HHS Public Access

Author manuscript

South Med J. Author manuscript; available in PMC 2017 February 01.

Published in final edited form as:

South Med J. 2016 February ; 109(2): 83–86. doi:10.14423/SMJ.0000000000000413.

Hepatic Dysfunction in Patients Receiving Intravenous Amiodarone

Ali Hashmi, MD, **Nicole R. Keswani, PharmD**, **Sharon Kim, MD**, and **David Y. Graham, MD**

Department of Medicine and Pharmacy Service, Michael E. DeBakey VA Medical Center, and Baylor College of Medicine, Houston, Texas

Abstract

Objectives—Amiodarone is a commonly used anti-arrhythmic drug. Hepatotoxicity following chronic oral administration occurs in 1% to 3% of patients. Hepatotoxicity following intravenous (IV) administration is infrequent but may be associated with dramatic increases in serum transaminases. We describe the incidence of liver toxicity among patients receiving IV amiodarone during a 5-year period.

Methods—This was a single-center retrospective review of patients receiving IV amiodarone for any cause. The outcome measures were development of elevated serum transaminases and the relation of transaminitis to all-cause 30-day mortality.

Results—A total of 1510 patients received amiodarone intravenously between 2005 and 2011; 77 (5%) developed elevated liver enzymes. Enzyme elevation was divided into mild (100–300 IU/L), moderate (300–1000 IU/L), and severe (>1000 IU/L). The median alanine aminotransferase was 189 (37–10,006) IU/L and aspartate aminotransferase was 253 (84–12,005) IU/L. The 30-day mortality among those with transaminitis was 22%; however, no patient died of amiodarone-related liver disease.

Conclusions—Amiodarone can cause severe elevation in liver enzymes. The incidence of severe transaminitis is low; deaths following IV amiodarone are rarely caused by drug-induced liver failure.

Keywords

amiodarone; intravenous; hepatotoxicity; arrhythmia; atrial fibrillation; mortality; polysorbate 80

Amiodarone is a class III antiarrhythmic drug used to treat atrial and ventricular arrhythmias.[1,2] Its adverse effects involve many organ systems and result in cessation of the medication in 10% to 15% of patients. Common adverse effects of oral amiodarone include thyroid dysfunction, corneal microdeposits, hepatic dysfunction, and pulmonary fibrosis,[3,4] and asymptomatic elevations in liver enzymes are reported in 15% to 50% of long-term

Correspondence to Dr David Y. Graham, Michael E. DeBakey VA Medical Center; 2002 Holcombe Blvd (111D), Houston, TX 77030. dgraham@bcm.edu..

The remaining authors have no financial relationships to disclose and no conflicts of interest to report.

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the Department of Veterans Affairs or of the National Institutes for Health.

users.[5,6] Symptomatic liver injury is rare but potentially fatal, occurring in 1% to 3 % of long-term users.[7–10]

Amiodarone often is given by intravenous (IV) bolus in the management of potentially life-threatening arrhythmias. Adverse effects following IV amiodarone administration include injection site reactions, diaphoresis, flushing, sinus bradycardia, atrioventricular block, and hypotension.[3,4] Acute amiodarone hepatotoxicity also may follow intravenous amiodarone.[7] The presentation of acute hepatotoxicity varies from mild asymptomatic increases in serum transaminases (transaminitis) to fulminant hepatic failure. The clinical presentations, incidence, and outcomes are less well described. The aim of this study was to determine the incidence, prevalence, and clinical manifestations of acute hepatitis following the IV administration of amiodarone. We retrospectively reviewed the clinical data from patients receiving IV amiodarone therapy at the Michael E. DeBakey Veterans Affairs Medical Center between July 2005 and July 2011. We also assessed potentially important variables possibly predicting the presence, severity, and outcome of acute hepatic injury.

Methods

This was a single-center, retrospective chart review of patients who received IV amiodarone for the treatment or prevention of arrhythmia. Patients who received IV amiodarone between July 2005 and July 2011 were identified using a pharmacy-generated computerized report; only patients receiving loading amiodarone doses for arrhythmias were included. Exclusion criteria included patients who had received oral amiodarone or IV amiodarone for up to 1 week before hospital admission, who received amiodarone as part of advanced cardiac life support, who had elevated liver enzymes at baseline, who were younger than 18 years old, and pregnant women. Clinical data and medication administration records for those who received intravenous amiodarone were reviewed. The study was approved by the Baylor institutional review board.

The primary objective was to determine the incidence of transaminitis in patients receiving IV amiodarone. Transaminitis was defined as a serum alanine aminotransferase (ALT) >100 IU/L and/or aspartate aminotransferase (AST) >100 IU/L within 48 hours after receiving intravenous amiodarone. An elevated total bilirubin was defined as >1.5 mg/dL and elevated alkaline phosphatase as >150 IU/L. Secondary objectives included 30-day mortality, all-cause mortality, and whether the presence of an impaired ejection fraction (<40%) or chronic liver disease influenced the occurrence or severity of transaminitis.

Amiodarone Administration

Amiodarone was prepared for IV infusion by diluting it in 100 mL of 5% dextrose. The loading dose of 150 mg was infused for 10 minutes and the maintenance dose was continued at 1 mg/min for 6 hours (360 mg) and then 0.5 mg/min for 18 hours (540 mg), giving a total dose of 1050 mg for 24 hours.

Statistical Analysis

Descriptive statistics were used to analyze baseline characteristics and study outcomes. Data are expressed as ranges, medians, and means.

Results

A total of 1510 patients received IV amiodarone in the 6-year period between July 2005 and July 2011; 77 (5%) developed transaminitis. Baseline characteristics are shown in Table 1. The median postamiodarone levels of serum transaminase were ALT 189 IU/L (range 37–10,006) and AST 253 IU/L (range 82–12,005). Elevations in transaminases were mild (100–300 U/L) in 39 (50.6%) patients, moderate (301–1000 U/L) in 26 (33.7%), and severe (>1000 U/L) in 12 (15.5%) patients. The median alkaline phosphatase was 79 IU/L (range 20–411) and total bilirubin was 1.65 mg/dL (0.5–20.5).

Comorbidities such as congestive heart failure, chronic kidney disease, diabetes mellitus, coronary artery disease, and/or underlying hepatitis were common in patients who developed elevated transaminases after receiving IV amiodarone. Hepatitis C antibody or hepatitis B surface antigen was present in 27 (35%) patients, congestive heart failure with an ejection fraction of <35% in 29 (37.6%), chronic kidney disease (glomerular filtration rate <60 mL/min) in 17 (22%), diabetes mellitus in 34 (44.1%), and coronary artery disease in 32 (41.5%). Each was categorized in relation to mild, moderate, or severe elevation in liver enzymes (Table 2).

The 30-day, all-cause mortality among the 77 patients with transaminitis was 22% (17 patients). The 30-day mortality among the patients with severe transaminitis (AST/ALT >1000 IU/L) was 9% (7 patients). The 30-day mortality in mild and moderate transaminitis was 10.2% and 2.5%, respectively; however, no patient died of amiodarone-induced liver disease.

Discussion

Acute hepatotoxicity following IV amiodarone administration is rare, occurring annually in approximately 1% of those receiving amiodarone intravenously, but it may be associated with a fatal outcome. In addition to the 12 patients described here with severe transaminitis (ALT/AST >1000 IU/L) after IV amiodarone administration, our literature review found 34 case reports.[7,8,11–16] Huang et al reported their experience with 802 patients receiving IV amiodarone, in which hepatotoxicity occurred in 12.6% (101/802); most cases were mild.[10] They reported severe transaminitis in only 1.1% (n = 9), which was 8.9% of those with transaminitis.[10] In our series with 17 patients, the overall mortality was 22% (all were acute in the hospital). All of the patients in the study had undergone a cardiothoracic surgical procedure and therefore differ considerably from our patient population, which had different indications for amiodarone infusion.

Amiodarone is an iodine-containing benzofuran derivative widely used to treat both atrial and ventricular arrhythmias. Its advantages include the lack of negative inotropic effects and high efficacy in resistant arrhythmias and is believed to be more efficacious than class I antiarrhythmics.[2] It also has advantages of having a long half-life and the ability of being given either orally or intravenously.[16–20] Acute liver injury following IV administration, however, is not believed to be caused by amiodarone; rather the hepatotoxicity is believed to

be related to the diluent polysorbate 80 and to be secondary to hepatic ischemia accompanying the hypotensive episode.[9,21]

Amiodarone is metabolized to mono-*N*-desethylamiodarone (DEA) by cytochrome P-450 enzymes (CYP3A4 and 2C8). This active metabolite possesses antiarrhythmic properties. Left ventricular dysfunction prolongs the half-life of DEA. Both amiodarone and DEA accumulate in fatty tissues, including the liver. Both compounds are directly toxic to HepG2 cells at high concentrations and are believed to be responsible for hepatotoxicity associated with chronic amiodarone administration.[22]

In contrast, amiodarone is not stable[22] in aqueous solutions and therefore must be dissolved in a solvent. The solvent used is a mixture of polysorbate 80 (polyoxenethylated sorbitan ester) and benzyl alcohol.[22] Rhodes et al were the first to link polysorbate 80 to amiodarone-associated hepatotoxicity.[9] Polysorbate 80 was previously implicated in E-ferol syndrome and the cause of hepatic toxicity in infants.[9] E-ferol is an IV preparation of vitamin E that contained both polysorbate 80 and polysorbate 20.[9,12] E-ferol syndrome is characterized by hepatomegaly, cholestatic jaundice, splenomegaly, renal failure, and thromobocytopenia. Liver histology shows Kupffer cell exfoliation, centrilobular accumulation of cellular debris, and central panlobular congestion. These histologic features are similar to the liver injury caused by amiodarone and suggest that the acute toxicity was related to the diluent rather than the drug itself. If polysorbate 80 is the cause of the acute hepatotoxicity, it would seem prudent for the pharmaceutical industry to find a more suitable diluent.[9,23–26]

Hepatic ischemia caused by hemodynamic instability from tachyarrhythmias and poor cardiac output also can be confused with amiodarone hepatotoxicity or may actually play a role in amiodarone-induced hepatotoxicity.[16,27] For example, Gluck et al reported similarities in histologic features of liver ischemia and amiodarone liver injury.[28] In our study, 38% (29 patients) with elevations in transaminases demonstrated systolic dysfunction, with 13.7% (4 of 29 patients) having severe elevations, suggestive of drug hepatotoxicity rather than ischemic injury. We attempted to assess whether comorbidities such as chronic kidney disease and congestive heart failure played a role in developing severe elevation of liver enzymes, but no comorbidity was present in more than approximately 20% of patients in any category.

The retrospective nature of our study and inconsistencies in laboratory monitoring following amiodarone administration precluded an accurate assessment of the duration of transaminitis. The available literature, however, is consistent with the view that amiodarone can be safely administered orally, even in patients who develop hepatitis following IV loading.[10,13]

The limitations of our study include our inability to determine the precise indication for amiodarone administration and to determine the average duration of transaminitis before resolution. Our population also was entirely men, which reflects the male predominance of the population served by the Veterans Affairs Medical Centers.

Conclusions

Amiodarone is a commonly used antiarrhythmic with many known adverse effects. Our study shows an incidence of transaminitis similar to other studies published in the literature. Severe elevations in liver enzymes are seen, but no fulminant hepatic failure was documented. Although amiodarone infusion is associated with an alarming increase in liver enzymes, it rarely causes fatal hepatic injury.

Acknowledgments

The study was supported in part by the Office of Research and Development, Medical Research Service, Department of Veterans Affairs.

D.Y.G. is supported by NIH Grant No. DK56338, which funds the Texas Medical Center Digestive Diseases Center; is a consultant to Novartis, RedHill Biopharma, and Otsuka Pharmaceuticals; and has received royalties from Baylor College of Medicine patents.

References

1. Goldschlager N, Epstein AE, Naccarelli G, et al. Practical guidelines for clinicians who treat patients with amiodarone. Practice Guidelines Subcommittee, North American Society of Pacing and Electrophysiology. Arch Intern Med. 2000; 160:1741–1748. [PubMed: 10871966]
2. Goldschlager N, Epstein AE, Naccarelli GV, et al. A practical guide for clinicians who treat patients with amiodarone: 2007. Heart Rhythm. 2007; 4:1250–1259. [PubMed: 17765636]
3. Roy D, Talajic M, Dorian P, et al. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. N Engl J Med. 2000; 342:913–920. [PubMed: 10738049]
4. Podrid PJ. Amiodarone: reevaluation of an old drug. Ann Intern Med. 1995; 122:689–700. [PubMed: 7702232]
5. Lewis JH, Ranard RC, Caruso A, et al. Amiodarone hepatotoxicity: prevalence and clinicopathologic correlations among 104 patients. Hepatology. 1989; 9:679–685. [PubMed: 2785079]
6. Hyatt RH, Sinha B, Vallon A, et al. Noncardiac side-effects of long-term oral amiodarone in the elderly. Age Ageing. 1988; 17:116–122. [PubMed: 3369337]
7. 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; 33:128–134. [PubMed: 15644659]
8. Agozzino F, Picca M, Pelosi G. Acute hepatitis complicating intravenous amiodarone treatment. Ital Heart J. 2002; 3:686–688. [PubMed: 12506529]
9. Rhodes A, Eastwood JB, Smith SA. Early acute hepatitis with parenteral amiodarone: a toxic effect of the vehicle? Gut. 1993; 34:565–566. [PubMed: 8491409]
10. Huang X, Yang Y, Zhu J, et al. Clinical applications and acute hepatotoxicity of intravenous amiodarone. J Int Med Res. 2009; 37:1928–1936. [PubMed: 20146893]
11. McGovern B, Garan H, Ruskin JN. Serious adverse effects of amiodarone. Clin Cardiol. 1984; 7:131–137. [PubMed: 6368073]
12. Chan AL, Hsieh HJ, Hsieh YA, et al. Fatal amiodarone-induced hepatotoxicity: a case report and literature review. Int J Clin Pharmacol Ther. 2008; 46:96–101. [PubMed: 18218290]
13. Pye M, Northcote RJ, Cobbe SM. Acute hepatitis after parenteral amiodarone administration. Br Heart J. 1988; 59:690–691. [PubMed: 3395527]
14. Simon JP, Zannad F, Trechot P, et al. Acute hepatitis after a loading dose of intravenous amiodarone. Cardiovasc Drugs Ther. 1990; 4:1467–1468. [PubMed: 2081138]
15. Maker AV, Orgill DP. Rapid acute amiodarone-induced hepatotoxicity in a burn patient. J Burn Care Rehabil. 2005; 26:341–343. [PubMed: 16006841]

16. Nasser M, Larsen TR, Waanbah B, et al. Hyperacute drug-induced hepatitis with intravenous amiodarone: case report and review of the literature. Drug Healthc Patient Saf. 2013; 5:191–198. [PubMed: 24109195]
17. Faniel R, Schoenfeld P. Efficacy of i.v. amiodarone in converting rapid atrial fibrillation and flutter to sinus rhythm in intensive care patients. Eur Heart J. 1983; 4:180–185. [PubMed: 6861767]
18. Aravanis C. Acute thrombophlebitis due to IV use of amiodarone. Chest. 1982; 82:515–516. [PubMed: 7116977]
19. Installe E, Schoevaerdts JC, Gadisseux P, et al. Intravenous amiodarone in the treatment of various arrhythmias following cardiac operations. J Thorac Cardiovasc Surg. 1981; 81:302–308. [PubMed: 7453241]
20. Morady F, Scheinman MM, Shen E, et al. Intravenous amiodarone in the acute treatment of recurrent symptomatic ventricular tachycardia. Am J Cardiol. 1983; 51:156–159. [PubMed: 6401373]
21. James PR, Hardman SM. Acute hepatitis complicating parenteral amiodarone does not preclude subsequent oral therapy. Heart. 1997; 77:583–584. [PubMed: 9227310]
22. Souney PF, Cooper WD, Cushing DJ. PM101: intravenous amiodarone formulation changes can improve medication safety. Expert Opin Drug Saf. 2010; 9:319–333. [PubMed: 20074019]
23. Gallik DM, Singer I, Meissner MD, et al. Hemodynamic and surface electrocardiographic effects of a new aqueous formulation of intravenous amiodarone. Am J Cardiol. 2002; 90:964–968. [PubMed: 12398963]
24. Somberg JC, Bailin SJ, Haffajee CI, et al. Intravenous lidocaine versus intravenous amiodarone (in a new aqueous formulation) for incessant ventricular tachycardia. Am J Cardiol. 2002; 90:853–859. [PubMed: 12372573]
25. Somberg JC, Timar S, Bailin SJ, et al. Lack of a hypotensive effect with rapid administration of a new aqueous formulation of intravenous amiodarone. Am J Cardiol. 2004; 93:576–581. [PubMed: 14996582]
26. Lahbabi M, Aqodad N, Ibrahimi A, et al. Acute hepatitis secondary to parenteral amiodarone does not preclude subsequent oral therapy. World J Hepatol. 2012; 4:196–198. [PubMed: 22761971]
27. Babatin M, Lee SS, Pollak PT. Amiodarone hepatotoxicity. Curr Vasc Pharmacol. 2008; 6:228–236. [PubMed: 18673162]
28. Gluck N, Fried M, Porat R. Acute amiodarone liver toxicity likely due to ischemic hepatitis. Isr Med Assoc J. 2011; 13:748–752. [PubMed: 22332445]
29. Schwartz A, Shen E, Morady F, et al. Hemodynamic effects of intravenous amiodarone in patients with depressed left ventricular function and recurrent ventricular tachycardia. Am Heart J. 1983; 106(4):848–856. Pt 2. [PubMed: 6613831]

Key Points

- Approximately 5% of patients receiving intravenous amiodarone developed elevated serum transaminases.
- Transaminase elevations exceeded 1000 in approximately 15% of patients with elevated transaminases.
- The 30-day mortality among the patients with severe transaminitis (aspartate aminotransferase/alanine aminotransferase >1000 IU/L) was 9% versus 10.2% with mild and 2.5% with moderate transaminitis.
- No patient died of liver failure.

Table 1

Baseline characteristics

Characteristics, n (%)	**n = 77**
Median age (range)	63 (26 – 99)
Male sex (%)	77 (100)
Race (%)	
White	59 (76)
Black	15 (19)
White Hispanic	3 (4)
Medical history (%)	
Ejection fraction <40%	29 (37.6)
Chronic kidney disease	17 (22)
Diabetes mellitus	34 (44)
Coronary artery disease	32 (41)
Hypertension	63 (81)
Hyperlipidemia	44 (57)
Mental health diseases	20 (26)
Chronic obstructive pulmonary disease	12 (15)
Cerebrovascular accident	8 (10)
Autoimmune disorders	1 (1)
Malignancy	12 (15)
Cirrhosis	8 (10)
Chronic hepatitis	27 (35)
Baseline medications (%)	
ACE inhibitor	29 (37)
Acetaminophen	54 (70)
Allopurinol	2 (3)
Angiotensin receptor blocker	3 (4)
Antipsychotic medications	15 (19)
Antiseizure medications	4 (5)
Aspirin/NSAIDs	53 (68)
Buproprion	1 (1)
Calcium channel blockers	12 (15)
Corticosteroids	7 (9)
SSRIs	5 (6)
Statins	32 (41)
Tricyclic antidepressants	1 (1)

ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.

Table 2

Comorbidities among patients receiving intravenous amiodarone

Comorbidity	Transaminitis n (%)*		
	Mild	Moderate	Severe
EF < 40% (n = 29)	15 (51.7)	10 (34.4)	4 (13.7)
CKD (n = 17)	8 (47)	5 (29.4)	4 (23.5)
DM (n = 34)	17 (50)	10 (29.4)	7 (20.5)
CAD (n = 32)	12 (37.5)	13 (40.6)	7 (21.8)
Hepatitis (B or C)	15 (55.5)	9 (33.3)	3 (11.1)

CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; EF, ejection fraction.

*Percentage of group (eg, of those with mild transaminitis).