Severe acute hepatitis following intravenous amiodarone : a case report and review of the literature

Amy Stratton[1], Joshua Fenderson[1], Patrick Kenny[1,2], Donald Lee Helman[1,3]

(1) Department of Internal Medicine, (2) Gastroenterology Service, (3) Critical Care and Pulmonology Service, Tripler Army Medical Center, Honolulu, Hawaï.

Abstract

Background and Aims : **Hepatotoxic complications of long-term oral amiodarone therapy have been well described ; however, liver injury secondary to parenteral infusion of amiodarone is uncommon, potentially fatal, and poorly understood. The hepatotoxicity is thought to result from the diluent polysorbate 80 and not the amiodarone its self. Theories suggest an allergic or immunologic response leading to alterations in the hepatocellular membrane while some propose that ischemia, not a drug reaction, is truly to blame.**

Methods : **Both the PubMed and Embase databases were searched for cases of acute hepatitis implicating intravenous amiodarone with a total of 25 cases from 1986 to 2012 identified. Each case was then carefully evaluated to determine the connection between parenteral amiodarone and acute hepatotoxicity while assessing for evidence of potential ischemia.**

Results : **Of the 25 published cases of amiodarone induced acute hepatotoxicity available for review, only 10 provide evidence to conclusively implicate parenteral amiodarone as the etiology. We add the eleventh reported case of parenteral amiodarone induced acute severe hepatitis to the literature and report the most comprehensive review of this topic to date.**

Conclusion : **There is sufficient evidence to support amiodarone induced acute hepatotoxicity as a unique entity separate from ischemic hepatitis. If suspected, parenteral amiodarone should be discontinued and held indefinitely.** (Acta gastroenterol. belg., **2015**, 78, **233-239**).

Key words : amiodarone hepatotoxicity, polysorbate 80, amiodarone hepatitis, severe acute hepatitis.

Introduction

Amiodarone is a class III antiarrhythmic agent that comes in both an intravenous and oral form with a half life of approximately 20–100 days. It acts to stabilize the myocardium predominantly blocking potassium channels ; in addition, it also has antagonistic effects on calcium channels, sodium channels, beta-adrenergic receptors, and alpha-adrenergic receptors. Amiodarone used in treatment of refractory atrial and ventricular arrhythmias as a means of rhythm control and for prevention of sudden death. The long-term side effects of oral amiodarone are the result of tissue deposition of the drug. Common side effects include hypothyroidism, hyperthyroidism, corneal microdeposits, bradycardia, atrioventricular block, and pulmonary fibrosis. A transient elevation in aspartanine aminotransferase (AST), and alanine aminotransferase (ALT) levels can be seen but hepatitis and cirrhosis are rare. Steel-blue skin discoloration is reported but is less common that photosensitivity. Intravenous amiodarone has few reported side effects, which include hypotension, bradycardia, ventricular arrhythmias, heart failure, hyperlipidemia, transfusion site reactions, and transient elevation of the ALT and AST without hepatitis.

Severe hepatitis secondary to amiodarone is rare and potentially fatal. The process was first described by J. Lupon-Roses in 1986 and since that time there have been 24 other documented case reports in the English language (1). It is associated solely with intravenous preparations of amiodarone and does not require toxic blood levels to occur. The pathophysiology is poorly understood, but is theorized to be secondary to alteration of cell-membrane structure and function by the diluent Polysorbate 80 and not the amiodarone itself (1-3). The hepatocellular injury that occurs is acute and thought to be reversible after discontinuation of the intravenous amiodarone. A second theory implicates an immunologic reaction resulting in hepatotoxicity. Conversely, there has been evidence presented which suggests hypotensive ischemia and not amiodarone as the culprit in these cases (1,4,5). The case presented here contributes to the limited clinical experience with acute liver injury secondary to parental amiodarone administration and the following review revisits all cases of amiodarone induced hepatitis that have been reported.

Case Presentation

An 80-year-old man presented to another hospital with an ST segment elevation myocardial infarction. He was managed medically with intravenous tenecteplase and heparin, and his chest pain resolved prior to transfer to our medical center for cardiac catheterization. He had a past medical history significant for coronary artery disease, hypertension, and hyperlipidemia. He had no history of liver disease. On arrival his blood pressure was 106/53 with a heart rate of 66, and a respiratory rate of 20. There were no documented episodes of hypotension

Correspondence to : Amy Stratton, D.O., Tripler Army Medical Center, 1 Jarrett White Road, Honolulu, 96859 Hawaï. E-mail : amynstratton@gmail.com

Submission date : 30/09/2013
Acceptance date : 16/02/2015

or hypoxemia during initial presentation or transfer. His exam was otherwise unremarkable with no evidence of hepatosplenomegaly or clinical evidence of cirrhosis. The patient underwent a cardiac catheterization which demonstrated three vessel coronary artery disease that was not amenable to percutaneous interventions. He subsequently underwent an uncomplicated, off pump coronary artery bypass surgery that same evening. His immediate postoperative course was without complication and there was no documented peri-procedural hypotension.

On post-operative day seven, the patient developed stable ventricular tachycardia for which he was treated with the standard dosing regimen of intravenous amiodarone (150 mg intravenous load, followed by 1 mg/min for 6 hours then 0.5 mg/min for 18 hours). There were no episodes of hypotension or ischemic EKG changes at this time. His blood total bilirubin, AST, and ALT levels drawn the day amiodarone therapy was initiated were 0.5 mg/dL (normal range 0.2-1.3 mg/dL), 47 units/L (normal range of 15-46 units/L), and 44 units/L (normal range of 13-69 units/L) respectively. His INR was 1.3 with a platelet count of 186 × 10(9)/L (normal range of 150-440 × 10(9)/L) and a serum creatinine of 1.18 mg/dL (0.57-1.25 mg/dL). The next day he was incidentally noted on routine morning labs to have an elevated total bilirubin of 1.6 mg/dL, ALT of 3969 units/L, and alkaline phosphatase of 127 units/L (normal range of 38-126 units/L). In addition to amiodarone, he had received a total of 1300 mg of acetaminophen in the preceding 24 hours. He also received atorvastatin, a drug which was part of his outpatient treatment regimen prior to admission. He had no history of trauma. A subsequent right upper quadrant ultrasound with Doppler imaging was normal and showed no evidence of common bile duct dilation/obstruction or decreased arterial or venous flow as seen in Budd Chiari disease (Fig. 1, 2). Viral serologies for hepatitis B and C were negative making acute viral hepatitis unlikely. A transthoracic echo was not obtained during the initial episode of ventricular fibrillation. He had remained on telemetry monitoring without evidence of hypotension or shock making ischemic hepatitis unlikely. His aminotransferase levels were closely monitored and, as shown in figure 3, within 48 hours of discontinuation of intravenous amiodarone, his aminotransferase levels declined rapidly. On post-operative day nine his ALT peaked at 4434 units/L and AST peaked at 7500 units/L after which both values slowly normalized (Fig. 3). In addition, his total bilirubin peaked on post-operative day 9 at 1.9 mg/dL. On postoperative day 11 his alkaline phosphatase peaked at 159 units/L and normalized within 2 days. Although his aminotransferase levels, total bilirubin, and alkaline phosphatase improved, because of overall failing health and the family's wishes, he transitioned to palliative care and expired on post-operative day 30.

Discussion

Severe hepatitis secondary to intravenous amiodarone is defined by acute and reversible hepatocellular injury (1,5). The entity was first described by J. Lupon-Roses in 1986 (1) and since that time there have been 24 other documented case reports in the English literature. Severe acute hepatitis secondary to amiodarone is associated solely with parenteral forms and does not require toxic blood levels to occur (5,15). The half-life of amiodarone is too long to be associated with the rapid improvement as was seen in our case where aminotransferase levels improved shortly after discontinuation of the medication (22). As a result, the acute hepatic toxicity is thought to be secondary to polysorbate 80, a nonionic emulsifier

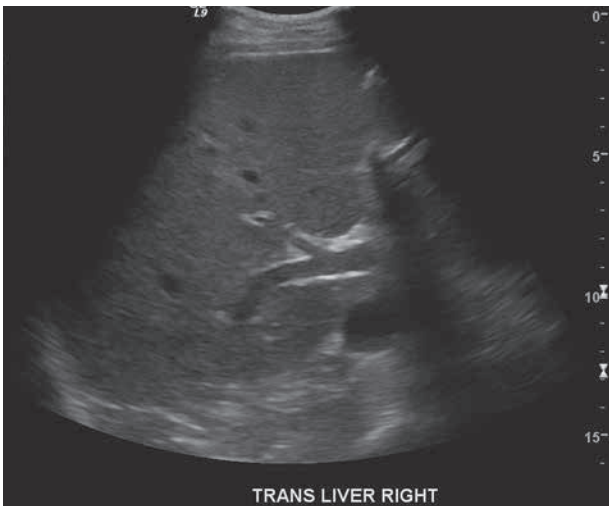

Fig. 1. — Ultrasound with a transverse view of the liver demonstrating normal hepatic architecture and echogenicity.

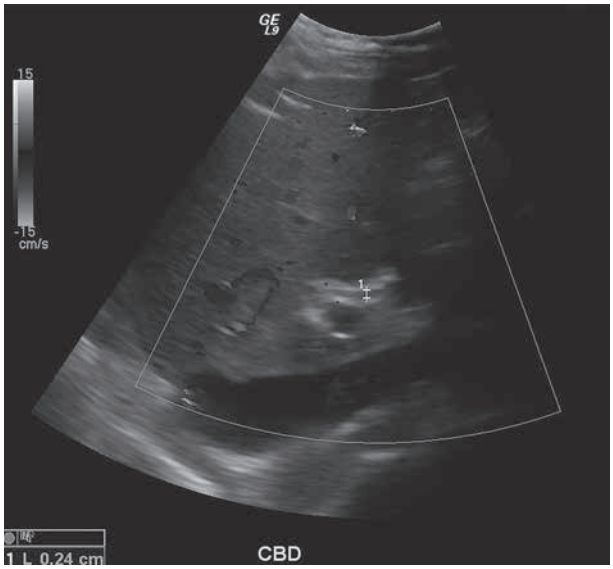

Fig. 2. — Doppler ultrasound of the liver demonstrating normal common bile duct size with surrounding normal arterial and venous flow.

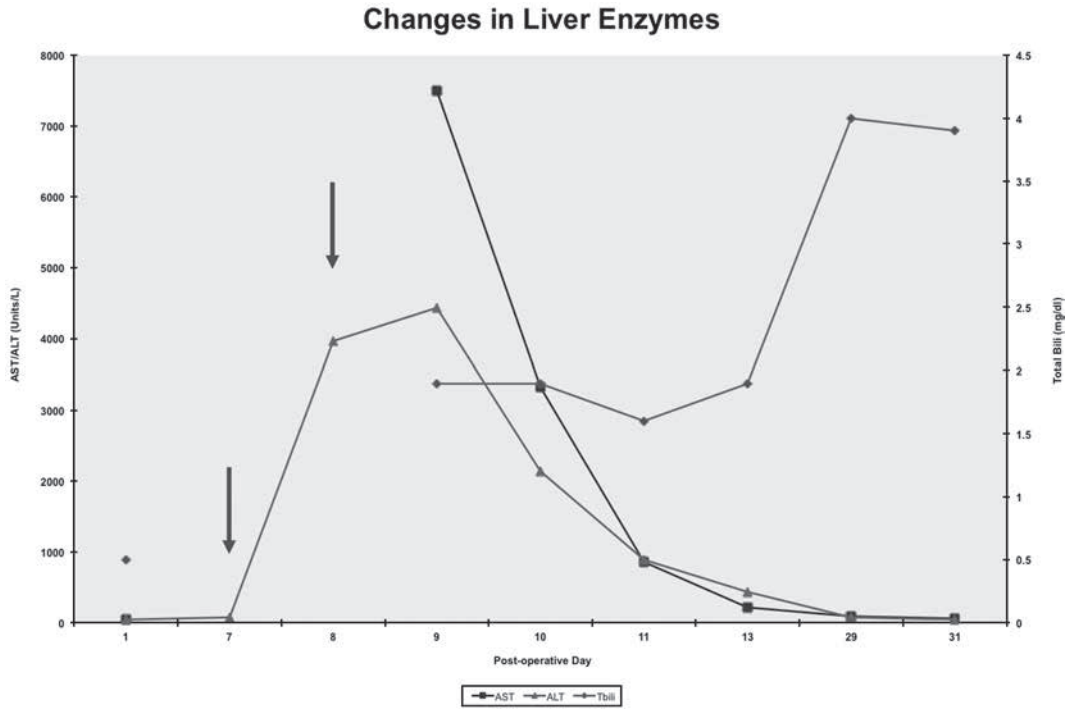

Fig. 3. — Graph demonstrating the trend of AST, ALT and total bilirubin over time. The first arrow highlights initiation of parenteral amiodarone on post-operative day 7. The second arrow highlights discontinuation of parenteral amiodarone on post-operative day 8.

used as a diluent in intravenous amiodarone, and not the active medication (1-3). Furthermore, the hepatotoxicity of polysorbate 80 was first noted in low-birth weight infants in association with e-ferol syndrome. E-ferol syndrome is fatal and presents with acute hepatic failure manifest as thrombocytopenia, ascites, cholestasis, and kidney injury. Hepatic histology, obtained from effected infants at autopsy, demonstrated progressive cholestasis, inflammation, and accumulation of cellular debris resulting in fibrosis and sinusoidal veno-occlusion (23).

The pathophysiology is poorly understood, but the resulting hepatitis is theorized to be secondary to polysorbate 80 mediated alterations to the structure and function of cell membranes (3,5). As with most suspected drug-induced toxicity, the diagnosis is made by excluding other risk factors and known causes of hepatocellular injury or cirrhosis in the setting of acute hepatotoxicity less than 48 hours after the initiation of intravenous amiodarone therapy (2). It is important to identify the presence of hepatocellular injury and discontinue intravenous amiodarone treatment to prevent further potentially irreversible hepatic failure.

The mechanism driving the liver injury is not currently known. It has been theorized that perhaps an allergic or immunologic process is involved. J. Lupon-Roses was the first to make this suggestion in 1986 due to the early presentation and elevated circulating IgA at levels greater the 2.5 times the upper limit of normal (1). In 1998, Breuer et al further supported an immunologic mechanism showing similar results as the 1986 case (4). Interestingly, they performed a re-challenge of a patient who had previously developed acute hepatitis after intravenous amiodarone administration and documented a very similar but longer lasting immunologic response with the second trial (4). These findings, along with the low doses of amiodarone required to induce the laboratory changes and rapid correction of these abnormalities when the drug was stopped, led the researchers to favor an immunologic mechanism over a toxicologic or ischemic etiology (4).

According to a case control retrospective study, performed by N. Gluck and colleagues, there is insufficient data to demonstrate that acute severe hepatitis secondary to intravenous amiodarone occurs at all (24). On their review of the literature, N. Gluck and colleagues concluded that the reported cases of intravenous amiodarone hepatitis were not due to toxicity at all, but rather, they were secondary to undiagnosed ischemic hepatitis (24-27).

We performed an extensive review of the literature and report the most thorough and comprehensive review of intravenous amiodarone induced hepatitis in the English language. Both the PubMed and Embase databases were searched for cases of acute hepatitis implicating intravenous amiodarone and found a total of 25 reported cases from 1986 to 2012 (Table 1). In addition, a RUCAM score was calculated for each reported case (Table 2) (28,29). Our case represents the twenty-sixth reported case implicating intravenous amiodarone as an etiology of acute hepatitis. An evaluation of the data demonstrated that 10 of the reported cases were more consistent with ischemic hepatitis based on history or documented hypotension (Table 2). There were 6 cases

Table 1

Year published	Reference	Age	Gender	Indication for Amiodarone	Intravenous Amiodarone Dose	Liver Enzymes Prior to Amiodarone (ALT/AST)	Days After IV Amiodarone Before Elevations in Transaminases	Days Until Peak Elevation in Transaminases (AST/ALT)	Peak ALT	Peak AST	Peak Alkaline Phosphatase	Peak Total Bilirubin	Day Until Normalization of Liver Enzymes	Patient Outcome
1986	Lupon-Roses *et al.*	77	M	Atrial tachycardia	300 mg load –> 900 mg/day ×2 days –> 300 mg/day	Normal	2	2	1571	1846	NR	6.3	14	Survived
1988	Pye *et al.*	48	F	Atrial fibrillation	300 mg load –> 900 mg/day ×2 days	20/35	1	2	1770	1860	185	15.5	16	Survived
1988	Pye *et al.*	70	F	Atrial fibrillation	300 mg load –> 1200 mg/day ×4	15/67	1	2	1600	2400	600	6	Did not fully resolve	Survived
1989	Stevenson *et al.*	59	M	Atrial fibrillation	450 mg/day x5 –> 200 mg/day ×2	NR/100	1	3	NR	450	250	3.5	20	Survived
1990	Simon *et al.*	59	M	Atrial fibrillation	1200 mg/24 hr	33/25	1	2	3270	2410	125	4.1	13	Survived
1991	Kalantzis *et al.*	28	M	Atrial fibrillation	1500 mg over 24 hours	48/52	1	2	20360	20040	60	6.8	14	Death (related to hepatic pathology)
1991	Kalantzis *et al.*	60	M	Atrial fibrillation	1500 mg over 24 hours	50/45	2	2	870	1200	45	5.6	Did not resolve	Death (related to hepatic pathology)
1991	Morelli *et al.*	58	M	Atrial fibrillation	300 mg load –> 50-65 mg/hr for 3 days	29/24	3	4	251	192	505	3.4	14	Survived
1991	Morelli *et al.*	68	M	Ventricular tachycardia	450 mg load –> 20-65 mg/hr for 7 days	26/37	2	4	128	160	482	3.3	14	Survived
1992	Fornaciari *et al.*	52	F	Ventricular tachycardia	12000 mg/day x2.5 days	Normal	1	4	2000	2500	NR	3.5	13	Survived
1993	Rhodes *et al.*	72	M	Ventricular tachycardia	300 mg load –> 900 mg/24 hr	69/50	1	1	7238	5236	NR	7.1	Did not resolve	Death (3 days after discharge from arrythmia)
1997	James *et al.*	50	M	Atrial fibrillation	1.2 gm amio IV	NR/28	1	8	85	8220	85	5.3	10	Survived
1998	Breuer *et al.*	64	M	Atrial tachycardia	300 mg load –> 1000 mg/day	36/18	3	6	3803	2555	NR	3	25	Survived
1999	Iliopouloum *et al.*	69	M	Frequent PVC	1500 mg load	NR/NR	1	NR	"Increased 50 fold"	"Increased 50 fold"	NR	NR	14	Survived
2002	Curran *et al.*	65	M	Atrial flutter	Dosing not reported	NR/NR	NR	NR	4700	NR	228	3.5	20	Survived
2002	Gregory *et al.*	74	F	Ventricular tachycardia	150 mg IV load –> 150 mg IV load –> 1 mg/min, restarted 1 day later at 0.5 mg/min	NR/NR	1	NR	759	1099	NR	NR	13	Survived
2002	MacFadyen *et al.*	64	M	Atrial fibrillation	1.2 gm over 30 hrs	NR/19	2	2	9308	NR	NR	16	Did not resolve	Death (unrelated to hepatic pathology)
2005	Rätz Bravo *et al.*	66	F	Atrial fibrillation	200 mg IV	33/59	1	13	2732	3822	216	2.6	> 13	Survived
2005	Rätz Bravo *et al.*	73	F	Atrial fibrillation	720 mg IV	8/28	1	5	7639	17471	566	1.8	> 15	Survived
2005	Rätz Bravo *et al.*	57	M	Atrial fibrillation	200 mg po x2 –> 150 mg IV load –> 60 mg/hr x6hr –> 30 mg/hr	52/37	1	25	3707	3091	150	6.1	25	Survived
2005	Maker *et al.*	54	M	Atrial fibrillation	150 mg IV –> 1 mg/min –> 0.5 mg/min	29/32	5	5	1303	739	NR	NR	6	Survived
2007	Rizzioli *et al.*	79	F	Atrial fibrillation	180mg/60 min –> 360 mg/5 hr	15/13	1	1	3387	4202	NR	2.2	Did not resolve	Death (unrelated to hepatic pathology)
2011	von Vital *et al.*	64	M	Atrial fibrillation	150 mg IV –> 1 mg/min	NR/NR	7	14	2028	932	104	13.4	32	Survived
2012	Rao *et al.*	44	M	Atrial flutter	300 mg IV over 30 min –> 900 mg over 24 hr	28/NR	1	3	4578	NR	194	4.5	10	Survived
2012	Akbal *et al.*	80	M	Ventricular tachycardia	300 mg load –> 900 mg over 24 hr	NR/NR	NR	30	1240	1300	99	3.6	7	Death (related to hepatic pathology)
2013	Our Case	80	M	Ventricular tachycardia	150 mg IV –> 1 mg/min –> 0.5 mg/min	44/47	1	2	4434	7500	159	1.9	2	Death (transitioned to palliarive care)

* NR : Not reported.

Table 2

Year published	Reference	Evidence of Hypotension	Other Possible Etiology for Elevated Liver Enzymes	Hepatic Imaging	Additional Testing	RUCAM score
1986	Lupon-Roses *et al.*	No hypotension or shock	None reported	None reported	Liver biopsy: centrilobular necrosis, hepatitis serologies, CMV neg, IGA 1090, IGG/IGM normal	8 (probable)
1988	Pye *et al.*	No hypotension or shock	Verapamil	None reported	Hep A/B, viral studies, anti-tissue Ab neg	6 (probable)
1988	Pye *et al.*	No hypotension or shock, cannot rule out ischemic hepatitis	Nifedipine	None reported	None reported	5 (possible)
1989	Stevenson *et al.*	Not Reported, cannot rule out ischemic hepatitis	None reported	Ultrasound: hepatic congestion, no evidence of obstruction (no doppler reported)	Hepatic serologies, anti-tissue Ab neg	2 (unlikely)
1990	Simon *et al.*	Not Reported	None reported	None reported	Hep serologies, mono, CMV, anti-mitochondrial, anti-smooth neg	9 (highly probable)
1991	Kalantzis *et al.*	No hypotension or shock	None reported	None reported	Liver biopsy: Confluent liver necrosis, centrolobular necrosis, Hep A/B, CMV, EBV, HSV neg	6 (probable)
1991	Kalantzis *et al.*	No hypotension or shock	None reported	None reported	Liver biopsy: Confluent liver necrosis, centrolobular necrosis, Hep A/B, CMV, EBV, HSV neg	4 (possible)
1991	Morelli *et al.*	No hypotension or shock	None reported	Ultrasound: normal (no doppler reported)	Hep A/B, viral studies neg	6 (probable)
1991	Morelli *et al.*	No hypotension or shock, cannot rule out ischemic hepatitis	Captopril	Ultrasound: normal (no doppler reported)	Hep A/B, viral studies neg	2 (unlikely)
1992	Fornaciari *et al.*	Report of Syncope, likely ischemic hepatitis	Enalopril	CT: hepatomegaly (no duct dilation or vascular pathology reported)	Hep A/B/C, CMV, HSV, EBV neg	2 (unlikely)
1993	Rhodes *et al.*	Report of Shock and Syncope	Enalopril	None reported	None reported	0 (relationship with drug excluded)
1997	James *et al.*	Not Reported	Ethanol	Ultrasound: hepatomegaly, no duct dilation (no doppler reported)	None reported	4 (possible)
1998	Breuer *et al.*	Hypotension reported	Hepatic steatosis, trandolapril	None reported	Amiodarone 1.8, pos coombs test	2 (unlikely)
1999	Iliopouloum *et al.*	No hypotension or shock	Enalopril, Ranitidine	CT: normal	Neg hep A/B/C, CMV, EBV, HSV	6 (probable)
2002	Curran *et al.*	Hypotension reported	Hereditary fructose intolerance	Ultrasound: Negative, no flow obstruction	GGT 228 u/L	2 (unlikely)
2002	Gregory *et al.*	Not Reported	None reported	None reported	Amiodarone 1.5 mg/L	-1 (relathionship with drug excluded)
2002	MacFadyen *et al.*	Hypotension reported	None reported	None reported	Post mortem liver bx: nutmed patern, fulminant hepatic necrosis without prior liver disease	0 (relationship with drug excluded)
2005	Rätz Bravo *et al.*	No hypotension or shock, cannot rule out ischemic hepatitis	Pravastatin, Acetominophen	None reported	None reported	3 (possible)
2005	Rätz Bravo *et al.*	No hypotension or shock	Pravastatin, Allopurinol, Amlodipine,Acetominophen, Phenytoin	None reported	None reported	3 (possible)
2005	Rätz Bravo *et al.*	No hypotension or shock	Acetominophen, Captopril	None reported	None reported	5 (possible)
2005	Maker *et al.*	Not Reported	Amphotericin, Erythromycin, Imipenem, Levafloxicin, levofloxacin, Ranitidine	Ultrasound: normal (no dopler reported); CT: normal	None reported	1 (unlikely)
2007	Rizzioli *et al.*	Not Reported	None reported	None reported	None reported	5 (possible)
2011	von Vital *et al.*	Not Reported	Steatohepatitis, Hepatocellular carcinoma	Ultrasound: normal, normal doppler	ERCP: negative/no obstruction, liver biopsy: apoptotic hepatocytes/canalicular cholestasis/no rejection	6 (probable)
2011	Rao *et al.*	No hypotension or shock, cannot rule out ischemic hepatitis	None reported	Ultrasound: normal	Not reported	3 (possible)
2012	Akbal *et al.*	No hypotension or shock	None reported	Ultrasound: gallbladder wall thickening/ edema	Neg hep B/C, HIV, CMV, EBV, antimitocondrial Ab, ANA	9 (highly probable)
2013	Our case	No hypotension or shock	Acetaminophen, Atorvastatin	Ultrasound: normal	Neg hep B/C	8 (probable)

† RUCAM score : Roussel Uclaf Causality Assessment Method validated to determine the hepatotoxic effects of a substance (28,29).

in which other etiologies of acute hepatitis had not been evaluated or, if evaluated, had not been documented and therefore amiodarone cannot be implicated in these cases. The remaining 10 cases reported did provide sufficient evidence to conclusively implicate amiodarone as the etiology of the patient's acute hepatitis (Table 1, 2). Further, Akbal et al reported a patient who had reproducible response with an elevation of hepatic enzymes within 24 hours after re-challenge with intravenous amiodarone that resolved shortly after withdraw of the medication (21).

Liver biopsy specimens were obtained from 5 patients with histologic findings of centrilobular necrosis, nutmeg pattern of the hepatocytes, apoptotic hepatocytes, and cannicular cholestasis (1,6,9,19). The findings from these biopsies, in addition to those from infants with e-ferol syndrome, are consistent with both drug induced liver injury and ischemic hepatitis. These findings support acute amiodarone induced hepatitis but cannot conclusively exclude ischemic hepatitis.

There are 6 cases documenting that re-challenge with oral amiodarone is well tolerated without recurrent hepatitis (2,6,10,12,15). In 1 of these cases, though, ischemic hepatitis is the likely cause of acute hepatitis and therefore oral re-challenge is futile to demonstrate a difference in effect (10). Additionally, in 3 case reports the work up to eliminate other etiologies of acute hepatitis was incomplete or not performed (2,12,15). In a 1988 case report by M. Pye and a 1991 case reported by S. Morelli oral amiodarone was re-introduced without evidence of toxic side effect (6,10). More evidence is needed with regards to oral re-introduction of amiodarone following a case of IV amiodarone induced acute hepatitis, but the limited data that is available suggest there is no increased risk for toxicity or other adverse events with subsequent exposure to oral amiodarone preparation (6,10). Additionally, these findings support the implication of polysorbate 80 in parenteral amiodarone preparations as the causative agent over an immune-mediated or allergic mechanism ; however, multifactorial etiology in some patients cannot be excluded.

Our patient adds to the limited number of cases where a thorough investigation implicates parenteral administration of amiodarone as the cause of acute hepatic injury. He remained on continuous telemetry throughout his admission with no evidence of unstable ventricular arrhythmia or hypotension making ischemic hepatitis unlikely ; and further workup, including viral serology and right upper quadrant ultrasound, did not lead to an alternate diagnosis. The 1300 mg of acetaminophen and his outpatient atorvastatin were considered unlikely to be the source of his hepatic injury. Furthermore, the downtrend of his ALT and AST within 24 hours of amiodarone cessation would not be expected with these other etiologies. In comparison to other reported cases this case is similar with regards to patient age, sex, and type of arrhythmia (atrial fibrillation or atrial flutter). The majority of cases were associated with congestive heart failure (CHF), cardiomyopathy or cardiac valvular surgery unlike this case in which the patient developed ventricular tachycardia immediately post cardiac bypass after a recent cardiac event. This case represents the tenth reported case of severe acute hepatitis secondary to intravenous amiodarone with evidence of exclusion of other possible etiologies.

Conclusion

Our review of the literature reveals that there is sufficient data to support the existence and clinical significance of intravenous amiodarone induced hepatotoxicity in 10 cases. In agreement with Gluck et al, there is evidence that 10 of the published cases that have implicated amiodarone administration as the cause of aminotransferase elevation are, in fact, more consistent with an ischemic hepatopathy. Additionally, our review suggests that 6 of the reported cases of amiodarone hepatotoxicity were actually inconclusive due to a limited or incomplete evaluation and workup for alternative and more common causes of liver injury. Contrary to Gluck et al, though, the presentations of 10 patients having high RUCAM score, absence of hypotension, and rapid resolution of aminotransferase elevations when amiodarone was withheld are very convincing for a hepatotoxic etiology caused by intravenous administration of amiodarone.

Care should be taken to fully evaluate and rule-out other causes of hepatic injury before the diagnosis of amiodarone induced hepatotoxicity can be made conclusively. A causality assessment method based on objective data, such as the RUCAM score, should be performed as an added evaluation measure to prevent erroneous diagnosis. Discontinuation of parenteral amiodarone should not be postponed during the diagnostic work-up. In addition, reintroduction of parenteral amiodarone as a diagnostic tool can be lethal. Therefore, the medication should be held indefinitely where amiodarone toxicity is considered the most likely cause of the acute severe hepatitis.

References

1. LUPON-ROSÉS J., SIMÓ-CANONGE R., LU-CORTEZ L., PERMANYER-MIRALDA G., ALLENDE-MONCLUS H. Probable early acute hepatitis with parenteral amiodarone. *Clin. Cardiol.*, 1986, **9** (5) : 223-225.
2. RÄTZ BRAVO A.E., DREWE J., SCHLIENGER R.G., KRAHENBUHL S., PARGGER H., UMMENHOFER W. Hepatotoxicity during rapid intravenous loading with amiodarone : Description of three cases and review of the literature. *Critical Care Medicine*, 2005, **33** : 128-134.
3. RHODES A., EASTWOOD J., SMITH S. Early hepatitis with parenteral amiodarone : a toxic effect of the vehicle ? *Gut*, 1993, **34** : 565-566.
4. BREUER H.W., BOSSEK W., HAFERLAND C., SCHMIDT M., NEUMANN H., GRUSZKA J. Amiodarone-induced severe hepatitis mediated by immunological mechanisms. *Int. J. Clin. Pharmacol. Ther.*, 1998, **36** (6) : 350-352.
5. GENÈVE J., SERGE E., DHUMEAUX D. Amiodarone-induced liver disease. *J. Hepatol.*, 1989, 9 (1) : 130-133.
6. PYE M., NORTHCOTE R., COBBE S. Acute hepatitis after parenteral amiodarone administration. *Br. Heart J.*, 1988, **59** : 690-691.

7. STEVENSON R.N., NAYANI T.H., DAVIES J.R. Acute hepatic dysfunction following parenteral amiodarone administration. *Postgraduate Medical Journal*, 1989, **65** : 707-708.
8. SIMON J.P., ZANNAD F., TRECHOT P., THISSE J.Y., HOUPLON M., ALIOT E. Acute hepatitis after a loading dose of intravenous amiodarone. *Cardiovasc. Drugs Ther.*, 1990, **4** (6) : 1467-1468.
9. KALANTZIS N., GABRIEL P., MOUZAS J., TINIAKOS D., TSIGAS D., TINIAKOS G. Acute amiodarone-induced hepatitis. *Hepatogastroenterology*, 1991, **38** (1) : 71-74.
10. MORELLI S., GUIDO V., DE MARZIO P., AGUGLIA F., BALSANO F. Early hepatitis during intravenous amiodarone administration. *Cardiology*, 1991, **78** (3) : 291-294.
11. FORNACIARI G., MONDUCCI I., BARONE A., BASSI C., BELTRAMI M., TOMASI C. Amiodarone-induced acute hepatitis : Case report. *J. Clin. Gastroenterol.*, 1992, **15** : 271-273.
12. JAMES P.R., HARDMAN S.C. Acute hepatitis complicating parenteral amiodarone does not preclude subsequent oral therapy. *Heart*, 1997, **77** : 583-584.
13. ILIOPOULOU A., GIANNAKOPOULOS G., MAYRIKAKIS M., ZAFIRIS E., STAMATELOPOULOS S. Reversible fulminant hepatitis following intravenous amiodarone loading. Amiodarone hepatotoxicity. *Int. J. Clin. Pharmacol. Ther.*, 1999, **37** : 312-313.
14. CURRAN B.J., HAVILL J.H. Hepatic and Renal Failure Associated with Amiodarone Infusion in a Patient with Hereditary Fructose Intolerance. *Critical Care and Resuscitation*, 2002, **4** : 112-115.
15. GREGORY S.A., WEBSTER J.B., CHAPMAN G.D. Acute hepatitis induced by parenteral amiodarone. *The American Journal of Medicine*, 2002, **113** : 254-255.
16. MACFADYEN R.J., PALMER T.J., HISAMUDDIN K. Rapidly fatal acute amiodarone hepatitis occurring in the context of multiple organ failure. *Int. J. Cardiol.*, 2003, **91** (2-3) : 245-247.
17. MAKER A.V., ORGILL D.P. Rapid acute amiodarone-induced hepatotoxicity in a burn patient. *J. Burn. Care Rehabil.*, 2005, **26** (4) : 341-343.
18. RIZZIOLI E., INCASA E., GAMBERINI S., SAVELLI S., ZANGIROLAMI A., TAMPIERI M. Acute toxic hepatitis after amiodarone intravenous loading. *Am. J. Emerg. Med.*, 2007, **25** (9) : 1082.e1-1082.e4.
19. VONVITAL J.M., KARACHRISTOS A., SINGHAL A., THOMAS R., JAIN A. Acute Amiodarone Hepatotoxicity After Liver Transplant. *Transplant*, 2011, **91** (8) : e62-e64.
20. RAO U., AGARWAL A. Amiodarone-induced acute hepatotoxicity. *Eur. J. Clin. Pharmacol.*, 2012, **68** : 449-450.
21. AKBAL E., BATGI H., KOÇAK E., CANATAN T., KÖKLÜ S. Low-dose amiodarone-induced fatal liver failure. *Drug and Chemical Toxicology*. http://www.ncbi.nlm.nih.gov/pubmed/22356138 (accessed, 2012 Sep 4).
22. LATINI R., TOGNONI G., KATES R. Clinical Pharmacokinetics of Amiodarone. *Clinical Pharmacokinetics*, 1984, **9** : 136-156.
23. BODE K., KOSMETATOS N., WEDIG K., FRANK D., WHITLATCH S., SALDIVAR V. et al. Vasculopathic hepatotoxicity associated with e-ferol syndrome in low-birthweight infants. *JAMA*, 1985, **254** : 2422-2430.
24. GLUCK N., FRIED M., PORAT R. Acute Amiodarone Liver Toxicity Likely Due to Ischemic Hepatitis. *IMAJ*, 2011, **13** : 748-752.
25. GUGLIN M. Occam's Razor and Ischemic Hepatitis. *IMAJ*, 2012, **14** : 402.
26. SEETO R.K., FENN B., ROCKEY D.C. Ischemic Hepatitis : Clinical Presentation and Pathogenesis. *Am. J. Med.*, 2000, **109** (2) : 109-113.
27. GIBSON P.R., DUDLEY F.J. Ischemic Hepatitis : Clinical Features, Diagnosis and Prognosis. *Aust. N. Z. J. Med.*, 1984, **14** (6) : 822-825.
28. BENICHOU C., DANAN G., FLAHAULT A. Causality assessment of adverse reactions to drugs--II. An original model for validation of drug causality assessment methods : case reports with positive rechallenge. *J. Clin. Epidemiol.*, 1993, **46** (11) : 1331-1336.
29. DANAN G., BENICHOU C. Causality assessment of adverse reactions to drugs : a novel method based on the conclusions of international consensus meetings : application to drug-induced liver injuries. *J. Clin. Epidemiol.*, 1993, **46** (11) : 1323-1330.