PNEUMONITIS, PULMONARY FIBROSIS AND AMIODARONE/Sobol and Rakita

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Pneumonitis and Pulmonary Fibrosis Associated with Amiodarone Treatment: A Possible Complication of a New Antiarrhythmic Drug

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SUMMARY  Six patients are presented who developed pulmonary infiltrates of undetermined origin while being treated for severe ventricular arrhythmias with amiodarone hydrochloride. Biopsy material was available in four patients and revealed interstitial or alveolar fibrosis and pneumonitis. Four patients recovered and two died of severe cardiopulmonary decompensation; all of the patients who recovered received corticosteroid therapy. Pulmonary fibrosis is a previously unreported complication of amiodarone therapy.

AMIODARONE hydrochloride is a benzo-furan derivative, introduced in Europe in 1961 as an anti-anginal agent and subsequently found to have important antiarrhythmic properties. It is widely used as an antiarrhythmic agent in Europe and in South America. Experience with large numbers of patients in the past decade1-8 has shown that the drug may be associated with side effects, of which the most common is corneal microdeposits, appearing in 90-100% of patients who receive chronic treatment. These are rarely symptomatic, and resolve when the drug is discontinued. Less frequent adverse effects include constipation, photosensitivity dermatitis, headache, nausea and hyperthyroidism. These symptoms are usually mild and only occasionally necessitate discontinuing the drug. Uncommon toxic effects have included hypo-thyroidism, gray-blue skin discoloration and peripheral neuropathy. Until 1980, there were no reports in the world literature of pulmonary toxicity due to amiodarone. However, Rotmensch and associates8 suggested that this drug may have been responsible for the appearance of pulmonary infiltrates in one of their patients.

In the United States, amiodarone is available in only a few centers as an investigational agent, and has been used on a limited number of patients.10-18 As this report was being prepared, 432 patients in this country were being treated with the drug; all had life-threatening or severely symptomatic arrhythmias and were either resistant or intolerant to treatment with standard antiarrhythmic drugs. Despite the small number of patients exposed, we know of six cases of pulmonary disease occurring unexpectedly in patients treated with amiodarone.

Case Reports

Patient 1
A 67-year-old man with severe mitral valve prolapse and recurring atrial flutter and ventricular ectopy was begun on amiodarone in December 1977. Doses were increased weekly from 200 to 800 mg/day; 800 mg/day was the maintenance dose. He did well until May 1978, when transient fever occurred with mild dyspnea, weight loss and weakness. In late June, bilateral upper lobe infiltrates were noted on chest

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x-ray (fig. 1). Extensive evaluation, including bacterial, fungal and viral studies, immunologic studies and transbronchial biopsy, failed to disclose a cause. Amiodarone was discontinued in early July. The pulmonary infiltrates were unchanged. Atrial flutter recurred and amiodarone was restarted in late July. Pulmonary infiltrates persisted. Open lung biopsy was performed in mid-September, and showed focal interstitial fibrosis, focal resolving pneumonitis and bronchiolitis obliterans (fig. 2). Amiodarone was discontinued shortly thereafter, and steroid therapy was begun. The patient’s dyspnea and weakness slowly improved in the following months, and by mid-January 1979 the chest x-ray had returned to almost normal (fig. 1).

Patient 2
A 56-year-old man had a history of acute myocardial infarction in May 1978, complicated by ventricular arrhythmias and severe congestive failure. One month later he was readmitted for increasing dyspnea and soon thereafter sustained a cardiac arrest. Severe ventricular arrhythmias persisted despite standard drugs, as well as tocainide, aprindine and overdrive pacing. He was eventually discharged on procainamide and aprindine. He was again admitted in September 1978 for syncope. An ECG revealed frequent multifocal premature ventricular complexes and R-on-T phenomenon. Chest x-ray showed minimal haziness of pulmonary vasculature and possible low-grade interstitial disease (fig. 3). Amiodarone was begun for arrhythmia control with a single loading dose of 1400 mg/day and then 600 mg/day. Aprindine was discontinued but procainamide continued. Subsequently, propranolol was also begun. After 4½ weeks of amiodarone treatment, the patient sustained an episode of symptomatic ventricular tachycardia that required cardioversion. At this time amiodarone was discontinued and aprindine was restarted. In the next week low-grade fever was noted, and chest x-ray revealed development of interstitial pulmonary edema with questionable right lower lobe infiltrate. During the next 5 weeks the chest x-ray showed an increasing pattern of interstitial edema (fig. 3). Swan-Ganz catheterization revealed a pulmonary wedge pressure of 5–13 mm Hg, ruling out congestive failure as a cause of interstitial edema.

The patient’s condition continued to deteriorate, with progressive respiratory impairment, eventually requiring intubation and ventilator assistance, and increasing ventricular arrhythmia. Irreversible ventricular tachycardia occurred during the tenth week in the hospital, and the patient died. Autopsy revealed chronic pulmonary interstitial fibrosis, with superimposed organizing pneumonitis.

Patient 3
A 61-year-old man with a history of Hodgkin’s disease (in remission over 3 years after chemotherapy and radiotherapy) and mild chronic obstructive...
FIGURE 2. Patient 1. (top) Photomicrograph of lung biopsy specimen showing interstitial fibrosis, macrophages, and protein debris in alveolar space. Magnification \( \times 100 \). (bottom) Higher-power view showing interstitial fibrosis, and early hyaline membrane formation lining alveolar spaces. Magnification \( \times 400 \).
Pulmonary disease had an acute myocardial infarction complicated by congestive heart failure with persistently high filling pressures and low cardiac output in late August 1978. One week later, ventricular fibrillation occurred. The patient was resuscitated, but continued to have severe ventricular arrhythmias, with recurring episodes of ventricular tachycardia refractory to all standard antiarrhythmic drugs and to the investigational agents encainide and aprindine. On October 24 he was started on amiodarone, 600 mg/day, without a loading dose. Over the ensuing 3 weeks good control of ventricular tachycardia was attained and he was discharged on the same dose on November 13. Two days later, however, syncope and sustained ventricular tachycardia recurred, and procainamide was added to his regimen. On December 14 he complained of increasing shortness of breath. The chest x-ray showed a diffuse alveolar pattern bilaterally, felt to be consistent with acute pulmonary edema. Despite treatment with diuretics and antibiotics, the patient’s status worsened and intubation and mechanical ventilation were required. Amiodarone and procainamide were both discontinued on December 18. Because of continuing respiratory failure despite therapy, an open lung biopsy was performed on December 20. Microscopic examination revealed fibrosing interstitial pneumonitis with hyaline membrane formation and atypical alveolar lining cell hyperplasia. No eosinophilia was noted and no cause determined. The patient’s respiratory status did not improve despite aggressive therapy, and on December 23 the patient suffered a cardiac arrest unresponsive to resuscitation.

**Patient 5**

A 40-year-old black female with pulmonic stenosis, treated by comissurotomy in 1972, had a history of ventricular tachycardia of obscure origin since June 1978. Treatment with quinidine and procainamide was initially successful but ventricular ectopy continued, and in June 1979 quinidine was discontinued because of syncope. Subsequently, procainamide, propranolol, phenytoin, tocainide and aprindine were given in combination and suppressed ventricular ectopy. However, aprindine resulted in cholestatic jaundice and was discontinued, and amiodarone was begun in July 1979. At doses of 600–1400 mg/day, arrhythmia control was achieved and other drugs were discontinued in July. In October, a permanent pacemaker was inserted because of bradycardia at a chronic amiodarone dose of 800 mg/day. On November 16, ventricular ectopy recurred, thought due in part to
pacemaker malfunction. The next day, a mild fever was noted. During the next week the fever persisted, and on November 23 she developed right-sided pleuritic pain. Chest x-ray showed right pleural effusion, RUL atelectasis and an RLL infiltrate. Pleural fluid showed acute and chronic inflammatory cells and protein, 3.1 g/l. Pleural biopsy showed only acute and chronic inflammation. All cultures were negative, as were viral studies. Tests for autoimmune disease included a negative lupus prep and negative antinuclear antibody test; a Raji cell assay was abnormal and IgE level was elevated. No eosinophilia was present. Amiodarone was discontinued and prednisone was begun on December 7. By mid-January, the chest x-ray had returned to normal.

**Patient 6**

A 67-year-old white male with a history of myocardial infarction, aortocoronary bypass surgery and ventricular pseudoaneurysm resection developed recurrent bouts of ventricular tachycardia. The arrhythmia was not controlled with standard drugs or mexiletine. An implanted, patient-activated overdrive pacemaker terminated some episodes, but additional control was necessary and amiodarone, 600 mg/day, was begun on March 20, 1980. Within 4 weeks, the Holter monitor showed excellent control with only rare isolated premature ventricular complexes, and amiodarone was continued.

On June 2, the patient was admitted to the hospital with a history of increasing exertional dyspnea. Chest x-ray showed extensive diffuse infiltrates that had characteristics of both alveolar and interstitial infiltration. Pulmonary edema was suspected, but Swan-Ganz catheterization revealed pulmonary arterial wedge pressures less than 18 mm Hg. Treatment with both antibiotics and high-dose steroids was begun. Amiodarone was discontinued. All sputum and blood cultures were negative, cold agglutinins were negative, and no cause was found. A lung biopsy was not done. The patient slowly improved, and was discharged 2 weeks later. The pulmonary infiltrates gradually cleared, and were virtually resolved within 3 months.

**Discussion**

The relationship of amiodarone therapy to the development of pulmonary abnormalities in our patients is not clear. Despite extensive use since 1967, amiodarone had not been reported to cause pulmonary disorders of any kind until the report of Rotmensh et al.9

The relatively high doses used in these patients may have been a contributory factor; in most reported series, the doses of amiodarone ranged from 200–600 mg/day. The patients discussed in this report received up to 1400 mg/day, at least until arrhythmias were controlled. However, maintenance doses as high as 800 mg were used in only two cases, and three patients never received more than 600 mg/day at any time. The cumulative amiodarone dose to the initial appearance of radiographic pulmonary abnormalities ranged from 14.6–142.2 g, and the duration of therapy ranged from 4½ weeks to 8 months (table 1). The patient reported by Rotmensh received only 400 mg/day for 1 month.

The clinical presentation was varied, but all patients experienced dyspnea. Two patients in this group concomitantly manifested other adverse effects of amiodarone: Patient 1 had severe peripheral neuropathy with lower-extremity weakness and sensory impairment and patient 5 had sinus bradycardia that required a permanent pacemaker. No other drug-related side effects were documented, except for the anticipated benign corneal microdeposits among patients on longstanding therapy.

All of the patients for whom pathologic specimens of lung parenchyma were available had interstitial fibrosis and pneumonitis. The finding of interstitial fibrosis in these cases does not, of itself, specify a common cause, as many conditions can result in this pathologic picture. However, none of the patients had obvious predisposing factors or pathologic findings that suggested an identifiable etiology, and cultures as well as microscopic examination failed to detect infectious agents. Eosinophilia was not present in any patient, excluding the syndrome of pulmonary infiltration with eosinophilia. Furthermore, no patient was being treated with a specific drug known to cause pulmonary fibrosis.17 Although all patients were treated with procainamide at some point, none had clinical manifestations of drug-induced lupus erythematosus. However, patient 3 did not develop pulmonary changes until after the addition of procainamide, and patient 2 had continuous treatment with procainamide during and after the period of amiodarone therapy.

<p>| Table 1. Amiodarone Dosage (Maximum, Maintenance and Total); Duration of Therapy Before Onset of Pulmonary Disease; Time to Recovery After Amiodarone Stopped; and Treatment with Steroids |
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<th>Pt</th>
<th>Dose (mg/day)</th>
<th>Total dose (g)</th>
<th>Duration of therapy (months)</th>
<th>Time to recovery (months)</th>
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<td>Maint 800</td>
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<td>1800</td>
<td>600</td>
<td>14.6</td>
<td>1</td>
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<tr>
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<td>600</td>
<td>600</td>
<td>31.2</td>
<td>2</td>
<td>Died</td>
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<tr>
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<td>600</td>
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<tr>
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<td>44.4</td>
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In four patients, symptoms and radiographic abnormalities resolved after discontinuing amiodarone. All of these received steroid therapy. The time interval between cessation of the drug and radiographic clearing ranged from 6 weeks to 4 months, and did not appear to be related to the antecedent dose or duration of treatment.

Two patients died. Both had severe cardiac disease and a history of myocardial infarction, congestive heart failure and cardiac arrest. Neither received corticosteroids.

Amiodarone has been in clinical use for almost two decades, with an accumulated experience of over 500,000 patient-years in one country alone by 1977. However, since the first report of its use in the United States, six cases of unexplained pulmonary infiltrates have occurred in a population of 432, an incidence of 1.4%. If this drug truly has a potential for causing pneumonitis and pulmonary fibrosis, it is remarkable that such an observation has not been made until now. Therefore, caution must be exercised and consideration given to the diversity of clinical presentations, radiologic findings, and pathologic findings — with the exception of pneumonitis and fibrosis — in patients treated with amiodarone. The role of other drugs must be weighed, since each patient except one had exposure to multiple antiarrhythmics, including other investigational agents. In particular, drug interaction and the role of amiodarone should be considered in our patient 2. This patient received two other investigational drugs and was on procainamide continuously. Also, although the persistence of amiodarone in tissues is well recognized and can result in very prolonged duration of biologic action, the onset of severe pulmonary changes and respiratory decompensation only after discontinuation of the drug must raise some doubt as to its role in this case.

Nevertheless, the unexpected appearance of clinical pulmonary disease without other clearly definable etiology in these six patients is cause for concern. Physicians who are treating patients with amiodarone, especially in high doses, should be alerted to the possibility of pulmonary toxicity, and should examine their patients for new respiratory symptoms and follow the chest x-ray at frequent intervals, at least during the first year of therapy.

We can make no definitive recommendations for treatment, in view of the small number of cases involved. However, it seems prudent to advise that amiodarone be discontinued in any patient who develops unexplained pulmonary symptoms and radiographic changes. Steroid therapy was used in all four patients who recovered, while the two patients who died did not receive steroids. The contribution of corticosteroid therapy to the recovery of the patients who improved is unknown, but the use of steroids in the treatment of drug-induced pulmonary fibrosis is supported by experience, and the outcomes suggest that such therapy may have been of benefit.

Acknowledgment

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References


Addendum

Since the submission of this manuscript, Drs. Heger and Zipes have reported their experience with amiodarone in 45 patients (Heger JJ, Prystowsky EN, Jackman WM, Naccarelli GV, Warfel KA, Rinkenberger RL, Zipes DP: Clinical efficacy and electrophysiology during long-term therapy for recurrent ventricular tachycardia or ventricular fibrillation. New Engl J Med 305: 539, 1981). Two of the patients in our report (patients 3 and 4) are also briefly discussed in their publication.
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