



Adherence to Monitoring Guidelines of Amiodarone Adverse Reactions

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Abstract

Background: Amiodarone treatment frequently causes adverse reactions. Clinical guidelines warrant a comprehensive assessment prior to chronic treatment with amiodarone and repeated monitoring for the appearance of adverse reactions.

Objective: To evaluate adherence to these guidelines.

Methods: A retrospective chart review of electronic medical records of adult patients treated with oral amiodarone for at least 12 months.

Results: One hundred patient records were analyzed; 97% of patients were evaluated for thyroid and liver functions prior to treatment. Liver functions were properly monitored every 6 months in 96% of patients and thyroid function in only 59%. Most (84%) patients completed a chest X-ray before treatment; only 2% completed a respiratory function test. None have performed a chest X-ray annually. Sixty-four percent of the patients were examined by an ophthalmologist prior to treatment; periodic ophthalmic surveillance was not consistent. Neurological and dermatological evaluations were not recorded for any of the patients, unless symptoms appeared. Only 50% were adherent to annual cardiac reassessment.

Conclusions: Adherence to recommended clinical guidelines for monitoring amiodarone adverse reactions is poor. Interventions to improve compliance with these guidelines are needed.

Keywords

amiodarone, monitoring, adherence, adverse reactions

Introduction

Amiodarone, a widely used antiarrhythmic drug, is associated with profound safety concerns.¹⁻⁴ During intravenous administration, hypotension and ventricular arrhythmia can occur.⁴⁻⁶ Long-term use with oral formulations is associated with a wide variety of adverse reactions.^{1-4,7-18} Disorders of thyroid function are common during chronic treatment with amiodarone. The reported prevalence is 4% to 30% for hypothyroidism and 5% to 6% for hyperthyroidism, depended on maintenance doses.^{9,19} Liver function disorders are recorded in 15% to 50% of amiodarone-treated patients.¹³ Pulmonary morbidity during amiodarone treatment is identified in 5% to 15% of patients; cough is the most reported initial symptom.^{1,2,7} Ophthalmic adverse reactions include corneal microdeposits that cause blur vision¹⁵⁻¹⁷ and optic neuropathy that can lead to loss of vision in 1% to 2% of patients after 10 years of treatment.^{15,20} Neurologic manifestations are reported in 3% to 30% of patients during amiodarone treatment, mainly peripheral neuropathy and ataxia.^{1,9} Dermal adverse reactions

following amiodarone include photosensitivity in 25% to 75% of patients and skin discoloration in less than 10%.¹ Amiodarone can cause by itself cardiac arrhythmias and blocks in 3% to 5% of patients.²⁰

The North American Society for Pacing and Electrophysiology recommends monitoring tests for early detection and mitigation of amiodarone adverse reactions.¹ Previous studies demonstrated limited adherence to these guidelines and unveiled difficulties of the surveillance efforts to identify the

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Table 1. Recommended Monitoring and Adherence Rate Results.

Recommended Monitoring	Recommended Timing		Adherence Rate	
	Before Treatment	During Treatment	Before Treatment	During Treatment
Thyroid function test	Once	Every 6 months	97%	59% full, 32% partial
Liver function test			97%	96%
Chest X-ray		Annually	84%	10%
Respiratory function test		According to clinical manifestation	2%	21% (6/29 symptomatic patients)
Ophthalmic evaluation			64%	N/A
Neurologic evaluation			0%	
Dermatologic evaluation			0%	
Cardiac evaluation + ECG		Annually	100%	55% full, 45% partial

Abbreviations: ECG, electrocardiogram; N/A, not applicable.

adverse outcomes. Yet, the studies evaluated only part of the monitoring recommendations, mostly those regarding thyroid and liver functions, and using mainly older records. There is a need for an updated comprehensive evaluation of the whole set of amiodarone adverse reaction monitoring recommendations. The objective of the present study was to evaluate adherence to these guidelines.

Methods

We conducted a retrospective review of electronic medical records of adult patients treated chronically with amiodarone. The source of records was Carmel Medical Center database, part of Clalit Health Services, Israel. These medical records include community, hospital, and pharmacy information. Computerized query randomly retrieved a sample of records of patients who were actively treated with amiodarone at any time between January 1, 2015, and December 31, 2016. Sampled records were screened thereafter. Exclusion criteria included patients treated with amiodarone less than 12 months (based on pharmacy dispensing records) and patients with chronic neuropathy, liver, thyroid, or pulmonary disease before starting amiodarone treatment.

After screening, demographic and clinical data were collected from each medical record. A full review of the medical chart was completed including general practitioner records, procedure reports, laboratory results, and specialist/medical advisor reports. Data were transferred to an electronic data sheet (Microsoft Excel 365) and subjected to descriptive analysis. The study was approved by the institutional review board of Carmel Medical Center.

Results

Of 138 retrieved records, 38 were excluded; 12 were treated less than 12 months and 26 had neuropathy, liver, thyroid, or pulmonary disease before treatment. One hundred patients were included in the statistical analysis after screening. Average age was 76.6 (± 10.5) years; 61% were males. All patients were treated for atrial fibrillation or flutter with an oral

maintenance dose of 200 mg/d. Average treatment duration was 36 (± 23.8) months.

Summary of the rates of adherence to the recommended monitoring tests before and during amiodarone treatment is presented in Table 1. Most (97%) patients have been tested for thyroid functions before starting amiodarone. Yet, only 59% were monitored every 6 months for thyroid functions. Liver functions were evaluated before and during treatment in almost all patients, 97% and 96%, respectively.

Most (84%) patients performed chest X-ray before amiodarone treatment, but during treatment, only 10% were compliant with performing chest X-ray annually. Recommended pulmonary function test, including spirometry and diffuse capacity of the lung for carbon monoxide (DLCO), was completed in only 2% of patients before amiodarone treatment and in only 6% during treatment.

Approximately two-thirds (64%) of patients had baseline ophthalmological examination; none have completed a neurological or a dermatological evaluation before treatment. Only about half (55%) of the patients were adherent to annual cardiac reassessment. Electrophysiological assessment during treatment was not performed for any patient.

Discussion

The overall adherence to recommended guidelines for monitoring amiodarone adverse reactions in the study was not satisfactory. Rankin et al retrospectively evaluated the monitoring of thyroid and liver functions in Scottish adult patients treated with amiodarone between 1989 and 2011.²¹ The recorded adherence was 46% for liver and 28% for thyroid. Huang et al retrospectively reviewed medical records of amiodarone-treated patients in Taiwan between 2008 and 2009 and found that only 36.4% had baseline thyroid functions and 8.6% performed regular thyroid function tests during treatment.²² The current study results show some improvement, but profound gaps still exist regarding repeated thyroid function tests.

Adherence to annual chest X-ray and pulmonary function tests was extremely low. There are limited published data regarding real-world performance of pulmonary monitoring

during amiodarone treatment. Gleadhill et al found that annual pulmonary function tests including DL_{CO} have a positive predictive value of only 21% for early diagnosis of pulmonary toxicity.⁸ Chest X-ray costs between US\$5 and US\$20 and pulmonary function test costs between US\$50 and US\$500, depending on the country and health-care system.²³⁻²⁶ Considering the high cost, burden, and technical difficulties of performing annual respiratory function tests and chest X-ray to all amiodarone-treated patients, and the doubt regarding their effectiveness in early detection, the current guideline should be reconsidered. It is suggested to rely on clinical respiratory evaluation of patients chronically treated with amiodarone. Any report from the patient of worsening dyspnea or cough should elicit a prompt assessment for pulmonary toxicity.²⁷ This approach may focus the efforts and lead to better diagnosis, treatment, and prognosis of amiodarone-related respiratory adverse reactions.

Monitoring of ophthalmic, dermatological, and neurological effects in treated patients was poorly performed. Improved awareness and repeated structured multisystem evaluation of amiodarone-treated patients may lead to early diagnosis and intervention.

Amiodarone can cause by itself cardiac arrhythmias and blocks.²⁰ It can also impair the proper action of intracardiac defibrillators (ICDs) by causing ventricular bradycardia and misleading the ICD from diagnosis of other ventricular arrhythmias. In addition, amiodarone main active metabolite desethylamiodarone may accumulate—depending on dose and interactions—and raise the defibrillation threshold, thus endangering patients.²⁸⁻³⁰ Annual electrophysiological evaluation using cardiac physical examination and routine electrocardiogram is recommended for all amiodarone-treated patients, not just 50%, as found in the present study.

The significant gaps in the adherence to amiodarone monitoring guidelines are probably the consequences of several factors. Low physicians' awareness and limited time and resources may play a role.³¹ Patients' cooperation can also influence practice and outcome. Many of these patients are old and have mobility limitations. Furthermore, cost is a major issue and not all recommended tests are affordable or compensated. Some of these obstacles can be solved by using automated alerts to physicians, automated referral letters to patients to improve their engagement, construction of a focused task force within the health providing organization, and awareness promotion campaign using different media platforms.^{27,31,32} In addition, adherence rate to amiodarone monitoring guidelines may be set as a publically reported quality measure for physicians and health organizations, thus encouraging them to comply. Regardless of the intervention, there is a clear need to be proactive and improve the adherence. Most of the adverse reactions of amiodarone are either preventable or mitigated with proper monitoring.¹

This study has limitations. It is a retrospective observational study of a small sample. But this is balanced with the updated comprehensive data collection on each participant.

In conclusion, adherence to recommended monitoring measures of amiodarone adverse reactions is still poor. A full set of recommended tests should be performed before initiating amiodarone treatment and annually during chronic treatment. Proactive interventions and increased awareness are needed for improvement. Larger, prospective and interventional studies are recommended.

Authors' Note

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Declaration of Conflicting Interests

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