

Adherence to the NASPE Guideline for Amiodarone Monitoring at a Medical University

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ABSTRACT

OBJECTIVE: Amiodarone is an effective antiarrhythmic, but the clinical usefulness of this agent is complicated by its extensive side-effect profile, which necessitates careful patient selection and frequent monitoring. The purpose of this study was to quantify adherence to published recommendations for baseline monitoring when initiating inpatient amiodarone therapy at a university teaching hospital and determine whether appropriate serial monitoring of chronic amiodarone therapy (≥ 6 months) is occurring in the outpatient setting.

METHODS: A retrospective review of electronic medical records was conducted for inpatients at the Medical University of South Carolina (MUSC) who received amiodarone between November 1, 2003, and March 31, 2004, and for a subset of outpatients who had received amiodarone therapy for at least 6 months. Their medical records were reviewed for demographic data; reason for, date of initiation of, and duration of amiodarone therapy; and the occurrence of laboratory and diagnostic tests. The amiodarone guideline from the North American Society of Pacing and Electrophysiology (NASPE) was used as the measure of appropriate monitoring for baseline and follow-up chest x-rays (CXRs), liver function tests (LFTs), thyroid function tests (TFTs), and pulmonary function tests (PFTs).

RESULTS: Over the 5-month period from November 1, 2003, through March 31, 2004, 277 adult patients received oral amiodarone as inpatients at MUSC. Of these, 45 patients (16%) were initiated on chronic amiodarone therapy during their hospital admission. Baseline assessments of CXRs, LFTs, and TFTs occurred in 82% to 87% of these patients. Baseline assessment of PFTs occurred in 24% of patients, and 55% of these assessments included a diffusion capacity (D_{LCO}). Overall, only 5 (11%) of the 45 patients initiated on amiodarone received all recommended monitoring tests. Twenty patients with available outpatient records in the MUSC system were identified as receiving chronic amiodarone therapy. Baseline assessments of LFTs, TFTs, and CXRs occurred in approximately 75% to 95% of these patients; baseline assessment of PFTs occurred in $\leq 30\%$, and 83% of these included a D_{LCO} . Chronic monitoring at recommended time intervals for LFTs and TFTs occurred in 35% and 20% of patients, respectively, whereas annual CXRs were performed appropriately in 50% of patients.

CONCLUSION: Our data suggest that opportunities exist for improved monitoring of amiodarone therapy according to the NASPE guidelines and provide support for the development of a protocol to ensure continuous amiodarone monitoring.

KEYWORDS: Amiodarone, Monitoring, Adverse effects, Safety, Guidelines

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Amiodarone (Cordarone) is approved by the U.S. Food and Drug Administration for the treatment of life-threatening ventricular arrhythmias.¹ However, it is also commonly used for atrial fibrillation. Although amiodarone is an effective antiarrhythmic, the clinical usefulness of this agent is complicated by its extensive side-effect profile, which necessitates careful patient selection and frequent monitoring. Amiodarone is an iodine-containing compound that is structurally similar to thyroxine. Since the drug has a long elimination half-life of 16 to 180 days (mean, 52 days), it takes months for blood concentrations to reach steady state.² The oral bioavailability of amiodarone is variable, ranging from 35% to 65%, and excretion via the kidneys is negligible.¹ Amiodarone is metabolized in the liver and has a major metabolite, desethylamiodarone, which is pharmacologically active.²⁻⁴

Because amiodarone has a large volume of distribution and is highly lipophilic, it accumulates and has the potential to cause toxicity in multiple organs, including the liver, lungs, thyroid, and skin²⁻⁴ (see Table 1). Whereas some adverse effects of amiodarone are relatively mild in nature (e.g., nausea, corneal microdeposits, photosensitivity, and skin discoloration), others can require intervention to avoid serious consequences. Serial monitoring of liver transaminase, for example, is imperative in order to detect elevated levels. Elevated liver enzymes may be benign and decline despite continued amiodarone use, or they may signal the development of hepatitis, which can be fatal. If hepatitis develops, amiodarone should be discontinued immediately and appropriate supportive therapies initiated.

Hypothyroidism can be medically managed fairly easily with the addition of levothyroxine to the medication regimen and appropriate follow-up to ensure appropriate thyroid replacement. However, undetected hypothyroidism can be very detrimental to the patient, especially one with cardiovascular comorbidities. Hyperthyroidism can be more emergent in nature, especially in the patient with underlying cardiovascular disease. Based on patient-specific factors, the management strategy may include withdrawal or continuation of amiodarone, use of antithyroid medications, corticosteroids, or surgical resection of the thyroid.

An insidious and potentially fatal toxicity associated with amiodarone therapy is interstitial pneumonitis.⁵ Its onset is characterized by dyspnea and a subacute cough, both of which are fairly nonspecific and common in the patient population prescribed amiodarone. Baseline pulmonary function tests (PFTs) and chest radiographs are essential in the event interstitial pneumonitis is suspected, as interval changes consistent with this diagnosis are preferred over an isolated assessment of these

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TABLE 1 Toxicities Associated With Amiodarone Use and Monitoring Recommendations

Adverse Effect	Incidence	Package Insert Recommendations ¹	NASPE Recommendations ⁵
LFT elevation (>3 times normal) Hepatitis	4%-50% ^{5,13,16} <3% ⁵	Liver Function Tests	
		– Baseline – Regularly	– Baseline – Every 6 months
Pulmonary toxicity	2%-17% ¹	Chest Radiograph	
		– Baseline – Every 3-6 months	– Baseline – Every 12 months
		Pulmonary Function Tests (Including D_LCO)	
		– Baseline	– Baseline – Additional PFTs may be obtained if the patient has symptoms of pulmonary toxicity or if there is a change in the CXR
Hyperthyroidism	2%-10% ¹³	Thyroid Function Tests	
Hypothyroidism	1%-22% ⁵	– Baseline – Periodically	– Baseline – Every 6 months

CXR=chest x-ray; D_LCO=diffusion capacity, a subset of the PFT; LFT=liver function test; NASPE=North American Society of Pacing and Electrophysiology⁵; PFT=pulmonary function test; TFT=thyroid function test.

parameters at the time this toxicity is suspected.

Between 34% and 93% of patients experience some type of adverse effect during the course of amiodarone therapy, with most occurring within the first year of therapy.^{6,7} Discontinuation of amiodarone due to adverse effects has been reported in 2% to 26% of patients.⁶ Because the frequency of some adverse effects is associated with cumulative amiodarone exposure (i.e., dose and duration of treatment),^{3,6-10} careful and continuous follow-up and monitoring are essential throughout the course of amiodarone therapy to identify significant toxicity and allow a management plan to be initiated. It is surprising that a medication with such a large number of serious adverse effects that are not extremely rare is commercially available without a structured monitoring program to ensure patient safety. It is also surprising that no evidence-based monitoring guidelines are available.¹¹ The absence of evidence-based guidelines may be due to the fact that widespread chronic use of amiodarone did not occur when it was first approved for life-threatening ventricular arrhythmias, but rather after its effectiveness was established for atrial fibrillation, a common and relatively benign arrhythmia.

The amiodarone package insert does not provide explicit and measurable recommendations regarding appropriate monitoring parameters. Recommended time intervals for monitoring are listed as “regularly” or “periodically,” which are subjective and make adherence difficult to measure. However, the North American Society of Pacing and Electrophysiology (NASPE) developed guidelines that include specific and clear recommended monitoring parameters for patients on amiodarone therapy.⁵ No other published consensus guidelines are available; therefore,

NASPE recommendations were used for this study.

Based on our own assessments during routine patient care, we sensed that laboratory and radiographic tests were not being obtained as recommended for many patients receiving amiodarone. Since chronic amiodarone therapy is associated with several commonly occurring adverse effects, some of which result in substantial morbidity, an assessment of adherence to published recommendations seemed a worthy endeavor. In a university-based teaching hospital with multidisciplinary, hospital-based practitioners providing inpatient care, and clinic-based practitioners providing the majority of outpatient care, it remains unclear who is responsible for monitoring amiodarone therapy. Anecdotally, some practitioners feel that the initial prescriber is responsible, but this is not a realistic expectation for the longitudinal parameters if therapy is initiated during hospitalization. Others feel that the primary care provider, who is usually clinic-based and will see the patient for the long term, should be the professional responsible for follow-up monitoring of amiodarone therapy, including evaluation of laboratory values. In a referral center, continued contact with many patients is not assured. If cardiologists are involved in outpatient care, noncardiologists will often assume that the cardiologists are managing all cardiac medications, including the recommended monitoring. The case could be made that the pharmacist involved in patient care should be the responsible clinician; however, pharmacists are not reliably present in all clinic and hospital settings. Ultimately, it is not clear who in our health system is responsible for amiodarone monitoring, and this uncertainty increases the likelihood of either suboptimal amiodarone monitoring or significant overlap and unnecessary duplicate monitoring.

TABLE 2 Baseline Characteristics and Amiodarone Monitoring Tests for Patients Initiated on Amiodarone as an Inpatient*

Characteristic	Amiodarone Patients (n = 45)
Age, mean (range)	67 years (38-84)
Men, number	35 (78%)
Race, number	
White	23 (51%)
African American	20 (45%)
Other	1 (2%)
Unknown	1 (2%)
Reason for amiodarone therapy, number (%)	
Atrial arrhythmias	32 (71%)
Ventricular arrhythmias	8 (18%)
Both	5 (11%)
Daily amiodarone dose, mean (range)	330 mg (100-1,600)
Length of chronic therapy (≥6 months), average (range)	2.2 years (0.67-5)
Baseline monitoring tests (%)	
LFT	39 (87)
TFT	37 (82)
CXR	39 (87)
PFT	11 (24†)
D _L CO (N = 11)	6 (55)

* Time frame: November 1, 2003, to March 31, 2004.

† Includes patients for whom PFTs were scheduled to be performed after discharge.

CXR=chest x-ray; D_LCO=diffusion capacity, a subset of the PFT;

LFT=liver function test; PFT=pulmonary function test; TFT=thyroid function test.

Objectives

The objectives of this study were to quantify adherence to published recommendations for baseline monitoring when initiating inpatient amiodarone therapy at a university teaching hospital and to determine whether appropriate serial monitoring of chronic amiodarone therapy (≥6 months) is occurring in the outpatient setting.

Methods

The NASPE makes several recommendations for monitoring patients on amiodarone. For the purposes of this study, we chose to focus on the 4 recommendations listed in Table 1 since monitoring of chest radiographs (CXRs), liver function tests (LFTs), thyroid function tests (TFTs), and PFTs detect the major adverse effects associated with amiodarone therapy.

The Medical University Hospital is a 700-bed tertiary-care teaching institution affiliated with the Medical University of South Carolina (MUSC). It serves as a statewide referral center for both inpatient care and numerous outpatient primary care and specialty clinics. Institutional Review Board (IRB) approval was obtained, and a retrospective, electronic medical record review was conducted. Adult inpatients who received oral

amiodarone therapy from November 1, 2003, through March 31, 2004, were identified via the MS-MEDS pharmacy medication order-entry database. Two types of patients were included in this study. The first group consisted of MUSC inpatients initiated on amiodarone therapy during hospitalization, thus permitting an assessment of amiodarone baseline monitoring. The second group consisted of patients with an MUSC outpatient provider, who received chronic amiodarone on an outpatient basis. This group permitted assessment of serial amiodarone monitoring.

Patients were excluded for the following reasons: they were admitted on prior amiodarone therapy and followed by a non-MUSC provider postdischarge because of the inability to obtain their medical records to document appropriate monitoring; they were cardiothoracic (CT) surgery patients (because these patients are commonly prescribed a limited course of amiodarone therapy postoperatively for atrial fibrillation prophylaxis); and they were scheduled to receive amiodarone therapy for a short duration (<1 month), as indicated in the discharge summary.

Study patients' medical records were reviewed by the primary author for the following information: demographic data; date of initiation of amiodarone therapy; reason for amiodarone therapy; duration of amiodarone therapy; and baseline laboratory and diagnostic tests, including CXRs, LFTs, TFTs, and PFTs. If PFTs were scheduled on an outpatient basis according to the discharge summary, this was also captured. Appropriate follow-up monitoring for LFTs and TFTs was defined as every 6 months, yearly for CXRs, and based on symptoms for PFTs according to the NASPE guidelines (Table 1). Data were entered into an Excel spreadsheet, and descriptive statistics were applied to determine the proportion of patients who received appropriate amiodarone baseline and follow-up monitoring.

Results

Over the 5-month period, 277 adult patients admitted or initiated on oral amiodarone therapy at MUSC were identified for our study. Excluded patients were 146 CT surgery patients and 52 short-term (<1 month) amiodarone patients, leaving 79 patients for possible analysis. Of the 79 patients identified, 45 (57%) were initiated on amiodarone therapy during their admission at the medical university. A majority of these patients were men, (78%) with a mean age of 67 years, who were on amiodarone for atrial arrhythmias (Table 2). Additionally, outpatient records within the MUSC system were available for 20 of the 79 patients to allow assessment of chronic amiodarone monitoring.

Of the 45 patients initiated on amiodarone while hospitalized, baseline LFTs, TFTs, CXR, and PFTs occurred in 39 (87%), 37 (82%), 39 (87%), and 11 (24%) patients, respectively (Table 2). Of the 11 patients who received baseline PFTs, only 6 of these (55%) included a diffusion capacity test (D_LCO, a subset of the PFT). Overall, only 5 (11%) of the 45 patients

received all baseline monitoring tests (Table 2).

Of the 20 patients receiving chronic amiodarone and followed by a MUSC provider, baseline assessment of LFTs, TFTs, and CXRs occurred in 19 (95%), 15 (75%), and 15 (75%) of patients, respectively (Table 3). Baseline PFTs occurred in only 6 (30%) of patients, 5 (83%) of which included a D_LCO (Table 3). The average duration of amiodarone therapy was 2.2 years (range, 0.67 to 5 years). Of these 20 patients, LFTs and TFTs every 6 months occurred in 7 (35%) and 4 (20%) of patients, respectively. Lastly, of the 20 chronic amiodarone patients, 16 patients had been on amiodarone for longer than 1 year, and a yearly CXR was performed in 8 (50%) of these patients. Overall adherence to the NASPE guideline for outpatients receiving chronic amiodarone therapy is summarized in Table 3.

Discussion

Several of the adverse effects associated with chronic amiodarone use are serious and occur with enough frequency that vigilant assessment and monitoring are recommended and encouraged.^{5,12,13} In this retrospective analysis, we identified clinical practice guidelines developed by NASPE for amiodarone monitoring and used these as our model to evaluate appropriate monitoring practices of amiodarone therapy at MUSC. When we evaluated this monitoring model at our institution, we discovered that there was opportunity for improvement, particularly in obtaining PFTs at baseline. At our institution, only 24% of patients initiated on amiodarone therapy received PFTs at baseline. This is almost a 2-fold lower adherence rate than that reported by Stelfox and colleagues, in which 52 (52%) of 99 outpatients at a tertiary care hospital received baseline PFTs.¹¹ However, our institution does appear to have a slightly better adherence rate to monitoring baseline LFTs, TFTs, and CXRs (75% to 95%), compared with their 56% to 61% adherence rate.

Overall, both this study and the study published by Stelfox and colleagues provide some insight regarding the amount and occurrence of chronic amiodarone monitoring. However, it is questionable whether these results are applicable to other health care systems. The number of referrals treated at each institution likely affects the providers' view of the utility of obtaining baseline parameter measurements within their health system and likely influences the sense of responsibility they and other providers feel for ensuring appropriate follow-up monitoring. However, the magnitude and clinical importance of these influences are not known.

Currently, there are no broadly accepted guidelines that are consistently applied to patients receiving amiodarone. The package insert does not provide specific monitoring recommendations, and only one clinical practice guideline from an authoritative body exists for amiodarone monitoring. The complexity of amiodarone monitoring may also contribute to

TABLE 3 Adherence to Amiodarone Monitoring Recommendations for Outpatients

Baseline Monitoring Tests (N=20)		Chronic Monitoring Tests (N=20)	
Test	N (% Adherence)	Test	N (% Adherence)
LFT	19 (95)	Every 6 months LFT	7 (35)
TFT	15 (75)	Every 6 months TFT	4 (20)
CXR	15 (75)	Yearly CXR (N=16)	8 (50)
PFT	6 (30)*		
D_LCO (N=6)	5 (83)		

* Includes patients for whom PFTs were scheduled to be performed after discharge. CXR=chest x-ray; D_LCO =diffusion capacity, a subset of the PFT; LFT=liver function test; PFT=pulmonary function test; TFT=thyroid function test.

the failure to monitor as recommended. A number of strategies could be used to improve amiodarone monitoring through coordinating the ordering and execution of laboratory and diagnostic tests. This could be done by developing an electronic order set or protocol for amiodarone monitoring, to be initiated when starting a patient on amiodarone therapy upon admission, and/or by developing computerized prescribing aids that would remind the practitioner to monitor the tests on follow-up visits.

Raebel and colleagues conducted a randomized trial at Kaiser Permanente of Colorado to determine whether computerized alerts were effective in increasing the percentage of ambulatory patients with laboratory monitoring at initiation of drug therapy.¹⁴ Physicians and pharmacists teamed up to develop organization-specific guidelines for monitoring a selected 15 drugs among 400,000 health plan members. During this study, pharmacists, in collaboration with physicians, were alerted to missing laboratory test results, ordered missing tests, reminded patients to obtain tests, assessed test completion, reviewed test results, and managed abnormal results. Of the 15 medications that were selected for this study, the greatest absolute difference in monitoring between the intervention group and usual care group was with amiodarone. In the intervention group, 78.6% of amiodarone (95% CI, 73.1%-83.5%) dispensing was monitored compared with 51.4% (95% CI, 44.4%-58.4%) in the group receiving usual care ($P < 0.001$). This study demonstrated that a computerized tool in addition to collaboration among health care professionals was effective in increasing the percentage of patients receiving laboratory monitoring at initiation of therapy.¹⁶

Multidisciplinary clinics have also been shown to have a higher adherence rate to amiodarone monitoring guidelines.¹² A specialized amiodarone clinic at the University of Illinois at Chicago provided care to its patients according to accepted monitoring guidelines, and increased adherence to guidelines from 23% prior to referral to 90% after clinic enrollment.¹² After a mean enrollment of 9 months, previously unrecognized

adverse effects were detected in 35% of patients. While the number of these adverse effects that would have been detected if previous follow-up had been continued is not known, this rate is nonetheless impressive. If patients are not adequately monitored, the risks of amiodarone therapy may outweigh its beneficial antiarrhythmic effects.^{15,16} Unfortunately, there are no additional outcome data associated with amiodarone monitoring guideline adherence. Yet, based on the frequency and seriousness of the adverse effects associated with the use of amiodarone, it seems likely that early detection through the recommended laboratory and radiographic assessments would result in improved patient outcomes.

Limitations

The foremost limitation of this study is that it is a care process evaluation and does not address clinical outcomes.

Second, the results are based on retrospective medical record review, in which the data were limited to those files available in the MUSC computer database systems and pulmonary function laboratory records. This leads to potentially incomplete data for patients who received additional outpatient care from non-MUSC providers (approximately 50% of the patients assessed had an outside provider).

Third, the data collection period for this study, the 5-month period ending March 31, 2004, preceded the warning letters sent to pharmacists and other health care professionals at year-end 2004, regarding the life-threatening arrhythmias and cardiovascular and hepatic toxicity associated with the use of amiodarone.¹⁷ It is possible that outpatient monitoring of amiodarone improved in 2005 following the heightened attention to the black-box warning in amiodarone labeling.¹⁸

Fourth, only those patients on chronic amiodarone therapy who were admitted to the hospital during the 5-month time frame of data collection and followed by MUSC providers were identified, making it likely that many chronic amiodarone patients receiving outpatient care within our health system were not identified.

Fifth, baseline and follow-up laboratory tests could have been obtained for reasons other than initiation or monitoring of amiodarone therapy, leading to an elevated level of monitoring due to hospitalization or other complaint. For example, a CXR is often obtained when a patient is admitted for any pulmonary or cardiac complaint, not just because the patient is on amiodarone therapy. Also, PFTs may have been obtained if the patient had an underlying pulmonary condition such as asthma, chronic obstructive pulmonary disease, lung cancer, or sarcoidosis. Physicians indicated in only 2 out of the 11 PFTs obtained for patients in our review that these tests were related to initiation of amiodarone therapy. The indication for pulmonary function testing is required on paperwork submitted by the requesting physician, and these data were captured for the small number of tests ordered at MUSC in our sample. All

other PFTs were at least partly obtained for other reasons. Lastly, because this study included a small number of patients, these data can only provide a very rough estimate of adherence to amiodarone monitoring guidelines at this university-affiliated teaching institution.

However, given these limitations, the results indicating that patients on amiodarone therapy are not adequately monitored for adverse effects are not discordant with the one other report in the literature.¹¹ With the paucity of data available concerning amiodarone monitoring, our results provide justification for a gross assessment of this issue in other health care settings, for a prospective assessment in a university-affiliated setting, and for an investigation exploring the relationship between quality of amiodarone monitoring and patient outcomes.

Amiodarone is an effective antiarrhythmic, but its use is associated with many serious adverse effects. Close clinical observation and routine laboratory monitoring are necessary components of the management of patients on long-term amiodarone therapy. Serial monitoring of CXRs, LFTs, TFTs, and PFTs allows for early detection of toxicity and permits the discontinuation of amiodarone and/or initiation of appropriate treatment before serious or irreversible sequelae occur.

Conclusion

The NASPE guidelines for the monitoring of patients receiving amiodarone were published in 2000. Data collected for the 5-month period ending March 31, 2004, revealed a 75% to 95% adherence rate for all amiodarone baseline monitoring parameters except for baseline PFTs, for which the adherence rate was $\leq 30\%$. Recommendations for chronic monitoring of outpatients receiving amiodarone were followed in $\leq 50\%$ instances in the set of patients for whom outpatient data were available.

DISCLOSURES

No outside funding supported this study. The authors disclose no potential bias or conflict of interest relating to this article. Author Courtney L. Bickford served as principal author of the study. Study concept and design were contributed by Bickford and author Anne P. Spencer. Data collection was the work of Bickford; data interpretation was primarily the work of Bickford, with input from Spencer. Drafting of the manuscript was primarily the work of Bickford; its revision was primarily the work of Spencer.

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