AMIODARONE PULMONARY TOXICITY: A REVIEW

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Amiodarone hydrochloride is a very potent antiarrhythmic agent with some desirable pharmacologic properties such as long half-life and no negative inotropic effect. However, it has been reported to cause a variety of cardiac and extracardiac side effects. The most serious of these is pulmonary toxicity which may result in fatal respiratory failure. Amiodarone must, therefore, be used judiciously and patients should be followed-up carefully for side effects, especially amiodarone pneumonitis. The diagnosis of lung toxicity may be difficult because its features are indistinguishable from those of congestive heart failure or pulmonary infection. The prompt recognition and management of this serious toxic effect, however, may be lifesaving.

AMIODARONE is an iodinated benzofuran derivative which was originally marketed as an anti-anginal agent in Belgium in 1967.1 It was later found to be a very potent antiarrhythmic agent which is effective in patients with ventricular and supraventricular tachyarrhythmias.2-6 It seems to be particularly useful in symptomatic individuals with the preexcitation syndrome.3,2 One of the major advantages of this extraordinarily effective antiarrhythmic agent is its minimal negative inotropic effect; it may, therefore, be used safely in patients with congestive heart failure. Also, because of a very long half-life of 13 to 107 days,9 its antiarrhythmic effect persists from 10 to 150 days after cessation of long-term treatment.9 Thus, this unique pharmacokinetic property provides the patient with continuing antiarrhythmic activity even when he forgetfully omits the occasional dose.

Over the past twenty years, a vast amount of clinical experience in the use of amiodarone has been accumulated in Europe, South America, and the United States. It was believed initially that this was the ideal antiarrhythmic drug since its toxic effects appeared negligible.6,10 However, several recent studies have shown a high incidence (73% to 93%) of side effects which include corneal micro-deposits, hepatitis, dermatitis, neurotoxicity, thyroid abnormalities, and pulmonary fibrosis.4,11-14 Though most of the adverse reactions are mild, the frequency of serious toxicity, including pulmonary involvement, is still disconcertingly high, necessitating discontinuation of the drug in 15% to 20% of the patients. Pulmonary dysfunction, including occasional fatal respiratory failure is, however, the most serious side effect repeatedly described in the United States and Europe.15,23 This most serious toxic effect of amiodarone is discussed in detail in this paper.

Incidence

Despite extensive use of amiodarone since the 1960s, the first account suggesting a possible association with pneumonitis in some patients was published only as late as 1980.15 Within three years of this first publication, a total of 35 cases (11 of whom died) was reported. Several large series published recently demonstrate that the incidence of pulmonary toxicity varies from 0.6% to 17%.24-28 A search of the literature (Table 1) revealed that about 23% of patients who developed amiodarone pneumonitis died. It must be noted, however, that some of these deaths were probably due to a combination of drug-induced lung damage superimposed on an already severely compromised cardiopulmonary system.16

Pathogenesis

The pathogenesis of the pulmonary lesions
caused by amiodarone is not known. Some workers have suggested that they represent a hypersensitivity reaction, but there has been no convincing proof for such a mechanism. On the other hand, Marchlinski et al\(^7\) have postulated that this drug may cause abnormalities of lipid storage since the amiodarone molecule is amphipathic. This theory is consistent with the histologic findings of foamy macrophages.\(^29\) However, the mechanism of pulmonary damage and the discontinuation of therapy result in total reversal of the abnormalities in a few days to several months.\(^6\)

Table 1. Reports of incidence of amiodarone-induced pulmonary toxicity.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Patients</th>
<th>Affected</th>
<th>%</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heger et al(^4)</td>
<td>1981</td>
<td>196</td>
<td>7</td>
<td>3.6</td>
<td>3</td>
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<tr>
<td>Marchlinski et al(^7)</td>
<td>1982</td>
<td>70</td>
<td>4</td>
<td>6.0</td>
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<tr>
<td>Waxman et al(^8)</td>
<td>1982</td>
<td>51</td>
<td>5</td>
<td>9.8</td>
<td>2</td>
</tr>
<tr>
<td>Fogoros et al(^2)</td>
<td>1983</td>
<td>96</td>
<td>6</td>
<td>6.6</td>
<td>3</td>
</tr>
<tr>
<td>Grabeys et al(^1)</td>
<td>1983</td>
<td>121</td>
<td>4</td>
<td>3.3</td>
<td>0</td>
</tr>
<tr>
<td>Greene et al(^13)</td>
<td>1983</td>
<td>130</td>
<td>7 (6)*</td>
<td>5.4</td>
<td>2</td>
</tr>
<tr>
<td>Haffajee et al(^25)</td>
<td>1983</td>
<td>173</td>
<td>1</td>
<td>0.6</td>
<td>0</td>
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<tr>
<td>Harris et al(^11)</td>
<td>1983</td>
<td>140</td>
<td>1</td>
<td>0.7</td>
<td>0</td>
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<tr>
<td>McGovern et al(^24)</td>
<td>1983</td>
<td>80</td>
<td>4</td>
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<tr>
<td>Morady et al(^26)</td>
<td>1983</td>
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<td>8</td>
<td>5.0</td>
<td>1</td>
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<tr>
<td>Peter et al(^27)</td>
<td>1983</td>
<td>181</td>
<td>8</td>
<td>4.4</td>
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<tr>
<td>Kudenchuk et al(^16)</td>
<td>1983</td>
<td>69</td>
<td>9</td>
<td>13.0</td>
<td>2</td>
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<tr>
<td>Margo et al(^28)</td>
<td>1988</td>
<td>89</td>
<td>15</td>
<td>17.0</td>
<td>2</td>
</tr>
</tbody>
</table>

* Number in parenthesis indicates number of cases with possible pulmonary toxicity.

**Risk Factors**

There is reasonable evidence suggesting that amiodarone pneumonitis is dose related.\(^16,30\) This probably explains the disparity in the incidence of pulmonary toxicity between Europe and the United States. The maintenance dose in the United States (where amiodarone is used only as a last resort in patients with serious dysrhythmias who were unresponsive to conventional therapy) is four to six times greater than in Europe.\(^6\) The majority of the patients with lung toxicity were receiving maintenance doses of more than 600 mg/day.\(^6\) Suarez reported a patient who tolerated a dose of 200 mg/day of amiodarone for 5 days but then developed a pulmonary reaction when this dose was increased to 800 mg/day.\(^19\) Interestingly, Leech noted symptomatic and radiographic improvements in another patient with amiodarone-related lung disease when the dosage was decreased from 400 mg to 200 mg/day.\(^20\) Nevertheless, several cases of amiodarone pneumonitis have been reported in patients receiving less than 400 mg/day,\(^14,15,21,22\) and, occasionally, even in patients receiving low dose intermittent therapy.\(^21\) A recent study showed that the range of the cumulative dose was very wide (30.4 to 303.6 g) and did not correlate to pulmonary toxicity, whereas the higher maintenance dose did appear to be related to development of pneumonitis. Therefore, it is important to use the lowest effective maintenance dose.

Age of patient, history of congestive heart failure, cigarette smoking, and total loading dose have not been found to be risk factors for amiodarone pulmonary toxicity. The presence of pre-existing pulmonary disease, in the form of abnormal chest roentgenogram or diffusing capacity for carbon monoxide, is controversial as a risk factor. Kudenchuk et al\(^22\) found that pre-existing lung disease is a risk factor for pulmonary toxicity, and in such patients, alternative therapy should be considered. On the contrary, Margo et al\(^28\) found that pre-existing lung disease is not a risk factor and amiodarone may be safely used, regardless of pre-existing lung disease. However, it seems prudent to avoid amiodarone in such patients because superimposition of amiodarone pulmonary toxicity might present a severe and even fatal complication.\(^32\)

**Diagnosis**

The diagnosis of amiodarone pneumonitis is difficult with findings often indistinguishable from those of congestive heart failure or pulmonary infection. The usual features include cough, dyspnea, pulmonary infiltrations, and restrictive changes on pulmonary function testing. Compatible histological features are very helpful, however, biopsy is not essential for the diagnosis. It is important to rule out congestive heart failure and pulmonary infection. It is also important to have a high index of suspicion because if not detected early and treated, it may result in respiratory fail
ure or even death. Several studies have suggested that changes in pulmonary function tests may have diagnostic value in amiodarone pneumonitis. In a recent study, Margo et al observed a decrease in the forced vital capacity (FVC), the oxygen partial pressure (pO2), and the diffusing capacity for carbon monoxide. They found that a ~ 15% decrease in the diffusing capacity identified the presence of pulmonary toxicity with a sensitivity of 100% and specificity of 89%. This study also showed that Gallium-67 scintigraphy revealed abnormal uptake in 10 out of 11 patients. Although abnormal Gallium-67 scan is not diagnostic for any particular disorder, it is a very useful supportive evidence for amiodarone lung toxicity.

Every patient should have a baseline chest roentgenogram and pulmonary function tests before amiodarone therapy is initiated. Whenever symptoms suggestive of amiodarone pulmonary toxicity are noted, these tests should be repeated, in addition to a Gallium-67 scan. Is routine screening by serial pulmonary function testing advisable? Further prospective studies need to be done to answer this question.

Management

As soon as amiodarone pneumonitis is suspected, the drug should be discontinued. Usually, this results in total reversal of the abnormalities. Complete recovery takes a few days to several months. Corticosteroids have been used, but their role in accelerating resolution of the lesion is at present unclear, since in some cases, the lung infiltrates have recurred when tapering the dosage of steroids. Other patients have developed amiodarone pneumonitis during treatment with steroids for coincidental illness.

Conclusion

1. Amiodarone is one of the most potent antiarrhythmic drugs. However, in spite of the potency and other advantages, its use may be limited by numerous side effects, the most serious being pulmonary dysfunction which may even be fatal.
2. Its use should be restricted only after failure of conventional antiarrhythmic drugs in patients with disabling or life-threatening arrhythmias. Moreover, the patients should receive the smallest effective maintenance dose of this drug.
3. A baseline chest radiograph and pulmonary function tests should be done before initiation of therapy. Careful clinical follow-up and regular chest radiograms are important. When amiodarone pneumonitis is suspected, additional testing by Gallium-67 scan and pulmonary function studies should be done.
4. When pulmonary toxicity is suspected, prompt withdrawal of the drug and possible addition of steroids should result in relatively rapid recovery.
5. Use of this drug in the Kingdom should be restricted to a few specialist centers.

References

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