

## Suspected amiodarone-hypersensitivity pneumonitis

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Amiodarone is an iodinated benzofuran derivative used in the treatment of supraventricular and ventricular arrhythmias refractory to conventional therapy. It has complex pharmacokinetics and the potential for a wide range of adverse effects. Amiodarone pulmonary toxicity is the most serious adverse event and is well documented in the literature. We report a fatal case of respiratory failure shortly after the initiation of amiodarone therapy.

### CASE

An 84-year-old woman presented to hospital with generalized weakness and a weight loss of 10 kg over three months prior to admission. Her medical history included a myocardial infarction, ischemic heart disease, congestive heart failure, atrial fibrillation, hypertension, hyperlipidemia, macular degeneration, gastroesophageal reflux disease, diverticulitis and chronic urinary tract infections. The patient had never smoked and did not require oxygen prior to admission. A report from a radiologist noted interstitial fibrosis on chest x-ray one month prior to hospital admission. There was no further work-up of this diagnosis noted in the patient's chart. Medications on admission included a nitroglycerin patch 0.4 mg/hr on at 0800h and off at 2000h, digoxin 0.25 mg daily, docusate sodium 200 mg daily, foscarnil 2.5 mg daily, furosemide 40 mg 2 times a day, omeprazole 20 mg daily, potassium 20 mEq daily and warfarin 2.5-5.0

mg daily. These were the maximum tolerated doses with further increases limited by hypotension and decreased heart rate. A cardiology consult suggested the recent aggravation of congestive heart failure was likely related to diastolic dysfunction aggravated by intermittent atrial fibrillation and ischemia. The consult recommended discontinuation of foscarnil and initiation of amiodarone 400 mg 2 times a day for 2 weeks, followed by 400 mg daily for 1 month, then decreased to 200 mg daily.

Two days after the initiation of amiodarone, the patient developed a sudden onset of dry cough and pleuritic chest pain, requiring increased effort to breathe. She was transferred from the geriatric assessment unit to a general medicine ward under the care of an internist. Her respiratory rate increased to 30-40 breaths per minute. Oxygen saturation on room air was 80%, and oxygen was instituted at 2 L/min, which increased oxygen saturation to 92%. Blood and urine cultures were negative. Body temperature was 39.2°C. No peripheral edema or increase in jugular venous pressure (JVP) was noted. On exam, there was decreased air entry bilaterally with basal creps notes. Amiodarone toxicity was suspected and the drug was discontinued after a cumulative dose of 2400 mg. Within 72 hours, a chest x-ray revealed consolidation. The patient was found to have an elevated digoxin level of 3.4 nmol/L (1.0-2.6 nmol/L), WBC 19.1 (4.0-10 x 10<sup>9</sup>/L) with a left shift, pH 7.43 (7.35-7.45), pCO<sub>2</sub> 21.4 (22-26 mmol/L). Oxygen was increased to 8-9 L/min to keep the oxygen saturation at 92%.

On the fourth day after initiating amiodarone, the patient was transferred to the intensive care unit as oxygen saturation dipped to 72% on 9 L/min of O<sub>2</sub>. On admission, she was afebrile with a pulse of 70 beats per minute, blood pressure of 134/64 mmHg, and respiratory rate of 30. JVP was not elevated, and there were no pedal edema, S3 or S4 heart sounds or murmurs. Her white-blood-cell count was 21.3 with a left shift, blood urea nitrogen 21.5 (2.1-7.5 mmol/L), and her serum creatinine 215 (60-130 µmol/L). The

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patient was on 100% oxygen via a high-flow mask and had the following blood gases: pH 7.37, pCO<sub>2</sub> 45.5 mmHg, pO<sub>2</sub> 34.5 mmHg and HCO<sub>3</sub> 25.7 mmol/L. Respiratory failure was thought to be bacterial or viral in origin or related to amiodarone. The patient was started on cefuroxime 750 mg IV every 8 hours, erythromycin 500 mg IV every 6 hours. The following day metronidazole 500 mg IV every 8 hours was added. However, blood, urine and sputum cultures were all negative. Viral serology, stain for pneumocystis, bronchial washing for cytomegalovirus and legionella, and all fungal cultures were negative. The bronchial washings were not tested for bacterial growth and there was no lung biopsy. After 3 days, there was no improvement in respiratory function and the antibiotics were changed to piperacillin/tazobactam 3.375 gm every 6 hours and doxycycline 100 mg every 12 hours. On day 7, the patient developed a gastrointestinal bleed, and on day 8 she was intubated and ventilated. Twelve days later, she developed a right pneumothorax and a chest tube was inserted. On day 15, candida albicans was cultured in the patient's urine and sputum. Piperacillin/tazobactam was discontinued and replaced with fluconazole 200 mg IV 2 times a day. Despite 10 days of treatment with fluconazole, the patient's respiratory status continued to decline and life support was withdrawn. She did not receive a course of corticosteroids during her hospital stay.

## DISCUSSION

Interstitial pneumonitis (or alveolitis), hypersensitivity pneumonitis and pulmonary fibrosis have been reported in up to 10–17% of patients receiving amiodarone.<sup>1–5</sup> Hypersensitivity pneumonitis has been reported in approximately one-third of these patients and may occur earlier than interstitial pneumonitis.<sup>4</sup> The mechanism of toxicity may be the result of phospholipid deposition in the lung tissue<sup>6–8</sup> or an immunologic reaction.<sup>2,3,7,9</sup> Other mechanisms proposed include oxidant mediated damage,<sup>7,10</sup> direct detergent effect or the toxic effect of iodide.<sup>3,7</sup>

There are two types of clinical presentations of amiodarone pulmonary toxicity: an acute type or the more common subacute/chronic type.<sup>2,4</sup> Early symptoms in most patients with pulmonary toxicity consist of exertional dyspnea,<sup>1–3,6,8,9,11–17</sup> nonproductive cough,<sup>1–3,6,8,9,11,13–15</sup> nausea,<sup>1,9,11</sup>

weight loss,<sup>1,3,6,8,14</sup> and occasionally a low-grade fever<sup>1–3,6,11,15</sup> without sweats or chills.<sup>6</sup> Several patients have complained of muscle weakness, fatigue and pleuritic chest pain.<sup>1–3,6,9,11</sup> Acute presentations of hypersensitivity pneumonitis may include fever, pleuritic chest pain and cough resembling infection. These features may also be present in the subacute/chronic type of presentation along with exertional dyspnea, malaise and weight loss. Our patient complained of a nonproductive cough and pleuritic chest pain, and she had a fever. Clinically, it looked like she had an infection, but she did not respond to broad-spectrum antibiotics.

Physical findings usually include rales or decreased breath sounds.<sup>2,6,14</sup> The white-blood-cell count is typically normal to markedly elevated.<sup>3,6,11,14</sup> The erythrocyte sedimentation rate (ESR) is elevated in most cases.<sup>3,6,9,14,16</sup> Liver function tests may be normal but lactate dehydrogenase (LDH) may be mildly elevated.<sup>3,6</sup> Radiographic findings characteristically consist of alveolar or interstitial infiltrates that can be bilateral and diffuse, or patchy and focal.<sup>1–3,6,8,9,11,15,18</sup> Gallium lung scan may reveal abnormal radioisotope uptake consistent with amiodarone pulmonary toxicity.<sup>1–3,19</sup> Bronchial alveolar lavage and biopsy would show the presence of foamy macrophages and lamellated cytoplasmic inclusions in the alveolar macrophages.<sup>2,3</sup> These lipid-laden alveolar macrophages may also be seen in patients treated with amiodarone, without evidence of pulmonary toxicity.<sup>2,3</sup> In patients treated with amiodarone, absence of these histopathologic changes within the alveolar macrophages makes the diagnosis of amiodarone pulmonary toxicity unlikely.<sup>2</sup> Our patient had an elevated white-blood-cell count and consolidation was noted on chest x-ray. On exam, she had decreased air entry bilaterally with basal creps. No tests were done for ESR and LDH. Unfortunately, neither a lung biopsy nor a gallium scan was carried out to confirm the diagnosis of amiodarone pulmonary toxicity.

It is not clear if pretreatment spirometric or lung volume measurements help to identify patients who may be predisposed to developing pulmonary toxicity.<sup>1,2,6</sup> Rikita<sup>6</sup> studied the effects of amiodarone on pulmonary function tests in 35 patients. Tests of vital capacity, including forced expiratory volume in

one second (FEV1), total lung capacity (TLC) and the diffusing capacity of carbon monoxide (DLCO) were conducted and reviewed by pulmonologists who were blinded to treatment with amiodarone. There was no significant correlation between the cumulative dose of amiodarone and FEV1, forced vital capacity, TLC or DLCO. Pulmonary function tests in patients with clinical pulmonary toxicity have shown a decrease in TLC, DLCO and vital capacity (VC).<sup>2,4</sup> A pretreatment DLCO decreased by at least 15% may be a potential risk factor for developing pulmonary toxicity.<sup>1-3,11</sup>

The literature suggests toxicity is more commonly seen with doses greater than 500–600 mg/day<sup>1,2,6</sup> but may occur with dosages between 100 mg/day<sup>8,13</sup> and 200 mg/day.<sup>9,12,14,16</sup> The CAMIAT trial reported the use of amiodarone maintenance doses of 300 or 400 mg/day.<sup>20</sup> Medication was stopped due to the development of pulmonary side effects in 1.2% of placebo patients versus 3.8% in the amiodarone group ( $p=0.005$ ). There were no deaths due to pulmonary toxicity. The EMIAT trial reported daily dosages of 200 mg/day.<sup>21</sup> Pulmonary adverse effects were reported in 4.0% of placebo arm versus 5.2% in the amiodarone group. There were 3 deaths from pulmonary fibrosis in the amiodarone group; however, 2 of these patients had existing pulmonary disease and, in the authors' words, "should have been excluded from the trial". Voperian<sup>22</sup> conducted a meta-analysis on the use of low-dose amiodarone (less than 400 mg/day). Pulmonary toxicity occurred in 0.7% of patients receiving placebo versus 1.9% receiving amiodarone. This difference was not statistically significant ( $p=0.073$ ). Dusman<sup>1</sup> noted patients who developed pulmonary toxicity were older at initiation of therapy (mean age of 62.17 years). Increased amiodarone and desmethylamiodarone plasma levels have been associated with toxicity.<sup>1,10</sup> Most cases of pulmonary toxicity occur during the first 12 months of therapy;<sup>1,11,12,16,17</sup> however, toxicity has been reported after 2–9 years.<sup>8,11,14,17,23</sup>

Amiodarone pulmonary toxicity has developed with 1 week of initiation of therapy. A 74-year-old man received a 300 mg intravenous bolus of amiodarone on days 1 and 5, followed by a continuous infusion of 50 mg/hr for 6 days.<sup>18</sup> Two days after being weaned off the ventilator he developed wheezing. Chest x-rays showed pulmonary infiltrates. The airway obstruction

did not respond to salbutamol and ipratropium, and an IV infusion of methylprednisolone 40 mg every 6 hours was started. Bronchoalveolar lavage revealed phospholipid accumulation of alveolar macrophages consistent with amiodarone pulmonary toxicity. The patient developed further complications and died 4 weeks later.

In another case, pulmonary toxicity occurred after 6 days of 800 mg/day of oral amiodarone.<sup>1</sup> The drug was discontinued because of a recurrent arrhythmia. The toxicity was discovered on preoperative evaluation 1 month later and the patient was found to have interstitial infiltrates on chest x-ray, mild dyspnea and an abnormal gallium lung uptake. Histologic examination of lung tissue obtained by bronchoscopy and confirmed by open lung biopsy was consistent with amiodarone-associated pulmonary toxicity.

A 7-month-old infant developed pulmonary toxicity after 8 days of IV amiodarone 10 mg/kg/day.<sup>24</sup> The patient's oxygen requirements did not allow him to be weaned or extubated from the ventilator. A chest x-ray showed diffuse alveolar and interstitial infiltrates. Bronchoalveolar lavage on the ninth day showed the presence of foamy macrophages. There were no other clinical signs consistent with an infectious process or congestive heart failure, and amiodarone was discontinued on day 11. Two days later, his respiratory status improved and he was weaned from the ventilator. At a 3-month follow-up, he continued to do well, and chest x-rays and pulmonary function tests were normal.

A 70-year-old man developed pulmonary toxicity after receiving an IV loading dose of amiodarone followed by an oral regimen of 400 mg/day for one week and a maintenance dose of 200 mg/day.<sup>25</sup> Fifteen days after initiating amiodarone, he was readmitted for progressive dyspnea and fever, and cough which had begun 5 days later. Two days before admission he experiences hemoptysis. On exam, he had decreased air entry with bibasilar rales. A chest x-ray showed bibasilar alveolointerstitial infiltrates. He had an elevated ESR of 105 mm (normal less than 20 mm/hr) and an elevated leukocyte count of 12.2 (4–10 x 10<sup>9</sup>/L). Blood and sputum cultures were negative. A transbronchial lung biopsy showed alveolar foamy cells and focal fibrosis. On day 11, amiodarone was discontinued and hydrocortisone was started.

Seventeen days later, he was discharged on oral prednisone.

Once amiodarone is discontinued, symptoms may resolve within weeks<sup>12,14,16</sup> to months<sup>3,6,8,9,11</sup> or prove fatal.<sup>8,11,17,18,20</sup> The time course from diagnosis to death has ranged from 4–30 days.<sup>1</sup> The mortality rate of amiodarone pulmonary toxicity is approximately 10%.<sup>4,5,7</sup> Patients who develop acute respiratory failure and require mechanical ventilation have a poor prognosis. The mortality rate for these patients ranges from 50–100% because of respiratory failure or complications of underlying cardiovascular disease.<sup>2</sup> Corticosteroids have been used to treat pulmonary toxicity.<sup>1,3,4,17,25</sup> Resolution of chest x-ray abnormalities and clinical symptoms occurred after a few weeks of treatment with prednisone, cortisone and methylprednisolone.<sup>12,14,16</sup> In some instances where steroids are discontinued within a few weeks, the patient may relapse.<sup>20,25</sup>

We report a case of possible amiodarone-induced pulmonary toxicity. Four reasons point to amiodarone as the cause of pulmonary toxicity in this patient. First, amiodarone was the only new medication added to the patient's regimen upon admission to hospital. Second, the patient had a history of pulmonary fibrosis of unknown etiology. Patients with a previous history of pulmonary disease may be at increased risk of developing pulmonary toxicity. Third, there were many symptoms consistent with previous reports of this adverse effect. Specifically, a nonproductive cough, pleuritic chest pain, fever, consolidation on x-ray and increased white-blood-cell count with negative cultures have been previously associated with this disorder. Fourth, the onset of amiodarone-induced hypersensitivity pneumonitis, a relatively common presentation of amiodarone pulmonary toxicity, may occur within the first week of therapy. No other cause for deterioration in respiratory function was identified.

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