Acute Amiodarone Liver Toxicity Likely Due to Ischemic Hepatitis

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ABSTRACT: **Background:** Hepatotoxicity due to intravenous amiodarone (HIVAD) is a rare side effect with a distinct pattern of enzyme disturbances compared to liver damage from oral amiodarone. Intravenous amiodarone is administered for acute arrhythmias often causing heart failure. The enzyme abnormalities and clinical setting are very similar to that of ischemic hepatitis, a far more common condition.

Objectives: To ascertain if acute HIVAD exists as a separate entity or whether reported cases may be explained by ischemic hepatitis.

Methods: In this case-control retrospective study the files of hospitalized patients with markedly elevated aminotransferases were reviewed for the diagnoses of HIVAD or ischemic hepatitis. Medline was searched for published cases of HIVAD. Pooled data of all patients with HIVAD were compared to a control group with ischemic hepatitis.

Results: There were no significant differences in the clinical characteristics, laboratory results or histological findings between HIVAD and ischemic hepatitis patients.

Conclusions: In our opinion, there is currently insufficient data to support the existence of distinct HIVAD, and ischemic hepatitis is a more probable diagnosis in most reported cases. Withdrawing amiodarone because of assumed hepatic damage could deprive patients of a life-saving therapy.

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KEY WORDS: amiodarone, hepatotoxicity, liver, ischemic hepatitis

Amiodarone is a widely used anti-arrhythmic drug, not uncommonly causing hepatotoxicity when given as chronic oral treatment. The elevation of enzymes is generally chronic, mild and reversible, and less than 1% of the patients require discontinuation of amiodarone due to clinical evidence of hepatitis, which usually develops after more than a year of therapy. Because of the long half-life of the drug, side effects sometimes persist for months even after drug discontinuation. Typical histological findings include steatohepatitis and phospholipidosis [1,2].

A much rarer liver injury, distinct in nature from that associated with chronic oral use, has been described following intravenous amiodarone administration. This disorder is acute, manifesting within 1–3 days following IVAD with markedly elevated aminotransferase levels, histological findings of centrilobular necrosis, and a potentially fatal outcome [3-12]. In most reported cases, the abnormalities resolved within days after the medication was discontinued. A search of the medical literature revealed 22 cases reported over 20 years.

IVAD is administered in patients with preexisting cardiac disease to treat arrhythmias, which reduce cardiac output and may cause hypotension and organ hypoperfusion. These clinical findings are also typical of ischemic hepatitis, a condition resulting from severe hypoxia to hepatocytes, characterized by acute marked elevations of aminotransferase and lactate dehydrogenase levels, which typically normalize within days following circulatory improvement, and by histological findings of centrilobular necrosis [13].

The diagnosis of ischemic hepatitis is often missed due to the complexity of the patients, as well as to confounding causes of liver damage, such as sepsis and the administration of hepatotoxic drugs. The reported incidence is 0.16–1.5% of hospitalized patients. However, ischemic hepatitis is considered the most common cause of markedly elevated aminotransferase levels in hospitalized patients and is responsible for up to 50% of the cases [14].

Physicians in the acute care setting may be reluctant to administer IVAD, with its potential hepatotoxicity, to patients already prone to biochemical liver disturbances resulting from impaired hepatic blood flow secondary to cardiac compromise. Conversely, IVAD is expected to improve hemodynamic status and liver blood supply, thus being actually therapeutic in these situations.

Due to the similar clinical setting and laboratory findings, we suspected that these two conditions – ischemic hepatitis and hepatotoxicity due to intravenous amiodarone – might easily be interchanged. Because of the extreme rarity of acute HIVAD and the distinct pattern of liver abnormalities in HIVAD compared with oral amiodarone, as well as the much higher prevalence of ischemic hepatitis coupled with unawareness of this diagnosis, we questioned the existence of a distinct HIVAD entity.

*** The first two authors contributed equally to this study**

IVAD = intravenous amiodarone
HIVAD = hepatotoxicity due to intravenous amiodarone

To address this question, we examined the possibility of ischemic hepatitis as an alternative diagnosis for patients diagnosed with acute HIVAD. We show almost complete similarity between HIVAD cases and ischemic hepatitis, thus raising doubt regarding HIVAD as a separate entity.

PATIENTS AND METHODS

We conducted a search of the laboratory database of the Tel Aviv Sourasky Medical Center for all patients admitted between January 2005 and December 2006 with markedly elevated aminotransferases and LDH, namely, aspartate and alanine aminotransferases > 500 U/L, LDH > 1000 U/L. All retrieved files were reviewed for diagnosis of HIVAD as well as for the possible diagnosis of ischemic hepatitis according to the criteria of Gibson and Dudley (1984): marked elevation (above 20 times normal) and rapid normalization of hepatocellular enzyme levels, with no other apparent cause for abnormal liver tests, in the appropriate clinical setting, namely, an acute illness with a reduction of blood pressure or of cardiac output. Histological confirmation is not required by these criteria [13].

To better study the characteristics of HIVAD patients, in light of the rarity of this condition and potential scarcity of HIVAD patients in our search, we sought to expand this group to include published cases with HIVAD. We conducted a Medline search using the key words: amiodarone AND liver, hepatotoxicity, hepatitis, hepatic necrosis, hepatic damage. All cases of acute IVAD-induced liver injury in the English literature during the years 1986–2009 were reviewed and included in the study, including all cases cited in the reference list of the published reports.

The available clinical and laboratory data of all patients with HIVAD (pooled from our records and from medical literature) were compared with a group of control patients matched for age and gender, selected from the subgroup that fulfilled the criteria for ischemic hepatitis in the above database. Statistical comparison used Fisher's exact test for the clinical findings and the paired *t*-test for laboratory findings.

Hypotension was defined as less than 90 mmHg or 60 mmHg systolic or diastolic pressures, respectively, or as mean arterial pressure under 70. When measurements of cardiac index or wedge pressure were not available we used clinical features typical of low cardiac output, including arrhythmias accompanied by pulmonary congestion or edema (demonstrated clinically or radiographically), severe oliguria, cool extremities, syncope, circulatory collapse, need for direct current shock or mechanical resuscitation, gross peripheral edema, jugular venous distension of > 5 cm from sternal angle, positive hepatojugular reflex, or congestive hepatomegaly. Renal deterioration was defined as a rise of more than 0.5 mg/dl of plasma creatinine levels. Time to normalization of enzymes was defined as the earlier event between normal levels and an improvement of 90% (1 log) from peak levels.

The standard RUCAM scoring system for assessing drug causality of adverse reactions was applied to the HIVAD group [15,16]. This score was designed specifically for drug-induced liver injury. Points are assigned according to time to onset from the beginning/cessation of the drug, course of biochemical abnormalities, presence of risk factors for drug-induced liver injury, concomitant confounding drugs, adequate ruling out of various non-drug causes, previous information on the hepatotoxicity of the drug, and response to rechallenge, if performed.

LDH = lactate dehydrogenase

RESULTS

A total of 220 patients with markedly elevated liver enzymes were admitted to our medical center between January 2005 and December 2006. A probable diagnosis of ischemic hepatitis could be made in 116 cases. Other common diagnoses included viral hepatitis, biliary disease and liver infiltration. HIVAD was diagnosed by the physicians in three cases, and Medline revealed 22 additional cases of HIVAD published in the English literature. Twenty-five patients from the ischemic hepatitis group matched the HIVAD patients for age and gender. Baseline characteristics and findings of both groups are summarized in Tables 1 and 2, respectively.

Background congestive heart failure was common in both groups. Also common to both were the clinical findings of hypotension, low cardiac output and renal deterioration. Importantly, in all cases, the episode of hypotension and/or low cardiac output occurred before IVAD administration and therefore was not a result of IVAD therapy.

Baseline aminotransferase levels were normal in all cases but one, with an AST of 200 and ALT of 100. IVAD was administered for 1–3 days in all cases. Both groups exhibited dramatic increases in aminotransferase levels and rapid

AST = aspartate aminotransferase
ALT = alanine aminotransferase

Table 1. Baseline characteristics of patients with HIVAD compared to patients with IH

	HIVAD (n=25)	IH (n=25)	*P* value
Patient age (mean yrs)	64.36	64.0	NA
Gender, male, n (%)	14 (56)	14 (56)	NA
Amiodarone dose (total mg)	1518 ± 816		NA
Background			
Congestive heart failure, n (%)	20 (80)	13 (52)	0.04
Renal failure (creatinine › 1.5), n (%)	7 (28)	8 (32)	0.38
Diabetes, n (%)	9 (36)	8 (32)	0.39

HIVAD = hepatotoxicity due to intravenous amiodarone, IH = ischemic hepatitis

Table 2. Clinical and laboratory findings of patients with HIVAD compared to patients with IH

	HIVAD (n=25)	IH (n=25)	*P* value
Clinical findings (no. of patients)			
Documented hypotension, n (%)	14 (56)	18 (72)	0.26
Low cardiac output, n (%)	18 (72)	19 (76)	0.49
Renal deterioration, n (%)	21 (84)	22 (88)	0.71
Laboratory characteristics (mean peak value ± SD)			
AST	2531 ± 2006	2507 ± 1922	0.29
ALT	2035 ± 1698	1762 ± 1050	0.21
LDH	5271 ± 3221*	4260 ± 2430	0.47
Days to normalization (mean ± SD)			
AST	6.2 ± 3.2	5.2 ± 2.5	0.10
ALT	11.6 ± 2.2	10.3 ± 2.7	0.46
LDH	3.8 ± 1.7	4.7 ± 1.2	0.67

*Data lacking in most published cases

HIVAD = hepatotoxicity due to intravenous amiodarone, IH = ischemic hepatitis, AST = aspartate aminotransferase, ALT = alanine aminotransferase, LDH = lactate dehydrogenase

normalization, with no significant differences between the groups in the enzyme values or normalization time. The time to peak aminotransferase levels from IVAD administration, but also from the acute event of hypotension or low cardiac output state to aminotransferase elevation, was 1–3 days in all cases. Most cases reported clinical and enzymatic improvement 1–2 days after IVAD withdrawal and nearly complete resolution in up to 7 days. In two cases enzyme levels normalized despite continuation of IVAD [6].

A positive rechallenge with IVAD was reported in two cases [7,8]. However, in two other cases, rechallenges with IVAD performed following clinical improvement were negative and resulted in normal liver enzymes [9,17].

Concomitant drugs that could influence IVAD toxicity or cause independent hepatotoxicity in the HIVAD group included acetaminophen, phenytoin, statins, metoprolol, furosemide, propofol, captopril, enalapril and aspirin. Most drugs were taken chronically before presentation.

Based on the above data, we next applied the RUCAM algorithm to the HIVAD group to assess the probability of a causal relationship between IVAD administration and the ensuing biochemical hepatocellular disturbance [15,16], assuming ischemic hepatitis could be an alternative cause for liver toxicity. Table 3 lists the diagnostic criteria of the algorithm met by the HIVAD cases.

Assigning the appropriate points designated by the scoring system to each case, 72% of HIVAD cases would obtain a score of 3 points (maximum 14) ("possible reaction"), 12% would score 2 points ("unlikely"), 8% would score 0 points ("ruled out"), and only 8% would score 6 points ("probable"). Of note, this algorithm relies heavily on a suggestive time-course of improvement when discontinuing the drug; however, this is the exact identical course in ischemic hepatitis.

Table 3. Assessment of HIVAD patients to assess drug causality by RUCAM score

Criteria	Results	No.	Assessment score (points)
Time to onset from beginning of drug	Compatible (< 5 days)	25	1
Course after cessation of drug	Highly suggestive (decrease of peak ALT > 50% within 8 days)	23	3
	Inconclusive (drug continued)	2	0
Risk factor for drug reaction	Age ≥ 55 Age ≤ 55	22 3	1 0
Concomitant drug(s)	None/no information/drug with incompatible time to onset	22	0
	Drug with compatible time to onset	3	-1
Non-drug related causes	Probable	25	-3
Previous information on hepatotoxicity of drug	Reaction published but unlabeled	25	1
Response to rechallenge	Positive Negative Not done	2 2 21	3 -2 0

HIVAD = hepatotoxicity due to intravenous amiodarone, ALT = alanine aminotransferase

A more recent algorithm weighs the same criteria with reference to two groups of senior experts' opinion and provides discrete probabilities of drug causation [18]. When applied to the HIVAD cases, the probabilities are 27%, 38%, and 50% for 24%, 68%, and 8% of the patients, respectively. Thus, 92% of the patients have a probability that is less than neutral.

Liver biopsy was performed in four HIVAD cases. Three demonstrated centrilobular necrosis [11,12], the typical histology for ischemic hepatitis, while one showed atrophy of hepatocytes with a granulocytic and eosinophilic infiltrate [8].

DISCUSSION

HIVAD has been accepted as a distinct cause for acute amiodarone-induced liver damage in major gastroenterology, hepatology and clinical pharmacology textbooks [19-21]. Therefore, the clinician treating patients suffering from acute heart failure and arrhythmia, who often have some degree of liver enzyme elevation, may be faced with the dilemma of whether to administer a drug that could potentially exacerbate liver biochemical abnormalities.

The criteria that could potentially establish a causal relationship between amiodarone and hepatotoxicity are exclusion of other drug- and non-drug-related causes, suggestive time to onset, improvement upon drug withdrawal, positive rechallenge, presence of risk factors for drug hepatotoxicity,

and the reaction being documented and labeled. Different algorithms are provided to determine the probability for a causal relationship between a drug and an adverse effect according to these criteria [15,16,18].

We suggest that most of the patients' findings could be explained by ischemic hepatitis, since the HIVAD patients fulfilled all the criteria required for diagnosis of ischemic hepatitis, at a similar or even increased incidence compared to the ischemic hepatitis group: an acute, marked elevation in aminotransferases, with rapid normalization upon circulatory improvement [22], decompensated heart failure, hypotension, low cardiac output and renal deterioration. Although liver histology is not required for the diagnosis of ischemic hepatitis, centrilobular necrosis – the characteristic finding in ischemic hepatitis – was present in the HIVAD group where histology was available.

Congestive heart failure was a common background diagnosis in both groups, more so in the IVAD group. This difference is understandable since IVAD is administered primarily to patients with known heart disease and arrhythmias, whereas ischemic hepatitis occurs in patients with acute liver hypoxia from various etiologies [23-25].

Some authors describing HIVAD rejected the possibility of ischemic hepatitis due to lack of documented hypotension. However, a very brief, easily overlooked hypotensive episode – 15 minutes – has been shown to be sufficient for causing ischemic hepatitis [23]. Numerous cases of ischemic hepatitis in the absence of bona fide hypotension have been reported, involving other causes of transient liver hypoperfusion, such as hypoxia, anemia or arrhythmias causing decreased cardiac output and relative hypotension, superimposed on right-sided heart failure with hepatic congestion [13,24,25].

The time to onset in most HIVAD cases (1–3 days), although compatible with a drug cause, is not suggestive of it [15]. However, it is highly indicative of ischemic hepatitis, which typically occurs acutely [13]. Age, considered a predominant risk factor for drug hepatotoxicity in these reported cases, is also a risk factor for ischemic hepatitis [23].

Most cases report rapid enzymatic improvement upon IVAD withdrawal. This is despite a drug half-life of 15–100 days and in contrast to hepatotoxicity from oral amiodarone which may consequently persist for months. We suggest that concurrent improvement in cardiovascular status and liver perfusion causes resolution of ischemic hepatitis and is responsible for this rapid improvement. This may also explain why in some cases enzyme levels normalized despite continued IVAD [6], while in others rechallenge with IVAD after circulatory improvement was negative [9]. Although rechallenge was positive in two cases [8,9], retreatment in both was due to recurrent arrhythmia, which may have caused an additional bout of ischemic hepatitis.

According to the algorithms we applied for causality assessment of drug-induced injuries, the vast majority of HIVAD cases would obtain a score of "possible drug reaction" at the most, or if quantified less than 50%.

A potential mechanism of HIVAD could be liver ischemia due to hypotension or an unknown mechanism. This would make the distinction between HIVAD and ischemic hepatitis very difficult, and perhaps discontinuation of IVAD appropriate. We cannot completely rule this out; however, in the clinical setup of arrhythmia causing decreased cardiac output, amiodarone is much more likely to improve liver perfusion, rather than worsen it, by correcting the rhythm problem and the cardiac output. In addition, when documented, hypotension always preceded IVAD administration rather than being a result of the drug administration.

Our study has several shortcomings. First, it was retrospective; therefore, not all the required data were available for all patients. Second, due to the small number of cases in our search, we had to broaden the group by including published cases, which provided less detailed data. Lastly, objective measurements of low cardiac output were lacking in many cases, requiring us to rely on clinical features.

In conclusion, medical background, clinical characteristics, and laboratory and histological findings in almost all cases with supposed HIVAD were strikingly similar to those with ischemic hepatitis. Presumptive HIVAD is exceedingly rare, while ischemic hepatitis is the most common cause of markedly elevated aminotransferases, particularly in patients with chronic cardiovascular illnesses. Given that HIVAD by an ischemic or other mechanism cannot completely be ruled out, it is our opinion that a patient presenting with an arrhythmia and acute low cardiac output, who develops a rise in aminotransferases after receiving IVAD, is much more likely to have ischemic hepatitis than HIVAD. Correcting the arrhythmia with IVAD treatment may increase liver blood flow and ameliorate ischemic hepatitis. Thus, reluctance on the part of the clinician to use amiodarone, or withdrawal of the drug when biochemical liver abnormalities appear, could deprive patients of an important and sometimes life-saving therapy. The possible risk and benefit of continuing or discontinuing amiodarone should be weighed in every case.

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