Amiodarone hepatoxicity

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Liver toxicity occurs in about 1% of patients treated with amiodarone. Although potentially life-threatening, it may be reversible if the drug is ceased as soon as toxicity is suspected.

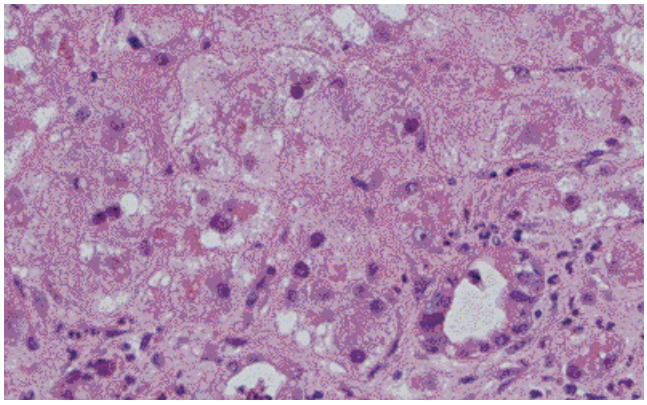

Figure. Liver biopsy specimen from case 2, showing severe acute necrotising hepatitis with prominent Mallory's hyaline.

Remember

- Amiodarone hepatotoxicity can occur even on low-dose amiodarone therapy.
- There is a significant mortality and morbidity (approximately 1%).
- It can present as acute or chronic liver disease, early or late in the course of therapy (see the case studies in the box on page 58).
- The risk increases with higher doses and longer durations of therapy.
- The indication for amiodarone should be reviewed and other agents considered.
- Monitoring of liver function tests (one to three-monthly) is recommended throughout the duration of amiodarone therapy and for 12 months beyond cessation.[1]
- Amiodarone should be ceased if the patient's serum alanine aminotransferase (ALT) level is more than three times the normal for the testing pathology laboratory (i.e. is above about 150 U/L).

Assessment

- Diagnosis of amiodarone liver toxicity is based upon liver biochemistry and histology (Figure), as CT and MRI changes reflect liver amiodarone deposition, which occurs in all patients.
- Liver function tests should be performed every month for six months, extending to three-monthly, during and for 12 months beyond therapy.
- An ALT level more than three times the upper limit of normal is the most sensitive sign of hepatotoxicity. Amiodarone treatment should be ceased and a liver biopsy performed.
- Liver histology is characterised by Mallory's hyaline and phospholipid laden lysosomal lamellar bodies within hepatocytes.
- Extensive necrosis and fibrosis, or cirrhosis, is seen in severe cases.

Management and recommendations

- There is no specific management for amiodarone hepatotoxicity beyond cessation of amiodarone, which should be done as soon as toxicity is suspected.
- The hepatotoxicity may be reversible if the drug is ceased as soon as toxicity is suspected.
- Prevention by using the lowest amiodarone dose possible (200 mg oral daily) helps maintain serum levels below 2.5 mg/L. A lower incidence of toxicity is seen at these serum amiodarone levels.
- Those patients with abnormal liver function tests prior to amiodarone therapy do not appear to be at greater risk. MT

Reference

1. Stelfox HT, Ahmed SB, Fiskio J, Bates DW. Monitoring amiodarone's toxicities: recommendations, evidence, and clinical practice. Clin Pharmacol Ther 2004; 75: 110-122.

Further reading

Gilinsky NH, Briscoe GW, Kuo CS. Fatal amiodarone hepatotoxicity. Am J Gastroenterology

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continued

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Amiodarone is an effective antiarrhythmic agent generally reserved for refractory ventricular tachyarrhythmias because of the risk of liver and lung toxicity. Although uncommon, this toxicity is potentially life-threatening. It is, however, reversible if recognised early. Liver damage occurs through mitochondrial injury, with free radical generation and apoptosis and necrosis of hepatocytes. Amiodarone toxicity can continue to worsen after drug cessation because of amiodarone's long half-life and its release from tissue stores into the bloodstream. Interstitial pneumonitis, lung fibrosis, thyroid toxicity, peripheral neuropathy and skin changes are other potential serious adverse effects of amiodarone. Recurrent toxicity with rechallenge is usual.

Liver toxicity occurs in approximately 1% of treated patients. Chronic liver disease similar to that seen with alcohol is well described, occurring even on low-dose oral amiodarone (200 mg/day) after an average treatment duration of two to three years. Cirrhosis and acute hepatitis may occur on low-dose oral amiodarone therapy, and subfulminant liver failure may be fatal. Asymptomatic abnormal liver function tests while taking amiodarone are common (in approximately 25% of cases), and need to be differentiated from toxicity.

Two cases of amiodarone hepatotoxicity are reported below.

Case 1

An 82-year-old woman who had been taking amiodarone 200 mg per day for three years for atrial fibrillation presented with two weeks of right upper quadrant pain, vomiting and increasing abdominal distension. There had been three months of anorexia, loss of weight and increasing fatigue. Liver function tests were normal until four months prior to presentation.

Examination revealed gross ascites, peripheral oedema and tender hepatomegaly. Investigations showed hepatitis (ALT and aspartate aminotransferase [AST] levels each above 500 U/L), and imaging revealed ascites, hepatomegaly and portal hypertension. Liver histology revealed severe hepatitis with hepatocellular necrosis, cirrhosis and Mallory's hyaline, consistent with amiodarone-induced hepatotoxicity.

Despite ceasing amiodarone she died within four weeks of presentation.

Case 2

A 79-year-old man presented with abnormal liver function tests (ALT, 400 U/L), acute renal failure and a four-month history of lethargy, nausea and 25-kg weight loss. He had been on amiodarone 200 mg per day for five years following an episode of nonsustained ventricular tachycardia.

Liver histology showed severe necrotising hepatitis, with large amounts of eosinophilic Mallory's hyaline, consistent with amiodarone toxicity (Figure).

He developed pneumonia, with progressive respiratory, hepatic and renal failure, and died seven days later.

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