Comparison of Amiodarone Compliance Monitoring: Usual Care, Electronic Prescribing Template and Pharmacist-Managed Clinic

Jeannie L. Poon, Allison C. Brenner and Michael J. Brenner

Veterans Affairs Ann Arbor Healthcare System, Ann Arbor 48105, MI, USA

Abstract: Objective: To assess whether adherence to amiodarone monitoring differed pre- and post-amiodarone restriction template and implementation of the pharmacist-managed clinic. Design: This was a retrospective chart review study. Setting: A large, academically-affiliated Veteran Affairs Healthcare System providing primary and tertiary care. Patients: 580 patients were identified as having an active prescription for amiodarone for at least 60 days from January 1, 2009 to August 31, 2013 and receiving primary care at the VAAHS (Veterans Affairs Ann Arbor Healthcare System). Results: Nearly all patients had TSH and LFTs at baseline regardless of study group. Significant associations between baseline rates for CXR, ECG, PFT, and ophthalmologic exams were found, with higher rates in the clinic and template arms compared to usual care. Similar patterns for all monitoring outcome rates were also found for both the 6- and 12-month measures. Conclusions: Patients on amiodarone who are followed by a pharmacist-managed clinic or where a restricted ordering template was used had increased compliance with amiodarone monitoring guidelines compared to usual care. Use of a restricted template may be a reasonable option in place of a pharmacist-managed service.

Key words: Amiodarone, pharmacist-managed, monitoring, Veterans Affairs, usual care, electronic template.

1. Introduction

Amiodarone is one of the most commonly prescribed antiarrhythmic medications in the United States [1]. It is a class III antiarrhythmic agent with multiple electrophysiological effects used to treat ventricular arrhythmias and atrial fibrillation. Numerous studies have shown amiodarone to be efficacious and safe in patients with known structural heart disease, post myocardial infarction and heart failure [1-4]. Although amiodarone is an effective antiarrhythmic, the clinical usefulness of this agent is complicated by its extensive side-effect profile and necessitates careful patient monitoring and follow-up.

Between 35% and 90% of patients experience some type of adverse effect during the course of amiodarone therapy, with most occurring within the first year of therapy [5]. Amiodarone accumulates and has the

potential to cause toxicity in multiple organs, including the liver, lungs, thyroid, and skin because it is highly lipophilic and has a large volume of distribution [1, 5, 6]. Since the drug has a long elimination half-life of 16 to 180 days (mean, 52 days), it may take months for side effects to manifest or be reversed [5, 6]; whereas some adverse effects of amiodarone are relatively mild in nature (e.g., nausea, photosensitivity and skin discoloration), others can require intervention to avoid serious consequences. Therefore, determining the best methodology for prevention of amiodarone-related toxicity is important.

Current standards, such as those proposed by the Heart Rhythm Society, recommend TSH (thyroid stimulating hormone) and LFTs (liver function tests) monitored at baseline and every six months. Patients are also recommended to have CXR (chest x-ray), ECG (electrocardiogram) and PFTs (pulmonary functions tests) at baseline and then repeated yearly

Corresponding author: Jeannie L. Poon, Pharm.D., PGY2 cardiology pharmacy resident, VAAHS. E-mail: jeanniep@usc.edu.

[7]. Finally, ophthalmologic evaluations are recommended at baseline if symptoms of visual impairment are present thereafter. Despite published consensus statements recommending these monitoring requirements, patients receiving amiodarone may not always be appropriately followed. A recent review suggested about 50% of the patients starting amiodarone received minimum baseline evaluation and less than 25% received the recommended ongoing surveillance [8]. Several studies have also been published describing the need for amiodarone drug monitoring [9, 10]; however, no universally accepted and feasible approach is available.

In January 2010, a pharmacist-managed service was established at the VAAHS (Veterans Affairs Ann Arbor Healthcare System) for amiodarone monitoring as part of the cardiology pharmacotherapy clinic. The aim is to provide an environment in which patients receiving amiodarone can be referred and managed according to published guidelines. Referrals primarily come from our electrophysiology or heart failure clinics. Adverse effects can also be detected in this way and their incidence and impact minimized. Since that time, a restricted ordering template was created in May 2011 within the VAAHS' CPRS (computerized patient record system) in an attempt to further improve compliance with recommended monitoring guidelines. All baseline and follow-up monitoring are embedded within the template.

In this study, we evaluated the impact on compliance with monitoring guidelines for amiodarone after implementing the restricted ordering template and establishing the pharmacist-managed monitoring service.

2. Methods

2.1 Study Design and Patient Population

This single-center, retrospective study was conducted at the VAAHS (Veterans Affairs Ann Arbor Healthcare System) and was approved by its institutional review board and research and

development committee. Patients with an active prescription for amiodarone for at least 60 days from January 1, 2009 to August 31, 2013 and receiving primary care at the VAAHS were eligible for inclusion in the study. These dates were selected in order to capture the true impact of the restricted template by looking at usual monitoring several years before its implementation.

2.2 Data Collection

The VAAHS database was queried to identify eligible patients and data were obtained via review of individual medical records in the CPRS. The following laboratory monitoring and exams were recorded for all patients: liver, thyroid and pulmonary (including D_LCO) function tests, chest x-ray film, electrocardiogram, and ophthalmologic evaluation. Additionally, statin therapy, including dosage, was collected for each of the patient. Monitoring rates were compared for three groups: usual care, CPC (cardiology pharmacotherapy clinic) and templated-ordering. Patients on amiodarone prior to implementation of the restricted ordering template and not enrolled in the CPC were assigned to the "usual care" group. The "CPC" arm comprised of patients referred to and followed by the pharmacist-managed clinic. Lastly, those patients on amiodarone after the restricted ordering template and not enrolled in the CPC were assigned to the "templated-ordering" group.

2.3 Outcomes

The primary outcome was adherence to recommended monitoring in patients on amiodarone therapy pre- and post amiodarone restriction template and implementation of the pharmacist-managed clinic. Patients were considered adherent if each test at baseline, 6 months and 12 months as recommended by guidelines were completed (Table 1). Grace periods of two and six months were used when collecting the 6- and 12-month monitoring outcomes, respectively. Besides monitoring rates, the proportion of patients on

Table 1 Recommended laboratory testing in patients receiving amiodarone*.

Type of test	Time when test is performed
Liver function tests	Baseline and every 6 months
Thyroid stimulating hormone	Baseline and every 6 months
Chest x-ray	Baseline and every 12 months
Electrocardiogram	Baseline and every 12 months
Pulmonary function tests (including D _L CO)	Baseline and every 12 months
Ophthalmologic evaluation	Baseline or for symptoms

D_LCO: diffusion capacity of carbon monoxide.

*If clinical circumstances warrant, more frequent follow-up will be necessary.

inappropriately dosed CYP3A4 statin therapy was identified in each of the three study groups described. Inappropriately dosed CYP3A4 statin was defined as simvastatin or atorvastatin greater than 20 mg and lovastatin greater than 40 mg. The dose accepted for atorvastatin is above the equipotent dose limitation of simvastatin because the VA Pharmacy Benefits Management allows up to 20 mg daily of atorvastatin with concurrent amiodarone.

2.4 Data Analysis

A priori power calculation indicated a minimum of 300 patients would be required to achieve 80% power

to detect a minimum 15% difference among rates in adherence to amiodarone monitoring. Recommended adherence rates at baseline, 6- and 12-month were compared between groups for each monitoring outcome using either Pearson's chi-squared or Fischer's exact test with a significance level (alpha) of 0.05. Pearson's chi-square test was used for rates where cell frequencies were greater than or equal to five patients, whereas Fisher's exact test was reported for rates where cell frequencies were between one and four patients. Furthermore, inappropriate statin therapy was reported using descriptive statistics for all three groups.

3. Results

A total of 580 patients were identified as having an active prescription for amiodarone for at least 60 days from January 1, 2009 to August 31, 2013 and receiving primary care at the VAAHS (Table 2). Inappropriately dosed CYP3A4 statin therapy was confirmed in 112 cases and was the highest in the "templated-ordering" (44/164, 26.8%) group compared to the "usual care" (34/194, 17.5%) and "CPC" (34/222, 15.3%) groups.

Table 2 Adherence rates for each monitoring outcome for each study group (N = 580)*.

Measures	Total N = 580 (%)	Usual care N = 194 (%)	CPC N = 222 (%)	Templated-ordering N = 164 (%)	χ^2	p
Baseline						
TSH	564 (97.2)	186 (95.9)	220 (99.1)	158 (96.3)	-	-
LFTs	575 (99.1)	193 (99.5)	222 (100)	160 (97.6)	-	-
CXR	509 (87.8)	153 (78.9)	217 (97.8)	139 (84.8)	36.28	< 0.001
ECG	523 (90.2)	163 (84.0)	218 (98.2)	142 (86.6)	-	< 0.001
PFT	472 (81.4)	118 (60.8)	201 (90.5)	153 (93.3)	81.75	< 0.001
Ophthy	320 (55.2)	82 (42.3)	141 (63.5)	97 (59.2)	20.35	< 0.001
6-month						
TSH	445 (76.7)	108 (55.7)	201 (90.5)	136 (82.9)	75.42	< 0.001
LFTs	456 (78.6)	123 (63.4)	194 (87.4)	139 (84.8)	40.55	< 0.001
12-month						
CXR	309 (53.3)	59 (30.4)	152 (68.5)	98 (59.8)	64.09	< 0.001
ECG	330 (56.9)	64 (33.0)	163 (73.4)	103 (62.8)	72.27	< 0.001
PFT	269 (46.4)	55 (28.4)	132 (59.5)	82 (50.0)	41.49	< 0.001

THS: thyroid stimulating hormone; LFTs: liver function tests; CXR: chest radiograph; ECG: electrocardiogram; PFT: pulmonary function tests; Ophthy: ophthalmologic evaluation.

*Numbers reported reflect frequencies and percentage in parentheses. Pearson's chi-square test is reported.

3.1 Baseline Measures

Nearly all patients had TSH and LFTs at baseline. Almost all patients in the “CPC” (97.8%) group had a CXR at baseline, whereas CXR rates in the “usual care” (78.9%) and “templated-ordering” (84.8%) groups were lower ($p < 0.001$). The results revealed a similar pattern for ECG rates—98.2% of patients in the “CPC” group had an ECG, while less patients in both the “usual care” and “templated-ordering” groups had an ECG (84.0% and 86.6% respectively, $p < 0.001$). Patients in the “CPC” and “templated-ordering” groups had higher rates of PFT monitoring (90.5% and 93.3% respectively) compared to “usual care” (60.8%), $p < 0.001$. The rates for ophthalmologic exams were also significant, $p < 0.001$, with higher rates in the “CPC” group (63.5%) and “templated-ordering” group (59.2%) compared to “usual care” (42.3%).

3.2 Six-Month Measures

At six months, the results revealed that the rate of TSH monitoring in the “CPC” and “template-ordering” groups (90.5% and 82.9%, respectively) was much higher than the “usual care” (55.7%) group, $p < 0.001$. Similarly, there was a significant difference in LFT monitoring. A greater proportion of patients in the “CPC” (87.4%) and “templated-ordering” (84.8%) groups had LFTs, whereas only 63.4% of those in the “usual care” group had LFTs, $p < 0.001$.

3.3 12-Month Measures

At 12 months, the “usual care” group had the lowest rates of CXR (30.4%), followed by the “templated-ordering” group (59.8%) and the “CPC” group (68.5%), $p < 0.001$. The “CPC” group had ECG rates over 70%, the “templated-ordering” group had lower rates (62.8%) and the “usual care” had the lowest rates (33.0%), $p < 0.001$. More than half of the patients in the “CPC” group had PFTs (59.5%), half of

the “templated-ordering” group had PFTs (50.0%) and less than one-third of the “usual care” group had PFTs (28.4%), $p < 0.001$.

4. Discussion

We found that patients on amiodarone enrolled in a pharmacist-managed clinic or where a restricted ordering template was used had an increase in the percentage of patients who received recommended baseline and surveillance monitoring compared with usual care. Nearly all patients had TSH and LFTs at baseline regardless of study group. Significant associations between baseline rates for CXR, ECG, PFT, and ophthalmologic exams were found, with higher rates in the clinic and template arms compared to usual care. Similar patterns for all monitoring outcome rates were also found for both the 6- and 12-month measures.

These results in monitoring rates are similar to those in the study by Johnson et al. and Sanoski et al. [9, 11]. Both studies showed improved adherence to recommended monitoring through implementation of an amiodarone monitoring service and a multidisciplinary clinic compared to usual care, respectively. Monitoring rates increased from 23% to 90% through the use of a multidisciplinary clinic [11]. These approaches differed from ours in that one study utilized an entire cardiology team to follow-up and dose-adjust the patients’ amiodarone and neither study looked at or used a restricted ordering template for amiodarone.

The use of a restricted ordering template for amiodarone was almost as good as the pharmacist-managed clinic on many of the outcome measures making it a rational option, especially for those facilities unable to allocate resources and personnel to run a monitoring service. There appears to be a continuing need for amiodarone monitoring strategies and implementing such a template is not only easy, but affordable. By using this approach, prescribers are consistently reminded of the

appropriate baseline and surveillance monitoring required at the time of prescribing; thus, allowing patients to receive the necessary ongoing care.

It was also evident that many patients are on concomitant CYP3A4 statin therapy dosed above what is recommended. This may in part be due to the notion that concomitant amiodarone therapy is relatively rare in statin-associated adverse events. One study reviewed adverse events reported to the United States Food and Drug Administration and found that the percentage of simvastatin reports with concurrent amiodarone use was 1.0%, compared with 0.7% of the atorvastatin associated reports ($p = \text{not significant}$) [12]. Regardless, clinicians should be vigilant about muscle toxicity that may arise in patients who are being treated with a statin and amiodarone, use of a non-CYP3A4 statin in this setting may be appropriate.

There are several limitations to our study. Due to the retrospective nature, there is the possibility of confounding variables. Relatively stringent criteria were applied in an attempt to minimize the risk. As arbitrary cut-off dates and grace periods were used, this may potentially underestimate certain monitoring rates, especially those services unable to accommodate walk-ins. Our patient population was also comprised strictly of veterans who predominantly receive care within our closed VA system, so caution should be exercised in extrapolating the results to other facilities. Finally, we were unable to capture results of testing performed outside for patients initiated on amiodarone prior to establishing care with the VAAHS, which can certainly impact adherence rates.

5. Conclusion

A pharmacist-managed clinic that offers service for amiodarone monitoring or use of a restricted ordering template helped to improve compliance with monitoring guidelines compared to usual care. Moreover, implementation of a restricted template may be a reasonable option in place of a

pharmacist-managed service.

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