Elevated liver enzymes associated with dronedarone for atrial fibrillation

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Abstract
A 51-year-old male with documented atrial fibrillation who was taking dronedarone 400 mg twice daily for approximately 3 months returned to the cardiologist for an ablation procedure. Baseline liver enzymes were within normal range prior to starting the medication and increased after the 3 months of therapy. Aspartate aminotransferase increased from 31 IU/L to 98 IU/L and alanine aminotransferase increased from 21 IU/L to 101 IU/L. Two and a half months after discontinuation of the medication, liver enzymes normalized (aspartate aminotransferase: 30 IU/L and alanine aminotransferase: 25 IU/L). The Food and Drug Administration has now alerted health-care professionals of the potential for liver injury based upon post-marketing surveillance. The chronological course of elevated liver enzymes noted in our patient is suggestive of a dronedarone-induced problem. Clinicians should have a heightened awareness of the potential for liver enzyme elevation and injury with dronedarone and should monitor enzymes periodically, especially within the first 6 months of use.

Keywords
Dronedarone, liver, enzymes, atrial fibrillation, hepatic, elevation

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Introduction
Dronedarone is a non-iodinated amiodarone analogue, which is Food and Drug Administration (FDA) approved in adults for atrial fibrillation and flutter. The exact mechanism of action is unknown, although it does exert antiarrhythmic effects that are similar to all four Vaughan–Williams classes. Like amiodarone, dronedarone inhibits the calcium, sodium and potassium channels and is an alpha- and beta-adrenergic receptor antagonist. Although possible hepatic effects have been recently noted through post-marketing surveillance data, such case reports are limited in the current literature. The author presents a case of elevated liver enzymes after short-term use of dronedarone in the outpatient setting.

Case
A 51-year-old male with documented persistent atrial fibrillation for 10 years has been followed in our anticoagulation clinic for approximately 4 years. In addition to atrial fibrillation, he has documented hypertension, hyperlipidemia, mitral valve prolapse, Barrett’s esophagitis and rosacea. His atrial fibrillation has not been controlled in the past, despite efforts with propafenone, flecainide and a prior ablation in 2007. On 1 September 2010, the patient’s cardiologist started dronedarone 400 mg twice daily because of continued episodes of atrial fibrillation. His other medications at this time included warfarin 15 mg on Mondays, Wednesdays and Fridays and 10 mg on all other days (since June 2007), ramipril 5 mg/day (since December 2006) and atorvastatin 10 mg/day (since March 2008), doxycycline 100 mg twice daily (since September 2006) and omeprazole 20 mg/day (since January 2010). He also takes vitamin D 400 IU/day, fish oil 1 g/day and glucosamine twice daily. He is adherent to all medications and has prescription coverage. The patient does not smoke and only drinks occasionally (i.e. one or two drinks on the weekend socially). At this time, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were 31 IU/L (normal range: 12–38 IU/L) and 21 IU/L (normal range: 10–45 IU/L). It should be noted that all previous liver function tests dating back to 2002 were within normal range. His International Normalized Ratio (INR) was 2.2. His ejection fraction was found to be 69%. At his 29 September 2010 visit with the cardiologist, he was noted to still have episodes of atrial fibrillation approximately every other day with episodes lasting 6–8 h typically. After a thorough discussion, it was decided to perform a catheter
ablation in November. In the meantime, he was to continue the dronedarone. On 22 November 2010, the patient had his ablation performed with no problems noted. Medications and doses at this time were the same as previously stated. The ablation was successful, and the patient was sent home on the ramipril, atorvastatin, omeprazole, doxycycline, fish oil, glucosamine and vitamin D. Warfarin was not continued, and the patient was given dabigatran 150 mg twice daily instead. Dronedarone was also discontinued. In January 2011, it was noted by the clinical pharmacist at the primary care physician’s office that the patient’s liver enzymes had been elevated on 22 November 2010, with AST 98 IU/L and ALT 101 IU/L. All other laboratory values were normal. It should be noted that the patient never complained of muscle aches or weakness throughout this time and had no symptoms of liver disease. The primary care physician was contacted and repeat liver enzymes were drawn on 4 February 2011. The enzymes had normalized, with AST 30 IU/L and ALT 25 IU/L, and the patient was doing well. At the time of the repeat test, the patient was taking all medications listed above, post-ablation. Dronedarone had now been discontinued for approximately 2.5 months.

Discussion

Hepatic enzyme elevations may result from a variety of disease states, including hepatitis, alcoholic liver disease and nonalcoholic fatty liver disease. With regard to medications, a variety of agents have been noted to be potentially hepatotoxic, including acetaminophen, allopurinol, amiodarone, azathioprine, corticosteroids, nonsteroidal anti-inflammatory drugs, hydralazine, isoniazid, methotrexate, methyl dopa, nitrofurantoin, quinidine, statins, tetracycline and valproic acid. Drug-induced liver injury has been the major reason for withdrawal of medications after FDA approval. Determining causality of drug-induced liver injury can be difficult, and it is often a diagnosis of exclusion. There are currently no specific diagnostic markers that can be used to verify suspected drug-induced liver injury. In most cases, a medication is suspected when there is a close temporal association with onset and the course of the liver injury after withdrawal of the suspected agent. When information related to previously documented hepatotoxicity of agent(s) is not available, published case reports can prove to be very valuable. Hy’s rule, defined as an ALT level greater than or equal to three times the upper limit of normal, has been advocated by the US FDA for use in the assessment of the hepatotoxicity of newly developed drugs. In addition, this rule is often applied when deciding whether to discontinue medications that might be causing liver injury.

Dronedarone is an antiarrhythmic agent that was approved by the FDA in 2009 for paroxysmal or persistent atrial fibrillation or atrial flutter. It has electrophysiologic effects that are similar to those of amiodarone. The chemical structure of dronedarone differs from that of amiodarone in its lack of iodine, which could minimize any impact on the thyroid and could also make dronedarone less lipophilic. In addition, dronedarone is more hydrophilic than amiodarone due to a chemical group attached to the benzofuran ring. Dronedarone may also be less likely to prolong the QT interval. Like amiodarone, dronedarone is a CYP3A4 substrate and inhibits CYP2D6; therefore, interactions with drugs metabolized by these isoenzymes could occur. The drug currently contains a black box warning, cautioning that it should not be used in patients with severe heart failure due to increased risk of mortality. In early 2011, the FDA alerted health-care professionals and patients about unpublished cases of rare, but severe liver injury, including two cases of acute liver failure leading to liver transplant. These two cases occurred at 4 and 6 months after initiation of dronedarone in patients with previously normal hepatic serum enzymes. Both patients were female and approximately 70 years of age. In addition, there are reports from animal experiments and in vitro work with cell cultures suggesting that dronedarone is hepatotoxic. Information about the potential risk of liver injury from dronedarone is now being added to the warnings and precautions and adverse reactions sections of the dronedarone labels. For patients taking dronedarone, it is recommended to obtain periodic hepatic serum enzymes, especially during the first 6 months of treatment.

Although there are several published reports of amiodarone leading to hepatic dysfunction, there are limited case reports related to dronedarone and elevated serum transaminase levels or hepatic injury. According to the Naranjo probability scale, a possible relationship existed between the liver enzyme elevation observed and the use of dronedarone in our patient. Because this adverse effect related to the liver, a hepatotoxicity-specific causality scale was used as well. The Council for the International Organization of Medical Sciences (CIOMS) Scale has been shown to produce reliable and reproducible assessments related to drug-induced liver disease. According to the CIOMS Scale, a possible relationship existed between the liver enzyme elevation observed and the use of dronedarone in our patient. When looking at the aminotransferase levels and relating it to the initiation and discontinuation of the dronedarone, the time frame for the development of enzyme elevation is consistent with drug-induced liver enzyme elevation. Because of this association, the health-care team recommended that the patient not receive dronedarone or amiodarone in the future, and this was documented in the outpatient medical record. The patient was not re-challenged with dronedarone.

Our patient had been taking his long-term medications for months before the enzyme elevations were seen. Although liver enzyme elevations have been documented with atorvastatin, omeprazole, and doxycycline, it is unlikely that any of these agents were solely responsible based upon the time factor. It is possible that liver enzyme elevations were in part due to the potential drug interaction between dronedarone and atorvastatin, causing an increase in plasma concentrations of atorvastatin itself. Our patient had no disease states or other
disorders which could have contributed to the elevations seen. In light of new FDA communication regarding possible liver injury with dronedarone, clinicians should have heightened awareness of this possible side effect, and liver enzymes should be monitored carefully. If hepatic injury is suspected, the medication should be discontinued immediately, and no rechallenge should be attempted.

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There are no conflicts of interest that exist related to this manuscript or the author.

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**References**

1. Laughlin JC and Kowey PR. Dronedarone: a new treatment for atrial fibrillation. *J Cardiovasc Electrophysiol* 2008; 19(11): 1220–1226.
2. Aragon G and Younossi ZM. When and how to evaluate mildly elevated liver enzymes in apparently healthy patients. *Cleve Clin J Med* 2010; 77(3): 195–204.
3. Kaplowitz N. Drug-induced liver disorders: implications for drug development and regulation. *Drug Saf* 2001; 24: 483–490.
4. Larrey D. Epidemiology and individual susceptibility to adverse drug reactions affecting the liver. *Semin Liver Dis* 2002; 22: 145–155.
5. Bjornsson E. Drug-induced liver injury: Hy’s rule revisited. *Clin Pharmacol Ther* 2006; 79: 521–528.
6. Dale KM and White CM. Dronedarone: an amiodarone analog for the treatment of atrial fibrillation and atrial flutter. *Ann Pharmacother* 2007; 41(4): 599–605.
7. Damy T, Pousset F, Caplain H, et al. Pharmacokinetic and pharmacodynamic interactions between metoprolol and dronedarone in extensive and poor CYP2D6 metabolizers healthy subjects. *Fundam Clin Pharmacol* 2004; 18(1): 113–123.
8. US Food and Drug Administration. [http://www.fda.gov](http://www.fda.gov) (accessed 21 March 2011).
9. Every Day Pharmacy. [http://www.pharmqd.com/](http://www.pharmqd.com/) (accessed 21 March 2011).
10. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse reactions. *Clin Pharmacol Ther* 1981; 30: 239–245.
11. Danan G and Benichou C. Causality assessment of adverse reactions to drugs I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J Clin Epidemiol* 1993; 46: 1323–1330.