



Baseline Testing for Amiodarone Toxicity and Major Clinical Events

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Abstract

Background/Objectives: Strategies to ensure safe long term amiodarone use include the baseline performance of lung, liver and thyroid studies at drug initiation. In this analysis we sought to determine if guideline-based recommendations for baseline lung, liver, and thyroid function tests are being performed, and reduce mortality or time to first hospitalization.

Methods: Analysis of hospital records from January 2010 to December 2015 in a single center University Hospital.

Results: The study included 801 patients. The most common indication for amiodarone was atrial fibrillation (73.4%, n=578). Lung testing was assessed in 90.6% (n = 725), thyroid function in 53.9% (n=432), and liver function in 83.4% (n=668) at baseline. Group A (n=392, 48.9%) had all three organ system assessed within three months of initiation of amiodarone, and Group B did not. Compared to Group B, Group A had more heart failure (61.5% vs. 42.1%, p<0.001), thyroid disease (33.7% vs. 16.4%, p=0.001), and current alcohol use (4.1% vs. 1.2%, p=0.014) but had less hypertension (53.8% vs. 62.8%, p=0.010) and hyperlipidemia (52.6% vs. 60.4%, p=0.025). In 90 days after discharge 64 (15.6%) Group A patients died compared with 53 (13.4%) in Group B. In a propensity analysis to adjust for baseline differences, Group A patients had a shorter median time to first hospitalization (209 days + 148 vs. 789 days + 618, p<0.0001) than Group B. Drug discontinuation at 90 days was comparable (40.5% vs. 34.9%, p=0.137).

Conclusion: Performance of baseline studies to monitor long-term amiodarone safety does not reduce early mortality or major clinical outcomes. Other strategies to monitor amiodarone toxicity should be considered.

Keywords

Amiodarone; Drug Toxicity; Baseline Testing

Introduction

Amiodarone is a commonly used antiarrhythmic medication with over three million prescriptions written yearly in the United States[1]. It is of established value in patients with cardiac arrest [2] and Haemodynamically unstable ventricular arrhythmias [3]. It is considered first line therapy for recurrent ventricular fibrillation or pulse less ventricular tachycardia in Advanced Cardiac Life Support (ACLS) algorithms [4]. It reduces the frequency of implantable cardioverter defibrillator (ICD) shocks in patient with life threatening ventricular arrhythmias[5,6]. Amiodarone prophylaxis reduces atrial fibrillation, ventricular arrhythmias, stroke, and length of stay in patients undergoing cardiac surgery [7]. It was the most effective and most commonly used rhythm control agent in The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study [8]. Although not specifically approved for use by the Food and Drug Administration for patients with atrial fibrillation, it is used in approximately 11% of patients with atrial fibrillation worldwide[9]. Amiodarone has multiple and potentially serious side effects. Elevation in liver transaminases occurs in about 15% of patients [10] but is often only transient. However, histologic evidence of hepatic necrosis has been reported with only minor abnormalities in liver function tests [11]. Amiodarone lung toxicity occurs in 2-5.8% of patients [12,13] and seems related to the dose and duration of amiodarone uses[14] although deaths have occurred within only weeks or months of exposure[15,16]. Amiodarone may cause hypothyroidism or hyperthyroidism, both conditions with important impacts on patients with cardiac arrhythmias. Optic neuropathy is associated with amiodarone [17] and is infrequent (0.3%) but insidious in onset (18), and blindness might be prevented by prompt discontinuation of amiodarone.

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Due to these potentially serious adverse effects, it is believed that laboratory or radiologic imaging can predict the early development of serious side effects related to amiodarone. It is recommended that, at minimum, baseline studies including liver function tests, thyroid function tests (TSH, free T4 and total or free T3), a CXR, and pulmonary function tests (with diffusing lung capacity) be performed when amiodarone is initiated[19-21]. For patients with visual abnormalities, a baseline ophthalmologic evaluation is also recommended. Despite these recommendations it is unclear if the acquisition of baseline tests to prevent amiodarone toxicity reduces mortality or major morbidity. The purpose of this analysis is to

- Determine the frequency in which recommended baseline safety testing is performed during the inpatient initiation of amiodarone in a single center University Hospital and
- Determine if the performance of selected baseline testing results in a reduction of mortality or major clinical events.

Methods

The project was approved by the University of Missouri Institutional Review Board

Patients admitted to the University of Missouri Hospital between January 2010 and December 2015 were eligible for this study if amiodarone was not listed on the admission medication list but was listed on the discharge medication list. Data were obtained from Cerner's PowerChart database (Cerner Millennium) and GE's billing database (GE IDX).

Baseline demographic information was obtained. Special attention was directed to the performance of several key baseline safety studies. For liver disease, this included the performance of a comprehensive metabolic panel. For thyroid disease, this included the performance of any thyroid testing including TSH, free T3 or free T4. For pulmonary disease, this included the performance of either a CXR, pulmonary function testing with diffusing lung capacity (DLCO), or chest CT scan. If liver, thyroid, and lung function tests were all performed within three months of the initiation of amiodarone, the baseline assessment was considered to be complete. All other patients were considered to have an incomplete baseline assessment. The frequency of obtaining a comprehensive ophthalmologic examination within three months of the initiation of amiodarone was also collected. The duration of amiodarone use and outcome data were assessed. If amiodarone was initiated and listed at the next patient encounter, it was assumed to be used for the entire interval. If discontinued, particular attention was paid to the reason for discontinuation.

The primary outcome of this study was all cause mortality. Patients who died in our facility were flagged as deceased through GE IDX. Patients who died outside our facility are identified either by family contact to the physician or by regular screening by hospital personnel of obituaries and by phone call in the event of a missed appointment. Additionally, the Medical Records Department provides updated mortality information when obtained. Because many deaths occurred outside of the hospital and access to important details just prior to death were not available, secondary classification into cardiovascular (CV) or non-CV deaths was not attempted. Secondary outcomes included all-cause hospitalizations along with total CV and non-CV hospitalizations. Hospitalizations for CV or non-CV causes were adjudicated by the authors based on established criteria[22]. A hospitalization was considered cardiovascular if the discharge diagnosis was coded for any of the following: arrhythmia (ventricular or atrial), angina or chest pain, acute systolic or diastolic heart failure, cardiomyopathy, hypertension or orthostatic hypotension, aortic or pericardial disease, cardiac arrest, myocardial infarction, coronary artery disease, valvular disease, cardiogenic shock, or stroke.

Kaplan-Meier methods were used to estimate survival time and time to first readmission. The log-rank test was used for comparisons of the time-to-event distributions. Survival times for patients who did

not die were censored at the time of their last visit. The complete and incomplete testing groups differ in statistically significant and clinically meaningful ways that could be expected to impact the study outcomes. To isolate the impact of baseline testing, propensity methods were used to select a subset of patients who were well matched with respect to demographics and medical conditions. In this application, the propensity score is the probability of a patient being in the complete testing group, given their comorbidities. Logistic regression was used to fit the propensity model and the propensity score was then used as the matching variable with a greedy 1-1 matching algorithm. The standardized difference along with statistical testing was used to evaluate the degree of imbalance between the two groups. An absolute standardized difference of 0.1 or greater was used as an indicator imbalance. (26) In estimating duration of amiodarone use it was assumed that for patients without a discontinuation order, amiodarone was continued until readmission, death, or last follow-up visit. The distribution of time on amiodarone is highly skewed and so the median along with a 95% confidence interval for the median is reported rather than the mean and standard deviation.

Results

A total of 801 patients met entry criteria for this study. The most common indication for amiodarone was atrial fibrillation (73.4%). Location and route of administration were obtained to help assess the severity of clinical illness. The majority of amiodarone initiation ($n = 528$, 65.9%) occurred in the non-ICU setting. Approximately 273 patients (34.1%) were started on amiodarone in the ICU out of which 118 patients (43.2%) received intravenous amiodarone. The mean duration of follow-up was 685.5 days, 711 days in the complete group and 665 days in the incomplete group. Of note, no follow-up at our institution was provided in 105 patients. The performance of baseline studies, as recommended by professional guidelines, was low in our study. Only 3.6% of patients who began amiodarone therapy had an ophthalmologic evaluation within three months of drug initiation. Liver function tests were obtained in 83.4% ($n=668$) of patients, a thyroid function test was performed in 53.9% ($n=432$) of patients, and lung imaging (CXR or chest CT) or PFTs were assessed in 90.6% ($n= 725$) of patients (Figure 1). Only 392 (48.9%) patients had what was considered a complete baseline evaluation as recommended by consensus documents including the performance of liver, thyroid and lung testing. The baseline demographic data of the patients who were considered to have complete baseline data ($n=392$) as well as those with incomplete baseline data ($n=409$) is shown in Table 1. Patients with complete baseline data were less likely to have hypertension (53.8% vs. 62.8%, $p=0.010$) and hyperlipidemia (52.6% vs. 60.4%, $p=0.025$). These patients were more likely to have heart failure (61.5% vs. 42.1%, $p<0.0001$), have current alcohol use (4.1% vs. 1.2%, $p=0.014$) and have thyroid disease (33.7% vs. 16.4%, $p<0.0001$). Patients were more likely to have complete evaluations if they had atrial fibrillation (76.8% vs. 70.2%, $p=0.034$) or ventricular arrhythmia (24.7% vs. 6.8%, $p<0.0001$).

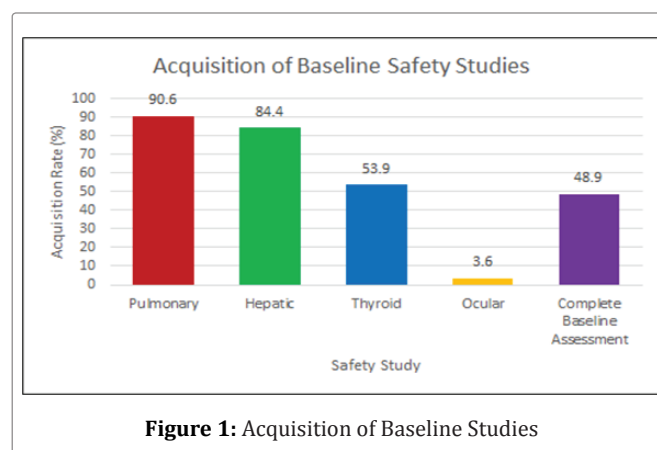


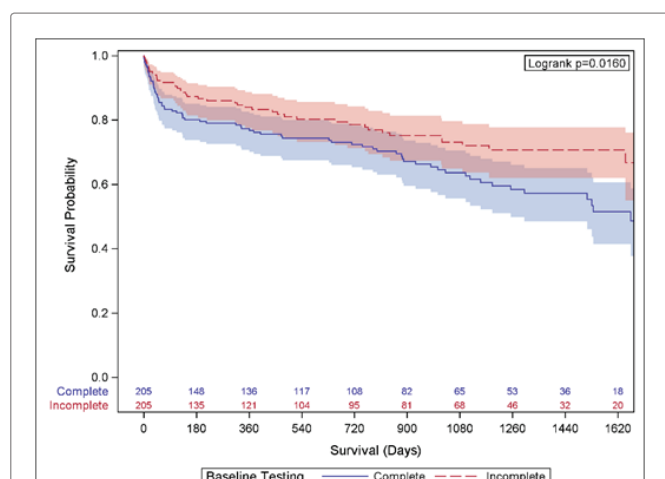
Figure 1: Acquisition of Baseline Studies

	Complete (Group A) (N=392)	Incomplete (Group B) (N=409)	P-value
Age1	69	70	0.357
BMI1	30.7	30.4	0.519
Male (%)	62.8	62.3	0.905
Risk Factors (%)			
Diabetes	32.7	29.8	0.389
Hypertension	53.8	62.8	0.01
Hyperlipidemia	52.6	60.4	0.025
Coronary Artery Disease	20.7	24.7	0.174
Myocardial Infarction	15.3	16.9	0.547
Coronary Artery Bypass	0	0.2	0.063
Peripheral Artery Disease	2.6	1.2	0.166
Stroke2	3.6	1.7	0.122
Heart Failure	61.5	42.1	<0.0001
Liver Disease2	3.6	1.7	0.122
Thyroid Disease	33.7	16.4	0.0001
COPD2	2	2.4	0.813
Ocular Disease	1.3	1	0.748
Alcohol Use2	4.1	1.2	0.014
Non-Skin Malignancy	13	15.9	0.247
Indication			
Atrial Fibrillation	76.8	70.2	0.034
Ventricular Tachycardia	24.7	6.8	<0.0001
Premature Ventricular Contraction	0.8	0	-
Pacemaker	8.9	6.8	0.274
Defibrillator	14.3	8.8	0.015

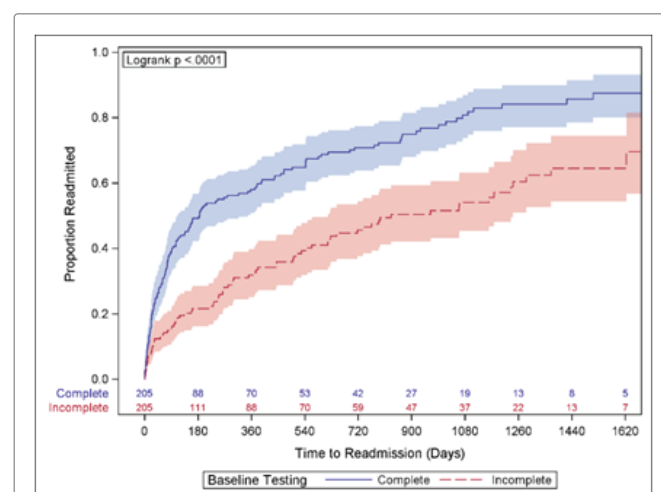
¹Fisher's Exact Test²Wilcoxon Signed Rank Test**Table 1:** Baseline Characteristics

Early mortality and the rate of early amiodarone drug discontinuation were high. In the first 90 days after discharge a total of 117 (14.6%) patients died, 64 (16.3%) in the group with complete baseline assessment and 53 (12.9%) in the group with an incomplete baseline assessment. The discontinuation rate of amiodarone in the first 90 days after discharge was 109 (40.5%) patients with complete baseline assessment and 147 (34.9%) (p=0.137) in the incomplete group. Many of the patients in whom amiodarone was discontinued early were due to planned short-term use post-operatively in the setting of cardiovascular surgery or no reason for discontinuation was documented. Overall mortality during the entire evaluation period was also found to be high at 23.6% (n=189). Four of the 189 deaths could be linked to amiodarone use. The overall rate of amiodarone discontinuation during the entire evaluation period was 20.8% (n=167). The reasons for discontinuation are detailed in Figure 4. The most common cause of discontinuation was failed therapy (n=30) followed by pulmonary (n=23), thyroid (n=16), and hepatic (n=13) causes. Only 2 patients (1.2%) had severe visual impairment or optic neuritis leading to discontinuation of therapy. Patients with pulmonary complications had amiodarone discontinued on average of 441+ 369.5 days after starting therapy, liver complications averaged 461+ 464.1 days until discontinuation, and thyroid complications 409+ 461.1 days until discontinuation. The first hospitalizations after amiodarone initiation were categorized as CV and non-CV causes. A total of 1078 firstre-hospitalizations were identified out of which 358 (33.2%) were CV and 720 (66.8%) were non-CV. Of the total re-hospitalizations, at least 15 were identified as amiodarone related causes for admission. Non-CV readmissions that were potentially related to amiodarone toxicity include: hepatic (n=5), thyroid (n=6), pulmonary (n=2), ocular (n=1), and drug interaction with warfarin leading to bleeding (n=1). CV readmissions were further subdivided into specific causes, outlined in Table 2.

Using a propensity analysis to adjust for baseline differences, patients with complete baseline testing had a shorter median time to first hospitalization (209 days +148 vs. 789 day + 358, p<0.0001) and a shorter mean time to death (1182 days +42 vs. 1321 +36, p=0.0002) than those with incomplete data (Figure 2 &3). The duration of amiodarone use was different between those with complete and incomplete baseline assessment. For those with complete baseline data, the mean duration of amiodarone use was 385.8 +469.4 days. Excluding the 189 patients who died, the mean duration of use was 463.9 +513.4 days. For those with incomplete baseline data, the mean duration of amiodarone use was 503.6 +

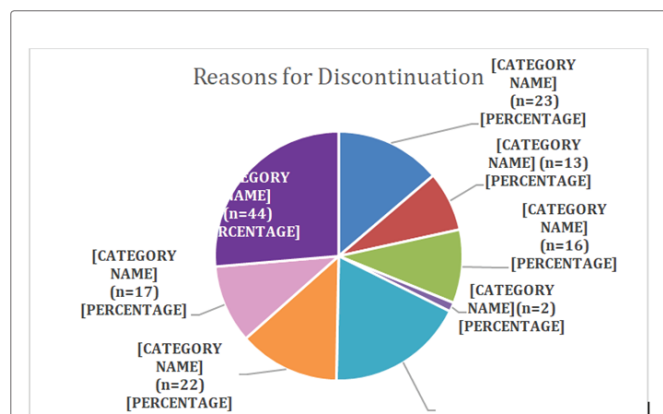
**Figure 2:** Time to Death, Propensity Analysis

Kaplan-Meier estimates of survival time following initiation of amiodarone for patients with complete and incomplete baseline testing. Mortality is all-cause and estimates are based on a propensity matched sample. Shaded regions are 95% confidence bands.

**Figure 3:** Time to Readmission, Propensity Analysis

Product-limit estimates of time to first readmission following initiation of amiodarone for subjects receiving complete and incomplete baseline testing in a propensity-matched data set. The curves are the cumulative probability of readmission and the shaded regions are 95% confidence bands.

Heart Failure	154
Arrhythmia	134
Myocardial Infarction	27
Stroke	18
Angina	11
Cardiogenic Shock	4
Coronary Artery Disease	3
Orthostatic Hypotension	3
Pericarditis	1
Valvular Disease	1
Non-Cardiovascular	720

Table 2: Reason for Hospitalization**Figure 4:** Reasons for Amiodarone Discontinuation

Other: failed therapy (n=30), reason for discontinuation not documented (n=16), normal sinus rhythm (n=14), patient refused (n=4), rate control strategy (n=4), left atrial appendage clot (n=2), drug interaction (n=2), polymorphic ventricular tachycardia (n=1), cost (n=1)

Side effect: erectile dysfunction (n=1), reaction with Coumadin (n=1), bradycardia (n=1), peripheral neuropathy (n=1), muscle weakness (n=3), confusion (n=1)

538 days. Excluding those who died, the mean duration of use was 566.2 + 563.1 days. Consequently, to evaluate the possibility that the results might be affected by discontinuation of amiodarone in the two groups, an analysis was performed to assess amiodarone use at the time of death. Of the 189 patients who died, amiodarone was present at the time of death in 44% of the complete baseline group and 50% in the incomplete baseline group. The difference were not statistically significant ($p=0.425$).

Discussion

In this study of hospitalized patients given amiodarone predominantly for atrial arrhythmias there were two main findings:

- Baseline data used to assist in monitoring amiodarone toxicity, as recommended in published guidelines, was incompletely obtained, and
- The performance of complete baseline safety data did not reduce early major clinical endpoints including mortality or time to first hospitalization.

Liver, thyroid and lung testing is recommended at initiation of amiodarone. However, only 49% of patients in this analysis had baseline liver, thyroid, and pulmonary testing. Previous studies have shown inconsistent monitoring for amiodarone toxicity [24-26] which might suggest non-adherence to guideline directed recommendations. There are several possible explanations for

the low acquisition of baseline lung, thyroid and liver tests after initiation of amiodarone. In selected patients, amiodarone might be intended for short-term therapy, as for patients undergoing coronary artery bypass surgery. Since therapy is intended only for weeks or months, baseline studies are not obtained. This may be an area where guideline recommendations should be altered to reflect this phenomenon. Another possibility for the infrequent use of baseline studies is that certain patients might be extremely ill with a poor long-term prognosis and therefore baseline studies are not considered necessary. Support for this theory is the high mortality rate of our patients within 90 days of discharge. If physicians were to follow baseline recommendations for the above mentioned populations, it may be a poor use of healthcare resources and the system may benefit from guideline alterations. While it makes good clinical sense to obtain baseline data to help follow patients who are anticipated to receive long term treatment with a medication which has frequent adverse effects, to our knowledge there are no data to demonstrate that improved early outcomes are associated with proper vigilance. This suggests another area where there may be a benefit to guideline modifications to begin such testing later in the amiodarone course to encourage strict follow up in a more select population.

After correcting for baseline differences with a propensity analysis, the patients with complete baseline testing appeared to have a higher mortality and shorter time to first hospitalization than those with incomplete baseline data. One conclusion could be that increased vigilance with appropriate testing resulted in discontinuation of amiodarone and more adverse outcomes. However the rate of discontinuation of amiodarone was similar in both groups. More likely, differences in the degree of illness between the two groups, not accounted for by the propensity analysis, could be the explanation for these findings. Regardless, these data do not demonstrate a reduction in early adverse outcomes in patients with appropriate baseline testing and raise the question as to whether these baseline testing modalities are necessary so early in the amiodarone course. Given the high discontinuation rate and the high mortality within three months of initiation, there might be selected patients with such a poor prognosis that long term use is anticipated to be brief and baseline information should not be obtained. In addition, selected patients including post-operative patients might be expected to receive amiodarone for a short, specified period of time and baseline studies should not be performed on these patients either. Another option is to perform lung, liver or thyroid function testing at selected times during follow-up, omitting baseline studies. More data is needed in this regard. There are limitations to this study. The sample size for amiodarone exposure is relatively small. The single center retrospective nature of the study has inherent bias in the determination of certain baseline characteristics and for the cause for hospitalization. A substantial number of patients who were discharged on amiodarone were not followed at our institution. Efforts to determine if death occurred were applied in a non-uniform fashion in the population. Finally, the acquisition of baseline data and follow-up hospitalization was limited to Cerner Power Chart and GE IDX databases. Certain baseline studies and additional hospitalizations could have occurred at other institutions and that data was not collected.

Conclusion

Amiodarone is a commonly prescribed antiarrhythmic drug associated with serious adverse effects. Acquisition of recommended baseline testing was found to be low at this single center study. Patients with complete baseline testing had higher 90-day readmission and mortality rates compared to those with incomplete baseline testing. Further studies are needed to determine an optimal way to monitor for long-term amiodarone toxicity.

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