Early Amiodarone-Induced Pulmonary Toxicity after Endovascular Aneurysm Repair: A Case Report

Uzung Yoon, MD, PhD¹ Laura Marinelli, MD¹ Sayed Ali, MD² Seymour Huberfeld, MD²
Rafael Barrera, MD¹ John B. Chang, MD¹

¹ Department of Surgery, Hofstra North Shore-LIJ School of Medicine, Manhasset, New York

² Department of Medicine, Hofstra North Shore-LIJ School of Medicine, Manhasset, New York

Address for correspondence: Uzung Yoon, MD, Department of Surgery, Hofstra North Shore-LIJ School of Medicine, 300 Community Dr, Manhasset, NY 11030 (e-mail: uzyoon@gmail.com).

Int J Angiol 2016;25:189–192.

Abstract

Amiodarone is an antiarrhythmic drug that has been commonly used to treat supraventricular and ventricular arrhythmias. This drug is an iodine-containing compound that tends to accumulate in several organs, including the lungs. Especially, its main metabolically active metabolite desethylamiodarone can adversely affect many organs. A very well-known severe complication of amiodarone therapy is the amiodarone-induced pulmonary toxicity. This article presents the case study of an 82-year-old male patient with acute amiodarone-induced pulmonary toxicity. The patient underwent endovascular aneurysm repair for rapidly increasing abdominal aortic aneurysm. During the postoperative period the patient developed rapid atrial fibrillation and amiodarone therapy was initiated. Subsequently, the patient went into acute respiratory failure and was requiring high supplemental oxygen support and a chest X-ray revealed bilateral pulmonary infiltrates. During the hospital course the patient required mechanical ventilator support. With discontinuation of amiodarone, supportive therapy and steroid treatment patient symptoms significantly improved. Amiodarone-induced pulmonary toxicity must be considered in the differential diagnosis of all patients on the medication with progressive or acute respiratory symptoms. Early discontinuation of amiodarone and aggressive corticosteroid therapy should be considered as a viable treatment strategy.

Keywords

- ▶ endovascular
- ▶ aneurysm
- ▶ amiodarone
- ▶ pulmonary toxicity

Amiodarone is a benzofuran-derivative antiarrhythmic drug that has been commonly used to treat supraventricular and ventricular arrhythmias. This drug is an iodine-containing compound that tends to accumulate in lung, liver, thyroid gland, kidney, heart, adipose tissue, muscle tissue, and brain. In addition, its main metabolically active metabolite desethylamiodarone can adversely affect these organs. Adverse effects, such as interstitial lung disease, pulmonary fibrosis, pleural effusion, thyroid dysfunction, hepatitis, corneal microdeposits, and neuropathies have

been reported in the literature. Amiodarone-induced pulmonary toxicity (APT) is one of the most serious side effects of amiodarone therapy. Often the clinical manifestation of APT resembles pulmonary infection, pulmonary edema, pulmonary thromboembolism or heart failure and makes the diagnosis of APT difficult. APT has been described mostly in patients who have received a large dose of amiodarone over prolonged periods of time. But literature has shown that APT can happen even with a very short course of therapy.^{1,2}

Case Report

An 82-year-old male patient with rapidly increasing abdominal aortic aneurysm presented for endovascular aneurysm repair.

The medical history included abdominal aortic aneurysm, intermittent atrial fibrillation on XARELTO (Bayer HealthCare AG, Leverkusen, Germany), benign prostatic hypertrophy, intermittent claudication, diabetes mellitus, gastroesophageal reflux disease, hypertension, hyperlipidemia, failure of penile implant, and laminectomy. Preoperative testing showed a normal electrocardiogram (ECG) with sinus rhythm and a normal chest X-ray.

Surgery was without major events and patient was extubated on postoperative day (POD) 1. On POD 2, patient's cardiac monitoring revealed atrial fibrillation with rapid ventricular response, which was confirmed by a 12-lead ECG. Intravenous (IV) injection of metoprolol and Cardizem (Hospira, Inc, Lake Forest, IL) was given and the patient's cardiac movement converted back into sinus rhythm. On POD 5 patient had a recurrent onset of atrial fibrillation with rapid ventricular response and Cardizem infusion was started. After unsuccessful attempt to control the heart rate with Cardizem infusion, amiodarone was started orally. Patient was started on a loading dose of 400 mg three times a day for a total of 4 days and subsequently 200 mg daily.

Four days (POD 9) after the administration of amiodarone, the patient was complaining about progressive dyspnea needing a high dose of supplemental oxygen, hypoxemia, and hypercarbia on blood gas analysis. White blood cell (WBC) count and cardiac enzymes were in normal limits. A chest X-ray revealed a new large left lung opacity, pulmonary edema, and bilateral pleural effusions (►Fig. 1). On worsening of the respiratory condition the patient was admitted to the surgical intensive care unit and continuous positive airway pressure, ventilator support was initiated. Laboratory studies revealed mild leukocytosis (WBC 14 K/ μ L) on POD 11, and empiric treatment with vancomycin and aztreonam antibiotic was started for possible pneumonia. The results of the blood and sputum culture were negative.

Despite the aggressive diuretic therapy and control of the arrhythmia the patient's respiratory status continued to

Fig. 1 Chest X-ray at postoperative day 9.

Fig. 2 Chest X-ray at postoperative day 13.

decline with worsening findings on chest X-ray (►Fig. 2). On POD 13 mechanical ventilation was instituted and bronchoscopy with bronchoalveolar lavage (BAL) was performed. Bronchial alveolar lavage cytology showed reactive ciliated bronchial epithelium, scattered alveolar macrophages, and mixed inflammatory cells. At this time due to high suspicion of APT amiodarone was discontinued. The patient received a total dose of 4,800 mg over 7 days. Steroid therapy was started with hydrocortisone 150 mg a one-time dose and prednisone 50 mg with taper for 1 week. The patient's respiratory status improved, and patient was extubated on POD 17. After 7 days amiodarone was discontinued, the patient was discharged in stable condition.

Discussion

Amiodarone is a widely used antiarrhythmic agent and often used for management of supraventricular and ventricular arrhythmias. It is categorized as a class III antiarrhythmic agent, and prolongs phase three of the cardiac action potential. Amiodarone is an iodine-containing compound with some structural similarities to thyroxine. Inhibition of thyroxine deiodination to triiodothyroxine may contribute to its antiarrhythmic efficacy.

Amiodarone is high lipid solubility and the large volume of distribution results in a delayed onset of action when taken orally (2–3 days) and an elimination half-life of up to 180 days. The active principal metabolite of amiodarone is desethylamiodarone, which is lipophilic and penetrates tissues and accumulates therein, thus providing a sustained source of release. Amiodarone is preferentially distributed in the decreasing order in lung, liver, thyroid gland, kidney, heart, adipose tissue, muscle tissue, and brain.^{3,4}

Incidence/Risk Factor

APT is a serious adverse event that occurs in approximately 2 to 5% of treated patients⁵ and mortality at day 90 was reported to be 37%.⁶

APT can develop as early as from the first few days of treatment to several years later and even after discontinuation of the therapy.⁷ Viswam et al reported an incidence of

APT on a 58-year-old male patient postcoronary artery bypass grafting after a day's loading dose of amiodarone.¹ Lee et al reported APT after 2 days of therapy and a total 1,635 mg of IV amiodarone for ventricular tachycardia after percutaneous coronary intervention on a 54-year-old male patient.²

The development of lung complications appears to be associated with older age, male gender, duration of treatment, and cumulative dosage and high levels of its desethylamiodarone metabolite.⁸ Especially, those with the highest risk are patients who are administered 400 mg/d cumulatively for greater than 2 months or 200 mg/d for 2 years.^{9,10}

There is evidence that history of cardiothoracic surgery and use of supplemental oxygen, use of iodinated contrast media, and probably preexisting lung disease as well as coexisting respiratory infections.¹¹ Exposure to supplemental O₂, especially in high concentrations, alone or when combined with mechanical ventilation, may potentiate APT.^{12,13}

Pathophysiology of Pneumonitis

Amiodarone and its metabolites may produce lung damage directly by cytotoxic radicals and indirectly by an immunological reaction. The latter is supported by the finding of cytotoxic T cells in BAL fluid from patients with diagnosed APT.^{14,15}

Pathologic findings also include alveolar septal widening with inflammatory infiltrate, type-II pneumocyte hyperplasia, interstitial fibrosis, and diffuse interstitial pneumonitis. The presence of accumulation of lipid-laden "foamy" macrophages in alveolar spaces is suggestive of APT, but is not diagnostic.^{16,17} In some cases, there is little evidence of an inflammatory process and the predominant finding is non-specific pulmonary fibrosis.¹⁸

Diagnosis

APT should be suspected in any patient taking amiodarone who has new or worsening pulmonary symptoms or new diffuse or patchy infiltrates on chest X-ray or computed tomography. Pulmonary function test usually reveals a restrictive or mixed restrictive/obstructive pattern with reduction in diffusing capacity of at least 15 to 20%.¹⁹ Bronchoscopy with BAL and transbronchial biopsy can be very useful. It may reveal evidence of an inflammatory or immune response with elevation of CD8+ lymphocyte, and increased phospholipid content.¹⁹ Due to its nonspecific nature and its ability to mimic other disease processes, such as congestive heart failure, pulmonary edema, pneumonia, pulmonary embolism the diagnosis of APT may be delayed or missed.

Treatment Option

If there is a suspicion for APT immediate discontinuation of amiodarone should be considered. Due to its high lipid solubility and long elimination half-life, pulmonary toxicity may initially progress despite drug discontinuation and may recur after steroid withdrawal. Discontinuation of amiodarone may be sufficient if the extent of the disease is limited. Corticosteroids should be administered in patients who show substantial involvement of the lung parenchyma on imaging studies with or without concomitant hypoxemia. When

treated early, most APT cases are considered reversible with good prognosis.²⁰

Conclusion

Acute amiodarone-induced pneumonitis is a severe complication after amiodarone therapy and should be considered in all patients on the medication with progressive or acute respiratory symptoms. Postoperative patients may be at higher risk due to supplemental oxygen therapy and careful monitoring is necessary. Prompt diagnosis, discontinuation of amiodarone, and early aggressive corticosteroid therapy should be considered as a viable treatment strategy.

Conflict of Interest

None.

Reference

- Viswam D, Nair SG, Patel V, Nagaraj Ultra-short course of low-dose amiodarone-induced post-operative fatal pulmonary toxicity. *J Assoc Physicians India* 2011;59:443-447
- Lee W, Ryu DR, Han SS, et al. Very early onset of amiodarone-induced pulmonary toxicity. *Korean Circ J* 2013;43(10):699-701
- Vassallo P, Trohman RG. Prescribing amiodarone: an evidence-based review of clinical indications. *JAMA* 2007;298(11):1312-1322
- Plomp TA, Wiersinga WM, Van Rossum JM, Maes RA. Pharmacokinetics and body distribution of amiodarone and desethylamiodarone in rats after oral administration. *In Vivo* 1987;1(5):265-279
- Goldschlager N, Epstein AE, Naccarelli GV, et al; Practice Guidelines Sub-committee, North American Society of Pacing and Electrophysiology (HRS). A practical guide for clinicians who treat patients with amiodarone: 2007. *Heart Rhythm* 2007;4(9):1250-1259
- Mankikian J, Favelle O, Guillon A, et al. Initial characteristics and outcome of hospitalized patients with amiodarone pulmonary toxicity. *Respir Med* 2014;108(4):638-646
- Papiris SA, Triantafyllidou C, Kolilekas L, Markoulaki D, Manali ED. Amiodarone: review of pulmonary effects and toxicity. *Drug Saf* 2010;33(7):539-558
- Ernawati DK, Stafford L, Hughes JD. Amiodarone-induced pulmonary toxicity. *Br J Clin Pharmacol* 2008;66(1):82-87
- Jessurun GA, Crijns HJG. Amiodarone pulmonary toxicity. *BMJ* 1997;314(7081):619-620
- Camus P, Martin WJ II, Rosenow EC III. Amiodarone pulmonary toxicity. *Clin Chest Med* 2004;25(1):65-75
- Wolkove N, Baltzan M. Amiodarone pulmonary toxicity. *Can Respir J* 2009;16(2):43-48
- Ashrafian H, Davey P. Is amiodarone an underrecognized cause of acute respiratory failure in the ICU? *Chest* 2001;120(1):275-282
- Saussine M, Colson P, Alauzen M, Mary H. Postoperative acute respiratory distress syndrome. A complication of amiodarone associated with 100 percent oxygen ventilation. *Chest* 1992;102(3):980-981
- Rosenow EC III. Amiodarone pulmonary toxicity. Recognition and pathogenesis (Part I). *Chest* 1988;93:1067-1075
- Martin WJ II, Rosenow EC III. Amiodarone pulmonary toxicity. Recognition and pathogenesis (Part 2). *Chest* 1988;93(6):1242-1248
- Yamada Y, Shiga T, Matsuda N, Hagiwara N, Kasanuki H. Incidence and predictors of pulmonary toxicity in Japanese patients receiving low-dose amiodarone. *Circ J* 2007;71(10):1610-1616

- 17 Dharmarajan TS, Shah AB, Dharmarajan L. Amiodarone-induced pulmonary toxicity: potentially fatal, recognize early during life! *J Am Geriatr Soc* 2008;56(7):1363–1365
- 18 Morera J, Vidal R, Morell F, Ruiz J, Bernadó LL, Laporte JR. Pulmonary fibrosis and amiodarone. *Br Med J (Clin Res Ed)* 1982; 285(6345):895
- 19 Gleadhill IC, Wise RA, Schonfeld SA, et al. Serial lung function testing in patients treated with amiodarone: a prospective study. *Am J Med* 1989;86(1):4–10
- 20 Nacca N, Bhamidipati CM, Yuhico LS, Pinnamaneni S, Szombathy T. Severe amiodarone induced pulmonary toxicity. *J Thorac Dis* 2012;4(6):667–670