Unexpected outcome (positive or negative) including adverse drug reactions

Acute hepatic failure following intravenous amiodarone

Robert Grecian,¹ Mark Ainslie²¹Wigan Hospital, Wigan, UK²Department of Cardiology, Wythenshawe Hospital, Manchester, UK

Correspondence to Dr Mark Ainslie, markpeterainslie@hotmail.com

Summary

A 73-year-old gentleman presented to the hospital after an episode of loss of consciousness. He had a defibrillator in situ, which on interrogation was found to have fired for an episode of ventricular fibrillation. As an inpatient he developed frequent episodes of self-terminating ventricular tachycardia, treated initially with oral amiodarone. A 24 h amiodarone infusion was started on day 3 of admission, following which the patient developed hyperventilation. Investigations revealed that this was secondary to acute hepatic and renal failure, requiring haemofiltration on the intensive care unit. Cessation of amiodarone was associated with normalisation of liver function over 48 h. The patient had normal blood and jugular venous pressures throughout days 1–4 of admission. We discuss the role of amiodarone as the predominant factor in the deterioration of this patient's liver function, versus the differential diagnosis of ischaemia-induced hepatotoxicity, citing recent research regarding this subject.

BACKGROUND

Although the long-term side effects of amiodarone are well documented and well recognised, acute complications are rare, less well known about and pose the risk of being missed even after the patient has deteriorated. Intravenous amiodarone can be associated with rapid hepatotoxicity. This case illustrates the importance of remembering to consider iatrogenic drug causes when inpatients become unwell.

CASE PRESENTATION

A 73-year-old gentleman presented to hospital following an episode of syncope. He recalled walking in his kitchen and then waking up on his back in the middle of the kitchen floor, after which he was able to get himself to his feet with assistance from his wife. He was not post-ictal, and there was no incontinence or tongue biting. Such an episode had not occurred previously.

The patient had a significant cardiac history including:

- ▶ Atrial fibrillation (anticoagulated with warfarin)
- ▶ Myocardial infarction
- ▶ Coronary artery bypass grafts
- ▶ Severe left ventricular dysfunction secondary to ischaemic heart disease (ejection fraction 30%)
- ▶ Biventricular implantable cardioverter defibrillator (ICD) pacemaker

The gentleman had no known drug allergies.

Examination was unremarkable and he was normotensive with a normal jugular venous pressure.

He was admitted under the acute medical team for further assessment of his collapse. A full baseline blood profile, including liver function tests, was normal except for a mildly raised urea at 9.8. His international normalised ratio (INR) was 3.1. His chest radiograph showed a cardiac resynchronisation therapy defibrillator in situ with no evidence of pulmonary oedema.

On the post-take ward round it was felt that a cardiac cause of syncope was likely. A cardiology opinion was therefore requested.

The cardiology team interrogated the ICD. This revealed that the patient had had five episodes of ventricular tachycardia and then received an appropriate 41 J shock for ventricular fibrillation (VF) which correlated with the time of his collapse. Resultantly, he was transferred to coronary care and put on cardiac monitoring which showed several short non-sustained runs of ventricular tachycardia. Interestingly, the patient was asymptomatic at all times with normal blood pressure and jugular venous pressure. The patient was initially treated with an increase in his β -blocker and the start of oral amiodarone.

Overnight there were some further runs of non-sustained ventricular tachycardia (VT). On the following consultant cardiology ward round (day 3 of admission), amiodarone 900 mg intravenously over 24 h was commenced. Blood tests, including liver function tests, were normal prior to the infusion.

The patient remained well throughout the day, but that night felt unwell and nursing staff noticed he was hyperventilating. A full medical assessment was not requested overnight, but the patient was reviewed by the registrar during his ward round on Sunday.

The registrar noted that the gentleman looked unwell with a respiratory rate of 24, but blood pressure (110/75 mm Hg) and pulse (75 bpm) were normal. The jugular venous pressure was normal and there were no signs of pulmonary oedema. A chest x-ray was requested and a full set of bloods and arterial blood gas were performed.

The blood gas showed severe metabolic acidosis (table 1), and the blood results were telephoned through due to significant derangements of liver and kidney function (table 2). The INR was greater than 15.

Table 1 Initial blood gas when patient became acutely unwell

Arterial blood gas on 2L oxygen	
pH	7.2
pO ₂	18.4
pCO ₂	2.0
HCO ₃ ⁻	5.7
Base excess	-19.6

The clinical picture suggested fulminant hepatic failure with the development of hepato-renal syndrome. Hyperventilation was secondary to the patients' severe acidosis.

DIFFERENTIAL DIAGNOSIS

The patient was discussed with the regional liver unit and differential diagnoses included:

- ▶ Drug-induced hepatic failure due to amiodarone toxicity.
- ▶ Ischaemic hepatic failure secondary to hypotension and hypoperfusion at the time of collapse.

Ischaemic hepatic failure is more common. However, this gentleman's deterioration was almost 72 h after the initial episode of VF and ICD shock. During this time he remained very well despite having non-sustained VT. In addition, he was normotensive and had a normal jugular venous pressure throughout (table 3). Since his LFTs were also normal before the amiodarone infusion on day 3, the principal diagnosis was of drug-induced hepatic failure.

TREATMENT

Amiodarone and warfarin were immediately stopped and the patient was catheterised to monitor urine output. The liver unit at Leeds recommended supportive treatment, and the patient was discussed with the cardiology and intensive care consultants. Despite intravenous fluids the patient became anuric with a progressive deterioration of liver and renal function (table 2). He was transferred to the intensive care unit. Vitamin K and fresh frozen plasma were given to lower the INR prior to central and arterial line insertion. Within 12 h haemofiltration was commenced.

OUTCOME AND FOLLOW-UP

By 48 h postcessation of intravenous amiodarone, liver function had dramatically improved. Kidney function responded well to haemofiltration. The patient was

transferred back to coronary care and discharged 6 days later with close to normalised blood tests. He was discharged with the increased dose of β -blocker. Warfarin was restarted at his normal dose.

Following discharge the patient was referred back to the regional cardiac centre where the biventricular ICD device was originally implanted. To date he has had no further ICD therapies.

DISCUSSION

Although long-term use of oral amiodarone is well known to be associated with asymptomatic rise of liver transaminases in approximately 25% of patients, less than 3% develop symptomatic hepatotoxicity.¹ Furthermore, the separate, and biochemically distinct entity of acute hepatotoxicity following amiodarone infusion, is even rarer.² This is characterised by more rapid and markedly elevated rise in liver transaminases, as seen in our patient.²

We carried out a Medline search using the keywords 'amiodarone AND hepatotoxicity' and also examined the references of a relevant review paper.³ We found 22 case report papers in the English language between 1986 and 2011, each describing between 1 and 3 patients with hepatotoxicity following parenteral amiodarone.

Typically these cases follow the following pattern:³

1. Occur within 24 h after starting amiodarone.
2. Predominant increase in transaminases >10 times the upper limit of normal (not obstructive picture).
3. Less commonly renal impairment or coagulation disorders.
4. Improvement after the withdrawal of amiodarone.

The mechanism of amiodarone-associated hepatotoxicity is unknown, and why there is a difference in presentation observed between oral and parenteral formulations is widely debated.

If toxicity is due to amiodarone itself, these differences may be related to higher plasma concentrations via the enteral route.³ Why toxicity only occurs in a small proportion of patients, may relate to differing abilities to metabolise the drug, or interactions of the drug with the cytochrome P-450 enzyme system affecting patients' metabolism of co-existent hepatotoxic medications.³

It has been postulated that rather than amiodarone itself, polysorbate 80, an organic surfactant used to dissolve the drug, may be the responsible agent for acute liver damage via a direct toxic effect on hepatocytes.⁴ This would also account for the difference in pattern of

Table 2 Table of blood results for the first 6 days of admission

Day of admission	Day 1	Day 2	Day 3 intravenous amiodarone started	Day 4 am	Day 4 pm	Day 6 following haemofiltration
Na ⁺	137	138	138	134	133	140
K ⁺	4.4	4.4	4.5	5.0	5.9	3.9
HCO ₃ ⁻	—	—	—	6	8	23
Ur	9.8	9.5	9.7	20.3	23.4	18.1
Cr	106	104	110	274	300	158
Bili	13	12	13	96	95	82
Alkaline phosphate	84	85	84	115	130	106
Alanine transaminase	17	18	18	2421	4157	1882
Albumin	38	38	38	34	43	29
Gamma-glytamyl transpeptidase	25	26	26	49	52	63

Table 3 Summary of blood pressures during admission (not all included but none showed significant hypotension)

Day of admission	Day 1	Day 2	Day 3 intravenous amiodarone started	Day 4 am	Day 4 pm	Day 6 following haemofiltration
110/70	115/74	114/72	115/76	110/75	105/72	108/70

toxicity between oral and parenteral formulations of amiodarone.

Most case reports describe the differential diagnosis of ischaemia-induced liver damage, which is much more common. This presents similarly both clinically and biochemically. Interestingly, a recent case-control retrospective study argues that hepatotoxicity due to intravenous amiodarone cannot be differentiated from ischaemic hepatitis, and claims that they are in fact the same entity.² Many authors of case reports in the past, have excluded this differential on the basis of clinical timing and due to the fact that their patients showed rapid improvement after cessation of amiodarone. We agree with this stance, and do not feel that the timing of our case fits with hypoperfusion (from the collapse) as the predominant cause. This argument is strengthened by the fact that during the first 3 days of admission our patient did not suffer any further episodes of hypotension and had normal liver function before the commencement of amiodarone. As amiodarone is a known vasodilator,⁵ we wonder if this is the reason it can produce a hypoperfused ischaemic looking clinical picture. We would argue that it is difficult to separate these two differential diagnoses and thus it is often hard to categorically state that amiodarone is the direct cause of hepatotoxicity. The vasodilator effect of amiodarone is often transient⁶ and it is possible a period of hypotension occurred that we did not record since he did not have continuous arterial monitoring. It is conceivable that in a gentleman with a severely impaired cardiac function and low blood pressure a transient period of hypotension may be enough to reduce perfusion pressure within the liver that could lead to ischaemia. Given the timing we believe it was amiodarone that led to this clinical scenario but one cannot be certain of the mechanism.

Learning points

- ▶ Intravenous amiodarone can cause acute hepatic failure, although this is rare.
- ▶ Presentation is similar to, and hard to differentiate from, ischaemic liver failure (a more common problem in the same patient population).
- ▶ Regardless of this, treatment is often the same for both.
- ▶ Iatrogenic drug causes should always be considered when inpatients deteriorate.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. Lewis JH, Ranard RC, Caruso A, *et al*. Amiodarone hepatotoxicity: prevalence and clinicopathologic correlations among 104 patients. *Hepatology* 1989;**9**:679–85.
2. Gluck N, Fried M, Porat R. Acute amiodarone liver toxicity likely due to ischemic hepatitis. *IMAJ* 2011;**13**:748–52.
3. 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.
4. Rhodes A, Eastwood JB, Smith SA. Early acute hepatitis with parenteral amiodarone: a toxic effect of the vehicle? *Gut* 1993;**34**:565–6.
5. Grossman M, Dobrev D, Kirch W. Amiodarone causes endothelium-dependent vasodilation in human hand veins in vivo. *Clin Pharmacol Ther* 1998;**64**:302–11.
6. Cheung A, Weiss S, Savino J, *et al*. Acute circulatory actions of intravenous amiodarone loading in cardiac surgical patients. *Ann Thorac Surg* 2003;**76**:535–41.

Copyright 2012 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit

<http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Grecian R, Ainslie M. Acute hepatic failure following intravenous amiodarone. *BMJ Case Reports* 2012;10.1136/bcr-2012-007080, Published XXX

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow