Amiodarone-Induced lung Toxicity

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Abstract

Amiodarone is one of the most frequently prescribed antiarrhythmic agents worldwide. Although it is extensively used in the treatment of life-threatening arrhythmias, it can act as a double-edged sword considering its potentially serious side effects which warrants careful patient selection. This is a review of amiodarone induced pulmonary toxicity, and its associated risk factors, pathogenesis, diagnosis, treatment and prognosis.


Keywords: Amiodarone “ Pulmonary toxicity ” Interstitial pneumonitis

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Introduction

Amiodarone is a class III anti-arrhythmic agent structurally related to thyroxine. Although originally developed as a new class of anti-anginal vasodilator, its derivative, desethylamiodarone, found to be a potent anti-arrhythmic agent with atypical class III Vaughan-Williams properties. It is one of the most frequently prescribed specific antiarrhythmic drugs in Europe and in the US. Amiodarone is an iodinated benzofuran drug with an adverse side effect profile, involving cornea, liver, lung, neuromuscular system, skin and thyroid. Until 1980, there were no reports in the world literature of pulmonary toxicity due to amiodarone. However, Rotmensh and associates suggested that this drug may have been responsible for the appearance of pulmonary infiltrates in one of their patients. In fact in spite of widespread use since 1967 amiodarone had not been reported to cause any form of pulmonary disorders until the report of Rotmensh et al., yet it was soon followed by Sobol et al. They reported 6 cases of potential amiodarone induced pulmonary toxicity in 432 patients who had life-threatening or severely symptomatic arrhythmias and were either resistant or intolerant to treatment with standard antiarrhythmic drugs. All of the reported patients for whom pathologic specimens of lung parenchyma were available had interstitial fibrosis and pneumonitis and none had clear predisposing factors or pathologic findings indicative of an identifiable etiology. Since then numerous reports have been published and amiodarone induced lung toxicity is now considered a recognized serious side effect which warrants frequent evaluation of treated patients.

Several forms of pulmonary disease occur among patients treated with amiodarone, the most common of which is chronic interstitial pneumonitis though bronchiolitis obliterans with organizing pneumonia, ARDS, a solitary pulmonary mass of fibrosis also occur. Prevalance

The incidence of pulmonary toxicity from amiodarone is not exactly known. Amiodarone pulmonary toxicity will develop in approximately 0.1% to 0.5% of patients that take up to 200 mg per day and 5 to 15% of patients that consume 500 mg or more per day. Recent studies have reported that the overall incidence is between 5 and 13%. A meta-analysis of amiodarone therapy estimated the risk of amiodarone pulmonary toxicity at 1% per year. Risk Factors

Potential risk factors for developing pulmonary toxicity are a high cumulative dose, a daily dose greater than 400 mg/day, duration of therapy exceeding 2 months, increased patient age, preexisting lung disease or an abnormal chest x-ray before the commencement of treatment with amiodarone and thoracic or non-thoracic surgery. Likewise, patients who undergo surgery and/or pulmonary angiography while on amiodarone therapy have an increased risk for developing amiodarone-induced pulmonary toxicity. Time course

In one third of cases, amiodarone pulmonary toxicity presents within weeks of commencement of the therapy. The patient typically complains of an abrupt onset of dyspnea, fever, and cough. The chest x-ray generally shows patchy alveolar infiltrates. This presentation occurs with doses of amiodarone as low as 100 mg per day. The more common form of amiodarone pulmonary toxicity has a gradual onset and typically presents after 2 or more months of therapy. This presentation is characterized by the progressive development of nonproductive cough, dyspnea, weight loss, and occasionally, low-grade fever. In this type, pulmonary infiltrates are more likely to be interstitial, and the usually occurs with higher doses of amiodarone which is usually 400 mg/d or more.

Pathogenesis

The mechanisms involved in amiodarone-induced pulmonary injury are incompletely understood. Several mechanisms have been proposed by which amiodarone results in pulmonary toxicity. Amiodarone impairs lipid metabolism, which increases cellular and phospho-lipid content, resulting in damage to the pulmonary endothelium. It can also produce toxic oxidants when exposed to high oxygen concentrations, further damaging cell membranes, which plays a part in the capillary leak syndrome related with adult respiratory distress syndrome. Hypersensitivity reactions have also been held responsible.
**Diagnosis**

Progressive dyspnea often is present for several weeks or months before the time of diagnosis. Malaise, non-productive cough and pleuritic chest pain also can be present. The physical examination often reveals bilateral inspiratory crackles, while clubbing is not seen. Radiology plays a key role in diagnosis. Chest x-rays show patchy or diffuse infiltrates, which are generally bilateral. High-resolution computed tomography (HRCT) scanning often reveals more advanced disease than noted on the chest x-ray. Parenchymal infiltrates that have high attenuation are typical and thought to be associated with the iodinated properties of the drug and its prolonged half-life in the lung. Yet it is not known whether this change in lung density indicates toxicity or the normal accumulation of amiodarone in lung tissue resulting from its therapeutic effects. Plasma levels of amiodarone are nondiagnostic, but elevated levels of its metabolite, desethylamiodarone, might be more frequent in patients with pulmonary toxicity.

**Treatment**

Once the diagnosis of amiodarone pulmonary toxicity is considered likely, the drug should be discontinued. After stopping, amiodarone resolution is likely to be slow and some degree of worsening may occur before improvement is noted. This has been attributed to the long elimination half-life of the drug and the tendency to concentrate in tissues such as the lung. Some authors have noted that the more insidious the onset of the disease, the slower the resolution. Discontinuation of amiodarone as the only therapeutic measure may be adequate, if disease extent is limited. The general consensus is that corticosteroid drugs should be given to patients who show extensive involvement on imaging or hypoxemia in the attempt to speed up the recovery process and perhaps to minimize the likelihood of lung fibrosis. Prednisone at 40 to 60 mg per day with a tapering dose over 2 to 6 months has been suggested as an appropriate regimen. If the patient’s pulmonary toxicity is not life threatening and amiodarone cannot be discontinued because it is the only or is the optimal therapy for a patient, lowering the dosage of amiodarone as much as possible along with administering low-dose steroids may be a option.

**Prognosis**

The prognosis of amiodarone lung disease is usually favourable when diagnosed early. However, more advanced disease may be fatal or result in pulmonary fibrosis. Clinical improvement and clearing of pulmonary opacities typically require 1–3 months. Radiological follow-up shows complete clearing in about 85% of patients; residual opacities persist in the remainder of patients. Mortality due to pulmonary toxicity is 5 to 10% when patients were on amiodarone dosages of more than 400 mg/d. Yet in patients who develop acute respiratory distress syndrome due to amiodarone pulmonary toxicity and require mechanical ventilation mortality is as high as 50 to 100%.

Despite frequent administration of amiodarone in our center, amiodarone induced pulmonary toxicity remains underrecognized.

**Conclusion**

Patients who should benefit from amiodarone should be carefully selected and the lowest effective dosage of amiodarone should be taken. Amiodarone-induced pulmonary toxicity is a diagnosis of exclusion. Pulmonary evaluation with chest X-ray and pulmonary function testing, including diffusion capacity for carbon monoxide is recommended when amiodarone is started.

**References**


