A Case of Drug-induced Hepatotoxicity: Amiodarone is Not Always to Blame

Brendan O’Hare, MD

Case Presentation

A 54 year-old male presented to the hospital with a two week history of new onset jaundice, anorexia and fatigue. The patient has a past medical history of hypertension, coronary artery disease, and ischemic cardiomyopathy with an ejection fraction of 10% to 15%. He also has a history of atrial fibrillation and paroxysmal ventricular tachycardia with an automated implantable cardioverter-defibrillator placed. He denied any history of blood transfusions, alcohol use, intravenous drug abuse, or known hepatitis. He also denied taking herbal medications or vitamins. The patient denied fevers, night sweats, nausea, shortness of breath, abdominal pain, blood in his stool, or easy bruising. Four weeks prior to admission, the patient was diagnosed with hyperthyroidism thought to be secondary to long-term amiodarone use which the patient had been taking for eight years for treatment of atrial fibrillation. At that time he was started on 10 mg of methimazole daily, and his amiodarone was stopped. All of his other medications were chronic and include atenolol, pantoprazole, aspirin, clopidogrel, and furosemide. He has no known drug allergies. Upon admission his methimazole was stopped since his symptoms could be attributable to this medication.

On presentation the patient was afebrile. His pulse was regular at 112 beats/minute, and his blood pressure was 91/61 mm Hg. He was orientated to person, place, and time. His exam was noteworthy for scleral icterus and jaundice. There was no ascites, asterixis, palmer erythema, spider angioma or other evidence of liver disease. His abdominal exam was benign, with no tenderness to palpation, organomegaly, or lymphadenopathy. He did have 2+ lower extremity swelling that was thought to be chronic and secondary to his heart disease.

Laboratory results are shown in Table 1. All other laboratory values were within the reference range. An EKG did not show any acute changes, and three consecutive troponins were negative. An abdominal ultrasound was notable for the presence of hepatosplenomegaly with the liver measuring 14.4 cm in sagittal length and the spleen measuring 14.4 cm. Color doppler ultrasound showed patent portal, hepatic, and splenic veins. There was no biliary ductal dilation, cholelithiasis or sludge.

On hospital day two the patient’s clinical status had not improved, and a liver biopsy was obtained to help differentiate the cause of hepatic dysfunction. The liver biopsy (Figure 1) showed severe cholestasis with mild inflammatory changes and mallory bodies on pathology. Given the time course of introduction to methimazole and the development of abnormal liver tests, the presumptive diagnosis of methimazole-induced hepatotoxicity was made. The patient experienced a relatively stable course until day six of his stay. At that time the patient became clinically unstable, went into cardiac arrest and died. It was presumed that the new onset liver failure proved to be too much of a stressor on an already weak heart.

Discussion

Methimazole and its precursor molecule carbimazole are common treatment options for hyperthyroidism but do not come without significant risk to the patient: methimazole is a known hepatotoxin. An extensive review of the literature has not identified any previous case reports of methimazole-induced liver injury leading to death in the United States. There

<table>
<thead>
<tr>
<th>Chem 7</th>
<th>Sodium 140 mmol/l</th>
<th>Potassium 4.1 mmol/l</th>
<th>Chloride 105 mmol/l</th>
<th>Carbon Dioxide 21 mmol/l</th>
<th>Urea-Nitrogen 58 mg/dl</th>
<th>Creatinine 2.2 mg/dl</th>
<th>Glucose 136 mg/dl</th>
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<tbody>
<tr>
<td>CBC</td>
<td>White Blood Cell 10.2 b/l</td>
<td>Hemoglobin 14.7 g/dl</td>
<td>Hematocrit 46.0%</td>
<td>Platelets 137 b/l</td>
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<tr>
<td>LFTs</td>
<td>Protein 5.1 g/dl</td>
<td>Albumin 2.8 g/dl</td>
<td>Total Bilirubin 26.8 mg/dl</td>
<td>Direct Bilirubin 11.4 mg/dl</td>
<td>Aspartate Aminotransferase 107 IU/l</td>
<td>Alanine Aminotransferase 107 IU/l</td>
<td>Alkaline Phosphatase 82 IU/l</td>
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<td>Coags</td>
<td>Protime 22.8 s</td>
<td>Prothrombin Time 33 s</td>
<td>INR 1.90</td>
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<tr>
<td>Serologies</td>
<td>HAV IgM (-)</td>
<td>HAV IgG (+)</td>
<td>HBV Ant (-)</td>
<td>HBV Core (-)</td>
<td>HBV Ab (-)</td>
<td>HCV Ab (-)</td>
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<tr>
<td>TFTS</td>
<td>Thyroid Stimulating Hormone 0.02</td>
<td>Thyroxine 4 1.5</td>
<td>Triiodothyronine 3 63</td>
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Table 1. Laboratory values at presentation.
was a case report of necrotizing hepatitis leading to death in 
Germany.1 There have been case reports associating fulminant 
hepatic failure and death with the antithyroid agent propyl-
thiouracil in the United States.2-3 However, up to this point 
methimazole liver injury has not been associated with any 
deaths in the United States.

There were many diagnoses in the differential that were 
sequentially ruled out during this patient’s admission, including 
chronic viral hepatitis, biliary and portal vein thrombosis, 
infiltrative and chronic passive congestion, and ischemic liver 
injury. One drug considered in addition to methimazole for 
causing hepatotoxicity in this patient was amiodarone. It was 
difficult to apply the established scoring systems for assessing 
causality between a drug and hepatocellular injury in this case 
because the patient expired before rechallenge of the potential 
offending agent was possible. However, considering the 
temporality of the treatment, it is likely that methimazole and 
not amiodarone was the cause of liver injury. The patient had 
been stable on amiodarone for eight years without any noted 
hepatotoxicity. In contrast, methimazole had been started four 
weeks prior to development of jaundice. The aforementioned 
scoring systems for deducing the cause of drug-induced liver 
injury put a much greater weight on drugs that cause injury in 
a window of roughly five days to three months. The patient’s 
amiodarone use did not fall into this time interval. In fact, the 
median time for liver disease associated with amiodarone is 21 
months after initiation.19

The liver biopsy was also not consistent with amiodarone-induced 
liver injury. Changes in pathology that are usually associated with 
amiodarone drug toxicity include Mallory’s hyaline, steatosis, 
ballooning of hepatocytes, focal necrosis, fibrosis, and in severe 
cases, cirrhosis.6 Although our patient did have Mallory bodies 
on specimen, none of the other defining characteristics of 
amiodarone toxicity were present. As mentioned, the biopsy 
showed diffuse cholestasis with intracanalicular bile plugging 
(Figure 1). As of 1999 there had only been seven case reports 
published of jaundice and cholestatisis presenting as the major 
clinical and pathological manifestations of amiodarone induced 
hepatotoxicity.7 Conversely, the majority of methimazole liver 
injury cases have reported cholestasis and associated jaundice.8-14

This case serves as an example of a serious but uncommon drug 
related liver injury. Generally, patients with severe liver injury, 
as defined by serum ALT being three times the upper limit of 
normal or the serum bilirubin being two times the upper limit of 
normal in the absence of biliary obstruction, have a mortality 
of at least 10%.15 In our case the patient had a bilirubin that 
was over 20 times normal levels. Additionally, our patient 
had two of the three hallmarks of acute liver failure: jaundice 
and impaired hepatic synthetic function. During the course 
of his admission he did not develop the third characteristic 
which is encephalopathy. If the full triad of manifestations is 
present in cases of drug induced hepatotoxicity, patients have 
roughly a 25% survival rate without liver transplant.16 However, 
prognosis also depends on agent as there is a 0% mortality of 
erythromycin induced liver failure versus 40% mortality with 
use of halothane.19

It is of crucial importance to recognize drug induced liver toxicity 
because it is now the leading cause of acute liver failure among 
patients referred for liver transplantation in the United States.17 
Hepatotoxicity related specifically to antithyroid agents occurs 
with an approximate frequency of 0.1% to 0.2%.18 It is plausible, 
however, that this number may be falsely low secondary to 
difficulty in diagnosis and underreporting.

In this case, the patient’s co-morbidities allowed for close 
physician follow up and an apparent drug induced liver injury 
was caught just four weeks after the inciting agent was started. 
However, not all patients will be followed so vigilantly after 
starting potentially hepatotoxic drugs. It is important for the 
responsible physician to be aware of potential liver injury that 

drugs such as methimazole may cause in order to prevent their 
rare but unfortunate complications.

References
1. Binder C, Lang W. Necrotizing hepatitis with a fatal outcome after carbimazole 
2. Williams KV, Natak S, Becker D, Reyes J, Burmeister LA. Fifty years of 
experience with propylthiouracil-associated hepatotoxicity: what have we 
37:224-228
4. Maria VAI, Victorino RMM. Development and validation of a clinical scale for 
5. Danan G, Benichou C. Causality assessment of adverse reactions to drugs. A 

novel method based on the conclusions of international consensus meetings:

Figure 1. Liver biopsy shows diffuse cholestasis, mallory bodies, 
and intracanalicular bile plugging. There were no viral inclusion 
bodies, steatosis, necrosis, or fibrosis.


Photograph courtesy of Esther Lee, MD