Acute hepatitis complicating intravenous amiodarone treatment

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We describe a case of acute hepatitis after a loading dose of intravenous amiodarone. An 83-year-old woman was admitted in emergency for recent-onset atrial fibrillation associated with left ventricular failure. Twenty-four hours after having started parenteral amiodarone, she developed biochemical alterations indicative of severe hepatic cytolysis associated with impairment of the synthetic capacity which rapidly reverted after suspension of the drug. No clinical sign or symptom of hepatopathy was noted except for mild icterus. A review of the literature regarding amiodarone-related hepatotoxicity is reported.

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Introduction

Amiodarone, an iodine-containing benzofuran derivative, is an extremely effective antiarrhythmic agent. Side effects, reported in up to 74% of patients at 1 year and in up to 94% of patients at 3 years, include atrioventricular and/or intraventricular conduction disorders, dermal and ocular photosensitivity, corneal deposits, peripheral neuropathy, pulmonary fibrosis, and thyroid dysfunction[1-5]. Asymptomatic elevation of serum transaminases is usually present in 15-50% of patients on long-term treatment[1-6] but acute hepatitis[7,8], severe cholestasis[9,10] and cirrhosis[11,12] have also been described. Only a few cases of acute hepatitis after intravenous amiodarone therapy have been reported[13-20]. We present a case of acute hepatitis, with alterations indicative of severe cytolysis and of an impaired synthetic capacity, developing less than 24 hours following the initiation of intravenous amiodarone treatment.

Case report

In April 2002, an 83-year-old woman was admitted in emergency with an 8-hour history of dyspnea and palpitations. The patient referred a diagnosis of cardiomyopathy 6 months before but she was taking no medication. On admission, she presented with clinical signs of left ventricular failure but no evidence of edema, ascites or hepatomegaly; her blood pressure was 105/70 mmHg. Twelve-lead electrocardiography revealed atrial fibrillation with a fast ventricular rate (150 b/min). Chest radiography showed marked cardiomegaly with a pulmonary vascular redistribution. Echocardiography confirmed left ventricular dilation with extensive hypokinesia and an estimated ejection fraction of 0.18. Laboratory investigations were normal except for mild renal failure. Initial treatment included furosemide, heparin and, in order to restore sinus rhythm, parenteral amiodarone (300 mg bolus followed by a daily infusion of 700 mg for a body weight of 50 kg). Within 24 hours of the initiation of amiodarone, sinus rhythm was restored and the patient's symptoms resolved. However, liver function tests revealed a marked rise in the plasma concentration of aminotransferase and a prolonged international normalized ratio. The patient developed oliguria with increased serum creatinine and urea levels. Toxic hepatitis was suspected and amiodarone and heparin were suspended with rapid improvement in the hepatic and renal function tests (Table I). Viral markers were found to be negative and abdominal ultrasonography showed a normal liver, pancreas, gallbladder and choledocus. No clinical sign or symptom of hepatic impairment was noted except for mild icterus. The patient was discharged on furosemide, digoxin and warfarin, 3 weeks after admission. She was still in good general conditions at a clinical follow-up visit performed 2 months after hospital discharge.

Table I. Patient's biochemical parameters.

Day	AST (U/l)	ALT (U/l)	Bilirubin (mg/dl)	INR	Urea (mg/dl)	Creatinine (mg/dl)
1 (admittance)	49	24	0.69	1.19	87	1.95
2	14620	7440	2.01	3.79	124	3.31
3	7090	5150	2.36	3.14	133	3.40
7	222	1189	2.83	3.39	88	1.99
12	54	313	2.10	2.00	69	1.65
16	39	122	1.12	1.30	58	1.43
Normal ranges	9-36	10-28	0-1	0.70-1.20	10-38	0.5-0.11

ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio.

Discussion

We believe that the clinical course and the absence of other causes of liver damage (viruses, alcohol intake, right ventricular failure) strongly suggest that amiodarone was responsible for the development of acute hepatitis in this patient. Episodes of acute hepatitis after amiodarone parenteral therapy have been reported in the literature[13-20] and were mortal in 3 cases[13,16]. Renal failure associated with reversible hepatic impairment has also been described[19]. Our report is characterized by high serum transaminase levels, with an impaired synthetic capacity but no clinical sign of severe liver dysfunction. Only biochemical investigations allowed us to detect the hepatic damages on time.

Hepatotoxicity is a well recognized adverse reaction to amiodarone. An asymptomatic elevation of the serum transaminase levels is the most common finding, present in up to 50% of patients with a frequency related to dosage[1-6]. The latency period varies from one week[6] to several months[2]. Liver enzyme serum levels are usually 2-4 times the normal values and can revert even if the drug is not suspended[2,3,6]. Acute hepatitis[7,8], sometimes with pseudoalcoholic[11,12] or cholestatic[9,10] features, has also been reported as a short time side effect. On the other hand, other clinical developments such as cirrhosis[11,12] have been associated with long-term therapy[7]. The exact mechanism of amiodarone-related liver toxicity is still unknown. In rats amiodarone depresses the action of hepatic oxidative enzymes in a dose-dependent fashion[21]. Multilamellar inclusion bodies have been found in hepatocytes and in biliary pigments[8,9,11] but phospholipidosis is not always correlated with the extent of the liver damage as evaluated clinically and at histology[22,23]. The evidence of granular cells characterized as macrophages suggests an immune mechanism for early amiodarone hepatotoxicity after oral therapy[24,25]. Needle liver biopsy performed immediately after death consequent to fulminant hepatitis in 2 patients who received a very high loading dose of amiodarone revealed unspecific lesions, with confluent and bridging necrosis[16]. The pathogenesis of acute hepatitis after intravenous administration is thought to be related to polysorbate 80, a component necessary to obtain stable solutions[19]. Hepatic dysfunction, as part of the E-ferol syndrome, has been described in infants who received an intravenous preparation of vitamin E containing both polysorbate 80 and polysorbate 20[26]. Further evidence in support of this hypothesis is the absence of liver abnormalities in patients receiving oral therapy after acute hepatitis complicating parenteral amiodarone[20]. Morelli et al.[17], however, described 2 cases of acute hepatitis during intravenous amiodarone administration in which liver function tests returned to normal despite continuation of drug infusion. Thus, the exact mechanism for hepatotoxicity during parenteral administration of amiodarone seems still unclear.

Acute hepatitis is an uncommon but potentially lethal side effect of intravenous amiodarone; monitoring of hepatic function during a parenteral loading dose should be suggested.

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