

## Acute hepatitis secondary to parenteral amiodarone does not preclude subsequent oral therapy

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### Abstract

Amiodarone chlorhydrate is a diiodated benzofuran derivative used to treat cardiac rhythm abnormalities. Hepatotoxicity is a relatively uncommon side effect of amiodarone and symptomatic hepatic dysfunction occurs in less than 1% to 3% of patients taking amiodarone. We report here on an unusual case of amiodarone-induced hepatotoxicity. A 29 year old woman with normal liver function was given amiodarone intravenously to treat her atrial fibrillation. She developed acute toxic hepatitis after 24 h. The intravenous form of amiodarone was immediately avoided and replaced by the oral form, using conventional loading doses as soon as the deranged liver function tests had normalized, without recurrence of the hepatitis. These observations show that the occurrence of acute hepatic impairment with intravenous amiodarone does not necessarily preclude the use of this drug by mouth and the necessity of monitoring the hepatic function of patients treated with amiodarone.

### INTRODUCTION

Amiodarone is an iodine-rich drug that is highly effective and widely used as an antiarrhythmic agent for the treatment of symptomatic supraventricular and ventricular tachyarrhythmias<sup>[1]</sup>. Amiodarone is associated with many adverse effects that involve different organs. Although these side effects are generally mild, 10% to 15% of patients require withdrawal of the drug as a result of toxicity. The most prominent adverse effects during long-term therapy include thyroid dysfunction, corneal microdeposits and pulmonary and hepatic toxicity. Transient rises in hepatic enzyme activity have been reported in 40% of patients who received the antiarrhythmic agent amiodarone. Asymptomatic elevation of serum aminotransferases occurs in 25% of those patients who are treated with amiodarone. Micronodular cirrhosis that was clearly due to amiodarone therapy has been confirmed in 12 cases<sup>[2]</sup>. However, the prevalence of severe liver injury has been estimated at only 1% to 3%<sup>[3]</sup>. We describe here a case of amiodarone-induced acute toxic hepatitis after treatment with 400 mg of intravenous amiodarone for one day.

## CASE REPORT

A 29 year old woman was admitted to our department complaining of palpitations. She had no risk factors for cardiovascular disease. She did not consume alcohol or tobacco. She was taking no medication. She presented with a six day history of permanent palpitations, without chest pain or disturbance of consciousness. Initial examination revealed a conscious anicteric patient. The respiratory rate was 18 breaths per minute, oxygen saturation was 94% (while she was breathing ambient air), pulse was irregular with an apical rate of 180 beats/minute, blood pressure 95/60 mmHg, temperature 37.5 °C, distal extremities were hot and her weight was 32 kg. The cardiovascular examination found no signs of right heart failure. Peripheral pulses were present and symmetrical. The initial cardiac auscultation was normal. The pleuropulmonary examination showed no lung crepitations. Biologically, the full blood count was normal, C-reactive protein 10.3 mg/dL, creatinine 70 micromol/L, urea 50 mg/dL and lactate dehydrogenase 263 IU/L. The liver function, including transaminases, gamma-GT, alkaline phosphatase and prothrombin level, was normal. Thyroid stimulating hormone was 4.4 U/mL with a normal free T4. An admission electrocardiogram confirmed atrial fibrillation with a fast ventricular response rate (200 beats/minute) with left ventricular hypertrophy. The chest xray found cardiomegaly. Echocardiography showed left ventricular dilatation with severe mitral regurgitation and pulmonary hypertension. Initial treatment with the ultimate intention of establishing sinus rhythm included 1.5 g of intravenous amiodarone, heparin and diuretics. One day after admission, she had reverted to sinus rhythm but repeat liver function tests revealed markedly elevated transaminases (ALT = 1050 UI/L). Gamma-glutamyl transferase (GGT) and alkaline phosphatase were respectively 56 U/L and 200 U/L, bilirubin was normal. An ultrasound examination of the liver was normal; hepatic echogenicity was homogeneous without dysmorphism and there were no bile duct abnormalities. The serology of viral hepatitis (A, B and C) and anti-tissue antibodies (antinuclear antibodies, anti-smooth muscle and antimitochondrial antibodies) were negative. Total creatinine kinase was normal. A diagnosis of acute toxic hepatitis secondary to amiodarone injection was made. So intravenous amiodarone was immediately avoided after 24 h and replaced by the oral form, using conventional loading doses (200 mg three times daily), without any derangement of liver function (Figure 1). The patient was discharged home on enalapril, furosemide, amiodarone and warfarin. Two months later, she remained in sinus rhythm on the same medications and her liver function, including transaminases, GGT and alkaline phosphatase, was normal. The patient was proposed for surgical treatment (mitral replacement).

## DISCUSSION

Amiodarone is an iodinated benzofurane derivative which is used in a wide variety of cardiac arrhythmias

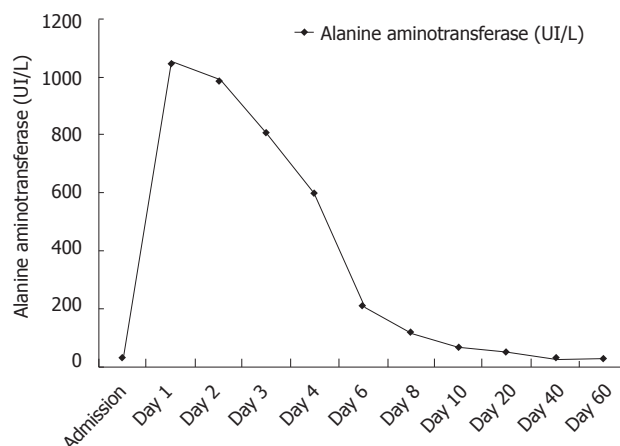


Figure 1 Evolution of liver function.

resistant to other treatments. It has a long half life and may be administered either orally or intravenously<sup>[4]</sup>. The drug has many extracardiac side effects. Severe acute hepatitis immediately after intravenous amiodarone has been reported<sup>[5-7]</sup>. In order to obtain stable solutions of amiodarone for intravenous use, the drug is dissolved in a mixture of polysorbate 80 (polyoxenethylated sorbitan ester) and a small amount of benzyl alcohol. Polysorbate 80 has been implicated in the E-ferol syndrome which has been described in infants. The E-ferol syndrome is characterised by hepatomegaly, splenomegaly, cholestatic jaundice, renal failure and thrombocytopenia. It is associated with the use of an intravenous preparation of vitamin E, E-ferol, which contains polysorbate 80 and polysorbate 20. The liver histology in this syndrome shows kupffer cell exfoliation, centrilobular accumulation of cellular debris and panlobular congestion, especially in central areas. The polysorbates are deemed responsible for these changes. The clinical features of the E-ferol syndrome show noticeable similarities to those found in cases of liver toxicity due to amiodarone<sup>[8,9]</sup>. This suggests that the hepatic insult may be a function of the diluent rather than the amiodarone<sup>[10,11]</sup>. This important distinction would not contraindicate oral amiodarone and was originally suggested by Rhodes *et al*<sup>[8,12]</sup> and others. Although this particular adverse reaction of intravenous amiodarone is rare<sup>[5]</sup>, it remains important because of the popularity of amiodarone for the treatment of severe life threatening cardiac arrhythmias. In the present case, oral amiodarone was administered as soon as the deranged liver function tests had normalized, without recurrence of the hepatitis. This supports the concept that acute hepatitis complicating intravenous amiodarone is related mainly to the diluents. On this basis, we suggest amiodarone can be safely administered by the oral route even in patients who develop hepatitis with the intravenous loading, provided that liver function and renal parameters must be closely monitored.

This observation supports the concept that acute hepatitis complicating intravenous amiodarone is related to the diluent rather than the drug. Indeed, amiodarone

can be safely administered by the oral route, even in patients who develop hepatitis with the intravenous preparation, provided hepatic function is closely monitored.

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