asthma.” A CT scan revealed and located the airway narrowings, preventing delay of the diagnosis. Management with self-expandable stents has kept the proximal airways patent. Without the stenting technology, the outcome of this patient’s case would be unpredictable and could be less than satisfactory.

REFERENCES

9 Chhajed PN, Malouf MA, Glanville AR. Bronchoscopic dilation in the management of benign (non-transplant) tracheobronchial stenosis. Intern Med J 2001; 31:512–516
10 Wang KP. Experiences of self-expandable wire stent or “wall stent” for bronchial obstruction. J Bronchol 1997; 4:120–124

Pulmonary Toxicity in Patients Receiving Low-Dose Amiodarone*

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Rationale: Although there have been reports of pulmonary toxicity with low-dose amiodarone, it is generally believed that low-dose therapy is safe. Methods: The clinical data for eight patients identified from a retrospective chart review are presented.

Results: All of the patients were receiving amiodarone, 200 mg/d, for an average of 2 years. The average age was 77 years (range, 65 to 89 years). Seven of the eight patients were male. Seven of the eight patients presented with dyspnea on exertion, and three of the eight patients presented with cough. All of the patients had a clinical diagnosis of amiodarone-induced pulmonary toxicity. Open-lung biopsies were obtained on two patients that were consistent with amiodarone-induced pulmonary toxicity. None of the patients were in congestive heart failure. Treatment involved cessation of amiodarone. In addition, three patients received corticosteroids. Five of the patients improved symptomatically with this conservative approach, and four patients improved radiographically. One patient died with progressive respiratory insufficiency (presumably from amiodarone pulmonary toxicity). One patient was unavailable for follow-up.

Conclusion: Amiodarone-induced pulmonary toxicity can occur at a daily dose of 200 mg. Clinicians must remain alert to this possibility even with this low-dose therapy.

Key words: amiodarone; antiarrhythmics; drug toxicity; pulmonary medicine

Abbreviations: BOOP = bronchiolitis obliterans organizing pneumonia; CABG = coronary artery bypass grafting; DLCO = diffusing capacity of the lung for carbon monoxide; TLC = total lung capacity

Pulmonary complications, including pneumonitis and ARDS, are well-documented risks of long-term amiodarone use, especially in the perioperative setting. Although there have been reports of pulmonary toxicity with low-dose amiodarone use (defined here as ≤ 200 mg/d), it is generally believed that low-dose therapy is safe. In addition, amiodarone has been associated with ARDS following coronary artery bypass grafting (CABG). One study has concluded that low-dose amiodarone is safe for cardiac surgery. We report a series of eight patients with pulmonary toxicity associated with low-dose amiodarone to emphasize that even low-dose therapy may have serious adverse pulmonary effects.

Materials and Methods

The clinical records of eight patients are presented. After receiving institution review board approval, a series of five case reports were compiled from the cardiology and pulmonology practices at Mayo Clinic in Jacksonville, FL, a referral-based, multispecialty group practice. In addition, we performed a retrospective electronic chart search of our outpatient clinic population using the key words amiodarone pulmonary toxicity and amiodarone-induced pulmonary toxicity from 1994 to 2001. Approximately 5,890,000 patient records from 520,000 patients were searched with this method. Sixty clinical notes involving 28 patients were identified as potential matches and were reviewed. Thirteen of these 28 patients were identified as receiving low-dose amiodarone. In the time of the evaluation, nine of these 13 were receiving at least 400 mg/d. The authors reviewed the clinical charts of the four patients receiving low-dose amiodarone at length to evaluate for the diagnosis of amiodarone-induced pulmonary toxicity, recognizing that this is usually a diagnosis of exclusion. Radiographs, biopsies, bronchoscopies, laboratory work, echocardiograms, and documented symptoms/examination findings were considered in making the presumed diagnosis. An example of this review is presented in the “Results” section.

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RESULTS

Of the patients identified with the electronic chart search, three of the four patients receiving low-dose amiodarone were confirmed to have pulmonary toxicity. The fourth patient did not have clear amiodarone-associated pulmonary toxicity.

All of the eight patients identified during the study were receiving 200 mg of amiodarone per day. No cases were identified at a dosage < 200 mg/d. There were no other medications known to be associated with pulmonary toxicity. The average age of the patients was 77 years (range, 65 to 89 years; Table 1). Seven of the eight patients were male. The patients had been receiving the medication an average of 2 years prior to having pulmonary complaints (range, 3 months to 5 years). Seven of the patients presented with dyspnea on exertion, and three patients presented with cough. One of the cases (patient 2) occurred after open-heart surgery. Four of the eight patients had a WBC differential measured at the onset of symptoms (patients 1, 2, 6, and 7). Only patient 7 had an increased percentage of eosinophils (8.2%, 1.09 absolute). The erythrocyte sedimentation rate was assessed in two patients and was normal. All patients underwent chest radiography, and six of eight patients underwent chest CT.

Chest radiograph and CT findings were variable but usually demonstrated bilateral disease. No high-attenuation infiltrates were seen by the radiologist or on review by the authors. No radiographic findings suggested congestive heart failure. Three of eight patients underwent fiberoptic bronchoscopy with negative results. Two of the bronchoscopies included a BAL, and one included a protected-specimen brush. Four of eight patients underwent pulmonary function tests (Table 1). Patient 1 demonstrated restriction (total lung capacity [TLC] ≤ 80% predicted) with a reduced diffusing capacity of the lung for carbon monoxide (DLco) ≤ 80% predicted). Patient 3 had normal pulmonary function. Patient 4 demonstrated restriction with a normal DLco, and patient 5 had an isolated reduction in the DLco.

None of the patients were in congestive heart failure based on clinical examination (including the absence of jugular venous distension or S3 gallop). Seven of the eight patients underwent transthoracic echocardiography. The ejection fraction was normal (≥ 60%) in four patients (patients 1 through 4), and reduced in three patients (patients 5, 7, and 8). Chest radiographs in the patients with a reduced ejection fraction did not demonstrate findings consistent with congestive heart failure (new unexplained effusions or increase in the vascular pedicle width compared with baseline).

Open-lung biopsies were performed in two patients. In patient 1, the biopsy showed a chronic interstitial pneumonia. Specifically, there was diffuse alveolar septal thickening due to a chronic inflammatory cell infiltrate and mild fibrosis. Patchy bronchiolitis obliterans organizing pneumonia (BOOP) was present but appeared to be only a minor component of the parenchymal changes (Fig 1). The biopsy in patient 2 revealed organizing diffuse alveolar damage with alveolar septal thickening due to fibroblast proliferation, type II alveolar cell hyperplasia, and remnants of hyaline membranes (Fig 2). Intra-alveolar collections of foamy macrophages were noted in both cases. There were no transbronchial lung biopsies, and the microbiologic results from the bronchoscopies were negative.

Treatment involved cessation of the amiodarone. Patients 1, 2, and 3 also received corticosteroids. Five of the eight patients improved symptomatically, and four of the patients improved radiographically with this conservative approach. Two of the three patients who received corticosteroids improved, although patient 3 worsened when the steroids were tapered. Patient 1 died from progressive respiratory failure. No autopsy was performed. Patient 6 was unavailable for follow-up.

The diagnosis of amiodarone-induced pulmonary toxicity was made clinically in six of eight patients. Patient 8 is presented in more detail to illustrate the typical evaluation that resulted in a clinical diagnosis. He is a 67-year-old white man with a known history of ischemic cardiomyopathy. He underwent a five-vessel CABG procedure 3 years prior to starting on amiodarone. In addition, he was a previous smoker with known moderate obstructive lung disease. Prior to amiodarone, the patient was doing extremely well without dyspnea on exertion, paroxysmal nocturnal dyspnea, or orthopnea. Indeed, he walked two to three miles daily without any symptoms.

Following a routine cardiolite stress test that revealed a fixed apical and inferior-lateral defect, the patient experienced atrial fibrillation/flutter with a rapid ventricular response. Subsequently, he was started on amiodarone, 200 mg/d, after a 3-day loading dose of 400 mg tid. Approximately 3 months later, the patient acquired some very mild dyspnea for which he did not seek medical attention. He subsequently fell while on a boat, suffering only a minor left chest wall bruise. The patient did not have any chest pain (except for mild point tenderness at the site of the bruise), orthopnea, paroxysmal nocturnal dyspnea, or edema. No environmental exposures could be elicited. The patient denied fevers, chills, night sweats, sick contacts, changes in weight, cough, sputum production, hemoptysis, history of tuberculosis, recent travel to areas endemic for histoplasmosis or coccidiomycosis, history of malignancy, illicit drug use, or known inhalation injury. He had not made any other recent changes to his medications, which included furosemide (stable dose), lanoxin, aspirin, pravastatin, and a multivitamin.

A chest radiograph was obtained that revealed new bilateral alveolar/interstitial infiltrates compared with his baseline radiographs; however, there was no change in the cardiac size or vascular pedicle width and there were no new effusions. The patient underwent chest CT, which confirmed multiple bilateral infiltrates. The radiographic changes were not felt to be cardiac in origin. His repeat transthoracic echocardiogram showed a stable pattern of mitral insufficiency, aortic sclerosis, and ejection fraction of approximately 35%. An open-lung biopsy was recommended, but was refused by the patient.

The only change made was to discontinue the amiodarone. Two months later, the mild dyspnea had resolved. Chest radiograph and chest CT demonstrated a significant decrease in the bilateral infiltrates. Four months after stopping the amiodarone, the chest radiograph showed a...
complete resolution of the changes. The patient has been followed up regularly for 3 years, both clinically and radiographically, with no return of symptoms or radiographic changes. A presumptive diagnosis of amiodarone-induced pulmonary disease was made clinically. The authors reviewed the medical record as well as the laboratory and radiographic results to confirm the accuracy of the diagnosis.

**Discussion**

Atrial fibrillation is an extremely common dysrhythmia, particularly in elderly patients and those with organic heart disease. Management of atrial fibrillation still represents one of the therapeutic challenges of modern cardiology. Atrial fibrillation increases the risk of embolic complications, especially cerebrovascular accidents. The decision whether to administer patients with atrial fibrillation antifibrillatory drug therapy is complex. The safety of long-term antiarrhythmic therapy must be balanced against the need to try to eliminate symptoms and prevent thrombotic complications.

Recent reports showed that low-dose amiodarone treatment is effective and is associated with very few side effects at 1 year. The Canadian Trial of Atrial Fibrillation randomized patients to amiodarone and to either propafenone or sotalol. There were fewer recurrences with amiodarone compared to sotalol. This trial suggests that amiodarone was twice as effective as the other two drugs. In addition, amiodarone had a more favorable safety profile. However, there have been no controlled, comparative studies specifically investigating long-term mortality rate with amiodarone or its long-term safety in atrial fibrillation.

Amiodarone-induced pulmonary toxicity has been observed in up to 10% of patients receiving this drug. There were fewer recurrences with amiodarone compared to sotalol. This trial suggests that amiodarone was twice as effective as the other two drugs. In addition, amiodarone had a more favorable safety profile. However, there have been no controlled, comparative studies specifically investigating long-term mortality rate with amiodarone or its long-term safety in atrial fibrillation.

Amiodarone-induced pulmonary toxicity has been observed in up to 10% of patients receiving this drug. An increased risk of pulmonary toxicity has been well described in several clinical settings, including pulmonary angiography and cardiothoracic operations. Reported pulmonary toxicities range from mild subacute illness to rapidly progressive and fatal ARDS. It has been difficult to predict which patients are at greatest risk for the development of amiodarone pulmonary toxicity.

### Table 1—Pulmonary Toxicity in Patients Receiving Low-Dose Amiodarone*  

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr</th>
<th>Gender</th>
<th>Duration of Therapy, mo</th>
<th>Clinical Signs</th>
<th>Chest Radiography</th>
<th>Pulmonary Function Tests†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>82</td>
<td>Male</td>
<td>24</td>
<td>Dyspnea on exertion</td>
<td>Bilateral pulmonary infiltrates</td>
<td>Moderate restriction, TLC 69%, DLco 36%, no obstruction</td>
</tr>
<tr>
<td>2</td>
<td>82</td>
<td>Male</td>
<td>60</td>
<td>Dyspnea on exertion, worse after CABG/MVR</td>
<td>Interstitial changes in lingula, small right effusion</td>
<td>Not done</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>Male</td>
<td>24</td>
<td>Dyspnea on exertion, cough</td>
<td>Bilateral infiltrates, minimal interstitial markings on right, prominent alveolar infiltrates left lateral mid-lung and left base</td>
<td>Normal</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>Male</td>
<td>14</td>
<td>Dyspnea on exertion, cough</td>
<td>Linear opacities in right upper lobe and lingula</td>
<td>TLC 78%, no obstruction, normal DLco</td>
</tr>
<tr>
<td>5</td>
<td>71</td>
<td>Male</td>
<td>36</td>
<td>Cough</td>
<td>Scattered fibrosis</td>
<td>No obstruction, reduced DLco</td>
</tr>
<tr>
<td>6</td>
<td>78</td>
<td>Male</td>
<td>23</td>
<td>Dyspnea on exertion</td>
<td>Bilateral interstitial changes with alveolar infiltrates bilateral bases</td>
<td>Not done</td>
</tr>
<tr>
<td>7</td>
<td>80</td>
<td>Female</td>
<td>7</td>
<td>Dyspnea on exertion</td>
<td>Patchy infiltrates bilateral bases and right mid-lung</td>
<td>Not done</td>
</tr>
<tr>
<td>8</td>
<td>67</td>
<td>Male</td>
<td>3</td>
<td>Dyspnea on exertion</td>
<td>Increased bilateral alveolar/interstitial infiltrates compared with baseline, no change in cardiac size or vascular pedicle width, no new effusions</td>
<td>Not done</td>
</tr>
</tbody>
</table>

*MVR = mitral valve replacement.
†Data presented as percentage of predicted.
Most of the published cases have been in patients receiving amiodarone in excess of 200 mg/d, usually ≥ 400 mg/d. The toxic effects of amiodarone seem to be related to dose and duration of therapy. Low-dose therapy has been deemed a safe alternative. Some studies indicate that there is no statistically significant difference in the rate of

<table>
<thead>
<tr>
<th>Chest CT</th>
<th>Fiberoptic Bronchoscopy</th>
<th>Echocardiography</th>
<th>Open-Lung Biopsy</th>
<th>Treatment</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scattered peripheral ground-glass opacities</td>
<td>Negative</td>
<td>Aortic stenosis, valve area 0.8 cm², ejection fraction 62%</td>
<td>Prominent alveolar macrophages with scattered foam cells, patchy chronic interstitial pneumonia and focal BOOP</td>
<td>Discontinue amiodarone, oral prednisone</td>
<td>No radiographic change, progressive hypoxemia and respiratory insufficiency, died</td>
</tr>
<tr>
<td>Upper and mid-lung interstitial infiltrates bilaterally</td>
<td>Negative</td>
<td>Ejection fraction 65%</td>
<td>Nonspecific interstitial pneumonitis vs diffuse alveolar damage</td>
<td>Discontinue amiodarone, IV methylprednisolone</td>
<td>Gradual radiographic and symptomatic improvement, discharged to home</td>
</tr>
<tr>
<td>Infiltrates in right lung with bilateral patchy areas of pneumonitis</td>
<td>Negative</td>
<td>Normal ejection fraction, aortic sclerosis</td>
<td>Not done</td>
<td>Discontinue amiodarone, oral prednisone</td>
<td>Resolution of alveolar infiltrates, minimal residual bilateral interstitial markings, decreased dyspnea and cough worse when prednisone was tapered quickly</td>
</tr>
<tr>
<td>Multiple subpleural opacities</td>
<td>Not done</td>
<td>Aortic sclerosis, right ventricular pressure 42 mm Hg</td>
<td>Not done</td>
<td>Discontinue amiodarone</td>
<td>Improvement in dyspnea on exertion, no significant radiographic changes</td>
</tr>
<tr>
<td>Peripheral fibrosis with mild honeycombing</td>
<td>Not done</td>
<td>Ejection fraction 30%</td>
<td>Not done</td>
<td>Discontinue amiodarone</td>
<td>Cough resolved, chest radiograph stabilized</td>
</tr>
<tr>
<td>Not done</td>
<td>Not done</td>
<td>Not done</td>
<td>Not done</td>
<td>Discontinue amiodarone</td>
<td>No follow-up available</td>
</tr>
<tr>
<td>Not done</td>
<td>Not done</td>
<td>Ejection fraction 32%</td>
<td>Not done</td>
<td>Discontinue amiodarone</td>
<td>Chest radiograph improved, no change in dyspnea on exertion</td>
</tr>
<tr>
<td>Multiple bilateral infiltrates</td>
<td>Not done</td>
<td>Severe mitral insufficiency, aortic sclerosis, ejection fraction 35%</td>
<td>Not done</td>
<td>Discontinue amiodarone</td>
<td>Improvement in dyspnea on exertion and chest radiograph returned to baseline</td>
</tr>
</tbody>
</table>

Most of the published cases have been in patients receiving amiodarone in excess of 200 mg/d, usually ≥ 400 mg/d. The toxic effects of amiodarone seem to be related to dose and duration of therapy. Low-dose therapy has been deemed a safe alternative. Some studies indicate that there is no statistically significant difference in the rate of

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**Figure 1.** Chronic interstitial pneumonia with associated foamy intra-alveolar macrophages (hematoxylin-eosin, original × 200).

**Figure 2.** Diffuse alveolar damage with alveolar septal thickening, remnants of hyaline membranes (arrow), and foamy macrophages (arrowhead) [hematoxylin-eosin, original × 200].
pulmonary side effects between placebo and low-dose amiodarone.\textsuperscript{7,28} However, this assertion has been called into question.\textsuperscript{29–34} In fact, the Canadian Myocardial Infarction Amiodarone Trial\textsuperscript{40} showed that low-dose amiodarone increased pulmonary toxicity compared to placebo (3.89\% vs 1.2\%). The risk for late adverse effects of low-dose amiodarone remains unknown.\textsuperscript{35} The disparity in the literature may contribute to the wide variation in the clinical practice of physicians caring for patients receiving amiodarone.\textsuperscript{36}

Previous studies predominantly focused on patients taking a daily maintenance dose of \( \geq 400 \) mg. Those studies have indicated that amiodarone induces several types of tissue reactions in the lung.\textsuperscript{37–40} The most common histologic finding in toxic patients is a chronic interstitial pneumonia with intra-alveolar accumulation of foamy macrophages.\textsuperscript{39,40} The macrophages have finely vacuolated cytoplasm at the light microscopic level and contain distinct cytoplasmic lamellar inclusions ultrastructurally.\textsuperscript{37–39} Foamy macrophages can also be found in nontoxic patients and are considered markers of amiodarone exposure rather than toxicity.\textsuperscript{39,41} BOOP is a less common manifestation of amiodarone toxicity and is often associated with a chronic interstitial pneumonia.\textsuperscript{39} Diffuse alveolar damage is seen in a minority of patients in whom it is accompanied by foamy macrophages.\textsuperscript{37,39} In our study of low-dose amiodarone toxicity, lung biopsy specimens were obtained in two cases. In patient 1, chronic interstitial pneumonia with associated foamy intra-alveolar macrophages and focal BOOP were seen. In patient 2, the biopsy showed diffuse alveolar damage with scattered collections of foamy intra-alveolar macrophages. Although patient 2 was in the setting of recent coronary artery bypass graft, there was no clinical evidence of heart failure or infection. Taken together, these observations suggest that the histologic spectrum of amiodarone-induced pulmonary toxicity can occur in patients receiving 200 mg/d.

Our study, although retrospective and limited in scope, serves as a reminder of the remaining clinical uncertainties of low-dose amiodarone. We have shown that 200 mg/d can increase the risk for pulmonary toxicity. This toxicity occurred as soon as 3 months after initiation of therapy in one patient, with a range of 3 months to 5 years. Although most patients presented with dyspnea, there was a wide range of clinical toxicities from cough to ARDS. Interestingly, patient 5, who presented only with cough, had no obstruction on pulmonary function, and his cough resolved with discontinuation of the amiodarone. The radiographic abnormalities were generally bilateral. Most of these patients improved with cessation of the amiodarone with or without corticosteroids. Of those patients with alveolar infiltrates and response to corticosteroids, BOOP is a consideration; however, the lack of other clinical signs and symptoms of BOOP such as fever and malaise make this less likely. In addition, BOOP can occur secondary to drug toxicity and would therefore fall into the category of amiodarone pulmonary toxicity.

Overall, low-dose amiodarone appears to be safer than conventional doses. A randomized prospective study may be able to determine the exact risk of low-dose amiodarone; however, there are significant practical limitations to such a study. The goal of this report is to reinforce the need for the clinician to recognize that low-dose amiodarone is associated with some risk for pulmonary toxicity.

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REFERENCES


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