Amiodarone Pulmonary Toxicity: Early Changes in Pulmonary Function Tests During Amiodarone Rechallenge

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Amiodarone is an investigational antiarrhythmic agent known to cause pulmonary toxicity. This report describes two patients with previous amiodarone pulmonary toxicity and complete resolution who at rechallenge 5 to 6 months later developed within 2 weeks of therapy a significant reduction in lung diffusion capacity before overt clinical toxicity occurred. This suggests that toxicity may present early with reduction in diffusion capacity and that such changes may warrant the need to alter treatment.

Case Reports

Case 1

A 60 year old black woman with recurrent, refractory ventricular tachycardia was treated with amiodarone from March 2 to June 17, 1983 (loading dose 1,200 mg/day for 14 days, 400 mg/day for 1 week and then 200 mg/day maintenance). Treatment was terminated on June 17 because of insidious development of dyspnea, hypoxia and pulmonary infiltrates (Fig. 1A), culminating in severe respiratory embarrassment necessitating transient respirator dependency. After amiodarone was discontinued, short-term corticosteroid therapy was instituted, pulmonary function returned to normal and the chest X-ray film cleared after 1 to 2 weeks.

The patient was readmitted on January 15, 1984 because of recurrent, incessant ventricular tachycardia. Because of failure with all conventional antiarrhythmic agents and several investigational agents, amiodarone was restarted at a low dose (100 mg/day) on January 18, 1984 after informed consent had been obtained. Baseline chest X-ray film and pulmonary function tests performed before amiodarone rechallenge are shown in Figure 1B and Table 1, respectively. After 1 week of therapy, nonsustained ventricular tachycardia persisted and thus the dose was increased to 600 mg/day for another week. During this 2 week therapy with amiodarone, there was no evidence of respiratory infection or congestive heart failure and no change in the patient’s weight or other medication. Although the patient had no respiratory symptoms and repeat chest X-ray film (Fig. 1C) at the end of the second week of amiodarone therapy was not significantly changed from the baseline film, repeat pulmonary function tests revealed a significant reduction in diffusion capacity to 67% of predicted value (50% reduction). Amiodarone was discontinued and corticosteroid therapy was instituted (prednisone, 40 mg/day administered over 1 week). On the following day, the patient developed mild to moderate dyspnea with no change in arterial blood gases...
Figure 1. Case 1. Chest X-ray films obtained (A) in 1983 when amiodarone pulmonary toxicity was evident, (B) in 1984, before amiodarone was re instituted and (C) 2 weeks after amiodarone rechallenge, when decreased diffusion capacity was present. Ls = left supine.

or repeat chest X-ray film. Repeat pulmonary function tests performed 1 week after discontinuation of amiodarone revealed no significant changes despite a slight decrease in dyspnea. Repeat pulmonary function tests at 2 weeks revealed significant improvement in diffusion capacity to 88% of predicted values (Table 1) and dyspnea had completely resolved.

Case 2

A 69 year old white woman with documented Wolff-Parkinson-White syndrome and recurrent, refractory supraventricular tachycardia was treated with amiodarone from March 1 to September 23, 1983 (loading dose 1,200 mg/day for 14 days and 200 mg/day maintenance dose). Treatment was discontinued because of insidious development of dyspnea on exertion, scattered areas of interstitial fibrosis on chest X-ray film (Fig. 2A) and significant reduction in diffusion capacity to 62% of predicted value from 100% baseline level. One week after amiodarone was discontinued, dyspnea resolved and diffusion capacity had normalized.

The patient was readmitted on February 8, 1984 because of recurrent, incessant supraventricular tachycardia. Treatment with conventional agents and several investigational agents was unsuccessful; therefore, amiodarone was re started at a low dose (600 mg/day) after informed consent was obtained. Baseline chest X-ray film and pulmonary function tests performed before amiodarone rechallenge are shown in Figure 2B and Table 1, respectively. Although the patient had developed no respiratory symptoms or change on repeat chest X-ray film (Fig. 2C) at the end of 1 week of therapy, repeat pulmonary function tests revealed a significant reduction in diffusion capacity to 62% of predicted value (43% reduction). Mild hypoxia was also noted, though the patient remained asymptomatic while confined to bed. During therapy with amiodarone, there was no evidence of respiratory infection, congestive heart failure or changes in the patient's weight or other medications. Amiodarone was discontinued and corticosteroid therapy was instituted (prednisone, 40 mg/day administered over 1 week). Repeat pulmonary function tests performed 1 week after amiodarone was discontinued revealed significant improvement in diffusion capacity to 82% of predicted value.

Discussion

We report on two patients with previous amiodarone pulmonary toxicity and complete resolution in whom amiodarone rechallenge resulted in significant reduction in diffusion capacity before overt clinical toxicity recurred. The

Table 1. Serial Pulmonary Function Tests at Baseline, During Therapy and After Discontinuation of Amiodarone

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
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<tbody>
<tr>
<td></td>
<td>Amiodarone Therapy</td>
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<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>FVC</td>
<td>2.1 (86%)*</td>
</tr>
<tr>
<td>FEV₁</td>
<td>1.8 (90%)</td>
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<tr>
<td>TLC</td>
<td>4.6 (111%)</td>
</tr>
<tr>
<td>DLCO</td>
<td>26 (134%)</td>
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<tr>
<td>P0₂</td>
<td>85</td>
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</tbody>
</table>

*Percent of predicted values. DLCO = lung diffusion capacity (ml/m per mm Hg); FEV₁ = forced expiratory volume at 1 second (liters); FVC = forced vital capacity (liters); P0₂ = partial pressure of oxygen at room air (mm Hg); TLC = total lung capacity (liters).
Figure 2. Case 2. Chest X-ray films obtained (A) in 1983 when amiodarone pulmonary toxicity was evident, (B) in 1984 before amiodarone was reinstituted and (C) 1 week after amiodarone rechallenge when decreased diffusion capacity was present. $^\dagger =$ upright.

degree of reduction in both patients was well beyond the accepted 10% variability in diffusion capacity noted in our laboratory. To our knowledge, this represents the first such observation since amiodarone pulmonary toxicity was first reported by Rotmensch et al. (2).

**Pulmonary function testing.** Although pulmonary function tests in patients with amiodarone pulmonary toxicity have revealed hypoxia and restrictive changes with reduction in total lung capacity and diffusion capacity (6,7), the value of pulmonary function tests in predicting toxicity is controversial. Whereas some investigators (4,5) noted a predisposition to pulmonary toxicity in patients with preexisting impairment in diffusion capacity (<80% of predicted) and total lung capacity (<80% of predicted values), others (3) found no consistent or predictive changes in pulmonary function tests.

Whether exposure to amiodarone itself produces a change in diffusion capacity or whether this change is a prelude to clinical toxicity is an important question. Our experience so far in a prospective study of 16 patients who have been treated with amiodarone and received serial diffusion capacity testing and have not developed clinical pulmonary toxicity through a mean of 8 months’ follow-up has revealed mean maximal changes of 10% from baseline level. These changes are within the accepted spontaneous variability noted in our laboratory.

**Mechanisms of pulmonary injury.** Amiodarone-induced pulmonary toxicity is thought to be, at least in part, dose-related and usually is evident a few months after the start of therapy (2,6,8). Our two cases are somewhat unusual in that both patients experienced significant changes with such low doses and short-term rechallenge. This would suggest that a direct toxic effect, hypersensitivity or possibly an immunologic memory cell-mediated mechanism led to early loss of effective alveolar-capillary surface area for gas exchange. Neither of the two patients had histologic confirmation of amiodarone-induced pulmonary toxicity at their first or second exposure to the drug and, thus, specific lung tissue changes could not be correlated with the physiologic impairment noted.

Although the role of corticosteroids in the treatment of amiodarone pulmonary toxicity is controversial, both patients received prednisone empirically. In one patient there was no apparent improvement in diffusion capacity after 1 week of corticosteroid therapy, whereas improvement was noted in the other patient, although previous toxicity had resolved without corticosteroid intervention. Thus, the role of corticosteroids remains unclear.

**Clinical implications.** Our observations suggest that earliest toxicity from amiodarone may present as asymptomatic significant reduction in diffusion capacity before a critical threshold is reached that results in overt clinical signs, symptoms or radiologic findings. Such early changes should lead to closer surveillance and perhaps result in a change in doses or therapy before clinical toxicity can occur. Defining subclinical toxicity, as judged by reductions in diffusion capacity, would also serve as an avenue to study the role of corticosteroids or other interventions on the course of toxicity.

We express our gratitude to Toni Haase for secretarial assistance.

References


