

Acute amiodarone syndrome after a single intravenous amiodarone bolus

Xin Rong Ng¹, Liang Yi Wee¹, Veerendra Chadachan², MRCP, FAMS

ABSTRACT Acute amiodarone toxicity after a single dose of intravenous amiodarone is very rarely seen. We report the case of a 64-year-old Chinese man who presented with atrial fibrillation and fluid overload due to congestive cardiac failure. He was treated with a single bolus dose of intravenous amiodarone, after which he developed elevated serum transaminases, coagulopathy, thrombocytopenia and acute renal failure. His parameters returned to normal after 25 days and his recovery was uneventful.

Keywords: acute renal failure, amiodarone, atrial fibrillation, hepatotoxicity, thrombocytopenia
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INTRODUCTION

Amiodarone is a commonly used anti-arrhythmic drug. It has been known to have several adverse effects, including thyroid dysfunction, bradycardia, hepatitis, corneal microdeposits and photosensitivity.⁽¹⁾ Many of these effects are due to tissue accumulation of amiodarone with long-term therapy.⁽²⁾ Acute toxicity, resulting in acute hepatitis and renal failure, has also been reported with short-term amiodarone therapy. It is a rare but recognised complication of repeated doses of amiodarone therapy, but its development after a single dose is comparatively less well known.⁽³⁾ We describe here a case of a 64-year-old Chinese man who was administered a single bolus of intravenous amiodarone for atrial fibrillation. Subsequently, he developed raised transaminase levels, coagulopathy, acute renal failure, and thrombocytopenia.

CASE REPORT

A 64-year-old Chinese man was referred to the emergency department of our hospital for tachycardia and atrial fibrillation detected on routine examination at a polyclinic. He had reported dyspnoea on exertion and decreased effort tolerance for the past one week prior to admission. This was not accompanied by dyspnoea at rest, orthopnoea or paroxysmal nocturnal dyspnoea. He did not report any chest pain, syncope, giddiness or palpitations, and had no fever, chills or rigors. He denied ingestion of any traditional Chinese medication prior to the symptoms. His past medical history included hypertensive nephropathy and previous cataract surgery. He had no known drug allergies, and no history of smoking or alcohol ingestion. He had no known history of liver disease and there was no baseline liver function test done before this particular admission.

On arrival at the emergency department, he was afebrile with irregular tachycardia of 150 beats per minute and had no evidence of respiratory distress. Physical examination revealed crepitus

over the bilateral lung bases, and bilateral pitting oedema up to mid-shin. There was no hepatomegaly and no sign of chronic liver disease. Electrocardiogram revealed atrial fibrillation with fast ventricular response. Chest radiography showed a small right-sided pleural effusion and cardiomegaly. Initial blood investigations showed hyperbilirubinaemia, but the rest of the liver function tests, renal function tests, blood counts and coagulation parameters were normal (Table I).

Atrial fibrillation was successfully terminated at the emergency department with intravenous amiodarone 300 mg given as a bolus dose. The patient did not receive any more doses of amiodarone. He was also given furosemide, 40 mg twice a day, for congestive heart failure and fluid overload. Clinically, the lower limb oedema resolved over the first three days, and the furosemide was stopped. The patient did not complain of increasing dyspnoea or productive cough during the hospital stay. However, he developed paroxysmal atrial fibrillation in the ward. In view of his current admission for congestive cardiac failure and past medical history of hypertension, which put him at moderate to high risk of cardioembolic stroke (CHADS₂ score = 2)⁽⁴⁾, prothrombin time (PT) was repeated in preparation to start anticoagulation therapy. Unexpectedly, this was shown to be markedly prolonged (PT of 39.2 seconds with an international normalised ratio of 4.24). This was associated with elevated total bilirubin, liver enzymes, activated partial thromboplastin time and serum creatinine with reduced platelets count (Table I). Other blood investigations done showed normal PT mixing studies and fibrinogen levels, negative dengue polymerase chain reaction test, negative hepatitis B serology and normal thyroid function tests. A transthoracic echocardiography was also done and showed severe biventricular failure with a left ventricular ejection fraction of 15%.

On the eighth day after amiodarone was given, the patient was asymptomatic, pitting oedema had resolved and the

¹Yong Loo Lin School of Medicine, National University of Singapore, ²Department of General Medicine, Tan Tock Seng Hospital, Singapore

Correspondence: Dr Chadachan Veerendra Melagireppa, Consultant, Department of General Medicine, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433. Veerendra_Chadachan@ttsh.com.sg

Table I. Patient's selected laboratory parameters.

Test	Days post-amiodarone administration									
	0	2	3	5	6	7	8	15	21	25
Albumin (g/L)	36	-	-	-	32	30	-	36	31	-
Total bilirubin (umol/L)	58	-	-	-	70	50	-	64	44	-
ALT (U/L)	25	-	-	-	1124	809	-	137	51	-
AST (U/L)	27	-	-	-	269	145	-	43	51	-
ALP (U/L)	102	-	-	-	124	132	-	129	123	-
GGT (U/L)	38	-	-	-	81	69	-	-	-	-
PT (secs)	15.3	39.2	31.8	19.7	17.7	-	-	-	-	-
INR	1.25	4.24	3.23	1.73	1.51	-	-	-	-	-
aPTT (secs)	30.7	-	38.9	31.8	-	-	-	-	-	-
Platelets ($\times 10^9$ /L)	166	-	-	90	-	85	76	131	-	168
Creatinine (umol/L)	110	388	249	109	106	-	-	132	98	-

PT: prothrombin time; INR: international normalised ratio; aPTT: activated partial thromboplastin time; ALT: alanine transaminase; AST: aspartate transaminase; ALP: alkaline phosphatase; GGT: gamma glutamyl transferase

liver enzymes were on a downward trend. However, in view of the thrombocytopenia and deranged liver function tests, anticoagulation for atrial fibrillation was not started during the admission. Since the patient was reluctant to stay on further, a decision was made to allow the patient to be discharged with an early follow-up appointment in two weeks when long-term anticoagulation would be considered. Medications at discharge were omeprazole 20 mg twice a day, bisoprolol 3.75 mg once a day and enalapril 2.5 mg once a day.

Unfortunately, our patient was hospitalised again on the 15th day of post-amiodarone administration for an episode of ischaemic stroke. Magnetic resonance imaging revealed acute infarcts in the territories of the left middle cerebral artery and left distal anterior cerebral artery. Blood investigations during the hospitalisation showed that all previously abnormal parameters were almost back to normal (Table I).

DISCUSSION

Amiodarone is commonly used in its oral or intravenous form for the treatment of serious ventricular and supraventricular arrhythmias. For patients who have been on long-term oral amiodarone therapy, the drug has been found to cause several adverse effects, including thyroid dysfunction, bradycardia, hepatotoxicity, corneal microdeposits and photosensitivity.⁽¹⁾ As for short-term intravenous amiodarone therapy, Giannattasio et al identified three cases of severe acute hepatitis after parenteral administration of amiodarone as a bolus dose followed by infusion.⁽⁵⁾ However, the development of amiodarone toxicity after a single bolus dose has been rarely, if at all, described in the literature.

Amiodarone-induced hepatotoxicity ranges from mild and reversible elevated serum transaminases to acute liver failure.⁽²⁾ Asymptomatic elevation of transaminases up to three times the upper limit of normal is frequently seen, with a reported incidence of approximately 24%–26%,^(6,7) whereas liver failure is rare, with an incidence of about 1%–3%.⁽⁶⁾ Our patient's test results show a clinical picture of acute hepatotoxicity with elevated

transaminases and coagulopathy. Subsequently, clinical and laboratory parameters normalised and the patient made a full recovery.

Rätz et al in 2005 summarised 25 case reports of acute liver toxicity, associated with intravenous amiodarone infusion, published between 1988 and 2004.⁽⁸⁾ Two-thirds of the patients received amiodarone for atrial fibrillation and one-third for ventricular arrhythmias, mainly ventricular tachycardia. In approximately 68% of the cases, abnormalities in liver function occurred within 24 hours after starting amiodarone administration – in 20%, within two to three days, and in the remainder, after a delay of more than three days. A tenfold increase in alanine transaminase and aspartate transaminase was seen in 22 of the 25 cases, and an increase in total bilirubin, with or without jaundice, was observed in 50% of the cases.

On hindsight, liver function tests should have been done more frequently in our patient in the first five days of post-amiodarone administration, as this would have indicated the peak value of liver enzymes and the onset of liver damage. However, clotting studies done on the day of admission showed normal PT, while clotting studies repeated on Day 2 of post-amiodarone administration showed an elevation of PT (Table I). Subsequently, PT showed a decreasing trend, suggesting an onset of hepatic dysfunction on or before Day 2 post-amiodarone administration. As coagulation studies were not done on the first day after amiodarone administration, we could not ascertain whether the onset of hepatic dysfunction was on Day 1. Nonetheless, this fits the clinical picture of amiodarone-induced hepatotoxicity, as 88% of such cases occur within three days of intravenous amiodarone administration.⁽⁸⁾

In patients whose cardiac arrhythmias are treated with amiodarone, hepatic dysfunction could be the effect of cardiac failure or amiodarone. In our patient, the cause of his acute hepatitis is likely due to amiodarone rather than cardiac failure, as his parameters became abnormal only after amiodarone was given. Hepatic dysfunction due to cardiac failure would have presented with abnormal parameters on admission, especially

since the patient started having symptoms of cardiac failure one week prior to admission.

The rapid time course of the deterioration in renal function, liver function and platelet counts suggests an acute cause that could be either drug-induced or a rapid decompensation in cardiac function. However, rapid decompensation in cardiac function is unlikely, as the patient was haemodynamically stable and displayed no features of cardiogenic shock throughout his stay. His atrial fibrillation was terminated in the emergency department and his fluid overload was successfully treated with furosemide. A similar clinical picture of hepatotoxicity, increased creatinine levels and thrombocytopenia has been reported in several case reports of patients given amiodarone infusion.^(3,6,9) The mechanism by which intravenous amiodarone causes hepatotoxicity is still open to debate. However, some evidence suggests that in some cases of toxicity after intravenous amiodarone therapy, polysorbate 80, a stabiliser used to obtain stable solutions of amiodarone for intravenous use, may be responsible instead. This is supported by two studies^(3,5) that have noted that some patients who developed amiodarone hepatotoxicity after intravenous amiodarone use did not develop any adverse effects when subsequently given oral amiodarone, which does not contain polysorbate 80. An analogous reaction that may be caused by a similar mechanism is the E-Ferol syndrome, which causes pulmonary deterioration, thrombocytopenia, liver failure, ascites and renal failure in preterm infants.⁽¹⁰⁾ This syndrome is postulated to be a polysorbate 80-mediated hepatotoxic reaction that develops after intravenous administration of a vitamin E formulation containing polysorbate as an excipient.⁽¹¹⁾ However, we were unable to ascertain whether our patient's hepatotoxicity was due to amiodarone itself or polysorbate 80, as the intravenous amiodarone formulation he was given contains both substances.

We thus conclude that a single bolus dose of amiodarone given intravenously can lead to an acute syndrome characterised by raised transaminase levels, coagulopathy, acute renal failure and thrombocytopenia. Hence, we suggest that acute amiodarone syndrome should be suspected in patients who develop abnormal liver biochemical results, raised creatinine levels and thrombocytopenia after receiving intravenous amiodarone, even if it is only a single dose. Given the relatively frequent usage of this drug in modern medical therapy, this syndrome should not be overlooked.

REFERENCES

- Katzung BG. Basic and Clinical Pharmacology. 10th ed. New York: McGraw Hill, 2007.
- Mehta N, Ozick L, Gbadehan E. Drug-Induced Hepatotoxicity. In: Medscape Reference (online). Available at: emedicine.medscape.com/article/169814-overview. Accessed June 27, 2012.
- Rhodes A, Eastwood JB, Smith SA. Early acute hepatitis with parenteral amiodarone: a toxic effect of the vehicle? *Gut* 1993; 34:565-6.
- Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001; 285:2864-70.
- Giannattasio F, Salvio A, Varriale M, et al. Three cases of severe acute hepatitis after parenteral administration of amiodarone: the active ingredient is not the only agent responsible for hepatotoxicity. *Ann Ital Med Int* 2002; 17:180-4.
- Lewis JH, Ranard RC, Caruso A, et al. Amiodarone hepatotoxicity: Prevalence and clinicopathologic correlations among 104 patients. *Hepatology* 1989; 9:679-85.
- Hyatt RH, Sinha B, Vallon A, Bailey RJ, Martin A. Noncardiac side-effects of long-term oral amiodarone in the elderly. *Age Ageing* 1988; 17:116-22.
- Rätz Bravo AE, Drewe J, Schlienger RG, et al. Hepatotoxicity during rapid intravenous loading with amiodarone: Description of three cases and review of the literature. *Crit Care Med* 2005; 33:128-34.
- Weinberger I, Rotenberg Z, Fuchs J, Ben-Sasson E, Agmon J. Amiodarone-induced thrombocytopenia. *Arch Intern Med* 1987; 147:735-6.
- Lorch V, Murphy D, Hoersten LR, et al. Unusual syndrome among premature infants: Association with a new intravenous vitamin E product. *Pediatrics* 1985; 75:598-602.
- Alade SL, Brown RE, Paquet A Jr. Polysorbate 80 and E-Ferol toxicity. *Pediatrics* 1986; 77:593-7.