Amiodarone-induced pulmonary toxicity (APT): A low dose fatal adverse event

Muhammad Imran Butt, Muhammad Asif Shahzad

ABSTRACT

Introduction: Amiodarone pulmonary toxicity (APT) can be a diagnostic challenge to clinicians as it has no pathognomonic clinical, laboratory, radiological or histological features. It can potentially be fatal particularly in high risk patients. Amiodarone pulmonary toxicity is dose dependent, however, low dosages have also been reported to cause severe pulmonary disease. Therefore, it should be considered in every patient with respiratory distress and on current or recent amiodarone therapy.

Case Report: We report a case of APT with fatal outcome in a 49-year-old female taking the recommended doses of amiodarone with history of atrial fibrillation, rheumatic heart disease and pulmonary hypertension. Our patient was taking amiodarone for three years. She presented with severe respiratory distress necessitating endotracheal intubation. Despite treatment with systemic corticosteroids and broad spectrum antimicrobials, patient died in intensive care unit (ICU) after one month of admission. Amiodarone pulmonary toxicity is usually dose-dependent, however, our patient was taking safe doses which make this case unique.

Conclusion: The knowledge of different safe dosage patterns is important for every working physician due to widely usage of the drug. The lowest effective dose of amiodarone should be determined for every patient requiring long-term treatment and needs a close and regular follow-up for early diagnosis of lung injury.

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CASE REPORT

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Keywords: Amiodarone, Fatal, Pulmonary, Toxicity

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Muhammad Imran Butt¹, Muhammad Asif Shahzad²

Affiliations: ¹MBBS, Medical Registrar, department of medicine, Sir Charles Gairdner Hospital, Perth, WA, Australia; ²MBBS, Advance trainee, department of medicine, Lyell McEwin Hospital, Adelaide, SA, Australia.

Corresponding Author: Muhammad Imran Butt, Department of Medicine, Sir Charles Gairdner Hospital, Hospital Avenue, Nedlands, Perth, WA, Australia, 6009; Email: drimran193@gmail.com

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INTRODUCTION

Amiodarone is an antiarrhythmic drug widely used to treat various arrhythmias. Despite various adverse effects, it is considered the most potent antiarrhythmic drug with safety proven in many clinical trials. Of major side effects, Amiodarone-induced pulmonary toxicity (APT) is the most serious adverse event that can lead to death. It occurs dose dependently, however can occur with any dose. Therefore, it is important for physicians to be aware of the safe dosage patterns of the drug to minimize the incidence and fatality.

CASE REPORT

A 49-year-old female presented with progressive dyspnea over two weeks along with generalized weakness, dry cough and reduced exercise tolerance over preceding four weeks. On presentation, patient's respiratory rate was 35 per min, heart rate 75 bpm, blood pressure 95/48 mmHg and oxygen saturation 90% with FiO₂ 45% on continuous positive airway pressure (cPAP). On chest auscultation there were diffuse crackles bilaterally. Jugular venous pressure was not elevated. Patient's respiratory condition did not improve on cPAP and few hours later patient was intubated due to type 2 respiratory failure (Arterial blood gas: pH 7.05, PCO₂ 88, PaO₂ 115, HCO₃ 25, sat 95%).

The past medical history of patient included atrial fibrillation (AF), mitral valve replacement due to rheumatic heart disease, pulmonary hypertension, hypothyroidism and hypertension. Her medications included warfarin, thyroxine, perindopril and amiodarone. Amiodarone was started three years ago with initial dose of 600 milligram per day and tapered down to maintenance dose of 100 mg per day in three weeks. Patient's chest X-ray done overseas was reported normal one year ago.

Initial laboratory tests revealed slight leukocytosis ($11.6 \times 10^9/L$) with rise in C-reactive protein (CRP) to 105 mg/L and normal procalcitonin level. Serial troponins were negative and ECG did not show any acute changes.

Chest X-ray (Figure 1) and computed tomography (CT) scan of the chest (Figure 2) showed diffuse bipulmonary interstitial infiltration. Serologic tests were negative for *Mycoplasma pneumoniae*, *Chlamydia* species and *Legionella*. The polymerase chain reaction of sputum and pharyngeal swabs were negative for influenza A, B and parainfluenza virus species. Extensive investigations ruled out any infective, autoimmune or neoplastic disorder. Coronary angiogram was normal and echocardiogram revealed takotsubo cardiomyopathy with ejection fraction of 30%. Pulmonary artery pressure was 45 mmHg. The patient underwent fiberoptic bronchoscopy and bronchoalveolar lavage (BAL) which revealed interstitial fibrosis and foamy macrophages. Lung biopsy was not performed due to the risk involved in the procedure.

Patient was started on broad-spectrum antibiotics for possible lower respiratory tract infection and amiodarone was immediately ceased. Patient was also given intravenous furosemide with no improvement in symptoms. Leukocytosis and CRP did not improve despite giving broad spectrum antibiotics. Computed tomography scan of chest was repeated which showed progressive pulmonary infiltrates in both lungs. Amiodarone toxicity was assumed the likely explanation and corticosteroid treatment was initiated two days after admission. Patient initially showed a quick response to steroids and came off ventilator (Figure 3). Steroids were stopped however the next day patient again developed severe dyspnea requiring

re-intubation. Systemic steroids were reinstituted on top of antibiotics but no further improvement was noted. A percutaneous tracheostomy was performed on 25th day of admission.

The patient also developed acute kidney injury requiring continuous veno-venous hemodialysis (CVVD) with improvement in renal functions.

Despite the above treatment patient did not improve. Extensive discussion was made with family regarding the lung biopsy and transplant. Biopsy was deferred due the risk of clinical deterioration. The patient died after 30 days of ICU admission due respiratory failure.

Figure 1: Chest X-ray on presentation with bilateral interstitial infiltrates.

Figure 2: Computed tomography scan of chest showing ground glass interstitial infiltrates.

DISCUSSION

Amiodarone is an amphiphilic compound and contains iodine in its formulation. It is globally used antiarrhythmic drug and tends to accumulate in some organs including lungs.

Amongst several side effects (thyroid dysfunction, liver dysfunction, skin photosensitivity, corneal deposits, coagulopathy, neuropathy and disturbances in the intraventricular conduction) pulmonary toxicity is the most serious adverse effect [1]. Amiodarone pulmonary toxicity can present as adult respiratory distress syndrome (ARDS) which has high mortality rate of 50% [2] and can progress to severe pulmonary fibrosis [3].

Incidence and mortality of APT have been described in several studies. In patients on long-term treatment the incidence of APT ranges from 0.5–17% [2, 4]. It was seen less frequent in some recent reports ranging between 1.6% [5] and 2.9% [6] likely due to lowest effective doses.

In recent studies, the mortality of APT was seen in 9% [7] and 7% [5] of patients, however, in previous studies it was described as 5% [8]. The time of onset ranges from several months to years after initiation of treatment and varies among cases.

Amiodarone appears to accumulate in adipose tissue and in highly perfused organs and usually has a higher absorption rate in lungs than heart [9]. Its half-life is long and with chronic oral dosing it can be 30–108 days but is subject to interpatient variation. The apparent volume distribution is about 5,000 liters [10]. Its active metabolite is desethylamiodarone which tends to accumulate in

lung tissues five times more than the original drug and provides a continuous release with variable serum levels [9]. Among the risk factors, age and duration of treatment are considered the most important risk factors of APT [11]. The patients taking doses of 400 mg daily for more than two months or 200 mg daily for two years are at much higher risk of developing APT [4]. Other risk factors include male gender, history of cardiothoracic surgery, previous airways disease, exposure to high levels of supplemental oxygen and iodinated contrast [3, 4]. Previous cardiac surgery, pulmonary hypertension and relatively longer duration of treatment put our patient in high risk category.

The mechanism of APT involves the direct toxic effects to lung tissues and immunologic reactions [12] leading to non-specific diffuse interstitial pneumonitis. Direct toxic effects include the accumulation of phospholipids due to less degradation and the generation of drug-mediated oxidants. The immunological reaction was found to be mediated by CD8 positive T-lymphocytes. These mechanisms lead to severe pulmonary fibrosis and explain the sudden onset and rapid progression of the disease after relatively smaller doses of amiodarone [12].

Patients may initially present with progressive and nonspecific symptoms such as generalized weakness, fever, cough, breathlessness, weight loss, pleuritic chest pain, and pleural effusion. However, these symptoms can be obscured by pre-existent heart failure or lungs disease [3]. Severe cases can present as ARDS.

As there are no confirmatory tests available [13], the diagnosis of APT is often of exclusion. It is based on history, clinical examination, radiographic features and exclusion of alternative causes of respiratory distress. Early radiographic features include localized or diffuse interstitial infiltrates or alveolar ground-glass appearances [2, 4]. Despite having ability to assess increased lung density, CT scan cannot exclude the normal drug accumulation in lung parenchyma [14]. Pulmonary function tests typically show a restrictive pattern with a decreased diffusion lung capacity of 15–20% but a mixed pattern can also be seen [15]. A decrease in the diffusion capacity for carbon monoxide is seen at the early stage of the disease [3]. Lung scintigraphy can help to distinguish any associated heart failure [13]. BAL may reveal a rise in polymorphonuclear leukocytes and CD8+ T cells indicating an inflammatory or immune reaction. The presence of foamy macrophages is in favor with the diagnosis but it is not a pathognomonic sign as these cells can also be seen in up to fifty percent of nontoxic patients [16]. If the diagnosis is uncertain, an open lung biopsy may be required. However, this should be avoided due to the risk of clinical deterioration after thoracic surgery.

In a study on 46 patients, it was found that severity of APT is proportional to the degree and rapidity of onset of lung injury. Those who survived improved slowly but with persistent progression [17].

The mainstay treatment is the discontinuation of amiodarone immediately. Due to its accumulation in fatty

Figure 3: Chest X- ray after brief response to steroids therapy.

tissues and long elimination half-life, pulmonary toxicity may initially progress despite drug discontinuation. Although systemic corticosteroids are also recommended for treatment, more well-controlled studies are required to demonstrate its efficacy. Prednisone should be initiated at 40 mg to 60 mg daily and tapered slowly over four to twelve months as early steroid withdrawal can cause relapse [18]. Obese patients with excess adipose tissue are more susceptible to recurrences with steroid tapering due to high lipophilicity of the drug [18].

No preventive measures have been described so far to prevent APT. However, identifying the smallest dose possible is considered an effective strategy. In an animal study, it was seen that vitamin E reduced the extent of lung injury after amiodarone administration [19]. However, more work needs to be done to find its role in prevention of APT.

There are several safe dosage regimens described. The recommended maintenance doses of amiodarone are 100–400 mg/day after initial doses of 600 mg/day over one month or 1000 mg/day for 1 week [20]. Other recommendations include 800–1200 mg/day for 1–3 weeks, reducing to 400 mg/day for further 2–3 months and maintaining therapy with up to 300 mg/day [21]. Maintenance doses are limited to 200–400 mg/d [22].

CONCLUSION

The incidence of amiodarone pulmonary toxicity (APT) has decreased in recent days with the use of lowest effective doses. However, due to increase usage of amiodarone and its fatal outcome, a strong clinical suspicion should be emphasized particularly in high risk groups. Amiodarone pulmonary toxicity occurs dose dependently, but low dosages have also been reported with severe lung injury after initiation of therapy. Clinical manifestations of pulmonary toxicity may be subtle, severe or life-threatening. Conscientious follow-up is required to identify the development of APT earlier and reduce its severity. The prognosis is favorable when diagnosed at early stage. Before starting amiodarone, patients should be educated about the potential adverse effects of the drug and asked to present early if they develop any new respiratory symptoms.

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Author Contributions

Muhammad Imran Butt – Substantial contributions to conception and study design, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Muhammad Asif Shahzad – Acquisition of data, Drafting the article, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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