CASO CLÍNICO

Acute pulmonary toxicity in a patient receiving short course therapy with low-dose amiodarone

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Resumen

La amiodarona es un medicamento antiarrítmico asociado a varios efectos adversos, de los cuales los pulmonares son los de mayor gravedad. Se presenta el caso de una paciente de 85 años con antecedentes de enfermedad pulmonar obstructiva crónica que después de seis días de recibir dosis bajas de amiodarona (200 mg/día) para tratamiento y profilaxis de fibrilación auricular, desarrolló insuficiencia respiratoria aguda, hipoxemia e infiltrados pulmonares. No respondió al manejo con diuréticos, inotrópico, ventilación mecánica y antibióticos. La evaluación diagnóstica del cuadro que presentó la enferma, se concluyó, fue secundario a la administración de amiodarona, ya que no se corroboraron otras posibles causas y por la excelente respuesta a la suspensión del medicamento y al empleo de esteroides. Con base en lo anterior, es recomendable considerar que la amiodarona aún a dosis bajas y por cortos periodos puede inducir complicaciones pulmonares graves caracterizadas por insuficiencia respiratoria, hipoxemia e infiltrados pulmonares.

Palabras clave. Toxicidad pulmonar, esteroides, agentes antiarrítmicos.

Abstract

Amiodarone is an effective antiarrhytmic drug. It's use may lead to several adverse effects, with lung toxicity being the most serious. We present the case of 85 year old patient with a history of chronic obstructive pulmonary disease who after 6 days of low dose of amiodarone therapy (200 mg daily) for treatment and prophylaxis of atrial fibrillation developed acute respiratory failure, hypoxemia and lung infiltrates. The patient failed to respond to diuretic, inotropic, mechanical ventilation and anti-infective therapy. Differential diagnosis of different causes of pulmonary infiltrates did not demonstrate any other abnormality therefore led to the diagnosis of amiodarone pulmonary toxicity. Pulmonary infiltrates and hypoxemia reversed with the suspension of amiodarone and treatment with steroids. Given the widespread use of amiodarone it's important consider this serious adverse effect as a differential diagnosis in patients treated with amiodarone even at low doses and for short periods who present respiratory symtomatology, hypoxemia or pulmonary infiltrates.

Key words. Pulmonary toxicity. Steroids. Anti-arrhythmia agents.

INTRODUCTION

Amiodarone is an effective antiarrhytmic agent for treatment of supraventricular and ventricular tachyarritmias and is associated to several cardiac and non-cardiac adverse reactions. Amiodarone-induced pulmonary toxicity (APT) is the most serious side effect and potentially fatal. It remains underdiagnosed and can have a variable presentation. The elderly population is at increased risk for APT, especially those who receive high doses. Thus, clinicians should prescribe the lowest dose possible in the elderly and have a low threshold to discontinue the amiodarone for anyone with fatigue, dyspnea, cough, fever and pulmonary infiltrates.[1,2]

The aim of this paper is to describe the case of an elderly patient who developed acute pulmonary toxicity with low doses of amiodarone and literature review.

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CASE REPORT

85 year old female with history of smoking and COPD is admitted to the intensive care unit (ICU) with hemorrhagic shock. During her stay in the ICU the patient developed atrial fibrillation (AF) with mean heart rate of 160 which condition hemodynamic deterioration. EKG showed left auricle dilation with a diameter of 6 cm, thickened left ventricle wall and diastolic dysfunction. Cardioversion was done without any improvement and amiodarone and beta blockers were started. Impregnation dose of amiodarone was 750 mg with a 300 mg/24 h drip. With this medical treatment heart rate was controlled and the arrhythmia disappeared. Progressively the patient started with dyspnea, cough, fever, and rales. Chest X-ray showed bilateral basal infiltrates, these findings were corroborated with a thorax computerized tomography (CT). The patient started with respiratory failure which deserved orothaqueal intubation and mechanical ventilation. To rule out cardiac insufficiency a new echocardiogram was done, it showed an ejection fraction (EF) of 65%, moderate diastolic dysfunction and moderate mitral valve insufficiency. Natriuretic peptide B was under normal limits. Cultures at all levels were done. CMV antibodies PCR determination was done. All cultures and CMV determination were negative. Bronchoalveolar lavage showed abundant lymphocytes and polymorphonuclear cells. Once all the possible causes of the infiltrates were ruled out, and without any

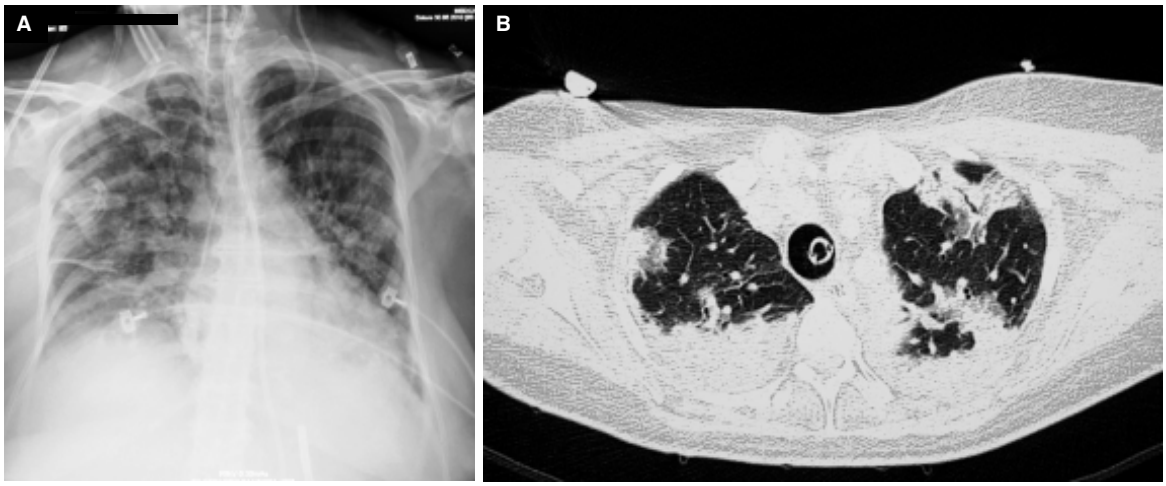

Figure 1. Imaging studies in a patient with amiodarone pulmonary toxicity. **A.** Chest X-ray with interstitial and reticulonodular infiltrates. **B.** Lung CT-scan with extensive areas of infiltration and consolidation.

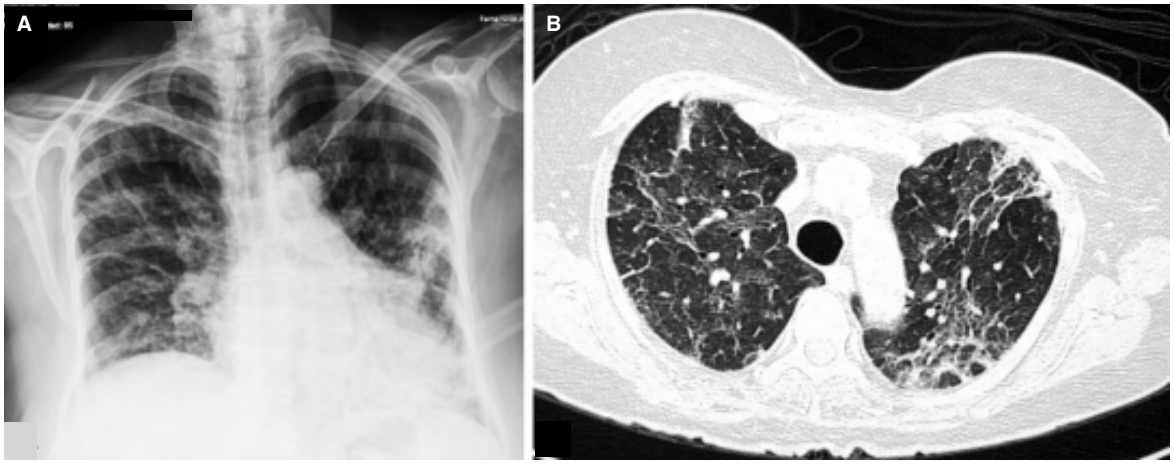

Figure 2. Improvement of pulmonary infiltrates following suspension of amiodarone and treatment with steroids. **A.** Chest radiography with resolution of infiltrates. **B.** Lung CT-scan with involution of the infiltrates and pulmonary condensation.

response to the diuretics, inotropics and antibiotics, amiodarone toxicity diagnosis was done (Figure 1). Amiodarone were suspended and Ibesartan (75 mg/day), vitamin E, and methylprednisolone (500 mg bolus) were started during three days. After this initial treatment prednisone (1 mg/kg/day) was started. With this treatment the patient improved, showing better gas exchange and showing no infiltrates, after all this, mechanical ventilation was stopped and was discharged from the ICU (Figure 2).

DISCUSSION

The popularity of amiodarone is explained by its efficacy and usefulness in reducing and preventing arrhythmias such as recurrent ventricular tachycardia and ventricular fibrillation. Amiodarone slows the ventricular response to atrial fibrillation and atrial flutter, in some patients convert atrial fibrillation to sinus rhythm, can maintain sinus rhythm in patients with paroxysmal atrial fibrillation and has been used prophylactically in the perioperative period in patients undergoing cardiac surgery.[3,4]

Amiodarone and monodesethylamiodarone accumulate in peripheral tissues over long periods because their peculiar pharmacokinetics, large distribution volume and long elimination half-life. An important property of amiodarone is its high lipid solubility. It tends to accumulate extensively in adipose tissue and highly perfused organs as the liver, lungs and spleen. Increase duration of therapy tends to increase the prevalence rate and risk of developing APT, principally in the first year. In the 1980's, the use of high doses of amiodarone was identified as a major cause of ATP.[5] Dussman[6] showed that the prevalence rate reached 9.1% and was 5.8% in total in patients receiving a daily dose of 400-500 mg. A meta-analysis of relative low dose (< 400 mg/24 h), placebo-controlled trials showed a 1.9% incidence de APT in 738 patients receiving amiodarone *vs*. 0.7% in 727 patients receiving placebo, the combined odds ratio was 2.2.[7]

In the 1990's the recommended maintenance dose of amiodarone was reduced of 400 to 200 mg daily to avoid adverse effects, however several reports concluded that APT could occur in patients receiving low (200 mg daily), or very low doses (100-150 mg daily) of amiodarone.[8,9]

Although pulmonary toxicity usually manifests after several months of therapy, it has been documented as early as within six days or secondary to impregnation dose even at low doses, which is related to the case reported. 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.[10,11]

Amiodarone and its metabolites can produce damage directly by a cytotoxic effect and indirectly by an immunological reaction. Amiodarone induce the production of toxic oxygen radicals and to promote the accumulation of phospholipids in tissues. Another mechanism of APT is attributed to stimulation of the angiotensin enzyme system leading to lung cell apoptosis and cell death. The inflammatory lung process in APT is supported by the finding of cytotoxic T cells in bronchoalveolar lavage fluid. The lungs of patients with APT show diffuse interstitial pneumonitis. The lung of patients with APT show a diffuse interstitial pneumonitis, hyperplasia of type II pneumocytes, lipid laden foamy macrophages in alveolar spaces, cytoplasmic lamellar bodies and less frequently patchy bronquiolitis obliterans, organizing pneumonia and in severe cases diffuse alveolar damage with hyaline membrane and alveolar hemorrhage. Amiodarone-induced pulmonary fibrosis develops in 5 to 7% of patients following amiodarone pneumonitis.[12,13]

The most common clinical presentation in patients with APT is an alveolar interstitial pneumonitis with subacute onset, but there are some cases characterized by acute onset of respiratory failure and acute respiratory distress syndrome (ARDS), especially in the immediate postoperative period of cardiac or lung surgery. APT is more frequent in man and elderly patients. There is evidence that exposure to supplemental oxygen especially in high concentration alone or combined with mechanical ventilation and thoracic surgery may potentiate APT. Patients usually present with progressive shortness of breath, nonproductive cough, malaise, fever and chest pain. Physical examination may be unremarkable in milder cases but in more severely affected individuals, diffuse rales, hypoxemia and respiratory distress be noted. In one series, symptoms of APT were most commonly dyspnea (71%), cough (25%), fever (21%), nausea (7%), weakness or fatigue (7%), weight loss (4%) and pleuritic chest pain (4%).[13-15]

Radiology plays a central role in diagnosis because laboratory studies and pulmonary function tests are nonspecific for the diagnosis. Laboratory data may reveal a leukocytosis. A nonspecific elevation in lactic dehydrogenase or serum KL-6, a mucin like glycoprotein, is often present. Pulmonary function tests usually reveals low lung volumes and a restrictive pattern. A reduced difussing capacity of the lung for carbon monoxide, at least 15-20%, is sensitive but nonspecific diagnostic marker.[16-18]

Chest X-rays reveal patchy or diffuse bilateral infiltrates. Some infiltrates have ground glass appearance. The right

lung is more frequently involved than left lung. Lung computed tomography scanning reveals bilateral interstitial, alveolar or mixed infiltrates, high attenuation areas in infiltrates, lung nodules, dense bibasal reticular opacities (fibrosis) and traction bronquiectasias. Ground glass opacities are often distributed in a peripheral manner and may be an early finding in APT.[19,20]

Diagnosis of APT is usually based on clinical and radiographic findings, the exclusion of differential alternatives, the demonstration of pulmonary function abnormalities compatible with APT, and foamy cells found in a lung biopsy specimen. APT often mimic heart failure, pulmonary emboli and pneumonia, requiring exclusion of these competing diagnoses. In a series of patients suspected of having APT, a final diagnosis of APT was made in 55% of the patients, the remaining were diagnosed with congestive heart failure (36%), pneumonia (6%) and pulmonary embolism (2%).[21]

Once the diagnosis of APT amiodarone should be discontinued. Systemic steroids are recommended. Prednisone is started in doses of 40 to 60 mg/day and tapered slowly. In severe APT, like ARDS, can start treatment with methylprednisolone. The prognosis of amiodarone lung disease is generally favourable when diagnosed early. However more advanced or severe disease may be fatal or result in pulmonary fibrosis. APT.[22]

The strategies that appears to be efficacious to prevent APT is that of using the smallest amiodarone dose possible and the concomitant use of vitamin E, ACE-I or ARB in patients taking amiodarone.[23,24]

CONCLUSION

Amiodarone is an antiarrhythmic agent commonly used to treat supraventricular and ventricular arrhythmias. It has been associated with a variety of adverse events. Of these events, the most serious is amiodarone pulmonary toxicity. Although the incidence of this complication has decreased with the use of lower doses of amiodarone, it can occur with any dose. Most patients diagnosed promptly respond well to the withdrawal of amiodarone and the administration of corticosteroids.

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