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Case Report

Amiodarone – a rare cause of acute hepatitis – case presentation

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Abstract

Amiodarone, a Class III antiarrhythmic agent, used in the treatment of supraventricular and ventricular tachyarrhythmias, may cause acute hepatitis. Although it is a rare complication, it can be fatal. We presented the case of a 59-year-old patient without any personal pathological background, chronic medication and cardiovascular risk factors, who came in the emergency Department where he is diagnosed with atrial fibrillation. Intravenous amiodarone treatment is instituted, but at 12 hours after initiation of treatment, there is a significant increase in the level of hepatic transaminases. The diagnosis of acute hepatitis is made, possibly drug-related. After we stopped the amiodarone administration, the evolution is favorable, with the remission of the cytolysis syndrome. This case highlights the need for careful monitoring of patients receiving intravenous amiodarone to identify any potential for hepatotoxicity.

Keywords: Intravenous amiodarone, acute hepatotoxicity, hepatic transaminases, amiodarone induced liver injury

Abbreviations

INR – international normalized ratio; AF – atrial fibrillation; AST – Aspartate aminotransferase; ALT – alanine aminotransferase; GGT – gamma glutamyl transferase; ADR – Adverse Drug Reaction; M&V System – Maria and Victorino System; RUCAM – RousselUclaf Causality Assessment Method; NT-proBNP – N-terminal pro b-type natriuretic peptide; HBV – hepatitis B virus; HCV – hepatitis C virus; AILI – amiodarone induced liver injury; NAC – N-acetylcysteine; ED – emergency department

INTRODUCTION

Amiodarone is a Class III antiarrhythmic agent widely used in the emergency department (ED) for the treatment of supraventricular and ventricular tachyarrhythmias, especially in patients with low ejection fraction and heart failure. For patients with atrial fibrillation (AF), the latest therapeutic guidelines recommend the use of amiodarone in patients with heart failure in order to maintain sinus rhythm (January, 2014, 2019; Kirchhof, 2016).

Approximately 25% of patients using amiodarone may develop a transient increase in plasma transaminase levels, which improve spontaneously or at dose reduction (Tsuda, 2018; Kocak, 2018). However, acute

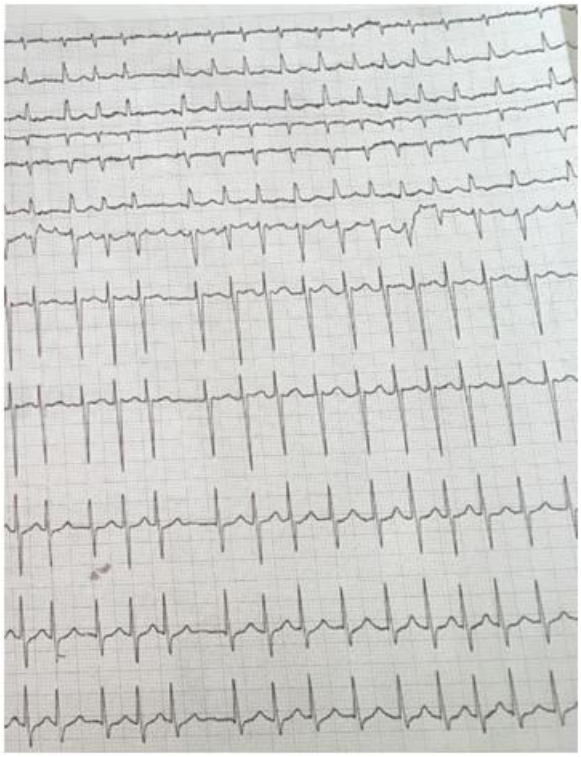

Figure 1. The appearance of the emergency department. electrocardiogram of the patient in the emergency department.

hepatotoxicity induced by amiodarone is extremely rare and occurs in less than 3% of patients treated with amiodarone (Kocak, 2018; Fonseca, 2015) and it is usually correlated with the use of the intravenous form (Chen, 2016). In patients with atrial fibrillation (AF) treated with amiodarone, this complication is easily overlooked as it is rarely encountered. Further, in this category of patients it is difficult to differentiate amiodarone-induced liver injury (AILI) from ischemic hepatitis and congestive hepatopathy.

CASE REPORT

We presented the case of a 59-year-old patient without any medical history or chronic medication, who came in the emergency department (ED) presenting dyspnea started 24 hours prior to the admission. The patient was not known to have any cardiovascular risk factors, did not consume alcohol and was not a smoker.

The patient had palpitation on the day of admission. The electrocardiogram that was made in theED shows atrial fibrillation with rapid ventricular allure 150 beats per minute (Figure 1).

At admission, he presented arterial blood pressure of 110/65 mmHg and partial pressure of oxygen of 90% and the patient showed no signs of right heart failure.

Pulmonary findings are bilateral basal subcrepital rales.

Cardiac ultrasound showed: hypokinesia of left ventricle with slight systolic dysfunction of the left ventricle (left ventricular ejection fraction 40%), aorta with normal size, no signs of pulmonary hypertension.

The biochemical balance at the admission shows normal values of hepatic transaminases plasma level (AST 29U/l, ALT 24 U/l), INR within normal limits (1.02) and the number of platelets was 174000/mm^3. Because the patient was hemodynamically stable, the pharmacological conversion with amiodarone is attempted. A dose of 300 mg of amiodarone is given intravenously over 60 minutes, followed by 900 mg amiodarone intravenously over 24 hours, as is specified in the therapeutic guidelines (January 2014, 2019; Kirchhof, 2016).

The biochemical reassessment 12 hours after admission revealed increased values of hepatic transaminases – AST and ALT (Figure 2), 50 times higher than their value upon admission (AST 6285 U/L and ALT 1543 U/L). But gamma-glutamyltransferase (GGT) shows slightly higher values of 79 U/L (normal value under 60 U/L). Also the spontaneous elongation of the INR at 2.69 appears (Figure 3), mild thrombocytopenia (148.000/mm^3) and slight changes in urea 58 mg/dL (normal value under 43 mg/dL) and

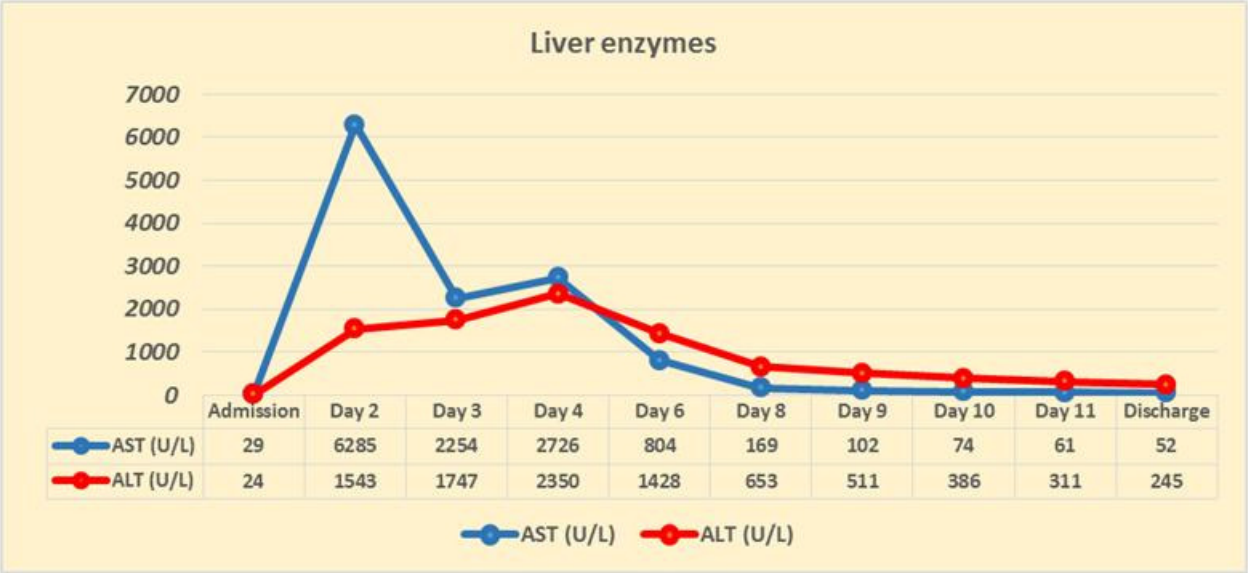

Figure 2. Dynamics of plasma levels variation of hepatic transaminases.

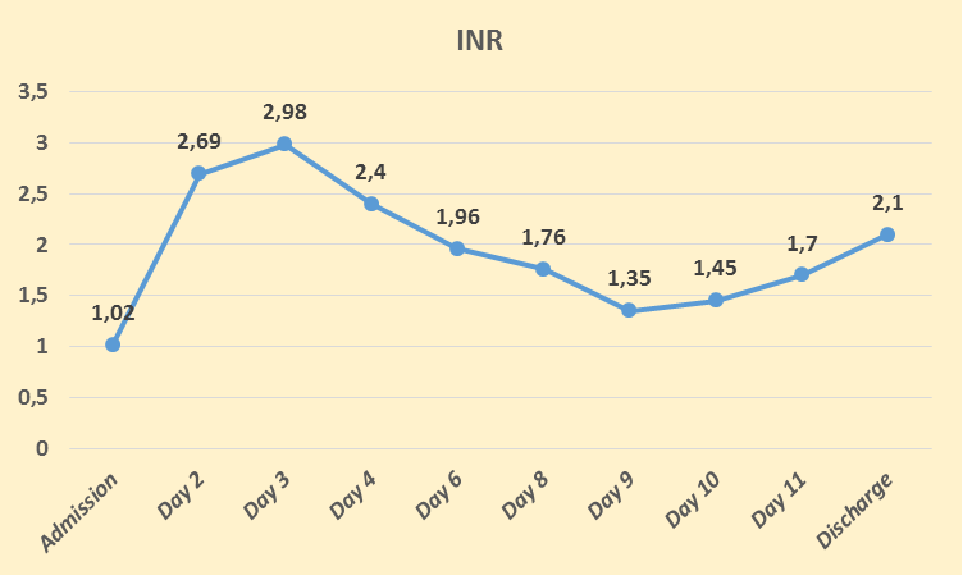

Figure 3. Variation of INR values during hospitalization.

creatinine 1.29 mg/dl (normal value under 1.2 mg/dL).

NT-proBNP showed moderately increased values – 353pg/mL (normal value in men being under 210pg/mL). Hepatic viral markers: anti-HAV IgM, anti-HCV and Ag HBs were negative. Also, the infection with cytomegalic virus, Epstein barr, simplex virus and human immunodeficiency virus (HIV) were excluded.

From the patient's anamnesis, we know that he didn't have any previous hepatic disorders, did not consume alcohol and did not take any hepatotoxic medication during his stay in the emergency department.

Pelvic and abdominal ultrasound shows liver within normal limits with increased homogeneous echogenicity without dilatation of intrahepatic bile ducts, excluding biliary obstruction. During hospitalization, he showed no signs of shock or hypoxia.

Considering the presence of marked hepatic cytolysis syndrome (50 times higher than normal value) the administration of amiodarone is stopped and hepatoprotective treatment, beta-blockers, and diuretics are instituted with the improvement of biochemical constants within 12 days. At discharge, the values of the recorded transaminases were: AST 52 U/L and ALT 245 U/L (Figure 2).

When the INR value was below 1.6, the oral anticoagulation with acenocoumarol was started with a target between 2-3 hours.

The patient is discharged after 12 days with recommended treatment with metoprolol 100 mg/day, digoxin 0.25 mg/day, furosemide 40 mg/day, spironolactone 25 mg/day and acenocumarol (for a target INR of 2-3).

DISCUSSION

The toxicity induced by the intravenous form of amiodarone is rare compared to that produced by chronic oral administration (Mudalel, 2015), but it can be fatal if not recognized early. In the literature, there are cited less than 50 cases of patients who have developed acute fulminant hepatitis after treatment with amiodarone; some had resulted in deaths, especially the ones with multiple comorbidities.

According to data presented in previous studies, about 15-25% of patients taking amiodarone (Pendyala, 2016; Nasser, 2013) may show a transient asymptomatic increase of hepatic enzymes that are corrected spontaneously or by dose reduction. Symptomatic hepatitis, hepatic cirrhosis or fatal liver failure induced by amiodarone are extremely rare in less than 3% of cases (Kocak, 2018; Fonseca, 2015).

In most cases reported liver abnormalities were found 24-48 hours after administration and improved 2-3 weeks after stopping treatment with amiodarone (Diab, 2017). In this presentation, we describe acute hepatitis that was identified 12 hours after intravenous administration of amiodarone (AST 6285 U/L, ALT 1543 U/L, INR 2,69) and which had a favorable evolution, liver tests being improved 12 days after stopping amiodarone administration.

The causal relationship between intravenous amiodarone exposure and acute hepatitis was established based on the following findings: changes in liver tests appeared suddenly, 12 hours after intravenous amiodarone administration, the initial values of liver tests being within normal limits; the presence of a model of hepatocellular injury with peak values of AST over 200 times the upper limit of the initial values; rapid improvement (in 8 days) of hepatic cytolysis syndrome after stopping the administration of amiodarone without any other therapeutic intervention; excluding other possible causes of liver damage (Fonseca; 2015).

Also the causal relation can be defined objectively by calculating the RUCAM score (7 points) as well as by using the Maria and Victorino system (13 points), which identifies the acute hepatitis of our patient as a “probable”/”possible” adverse drug reaction (Danan, 1993; Benichou, 1993; Vasco, 1997). Both scales were developed specifically for the assessment of the drug-induced liver injury.

Regarding the mechanism of acute hepatic impairment following intravenous amiodarone administration, this is controversial and still unknown.

Ischemic hepatitis is a much more frequent condition and has many clinical and histological features similar to those observed in amiodarone-induced liver injury (Nasser, 2013). In their work Gluck et al. hypothesized that acute hepatic lesion induced by intravenous amiodarone is caused mainly by liver ischemia rather than by direct toxicity of the drug (GlucK, 2011). The Ischemic lesion caused by hemodynamic instability that may occur during intravenous amiodarone administration are incriminated, but in our case, this mechanism is excluded as the patient was continuously monitored during the treatment with amiodarone and blood pressure remained constant above 110 mmHg, which makes the diagnosis of ischemic hepatitis unlikely. Also during the entire stay in the emergency department and during the hospitalization, there were no signs of hypoxia or shock. Also, the patients showed no signs of severe congestive heart failure, which could have explained a possible congestive hepatopathy.

But on the other hand, it is known that amiodarone is a lipophilic agent and it has the tendency to accumulate in organs loaded with lipids such as the liver (Tsuda, 2018). In some studies, a concentration of amiodarone and its metabolite – N-desethylamiodarone is reported, in the liver, more than 500 times above the serum level (Brien, 1987). Therefore, the direct toxicity of amiodarone cannot be excluded from acute hepatic impairment.

In other studies it is suggested that the solvent of the intravenous form of amiodarone – Polysorbate 80 – might be involved in this adverse effect because this solvent is present only in the intravenous formula but not in the oral formula of amiodarone (Rhodes, 1993; Giannattasio, 2002). Polysorbate 80 has a short plasma half-life, which may explain the rapid recovery of hepatic impairment after the discontinuation of intravenous amiodarone treatment (Fonseca, 2015). As a result, in 2008 FDA approved formula of intravenous amiodarone without polysorbate 80 but which is not yet available in Romania.

For the specific treatment of AILI, there are studies that show that N-acetylcysteine can improve amiodarone-induced liver cytolysis syndrome (Mudalel, 2015). Also using cell culture model Durukan et al. reported that NAC can treat amiodarone toxicity (Durukan, 2012).

CONCLUSIONS

Hepatic acute toxicity of amiodarone is a rare but potentially lethal adverse effect. The exact mechanism for acute hepatic insufficiency induced by intravenous amiodarone is not well defined and further studies are needed to elucidate the exact mechanism but especially to identify patients at high risk. Meanwhile, it is important

for clinicians to be aware of this rare, but potentially fatal complication of intravenous amiodarone, so that administration of amiodarone is stopped at the first sign of liver failure. If available, consideration should be given to the use of amiodarone injection without polysorbate 80. The present case highlights the need for careful monitoring of liver function during intravenous amiodarone treatment to prevent a fatal outcome.

Informed consent

The patient's informal approval has been obtained and recorded in the chart.

Author contributions

All the authors have equal contributions in this presentation.

Ethical approval

This article does not contain any studies with human participants performed by any of the authors.

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