found no excess of instances of acute liver injury among 1727 who were started on dronedarone therapy).

Hohnloser SH. Dronedarone: "Real-world" data vis-à-vis data from randomized clinical trials. J Am Coll Cardiol 2014; 63: 2385-7. PubMed PMID: 24727252.

(Editorial in response to analysis of a Swedish registry by Friberg [2014]).

Arif SA, Drury R, Ader P. Impact of Food and Drug Administration hepatotoxicity warning on prescribing and monitoring of dronedarone in a tertiary teaching hospital. Int J Pharm Pract 2015; 23: 456-60. PubMed PMID: 26382915.

(Retrospective analysis of frequency of prescriptions for dronedarone for the year before and year after the FDA issued a warning letter concerning liver injury at a single medical referral center showed a 50% decrease in number of prescriptions, but no increase in rate of ALT monitoring of recipients).

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.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 5 cases were attributed to amiodarone and 2 to dronedarone).