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Amiodarone-Induced Pulmonary Toxicity

Predisposing Factors, Clinical Symptoms and Treatment

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Summary

Amiodarone is frequently used for the treatment of cardiac arrhythmias. Although the therapeutic efficacy of amiodarone has been established, its use is limited by its safety profile. Amiodarone-induced pulmonary toxicity is one of the most life-threatening complications of this therapy. It is a relatively rare adverse effect of amiodarone and is easily missed by any physician who is suddenly confronted with nonspecific pulmonary complaints during amiodarone treatment. There are several cumulative factors which may enhance the susceptibility of patients for amiodarone-induced pulmonary toxicity, such as advanced age and pre-existing pulmonary dysfunction. Several case studies and clinical trials of amiodarone have shown the possible occurrence of amiodarone-induced pulmonary toxicity during low dose and short-duration therapy. Therefore, the dose and duration of amiodarone treatment are not the only determinants of toxicity risk.

Amiodarone-induced pulmonary toxicity is characterised by various clinical manifestations such as coughing, dyspnoea, fever, bodyweight loss, respiration-related chest pain and bilateral lung infiltrates with no escavated nodules.

Once amiodarone-induced pulmonary toxicity has been diagnosed, therapeutic options are limited, but in most cases the disease is reversible, if diagnosed at an early stage.

Amiodarone is frequently used for the treatment of cardiac arrhythmias. This class III antiarrhythmic drug was originally developed as an antianginal agent because of its vasodilatory properties. Amiodarone has become a reliable therapeutic agent in patients with severe underlying cardiomyopathy or coronary artery disease complicated by supraventricular or ventricular rhythm disturbances.[1,2] Although the therapeutic efficacy of amiodarone has been established, its general use is limited by its poor safety profile. The need for careful consideration of the risks and benefits of treatment before implementation of amiodarone is supported by the possible occurrence of a wide array of potentially serious adverse effects, such as abnormal liver function tests, thyroid dysfunction, etc. Noncardiovascular adverse effects occur more frequently than cardiovascular adverse effects such as proarrhythmia or exacerbation of heart failure.

Amiodarone-induced pulmonary toxicity remains one of the most life-threatening complications of this agent.[3] To decrease the adverse effects of amiodarone, the recommended maintenance dosage has been reduced to less than 300 mg/day.[4-9] In addition, it is desirable to identify possible risk factors in each patient before commencing amiodarone therapy. Subsequently, patients at an increased risk for amiodarone toxicity should be monitored more closely, or protective measures should be implemented or alternative therapeutic options used.

1. Pharmacology

Physicians who prescribe amiodarone should be aware of several important aspects of its complex pharmacokinetic profile. This will enable potential adverse effects to be anticipated.

Non-soluble amiodarone is prepared with the solvent polysorbate 80 which contributes to the hypotensive effect during intravenous administration. In addition, polysorbate 80 decreases the heart rate, depresses atrioventricular node conduction and increases the refractory period of the atrial and ventricular myocardium.[4] After intravenous administration, amiodarone is widely distributed in a 3-compartment model which explains the observed phases of plasma elimination. A short initial half-life is followed by a longer elimination period. In addition to a small central compartment, there is a large deep compartment which consists of the lymph nodes, liver, lung and fat tissue and a peripheral compartment composed of muscle and brain. The longer the duration of the intravenous amiodarone infusion, the greater the amount of parent drug and metabolite that is deposited in the deep compartment. The large accumulation of amiodarone in the deep compartment accounts for the delay in onset of the therapeutic effect of this agent.

The bioavailability of oral amiodarone varies from 30 to 70% of that of intravenous amiodarone and appears to be lower in elderly patients and those with cardiopulmonary disease. The dosage does not need to be adjusted in patients with renal failure, because the agent is eliminated through the biliary system.

Serum amiodarone concentrations are decreased by concomitant administration of barbiturates and increased by concomitant administration of cimetidine.

Amiodarone may induce a clinically significant reduction in the defibrillation threshold. Hypotension is a predominant haemodynamic effect of intravenous amiodarone and occurs in 10 to 30% of patients treated with this agent by this route. The hypotension is caused by a combination of arterial vasodilation and negative inotropy. Low blood pressure may be reduced by slowing the infusion rate. The direct negative inotropic effect caused by the antisympathetic action of amiodarone is minimal and transient. Long term oral amiodarone therapy increases the refractory periods of all cardiac tissues. In contrast, intravenous administration of amiodarone only influences the atrioventricular node. Moreover, a significant increase of conduction delay at faster heart rates (use-dependent effects) that is observed during oral therapy remains absent when amiodarone is administered intravenously.[10]

2. Pulmonary Toxicity

Amiodarone pulmonary toxicity was first described by Rotmensch in 1980.[11] The incidence of amiodarone pulmonary toxicity varies from between 5 and 10% of patients who receive the agent, and the outcome is fatal in a considerable number of patients.[12] However, in recent heart failure and post–myocardial infarction trials amiodarone-induced pulmonary toxicity occurred in relatively few patients.[2,6,8]

Amiodarone-induced pulmonary toxicity is characterised by various pulmonary manifestations.[13] The association between the clinical pulmonary symptoms and amiodarone therapy may not be immediately recognised. Moreover, amiodarone-induced pulmonary toxicity is often difficult to establish in patients with cardiomyopathy or serious coronary artery disease who present with nonspecific pulmonary symptoms and findings. The differential diagnosis may include complications of these underlying diseases, such as manifest cardiac failure, pneumonia and pulmonary embolism.

2.1 Mechanisms

The cause of amiodarone pulmonary toxicity is probably multifactorial.[14] Amiodarone and its metabolites can damage lung tissue indirectly, via immunological reactions, or directly, via a cytotoxic process. In patients with amiodarone-induced pulmonary toxicity, CD8-positive, cytotoxic T cells have been found in the bronchoalveolar lavage,[15,16] often in combination with polymorphonuclear cells. It has been shown that amiodarone influences the production of toxic oxygen radicals.[17] Moreover, amiodarone may induce accumulation of phospholipids in the tissues. These phospholipids have a direct cytotoxic effect on the alveolar-capillary membrane in the lung. Although, plasma amiodarone concentrations correlate with an increased risk of developing adverse effects,[18] it is not possible to predict or confirm the presence of amiodarone-induced pulmonary toxicity by plasma or tissue concentrations.

Clinical evidence suggests that the risk of a patient experiencing amiodarone-associated adverse effects increases as dosage and duration of therapy increases.[19-21] Most amiodarone-induced pulmonary manifestations are found to occur when the dosage exceeds 400 mg/day administered for more than 2 months or when a lower dosage is given for more than 2 years.[19-21] We reviewed the current clinical use of amiodarone therapy and concluded that amiodarone-induced pulmonary toxicity may also appear during low dose therapy and following a relatively short course of treatment in high risk patients.

The overall risk of amiodarone pulmonary toxicity may correlate with the total cumulative dose,[22] but not with the daily dosage and plasma concentrations.[3] However, since the incidence of this adverse effect is small, this cannot be verified with certainty.

2.2 Clinical Presentation

Patients with amiodarone-induced pulmonary toxicity usually present with insidious, evolving, nonspecific symptoms, such as coughing, dyspnoea, fever, bodyweight loss, respiration-related chest pain and bilateral lung-infiltrates without escavated nodules. It is important to realise that nonspecific complaints caused by amiodarone-induced pulmonary toxicity may be masked at first by the symptoms of overt cardiac failure on admission of a critically ill patient. The symptoms of amiodarone-induced pulmonary toxicity may subsequently emerge only after treatment of the underlying cardiac or pulmonary disease.[23,24] In fact, this may delay establishing the diagnosis of amiodarone-induced pulmonary toxicity, thereby increasing the risk of a fatal outcome.

The diagnosis of amiodarone-induced pulmonary toxicity is made after other causes of pulmonary disease are excluded, such as malignancy, infection or collagen disorders. A combination of clinical, radiological (reticular pattern, hyperinflation, or ground glass),[25] lung function tests (often obstructive, sometimes mixed or restrictive), and histological findings may support the diagnosis of

amiodarone-induced pulmonary toxicity. In addition, nuclear scans may contribute to the diagnosis of the clinical syndrome. Bronchoalveolar lavage and lung biopsy should not show any signs of malignancy or infection. There is, however, an increase in the number of CD8 lymphocytes, polymorphonuclear cells and 'foamy' macrophages. The presence of lamellar inclusion bodies is a specific histopathological finding which is associated with the cytotoxicity of amiodarone. Laboratory findings, though not pathognomonic, may help in the differential diagnosis by showing high levels of lactate dehydrogenase, hypergammaglobulinaemia and leucocytosis.

The variety of clinical-radiological presentations of amiodarone pulmonary toxicity, its evolution and response to therapy, make it necessary to differentiate between bronchiolitis obliterans, bronchiolitis obliterans organising pneumonia, and other infiltrative pulmonary abnormalities such as chronic eosinophilic pneumonia and interstitial pneumonitis. Both bronchiolitis obliterans and bronchiolitis obliterans organising pneumonia are associated with a more benign course and respond better to corticosteroids than the other infiltrative pulmonary diseases.[26] Bronchiolitis obliterans organising pneumonia is a pathological-anatomical entity which is characterised by destruction of the small airways by a nonspecific inflammation.[27] The possible association between amiodarone and the development of bronchiolitis obliterans organising pneumonia has rarely been described.[23]

2.3 Risk Factors

It is generally assumed that amiodarone-induced pulmonary toxicity only occurs when high dosages of amiodarone are used for an extended period of time. However, a low maintenance dosage (<300 mg/day) of amiodarone might also be toxic.[6,8,9,28,29] Moreover, there is an early peak incidence of amiodarone-induced pulmonary toxicity in the first 12 months after initiation of amiodarone treatment even if the agent is given at a low dosage.[12]

This early peak incidence is seen because of the existence of several potential predisposing factors for amiodarone-induced pulmonary toxicity, such as advanced age, pre-existent pulmonary abnormalities or other as yet unrecognised factors.[16,30] In pre-existent lung disease, it is possible that a reduced amount of functioning lung tissue is exposed to a higher tissue concentration during standard dose therapy with amiodarone.[31] Therefore, in certain subsets of high risk patients low dosage amiodarone may produce early onset pulmonary toxicity.[32,33] Cardiopulmonary surgery combined with the administration of oxygen giving a high oxygen concentration appears to predispose patients to amiodarone-induced lung toxicity.[34-37] We do not have any firm recommendations concerning routine baseline measurements for the prevention of amiodarone-induced pulmonary toxicity. However, we suggest that at least 1 chest x-ray should be taken before amiodarone treatment is started. Pulmonary function tests have no predictive value for toxicity.[38,39] The recognition of the high risk patient should lead to regular follow-up visits with subsequent diagnostic procedures according to clinical findings.

2.4 Treatment

Once amiodarone pulmonary toxicity has been established, the therapeutic alternatives are limited. In our experience, cessation of the therapy with amiodarone is the first option, but there is a risk that life-threatening arrhythmias will recur. This risk can be decreased by substitution of another antiarrhythmic alternative such as a IA, IC or other class III agent. However, the negative inotropic and proarrhythmic effects of these alternative drugs remain a potential disadvantage.

A second treatment option is to withhold amiodarone for several days and reduce the dosage to the lowest effective level. At present, most electrophysiologists will consider nonpharmacological therapeutic methods, such as radiofrequency ablation of the causative re-entry mechanism or implantation of an automatic cardioverter defibrillator.

Even when amiodarone therapy is discontinued, the toxic effect may persist, because of the long

elimination half-life of the agent (up to 45 days). The value of corticosteroid therapy in this setting is uncertain. However, it seems that early treatment with corticosteroids of amiodarone-related bronchiolitis obliterans organising pneumonia increases the likelihood of reversal. More than 60% of patients with subacute bronchiolitis obliterans organising pneumonia resulting from amiodarone toxicity respond successfully to corticosteroids. If no corticosteroid therapy is given, the mortality is 50%. However, 25% patients are unresponsive to, and 15% die despite of, corticosteroid treatment.[27,33] In general, we recommend at least 6 months of maintenance therapy with corticosteroids because of the chance of relapse of the pulmonary disorder.

3. Conclusion

Amiodarone pulmonary toxicity is a complex lung syndrome, which may have a fatal outcome. The clinical presentation of the damaging effect of amiodarone on pulmonary function is easily masked by a pre-existent cardiopulmonary disorder. The presence of underlying lung disease in the high-risk patient may enhance amiodarone-induced pulmonary toxicity even if low amiodarone dosages are used. Therefore, the cumulative influence of other risk factors, such as cardiac, liver or pulmonary dysfunction, must be considered in each patient in the evaluation of the benefit : risk ratio of amiodarone therapy. Clinicians should be alert to amiodarone-induced pulmonary toxicity, regardless of the dosage and duration of amiodarone therapy. In the presence of nonspecific pulmonary symptoms, pre-existent lung disease and the older patient group, amiodarone-related toxicity symptoms should be considered after other causes such as pulmonary embolism and cardiac failure are excluded or treated. In most cases of amiodarone-induced pulmonary toxicity, in particular bronchiolitis obliterans and bronchiolitis obliterans organising pneumonia, the disease is reversible unless the diagnosis is established at an early stage.

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