Amiodarone Hepatotoxicity in the Context of the Metabolic Syndrome and Right-sided Heart Failure

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Abstract

Background: Amiodarone is associated with varying degrees of hepatotoxicity. **Aims**: to study the association between the presence of the metabolic syndrome or right-sided heart failure and the prevalence of amiodarone induced liver disease. **Methods:** Retrospective chart review of patients who received amiodarone for ≥60 days at a university affiliated community hospital. We collected information about clinical progression and liver chemistries on 409 included patients. Subgroup analysis was based on the presence or absence of right-sided heart failure and the metabolic syndrome. **Results**: The 409 patients (58% male, 55% Caucasian) had a mean age of 62 years, mean follow up of 37.6 months and mean cumulative amiodarone dose of 295±404 grams. No subjects developed clinical hepatitis, cirrhosis or death related to amiodarone. Eight patients developed amiodarone hepatotoxicity, 5 required discontinuation and 3 required dose reduction of the medication with resolution of the transaminitis in all. No differences in liver chemistries at follow up between patients with or without the metabolic syndrome and with or without right cardiac dysfunction were noted. **Conclusion**: Administration of amiodarone was associated with a low incidence of hepatotoxicity without relationship to cumulative dose. The presence of the metabolic syndrome or right-sided heart failure does not increase the incidence of amiodarone hepatotoxicity.

Keywords

Amiodarone – liver – drug-induced hepatitis – metabolic syndrome – congestive heart failure.

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Introduction

Amiodarone has widespread applications in the treatment of supraventricular and ventricular tachyarrythmias [1, 2]. The chronic use of amiodarone is associated with varying degrees of hepatotoxicity. In most cases, the liver injury is limited to an asymptomatic transaminitis (4 to 50%) which resolves spontaneously or after dose reduction [3-8]. Rarely (0 - 3%) has amiodarone caused severe disease including liver failure or death [3, 4, 9]. Recommendations have been issued to monitor the hepatic enzymes levels on a regular basis [3, 10, 11]. Cardiac patients who receive amiodarone have a high prevalence of cardiovascular risk factors including the metabolic syndrome that has been associated with Non Alcoholic Fatty Liver Disease (NAFLD) and Non Alcoholic Steatohepatitis (NASH) [12-14]. Also this population has a high frequency of congestive heart failure (CHF) that may lead to hepatic congestion and similarly cause liver chemistries abnormalities. The aim of this study was to characterize the prevalence of amiodarone hepatotoxicity in a cohort receiving chronic amiodarone therapy, and to determine if the presence of the metabolic syndrome or right-sided heart failure predicts a higher incidence of liver chemistries abnormalities and hepatic complications in the context of amiodarone therapy.

Patients and Methods

We retrospectively reviewed the electronic medical record database at Wishard Memorial Hospital, Indianapolis, IN. We identified 1,021 patients who were prescribed amiodarone at our institution between January 1994 and December 2005. Six hundred and twelve patients were excluded due to treatment duration less than 60 days, incomplete baseline information, or imprecise amiodarone regimen. We collected and analyzed three types of datasets on the remaining 409 patients.

A main dataset included: 1) clinical progression (hepatitis, cirrhosis, or death); 2) radiological characteristics of the liver (abdominal computed tomography (CT), ultrasound (US) and magnetic resonance imaging (MRI); 3) co-

morbidities (alcoholism, diabetes mellitus, hypothyroidism, hypertension, CHF, chronic liver disease); 4) body mass index (BMI); 5) HDL and triglycerides (TG) levels; 6) left and right ventricular functions, and 7) degrees of right atrial dilation, tricuspid regurgitation and stenosis if any. In a second dataset we recorded the monthly dosing of amiodarone in every patient, and we followed any changes in the dosing from the date of the first prescription until the date of discontinuation. The discontinuation could be due to adverse effects, a decision from the cardiologist or death. The initial loading dose during hospitalizations was not accurate in most cases and was not counted in our study. In a third dataset we recorded the levels of ALT, AST, bilirubin, albumin, alkaline phosphatase, and platelets at baseline (before amiodarone administration) and during the entire period of amiodarone use.

Subgroups were categorized as follows: Patients with moderate or severe right atrial dilation, right ventricle (RV) dysfunction (visual or based on an RV ejection fraction (EF) ≤30%), tricuspid regurgitation or stenosis were considered to have right-sided heart failure. Patients with 3 or more features of the metabolic syndrome (diabetes mellitus, hypertension, TG≥150 mg/dL, HDL<50 mg/dL for women and <40 mg/dL for men, or BMI≥30 Kg/m^2) were considered to be in a group at risk of NAFLD and NASH (not biopsy proven). The number of times liver tests were determined in each group was controlled for in the analysis. The study protocol was approved by the Indiana University Institutional Review Board.

Statistics

The cumulative amiodarone dose for every patient was used to create 4 categories of patients (1 to 4). Thresholds for every category were based on keeping the numbers of patients similar among the 4 categories. In addition, units of cumulative dose in increments of 5000 mgs were expressed as Cumulative Dose Increments (cumulative dose divided by 5000 rounded to the nearest lower integer). Analysis used continuous values for cumulative dose increments: laboratory values were followed from the amiodarone start date until 3 months after the discontinuation date. The upper 2.5 % of the data was excluded for each laboratory test to eliminate extreme values, which occurred during acute illnesses. All tests were conducted as two-sided at alpha=0.05 significance level. Analysis was performed in SAS version 9. Distributions of laboratory values were examined for and met assumptions of normality. Means ± standard deviation were reported. Medians were reported for skewed data distributions. Linear regression was used to evaluate the association of laboratory values with amiodarone cumulative dose, or metabolic syndrome, or right-sided cardiac function. Eject fraction data were analyzed using Mann-Whitney U-test. Kaplan-Meier survival analysis was used to estimate median survival.

Results

The 409 patients included 236 (58%) male, 225 (55%) Caucasian and 169 (41%) African American. Mean age was 62 years (range 21-97), and mean duration of follow up 38 ± 39 months (range 2 - 220 months). The mean cumulative dose of amiodarone was 295 ± 404 grams (range 13 – 4756 grams). Median survival age was 69 years (95% CI: 57-90). The mean left ventricle EF was lower than normal at 42 ± 18%. Mean lowest HDL levels was 37.7 ± 12.7 mg/dl and mean highest TG levels was 301 ± 550 mg/dl (median=177). Table I reports the distribution of our sample based on the cutoff points for right-sided heart failure and the metabolic syndrome.

Table I. Distribution of subgroups with or without metabolic syndrome

Parameter	Frequency (%)
Diabetes Mellitus N=409	214 (52%)
Hypertension N=409	355 (87%)
Triglyceride (TG) ≥150 N=327	191 (58%)
High Density Lipoprotein (HDL) ≥40 (men) or ≥ 50 (women) N=312	89 (29%)
Body Mass Index (BMI) ≥30 N=376	180 (48%)
Patients with the metabolic syndrome* N=342	253/342 (74%)
Presence of right-sided heart failure** N=409	109/409 (27%)

*At least 3 of diabetes mellitus, hypertension, TG≥ 150mg/dL, BMI ≥30, or HDL ≥40mg/dL (men) or ≥ 50mg/dL (women) or **right-sided heart failure (at least one of moderate or severe: tricuspid regurgitation, tricuspid stenosis, right atrial dilation, or right ventricule (RV) dysfunction visually, or an RV ejection fraction (EF) ≤ 30%.

Sixty five (16%) patients had a history of chronic liver disease prior to amiodarone administration or on follow up developed increased liver enzymes during various periods of time. Among the 65 patients, 4 had cirrhosis at baseline and 2 others developed cirrhosis during follow up. Two hundred and four (50%) patients were on simvastatin during their course of amiodarone. No subjects developed clinical hepatitis, cirrhosis or death related to amiodarone administration. Eight patients (2 %) developed amiodarone - induced transaminitis with ALT levels ranging from 36 to 339 IU/L; in 5 patients it required discontinuation of amiodarone, and in the remaining 3 it required dose reduction. In all 8 cases the transaminitis resolved. Three of the 8 patients had ALT (36 and 44 IU/ml) or AST (92 IU/ml; ALT not available) levels that ranged below 3 times the upper limit of normal, and in whom the dose was either reduced (2 cases) or discontinued (1 case) just due to concerns of rising enzymes. The mean EF was available for 5 patients among those who developed the transaminitis and was 60 ± 5 %, which was higher than the EF of 41 ± 18 % for the rest of the sample (p=0.02).

When the 4 groups of cumulative dose were compared, we did not find any significant difference for ALT (N=278, p=0.17), AST (N= 323, p=0.69), and platelets (N= 291, p=0.28) levels. There was an inverse association with bilirubin values (N=316, p=0.02). Linear regression using

Table II. ALT levels among patients distributed per cumulative doses of amiodarone, and per presence or absence of right-sided heart failure or the metabolic syndrome

Amiodarone cumulative dose categories	Non right-sided heart failure group mean ALT N		Right-sided heart failure group mean ALT N		Non-metabolic syndrome group mean ALT N		Metabolic syndrome group mean ALT N	
1	41	37.73±28.19	27	36.74±30.93	11	32.18±42.82	42	34.10±18.12
2	56	41.64±40.64	13	55.92±35.99	19	48.11±37.94	38	38.18±29.75
3	52	31.42±19.61	22	31.95±13.77	11	26.09±15.85	52	32.44±16.89
4	51	35.41±27.96	16	30.88±23.51	18	25.89±17.41	39	36.97±30.36

Distribution among cumulative doses categories from 1 to 4 is based on keeping the numbers among the 4 groups similar. There were no significant differences between horizontal (p=0.17) or vertical categories (p=0.12).

cumulative dose increments showed that ALT (p= 0.23), AST (p= 0.35), bilirubin (p= 0.33) and platelets levels (p= 0.15) were not associated with cumulative dose increments. The patient with the highest cumulative dose was an outlier and was excluded based on leverage diagnostic h>0.4. Also there were no significant differences in ALT (p=0.82), AST (p=0.73), bilirubin (p=0.70) or platelets (p=0.72) levels between patients with or without the metabolic syndrome. Similarly the presence of right-sided cardiac failure did not significantly affect ALT (p=0.86), AST (p=0.50), bilirubin (p=0.15) or platelets (p=0.15) levels. Table II shows the distributions based on cumulative doses categories and subgroups. There were no differences in the frequency of follow up testing, prevalence of alcohol consumption or viral hepatitis among the subgroups.

Discussion

Long-term amiodarone administration is well known to cause a full spectrum of hepatic manifestations from benign increases in aminotransferases levels to fatal hepatitis and cirrhosis. The mechanism of injury is not fully elucidated. Phospholipidosis is a morphological alteration that is a marker of the accumulation of the drug, which may be independent of the biological alterations seen with amiodarone administration [15-17]. Amiodarone impairs the mitochondrial β-oxidation and uncouples the oxidative phosphorylation. This induces microsteatosis, apoptosis and necrosis of the hepatocytes [18-20]. The current recommendation is to monitor patients on a regular basis. If enzyme levels increase beyond three times the upper limit of normal or beyond two times the initial aminotransferase level in patients with an elevated baseline, then amiodarone has to be reduced or stopped [3, 10, 11].

The prevalence of amiodarone hepatotoxicity in our group is in the same range as a recent meta-analysis of four placebo-controlled studies that included 738 patients randomized to amiodarone and 727 randomized to placebo. The incidence of adverse hepatic effects of 1.2 % in the amiodarone group was not statistically different from the 0.8% observed in the placebo group [21]. We did not observe any case with clinical manifestations of liver injury or serious outcomes due to amiodarone.

Bilirubin levels were lower in patiens in the highest cumulative doses categories. This could be explained by the optimization of the cardiac function after initiation of amiodarone and the resulting improvement in congestive hepatopathy and hepatic perfusion in some patients. Otherwise, liver enzymes and platelets levels were similar among all groups and did not correlate with the increase in the cumulative dose.

This is not surprising since exposure risk is only related to cumulative dose during the loading phase, prior to reaching steady state. Thereafter, degree of exposure is related to dosing rate and individual patient absorption profile. For example, risk goes down when dosing rate is reduced, a situation that often occurs during long-term therapy at a time when cumulative dose is high. Prospective studies showed that amiodarone hepatic toxicity correlates to steady state serum levels of amiodarone rather than daily or cumulative doses [3, 10, 11, 22]. Pollak et al, in two prospective studies showed significant hysteresis between changes in amiodarone concentration and the resulting change in ALT. This means that, given the 55-day half-life of amiodarone, changes in dose produce a slow change in serum concentration which have an even longer lag in producing tissue effects on liver chemistry, whether up or down. Since cumulative dose can only go up, it cannot correlate with the stable or declining liver chemistry values seen with lower serum concentrations. [3, 10, 11].

Furthermore, the presence of the metabolic syndrome or right-sided heart failure did not predict higher liver chemistries profiles.

Lewis et al reported in a combination of several large series that 23% (range 14 to 82%) of patients on amiodarone had mild transaminitis, and 0.5% developed clinically overt hepatic disease [4]. In previous reports with a high incidence of amiodarone hepatotoxicity, the diagnosis was not confirmed by biopsy [4-8, 10, 22, 23], nor was the etiological evaluation of the transaminitis reported [4-8, 22]. Histological features of amiodarone deposition are very diverse, common, and do not correlate well with the degree of liver injury, making a diagnosis of amiodarone hepatotoxicity difficult [4, 6, 15, 16, 24]. Similarly, at the radiological level, in our study and in others (25) there was no correlation between the finding of amiodarone deposition

in the liver and the increase in hepatic chemistries.

Many patients with mild liver chemistries elevation normalize while still on the same dose of amiodarone [3, 6]. Our data suggests that most of the elevations in liver chemistries seen in these patients are due to acute exacerbations of their medical conditions (e.g. heart failure), rather than to amiodarone hepatic toxicity. In most cases, when the acute illness resolved, the transaminitis returned to normal while patients were still on the same dose of amiodarone. Kum et al noted that 50% of patients with increased enzymes while on amiodarone did not improve after 1.5 years of withdrawing the drug, and suggested that these patients may have underlying hepatic disease different from amiodarone hepatic toxicity as has been noted by others [5-8, 16].

Based on our study and others [3, 10, 11], it does not seem that the cumulative dose has a major impact on the prevalence of amiodarone hepatotoxicity. Withdrawing the medication should only be done in very rare instances, after all other etiologies of hepatitis have been ruled out. When needed, a liver biopsy may help distinguish the underlying etiologies of hepatitis in a cardiac patient on amiodarone [4].

There are of course limitations to our study. Due to the retrospective nature of our review, we relied on risk factors for NAFLD, NASH and congestive hepatopathy rather than a confirmed pathological diagnosis. The same limitation applies to the diagnosis of amiodarone hepatotoxicity, where assumptions were made by the treating physicians, and no biopsy confirmed the diagnosis. We had many patients without complete evaluation of their hepatitis, which may have missed cases of amiodarone hepatotoxicity. Finally, some patients lacked testing of their liver chemistries at regular intervals, thus transient elevations could have been missed.

Conclusions

In our cohort, amiodarone hepatotoxicity was a rare event. Amiodarone seems to be safe to be administered in patients with metabolic syndrome as well as those with evidence of right-sided heart failure. As amiodarone hepatotoxicity remains a diagnosis of exclusion, any increase in liver enzymes in patients on amiodarone should be investigated before considering amiodarone as the etiology. In cases where amiodarone is suspected, continuation or dose reduction may be sufficient to allow the hepatitis to resolve. Discontinuation of amiodarone should be a very rare occurrence.

Conflicts of interest

None to declare.

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