Low dose amiodarone causing pseudo-alcoholic cirrhosis

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Abstract

Amiodarone is a commonly used anti-arrhythmic in elderly patients. Abnormal liver function is frequently reported with its use but clinically symptomatic disease is rare. Hepatomegaly, cholestasis, acute hepatitis and rarely fulminant liver failure have been recorded [1, 2], however amiodarone toxicity presenting with cirrhosis is exceedingly rare. Toxic effects of amiodarone are well described with higher dosage but severe hepatic toxicity and cirrhosis with low dose amiodarone has not been reported in the English language literature.

We present a report on a patient with pseudo-alcoholic cirrhosis with low dose amiodarone.

Keywords: amiodarone, cirrhosis

Case report

A 79-year-old male was admitted to hospital with an episode of coffee ground vomit and a 2-month history of lethargy. In the past he had a coronary artery bypass graft, hypercholesterolaemia and hypothyroidism. He had a permanent pacemaker and had been on amiodarone 200 mg a day for 33 months. His daily medications included thyroxine 100 µg, frusemide 40 mg, aspirin 300 mg, atorvastatin 20 mg and ranitidine 150 mg. He was independent prior to admission and rarely consumed alcohol (<2 units per month). The history of occasional alcohol intake was independently confirmed by the patient's family. There was no history for the use of complementary medicines or herbal medication.

Examination revealed signs of chronic liver disease including spider naevi, gynaecomastia, palmar erythema and moderate ascites. The rest of the examination was unremarkable.

Investigations revealed a haemoglobin of 7.5 g/dl with blood film suggestive of iron deficiency. Liver function was deranged with albumin of 27 g/l, bilirubin 14 µmol/l, aminotransferase 67 iu/l, alkaline phosphatase 216 iu/l, and gamma-glutamyl transferase of 443 iu/l. Clotting tests were normal. Ascitic fluid examination showed no organisms and the cultures showed no growth. There were no malignant cells on cytological examination.

A gastroscopy showed grade IV reflux oesophagitis with confluent erosions and exudative gastritis. A CT scan of the abdomen confirmed extensive ascites and irregular liver margins consistent with the diagnosis of cirrhosis. There was no evidence of portal hypertension. Investigations for hepatotrophic viruses, autoimmune liver disease, haemochromatosis and Wilson's disease were negative.

Liver biopsy confirmed established cirrhosis with extensive fibrosis. There was evidence of polymorphonuclear infiltrate and reduplicating bile ducts within hepatic nodules. Degenerating hepatocytes with Mallory hyaline were also seen. Special stains for copper, iron and alpha-1 antitrypsin globules were negative and there was no evidence of malignancy.

Amiodarone was discontinued following admission but the patient progressively deteriorated with worsening ascites. His liver function deteriorated and he developed heart failure, renal failure and hepatic encephalopathy. He died 3 months after the discontinuation of amiodarone.

Discussion

Abnormal liver function is common with amiodarone. Elevation of serum aminotransferase is noted in 25% of patients on long-term treatment [3]. Clinically
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symptomatic disease is rare but hepatomegaly, hepatitis and chronic liver disease have been reported. Histologically, changes of amiodarone induced hepatotoxicity mimic alcohol-induced liver injury [4–6]. In these cases macro and microvesicular steatosis with fibrosis are frequently seen. Mixed inflammatory infiltrate, cholangitis and Mallory hyaline are also common features. Electron microscopy shows characteristic intra-lysosomal deposits suggestive of phospholipidosis with large amounts of iodine within these lysosomal deposits. Amiodarone contains 37.5% of iodine by weight and hence phospholipidosis is a morphological marker of intrahepatic accumulation of the drug. It is distinct from pseudo-alcoholic cytotoxic changes which tend to occur in susceptible patients who, for unknown reasons have sub-optimal metabolism of amiodarone [5, 6]. Phospholipidosis of the liver on abdominal CT scan have an abnormally high attenuation, which is due to the accumulation of amiodarone metabolite in the liver [7].

Amiodarone has a half-life of 2–3 months and the drug can be present in the body for many months after its discontinuation. Toxicity has been recorded 10 months after withdrawal of the drug and levels have been detected 280 days after discontinuation of amiodarone, highlighting slow elimination [3, 4]. Evidence suggests that the cumulative dose of amiodarone rather than the daily dose causes hepatic injury [8]. There is also evidence that left ventricular impairment may predispose patients to hepatic side effects [9]. Though atorvastatin and ranitidine could cause abnormal liver function, these drugs have never been known to cause cirrhosis. It is, however, plausible that the presence of other hepatotoxic drugs may have acted as a catalyst for severe hepatic injury by amiodarone, even at a lower dose. Cryptogenic cirrhosis is yet another possibility and may have developed independent of amiodarone although the histological evidence in this case is less supportive of this diagnosis.

Our case report highlights several important issues. The patient had been on a relatively low dose of amiodarone for 33 months. He presented for the first time with advanced cirrhosis and ascites with only a short history of non-specific symptoms. Despite discontinuation of amiodarone, he followed a downhill course. The liver biopsy closely simulated alcoholic cirrhosis with signs of activity; however, the patient had no history of significant alcohol intake. He was neither obese nor diabetic, which rarely produce changes simulating alcohol-induced hepatic damage.

We recommend monitoring of liver function in all patients receiving amiodarone, irrespective of the dose given, as the patient may have no symptoms despite severe hepatic involvement. Discontinuation of amiodarone should be considered in every patient with worsening liver function or hepatomegaly.

Key points
- Amiodarone-induced hepatic toxicity is rare but could be fatal.
- Cirrhosis secondary to amiodarone mimics alcohol-induced liver damage.
- Patient may have no symptoms despite severe hepatic involvement.
- Regular monitoring of hepatic function should be mandatory with amiodarone.

References

Received 30 January 2002; accepted in revised form 9 October 2002