Amiodarone Pulmonary Toxicity: A Patient with Three Recurrences of Pulmonary Toxicity and Consideration of the Probable Risk for Relapse

Kaori Okayasu¹, Yuichiro Takeda¹, Jun Kojima¹, Atsuto Yoshizawa¹, Nobuyuki Kobayashi¹, Haruhito Sugiyama¹ and Koichiro Kudo²

Abstract

A 44-year-old man was treated with amiodarone for dilated cardiomyopathy. After 53 months, he developed amiodarone-induced interstitial pneumonia. Amiodarone treatment was terminated, and the patient was given corticosteroids. These treatments were effective. However, pneumonitis recurred whenever prednisolone was reduced to less than 5 mg per day. Considering the patient’s background characteristics, we considered his body mass index (BMI, kg/m²) and found his to be high. When four additional patients with amiodarone pulmonary toxicity were reviewed at our institute, a correlation between BMI and the duration of shadow disappearance was found ($R^2=0.8695$). Because amiodarone is lipophilic, the patient’s high BMI might have influenced the repeated appearance of pulmonary toxicity.

Key words: amiodarone-induced interstitial pneumonia, relapse, body mass index, lipophilic

(DOI: 10.2169/internalmedicine.45.1800)

Introduction

Amiodarone hydrochloride, a benzofuran derivative, began to be used for the treatment of angina pectoris in Europe in 1967. Its potent suppressive effect on supraventricular and ventricular dysrhythmias led to its expanded use as a class III antiarrhythmic agent (1-3). However, significant adverse effects were noted in more than 50% of the patients who received this drug. The reported major adverse effects included gray-blue skin discoloration, photosensitivity, corneal micro-deposits, neurological and muscle disturbances, clinical and chemical thyroid abnormalities, and hepatic and gastrointestinal dysfunction (3-6). In 1980 (7), amiodarone-induced pulmonary toxicity was recognized as the most significant and potentially lethal adverse effect of amiodarone. The incidence of pulmonary toxicity was reported to be 5 to 15%. Once it appeared, the mortality rate was 5 to 10% (6, 8-12).

A few reports have described recurrences of amiodarone-induced pulmonary toxicity (13-15). Here, we describe a case that had persistent relapses of amiodarone-induced interstitial pneumonia despite undergoing effective corticosteroid therapy. Furthermore, the possible risk of recurrence of amiodarone-induced pulmonary toxicity is discussed.

Case Report

A 44-year-old man with dilated cardiomyopathy was admitted to hospital at the end of January 2004 because of dyspnea on effort. He had been receiving amiodarone (200 mg per day after loading with 400 mg per day for 7 days) since August 1999. The cumulative dose of amiodarone was 325 g, and his serum amiodarone concentration was 0.576 mg/l. Upon examination, the patient was found to be afebrile and fine crackles were audible at both lung bases. The fine crackles persisted even after the administration of diuretics. His white blood cell count and serum lactate dehydrogenase level were normal. His serum KL-6 concentration was 371 U/ml. His partial pressure of oxygen and carbon
Figure 1. Chest X-rays obtained at the time of the first admission (Fig. 1-Left) and the first relapse (Fig. 1-Right). The chest X-ray taken at the time of the first admission (Fig. 1-Left) shows enlarged cardiac shadow and bilateral reticular shadows in the middle-lower regions of the lungs. The chest X-ray taken at the time of the first relapse (Fig. 1-Right) shows reticular shadows in the left lung.

Figure 2. High-resolution computed tomography (HRCT) study of the chest performed at the time of the first admission (Fig. 2-1), after corticosteroid therapy (Fig. 2-2), and at the time of the first relapse (Fig. 2-3). High-resolution CT study performed at the time of the first admission (Fig. 2-1) shows diffuse ground-glass opacities throughout the lobes. After corticosteroid treatment, the ground-glass opacities improved (Fig. 2-2). High-resolution CT study performed at the time of the first relapse (Fig. 2-3) shows new ground-glass opacities and a consolidation, mainly in the left lung.

dioxide were 48.0 and 25.9 mmHg at room air, respectively. His blood pH was 7.551. A chest X-ray showed an enlarged heart caused by dilated cardiomyopathy and bilateral reticular shadows in the middle and lower regions of his lungs.
Administration of amiodarone was started with a loading of 400 mg per day for 7 days and continued at a dosage of 200 mg per day. The patient was admitted because of amiodarone pulmonary toxicity 4.5 years after the start of amiodarone treatment. Corticosteroid therapy was effective, but amiodarone pulmonary toxicity relapsed three times, whenever the prednisolone dosage was reduced to less than 5 mg per day.

Figure 3. Administration of amiodarone was started with a loading of 400 mg per day for 7 days and continued at a dosage of 200 mg per day. The patient was admitted because of amiodarone pulmonary toxicity 4.5 years after the start of amiodarone treatment. Corticosteroid therapy was effective, but amiodarone pulmonary toxicity relapsed three times, whenever the prednisolone dosage was reduced to less than 5 mg per day.

Figure 4. Correlation between body mass index (BMI, kg/m²) and the duration of the disappearance of shadow (DDS, in days). The best fitting curve was expressed by the following exponential equation: $\text{DDS} = 0.0542 \times e^{0.2999 \times \text{BMI}}$.

Fig. 3 shows the clinical course of this patient. Amiodarone was discontinued soon after the patient’s admission to hospital. Instead, he was treated with 1 g of methylprednisolone per day for three days, followed by 1 mg/kg body weight per day of prednisolone. After these treatments, his symptoms, chest X-ray findings, CT findings, and hypoxemia improved (Fig. 2-2). The corticosteroid dosage was gradually reduced to 5 mg per day, but the patient’s pulmonary toxicity relapsed, with increasing sputum and a consolidation visible in the left lung of his chest X-ray (Fig. 1-Right). New ground-glass opacity and consolidation, mainly in the left lung, was visible on a chest CT study (Fig. 2-3). The abnormal shadow on the patient’s chest X-ray did not improve even after the use of empiric antibiotics. We subsequently diagnosed the patient as having a relapse of amiodarone-induced pulmonary toxicity. After increasing his prednisolone dosage to 0.5 mg/kg body weight per day (40 mg/day), his symptoms and chest X-ray findings improved.

However, the interstitial pneumonia relapsed again when the corticosteroid dosage was reduced to 5 mg per day. He complained of dyspnea on effort, and a reticular shadow was visible in his left lung on a chest X-ray. These chest X-ray findings persisted even after the administration of diuretics and antibiotics. The patient’s serum amiodarone concentration remained detectable at 0.167 mg/l, and his laboratory data suggested hypothyroidism. After the patient was again treated with 0.5 mg/kg body weight of prednisolone, his symptoms and chest X-ray findings improved. Nevertheless, the patient was admitted for a fourth time because of heart failure. Since his serum amiodarone concentration was no longer detectable at this time and there were no sign of pul-
monary toxicity, the prednisolone dosage was slowly reduced to 2.5 mg per day. However, a new consolidation again appeared in his left lung, and his heart failure further deteriorated, leading to the patient’s death in December 2004.

Upon autopsy, congestion of the lungs, dilated cardiomyopathy with interstitial fibrosis in the myocardium, and congestion and bile stasis of the liver were noted. The histopathological findings for the lung tissues showed irregularly distributed interstitial fibrosis of the alveolar septum. No active infiltration of inflammatory cells was observed.

The medical records of four additional patients who had been treated for amiodarone pulmonary toxicity at our institute from 2003 to 2005 were also reviewed. Two patients improved with corticosteroid therapy, and two patients improved with only the discontinuation of amiodarone treatment. Including the present patient, their body mass index (BMIs, kg/m^2) ranged from 19.5 to 28.5. The duration of the disappearance of shadow (DDS) was defined as the time from the date of cessation of amiodarone treatment until the date on which the pulmonary shadows had disappeared from the chest X-ray or CT studies. Their DDSs ranged from 19 to 312 days. A correlation between BMI and DDS was found [R^2=0.8695, DDS=0.0542*exp (0.2999BMI); see Fig. 4].

### Discussion

Amiodarone is an amphiphilic, iodinated benzofurane derivative that binds strongly to plasma proteins and tissues (16). Its bioavailability varies, while its uptake and distribution display a biphasic pattern. As a result, the drug has a delayed onset of action and usually requires high initial loading doses (17). Because of its lipophilic nature, amiodarone tends to accumulate in adipose, liver, and lung tissues (6). Therefore, the terminal elimination half-life is relatively long, averaging 52 days, but varying from one patient to another (18). These pharmacologic properties make monitoring difficult, and amiodarone’s toxic effects may persist long after the cessation of its use.

Amiodarone pulmonary toxicity is thought to be a direct injury related to the intracellular uptake of phospholipids and T cell-mediated hypersensitivity pneumonitis (12). The risk of developing adverse reactions is reportedly related to the serum amiodarone concentration. Adverse reactions are common in patients with serum values exceeding 2.5 mg/L. However, pulmonary toxicity may appear at even a lower concentration (19).

The present patient improved with the withdrawal of amiodarone treatment and corticosteroid therapy, but his pulmonary toxicity relapsed three times—whenever the prednisolone dosage was reduced to less than 5 mg per day. To our knowledge, no patients with more than three relapses of pulmonary toxicity have been previously reported. In fact, the present patient’s serum amiodarone concentrations were relatively low at the time of the 2nd and 3rd relapses. Haffajee et al reported that amiodarone concentrations in tissues were significantly higher than those in the serum: The concentration of amiodarone in mesentry fat was 385 times as high as that in plasma (17). When we further examined the patient’s background characteristics, a large BMI was noted. This patient had been treated with amiodarone for quite a long time. As a result, the cumulative administrated dose was high. Because amiodarone is lipophilic, a long time was probably needed for the amiodarone concentration in this patient’s adipose tissues to decrease. Thus, his high BMI might have influenced the repeated appearance of pulmonary toxicity. When 5 patients with amiodarone pulmonary toxicity were reviewed, a non-linear regression correlation was found between BMI and DDS. Although the number of patients in this series was small, DDS might be predicted by the resulting exponential equation. Further studies involving large numbers of patients with amiodarone pulmonary toxicity are needed to validate this exponential equation. If patients have a high BMI, amiodarone might remain in their adipose tissues for a long time.

### References