

A late presentation of amiodarone - induced hepatotoxicity

Abstract

A 74-year-old man with heart failure and atrial fibrillation was admitted to hospital in case of persistent dyspepsia and disturbed liver test functions. Ultrasound and detailed laboratory tests didn't reveal infectious disease of the liver or biliary obstruction. A diagnosis of hepatotoxicity due to amiodarone use was made. Withdrawal of the drug led to complete recovery of symptoms and normalization of laboratory tests.

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Introduction

Amiodarone chlorhydrate is a class III antiarrhythmic drug. It is used to treat cardiac rhythm disorders, supraventricular and ventricular as well. The medication will be prescribed, both in the acute setting as an intravenous infusion, and for chronic oral maintenance therapy. A wide range of side effects has been reported, which tempted editors to describe the drug as Pandora's box, Offerhaus.¹ Hepatotoxicity is a relatively uncommon side effect of amiodarone, and, although asymptomatic elevation of aminotransferases is reported in up to a fourth of all patients, symptomatic hepatic dysfunction occurs in less than 2% of the patients on chronic amiodarone therapy, Kim et al.²

Case report

A 74-year old man was referred for analysis of progressive abnormal liver tests, which had started 15 months before presentation. Medical history included hypothyroidism, mitral valve plasty, and paroxysmal atrial fibrillation, which was managed with initiation of fenprocoumaron and oral amiodarone 200mg once daily, 24 months before presentation. Further medication consisted of perindopril 2mg, bumetanide 2mg, levothyroxine 50mcg, rabeprazol 20mg and allopurinol 100mg. On admission there were complaints of long-term nausea and dyspepsia only. He had no history of jaundice, dark urine of pale stools, and denied alcohol abuse or using any herbal or over-the-counter drugs. He had no history of obesity, and no family history of liver disease. He had not received any blood transfusions, and denied unprotected sexual contacts. On physical examination there were no signs of chronic liver disease. His blood pressure was 120/70Hg and the pulse was 72, regular, the temperature was 36.6 degree Celsius. There were no key findings pointing to heart failure or infectious disease. Liver chemistries were abnormal: ASAT 171U/L (normal < 37), ALAT 191U/L (n < 41), alkaline phosphatase 115U/L (n 75-120), GGT 259U/L (n < 50), bilirubin 9µmol/L (n < 18), albumin 37g/L (n > 35), INR 3.7. Hepatitis B and C serologies were negative. Auto-immune serologies were negative and serum Ig levels were normal. Serum ferritin, ceruloplasmin, and α-1 antitrypsin were normal. Computer tomography scanning (CT-scan) of the liver demonstrated no signs of liver cirrhosis or portal hypertension, and no focal lesions, yet revealed a bright texture of the liver, suggestive of diffuse liver fatty infiltration. Upper gastro intestinal tract endoscopy showed mild candida oesophagitis, where stomach and proximal duodenum were

normal. Drug-induced hepatotoxicity seemed to fit well as a possibility in view of the temporal association of development of abnormal liver test values after initiation of amiodarone, and the exclusion of other causes of liver disease. Amiodarone was stopped, and resulted in relief of complaints and normalization of liver chemistries six months after discontinuation of amiodarone.

Discussion

Chronic amiodarone toxicity usually presents as a mild asymptomatic increase of liver transaminases, of which the reported incidence varies between 14 and 82%. It will result in end-stage liver disease incidentally, as reported earlier by Atiq et al.³ Toxicity following acute intravenous administration is rarely seen, but may provoke severe transaminitis and risk of death, Hashmi et al.⁴ Taking this point into account it is worthwhile to refer to a recent comparative study by Ortiz et al.⁵ They found that iv administration of procainamide was associated with less major cardiac events. In the case presented here, liver tests abnormalities had developed the second year following the start of oral antiarrhythmic treatment. A large, although retrospective report suggested recently that the duration of treatment, even in low dose administration, is an important predictor of adverse effects, Kim et al.² The question may rise: is it possible to identify patients at risk? Although the exact mechanism is not fully elucidated, it has become clear that amiodarone induces steatohepatitis of the liver, is compatible with the picture of non-alcoholic steatohepatitis (NASH), Satapathy et al.⁶ In patients already prone to NASH or known with this status of the liver, an extra word of caution might be warranted. Awareness helps the doctor firstly. On the other hand: in particular asymptomatic cases imaging studies might be helpful, complementary to laboratory tests. Kim et al. Reported the case of a patient, who developed steatosis without any liver function test abnormalities.^{5,7} Symptomatic liver disease due to oral amiodarone, as described in the case here, is rather uncommon. The persistent complaints of nausea and dyspepsia resolved completely, however, after discontinuation of treatment. Other well-known adverse effects, such as thyroid-, pulmonary- or dermatologic toxicity were not found. In the clinical workup to make a definite diagnosis we excluded a number of diseases. Since polypharmacy was apparent in our patient, we considered a hepatotoxic drug effect as underlying problem. In case of the oral coagulation use, which in itself is able to

induce icterus as shown by de Bruijne et al, we decided to postpone a liver biopsy.⁸

Since aminotransferase elevations are usually reversible after dose reduction or drug discontinuation, most guidelines recommend baseline and periodic (3 to 6 months) monitoring of aminotransferases. It is unknown whether patients with abnormal liver tests should definitely discontinue amiodarone. A decision to continue should be based on an individual risk-benefit ratio.

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Conflict of interest

The author declares no conflict of interest.

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