Hyperacute drug-induced hepatitis with intravenous amiodarone: case report and review of the literature

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Abstract: Amiodarone is a benzofuran class III antiarrhythmic drug used to treat a wide spectrum of ventricular tachyarrhythmias. The parenteral formulation is prepared in polysorbate 80 diluent. We report an unusual case of acute elevation of aminotransaminase concentrations after the initiation of intravenous amiodarone. An 88-year-old Caucasian female developed acute hepatitis and renal failure after initiating intravenous amiodarone for atrial fibrillation with a rapid ventricular response in the setting of acutely decompensated heart failure and hepatic congestion. Liver transaminases returned to baseline within 7 days after discontinuing the drug. Researchers hypothesized that this type of injury is related to liver ischemia with possible superimposed direct drug toxicity. The CIOMS/RUCAM scale identifies our patient's acute hepatitis as a highly probable adverse drug reaction. Future research is needed to understand the mechanisms by which hyperacute drug toxicity occurs in the setting of impaired hepatic perfusion and venous congestion.

Keywords: intravenous amiodarone, acute hepatotoxicity, liver transaminases, drug-induced liver toxicity

Introduction

Amiodarone is a benzofuran class III antiarrhythmic drug used to treat a wide spectrum of ventricular and supraventricular tachyarrhythmias. The mechanism of action is complex. It involves antagonism of the delayed rectifier potassium channels, in particular the rapid component, thereby increasing membrane refractoriness. This agent also affects inactivated sodium channels (Phase 0), sympathetic activity, and calcium channels (L-type).¹ Long-term therapy is associated with various adverse effects due to accumulation of the drug in tissue. The intravenous (IV) preparation of amiodarone has been linked to adverse hepatic reactions such as hypotension, cardiac arrest, bradycardia, heart failure, and hepatic abnormalities.² We report an unusual case of acute hepatitis immediately after the initiation of IV amiodarone.

Case description

An 88-year-old Caucasian female presented to the emergency room complaining of shortness of breath with minimal exertion. This was associated with intermittent heart palpitations and fatigue. Her symptoms had gradually worsened over the prior month in response to family and emotional stress. She denied chest pain, cough, hemoptysis, nausea, vomiting, or diarrhea.

Her past medical history consisted of hypothyroidism, hypertension, and depression. Her only prior surgery was a hysterectomy. A recent echocardiogram

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revealed a normal ejection fraction with Grade 1 diastolic dysfunction. Family history was unremarkable. She did not use tobacco, alcohol, or illicit drugs. Her home medications included sertraline 25 mg daily, levothyroxine 25 mg daily, and lisinopril 20 mg daily.

A physical examination revealed the following vitals: a blood pressure of 147/52 mmHg, a temperature of 97.6°F, a respiratory rate of 20 breaths/minute, and a heart rate of 130 beats/minute. Cardiac auscultation demonstrated an irregular rhythm with a diastolic murmur heard best at the left upper sternal border, likely to be aortic in origin. An S3 gallop was present, and point of maximal impulse was laterally displaced. Auscultation of the lungs revealed bibasilar rales. Peripheral pulses were strong and equal bilaterally. There was moderate edema present in the lower extremities, and hepatjugular reflux was noted.

Laboratory testing identified the following values: white blood cell count of $8.8 \times 10^3/\mu\text{L}$, hemoglobin of 13.1 g/dL, platelet count of $277 \times 10^3/\mu\text{L}$, glucose level of 108 mg/dL, creatinine of 61.88 $\mu\text{mol/L}$, aspartate aminotransferase (AST) of 24 units/L, alanine aminotransferase (ALT) of 16 units/L, bilirubin total of 8.5 $\mu\text{mol/L}$, alkaline phosphatase of 98 units/L, and thyroid-stimulating hormone of 2.92 $\mu\text{IU/mL}$. All electrolytes were within normal limits. An initial electrocardiogram (ECG) revealed atrial fibrillation with a rapid ventricular response (Figure 1).

Intravenous diltiazem was initiated in order to control the ventricular rate. Shortly after, the patient's rhythm converted to normal sinus rhythm spontaneously. She subsequently developed sinus pauses lasting up to 6 seconds; consequently,

diltiazem was discontinued. Until a permanent pacemaker could be inserted, IV amiodarone was commenced in order to maintain sinus rhythm and prevent a rapid ventricular response. Following a loading dose of 150 mg, we administered 360 mg of amiodarone infused at a rate of 1 mg/min over 6 hours, after which a maintenance infusion rate of 0.5 mg/min was continued.

The next day, a routine laboratory evaluation illustrated an acute elevation to the following measurements: AST 1,881 units/L (normal high 35 units/L), ALT 1,048 units/L (normal high 35 units/L), alkaline phosphatase 143 units/L (normal high 129 units/L), total bilirubin 15.3 $\mu\text{mol/L}$ (normal high 17 $\mu\text{mol/L}$), and creatinine 97.2 $\mu\text{mol/L}$ (normal high 88 $\mu\text{mol/L}$) (Table 1). At that point, we reviewed all medications and obtained a hepatitis panel, which was normal. She had been on the same home medications for months without any change. A hepatic ultrasound identified venous congestion. We suspected amiodarone as a cause; thus, it was discontinued after administering a total dose of 960 mg over a 10-hour period. Signs of a hypersensitivity reaction such as itching, rash, or eosinophilia were not seen. Liver transaminases returned to baseline within 7 days. Further investigation with a cardiac echocardiogram demonstrated a left ventricular ejection fraction (LVEF) of 35%. Subsequently, a left heart catheterization revealed significant coronary artery disease with no clear revascularization targets, and a LVEF of 30%. She then received a permanent pacemaker, made an uneventful recovery, and was discharged on carvedilol, lisinopril, warfarin, and levothyroxine. Over the next 12 weeks, the patient suffered from progressive heart failure, which was

Figure 1 Standard 12-lead electrocardiogram demonstrating atrial fibrillation with rapid ventricular response.

Table 1 Liver–enzyme measurements

Day of hospitalization	AST (U/L)	ALT (U/L)	Alk Phos (U/L)
Day 1	24	16	98
Amio started			
Day 2	1,881	1,048	143
Amio discontinued			
Day 3	613	678	155
Day 4	328	578	174
Day 5	221	470	160
Day 6	161	339	129

Abbreviations: Alk Phos, alkaline phosphatase; ALT, alanine aminotransferase; Amio, amiodarone; AST, aspartate aminotransferase.

managed both in the office and at home. Eventually, she died of advanced pump failure with progressive edema and respiratory failure.

Discussion

Major side effects of oral amiodarone are related to drug accumulation in tissue when given over a long period of time. Adverse reactions include thyroid dysfunction, sinus bradycardia, ventricular arrhythmias, and pulmonary and hepatic toxicity. Approximately 25% of patients taking this medication develop a transient asymptomatic rise in serum aminotransferase levels. Symptomatic hepatitis, cirrhosis, and hepatic failure are rare complications which involve less than 3% of patients.^{3,4} Histological features of oral amiodarone hepatitis are similar to alcoholic hepatitis and include

steatosis, fibrosis, and phospholipid laden lysosomal lamellar bodies. The CIOMS/RUCAM scale identifies our patient's acute hepatitis as a highly probable adverse drug reaction.⁵ There was a mild total bilirubin elevation to 0.9 mg/dL; therefore, this case of drug-induced liver injury (DILI) did not meet Hy's Law criteria, which states that hepatocellular injury accompanied by a total bilirubin elevation over twice the upper limit of normal is of significant concern and has a mortality of 10%–15%.⁶

Intravenous amiodarone is typically used as a short-term therapy for various arrhythmias (as mentioned previously). It is metabolized to N-desethylamiodarone (DEA) by cytochrome P450 enzymes (CYP3A4 and CYP2C8). Its metabolite is also an antiarrhythmic. Amiodarone is primarily eliminated by biliary excretion. Left ventricular dysfunction prolongs the half-life of DEA. Acute hepatitis, due to parenteral therapy, is extremely rare.⁷ Our literature review identified 33 previously reported cases. The underlying mechanism is controversial and still unknown. Ischemic hepatitis, a much more common condition, shares many clinical and histological characteristics that are seen in parenteral amiodarone-induced liver injury. It has been hypothesized by Gluck et al that the acute liver injury following the IV formulation is related to liver ischemia, rather than direct drug toxicity.⁸ This was based on the observation that the two conditions show similar histological features and clinical events. Furthermore, DILI caused by oral and IV amiodarone

Figure 2 Pattern of hepatocyte injury with oral amiodarone, intravenous amiodarone, and hepatic hypoperfusion.

Notes: Intravenous amiodarone is thought to have direct cell toxicity with free radical formation and impairment of mitochondrial function, which leads to centrilobular necrosis.

Abbreviation: Amio, amiodarone; HO, hydroxyl radical.

Table 2 Published cases of fatal intravenous amiodarone-induced acute hepatitis

Year	Authors	Age	Sex	Indication	Associated conditions	AST/ALT (xULN)
1986	Lupon-Roses et al ¹¹	77	M	Atrial tachycardia	Jaundice	AST: 47 ALT: 29
1988	Pye et al ¹²	48	F	Atrial fibrillation	MR (moderate)	AST: 47 ALT: 32
1988	Pye et al ¹²	70	F	Atrial fibrillation	HF, MI, MR, PH	AST: 60 ALT: 26
1989	Stevenson et al ¹³	59	M	Atrial fibrillation	HF, hepatomegaly, jaundice	AST: 10
1990	Simon et al ¹⁴	59	M	Atrial fibrillation	Pulmonary edema	AST: 37 ALT: 38
1991	Morelli et al ¹⁵	58	M	Atrial fibrillation	Jaundice, nausea	AST: 15 ALT: 5
1991	Morelli et al ¹⁵	68	M	Ventricular fibrillation	Hepatomegaly, edema, HF	AST: 4 ALT: 2
1991	Kalantzis et al ¹⁶	28	M	Atrial fibrillation	Jaundice, hepatomegaly, renal failure	AST: 501 ALT: 370
1991	Kalantzis et al ¹⁶	60	M	Atrial fibrillation	Hepatomegaly, renal failure	AST: 30 ALT: 10
1992	Fornaciari et al ¹⁷	52	F	Ventricular tachycardia	Hepatomegaly	AST: 50 ALT: 45
1993	Rhodes et al ¹⁸	72	M	Ventricular tachycardia	Oliguria, hepatic encephalopathy	AST: 131 ALT: 132
1995	Tosetti et al ¹⁹	66	M	Atrial fibrillation	Nausea, oliguria	AST: 9 ALT: 11
1996	Paniagua et al ²⁰	80	F	Atrial fibrillation	Hepatomegaly	AST: 82 ALT: 59
1997	James et al ²¹	50	M	Atrial fibrillation	Dyspnea	AST: 205
1997	Tagliamonte et al ²²	61	M	Ventricular tachycardia	Jaundice	AST: 243 ALT: 122
1998	Breuer et al ²³	64	M	Atrial fibrillation	HF, renal failure, anemia, hypotension	AST: 63 ALT: 69
1999	Iliopoulou et al ²⁴	69	M	Premature ventricular complexes	Angina	AST: 50 ALT: 50
1999	Lopez-Gamez et al ²⁵	60	M	Ventricular tachycardia	Jaundice	ALT: 57
2000	Luengo et al ²⁶	68	F	Atrial fibrillation	Hepatomegaly	AST: 14 ALT: 37
2002	Gregory et al ²⁸	74	F	Ventricular tachycardia	Dyspnea	AST: 13 ALT: 8
2002	Gonzalez et al ²⁷	69	F	Atrial fibrillation	Jaundice	AST: 195 ALT: 227
2002	Agozzino et al ²⁹	83	F	Atrial fibrillation	HF, oliguria	AST: 365 ALT: 135
2002	Giannattasio et al ³⁰	65	M	Supraventricular tachycardia	Jaundice, hepatomegaly, edema	ALT: 100
2002	Giannattasio et al ³⁰	55	M	Atrial fibrillation	Core pulmonaly, hepatomegaly	ALT: 10
2002	Giannattasio et al ³⁰	75	F	Supraventricular tachycardia	Jaundice, ascites	ALT: 60
2005	Rätz Bravo et al ³¹	66	F	Atrial fibrillation	HF, postop	AST: 106 ALT: 66
2005	Rätz Bravo et al ³¹	73	F	Atrial fibrillation	Postop, no hypotension	AST: 485 ALT: 206
2005	Rätz Bravo et al ³¹	57	M	Atrial fibrillation	HF, post CABG, low MAP during surgery	AST: 44 ALT: 51

ALK PHOS/BILI (xULN)	Creatinine (μmol/L)	Latency period	Cumulative amio dose (mg)	Oral rechallenge test	Fatality
BILI: 5	–	3 days	2,300	–	–
BILI: 7	–	1 day	1,200	Negative test	–
BILI: 3	–	7 days	8,700	–	–
ALK PHOS: 2	–	1 day	450	–	–
BILI: 17	–	1 day	1,200	Positive test with intravenous amiodarone	–
BILI: Nrml	–	1 day	1,200	Negative test	–
ALK PHOS: 5	–	3 days	3,070	–	–
BILI: 3	–	6 days	2,375	Negative test	–
ALK PHOS: 5	–	6 days	2,375	–	–
BILI: 3	–	6 days	2,375	–	–
BILI: 6	963-required HD	1 day	1,500	–	Died after 14 days of hepatorenal failure and coma
BILI: 5	274	1 day	1,500	–	Died after 4 days of hepatic coma and renal failure
BILI: 29	–	36 hours	1,200	–	–
BILI: 3	328	12 hours	1,200	Negative test	–
ALK PHOS: 1.3	–	1 day	400	–	–
–	254	1 day	750	–	–
–	–	1 day	1,200	Negative test	–
ALK PHOS: 2.5	–	1 day	–	–	–
BILI: 10	–	4 days	3,400	–	–
–	–	4 days	3,400	–	–
BILI: increased	–	1 day	1,500	–	–
BILI: 8	–	7 days	2,400	Negative test	–
–	–	5 days	1,300	–	–
–	–	1 day	1,740	Negative test	–
BILI: 4	–	1 day	1,200	–	–
BILI: 19	300	1 day	1,000	–	–
BILI: 4	–	1 day	600	–	–
–	–	3 days	600	Negative test	–
BILI: 19	–	1 day	600	–	Died after 31 days of hepatic failure
ALK PHOS: Nrml	–	1 day	200	–	–
BILI: Nrml	–	1 day	200	–	–
ALK PHOS: 2	–	14 hours	720	–	–
BILI: Nrml	–	14 hours	720	–	–
ALK PHOS: Nrml	–	1 day	890	–	–
BILI: 2	–	1 day	890	–	–

(Continued)

Table 2 (Continued)

Year	Authors	Age	Sex	Indication	Associated conditions	AST/ALT (xULN)
2008	Chan et al ³⁴	72	F	Atrial fibrillation	Hypotension, jaundice, oliguria	AST: 33 ALT: 42
2008	Cataldi et al ³²	77	F	Atrial fibrillation	HF, fluid overload	AST: 53 ALT: 40
2009	Murphy et al ¹⁰	59	M	Atrial fibrillation	LVH	AST: 172 ALT: 83
2012	Lahbabi et al ⁹	29	F	Atrial fibrillation	Severe MR, LV dilation	ALT: 19
2012	Grecian et al ³³	73	M	Ventricular tachycardia	Hx of HF, fulminant hepatic failure	ALT: 44

Abbreviations: ALK, alkaline; PHOS, phosphatase; BILLI, bilirubin total; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HF, heart failure; MR, mitral regurgitation; PH, pulmonary hypertension; MAP, mean arterial pressure; CABG, coronary artery bypass grafting; MI, myocardial infarction; HD, hemodialysis; Nrml, normal; Amio, amiodarone; LVH, left ventricular hypertrophy; ULN, upper limit of normal; Hx, history; LV, left ventricle.

demonstrate different histologic findings. The majority of patients receiving the IV form are suffering from unstable tachyarrhythmias, which may result in a decreased cardiac output, hypotension, and ischemia. Most patients described in the reviewed cases had evidence of poor forward output, hepatic venous congestion, impaired circulation and acute kidney injury, predisposing them to ischemic hepatitis. Finally, another report by Lahbabi et al ascribes responsibility of liver toxicity to solubilizers such as polysorbate 80 in the IV amiodarone preparation.⁹ Polysorbate 80 has been

implicated in the E-Ferol syndrome characterized by renal failure, hepatosplenomegaly, and jaundice. Eliminating polysorbate 80 by the oral route demonstrated the safe use of amiodarone even after acute hepatitis in several studies.

Our patient showed evidence of impaired left ventricular function with an LVEF of 30% by ECG (decreased from 50% one month prior to admission). Also, there was evidence of acute elevation of her creatinine from 0.7 to 1.1 mg/dL, suggestive of a degree of hypoperfusion. Hepatojugular reflux was elicited and central venous pressure was elevated

Figure 3 Schematic representation of multiorgan failure contributing to systemic inflammation, oxidative stress, and apoptosis, which contributes to progressive pump failure and death.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; O₂, Oxygen; CO₂, carbon dioxide.

ALK PHOS/BILI (xULN)	Creatinine (μmol/L)	Latency period	Cumulative amio dose (mg)	Oral rechallenge test	Fatality
ALK PHOS: 1.5 BILI: 1.1	274	1 day	2,550	–	Died after 20 days of hepatic coma and renal failure
BILI: 2	–	1 day	750	–	Died after 29 days of multiorgan failure
ALK PHOS: 1.5 BILI: 68	236	1 day	1,200	–	Died after 4 days of acute hepatic failure
ALK PHOS: Nrml BILI: Nrml	70	1 day	1,599	Negative test	–
BILI: 5	274	1 day	900	–	–

subsequent to liver injury. The causal correlation is not clear as to which condition (cardio–renal dysfunction or liver failure) induced the other. We believe that in susceptible elderly patients, even the standard intravenous amiodarone dose may cause direct drug toxicity and hypotension, especially in the setting of heart failure, leading to hepatic injury.

Further research is needed to support a true acute amiodarone hepatotoxicity versus other proposed or even unknown mechanisms (Figure 2). Six fatal cases of IV amiodarone hepatitis have been reported, suggesting the severity of this condition (Table 2).^{10–34} Elevation of transaminases occurred within 24 hours of drug administration in most patients. The majority of these cases were associated with some degree of cardiac dysfunction and renal failure. Our case was fatal in 12 weeks due to progressive pump failure, and the DILI event may have been a harbinger of mortality. The mechanism of progressive left ventricular failure may have been secondary to the impact of systemic inflammation, neurohormonal stress, and microcirculatory dysfunction caused in part by the acute organ failure of the liver (Figure 3). We believed persistent hepatic venous congestion played a role and may have been a determinant. This case suggests that one should regularly obtain a liver function panel subsequent to parenteral amiodarone initiation and proceed with caution in the setting of heart failure and hepatic congestion.

Conclusion

Amiodarone is often used to treat life-threatening arrhythmias in the setting of acutely decompensated heart failure. In the presence of hepatic congestion, the IV preparation of amiodarone may cause acute liver injury, which can be a harbinger for a fatal outcome in the days to months after administration.

Future research is needed to understand the mechanisms by which hyperacute drug toxicity occurs in the setting of impaired hepatic perfusion and venous congestion.

Disclosure

The authors report no conflicts of interest in this work.

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