CASE REPORT

Bronchiolitis Obliterans Secondary to Amiodarone

J. Heipel, J. Dawdy, C.F.P. George and C.D. Bayliff

Amiodarone is a benzofuran derivative that was first introduced in 1967 for the treatment of angina, but has increasingly been used for its unique antiarrhythmic properties.[1] While efficacious for many life-threatening arrhythmias, amiodarone is known to cause a wide range of adverse effects including pulmonary toxicity.[2-4] Although the relationship between dose and duration has not been firmly established, most cases of amiodarone pulmonary toxicity occur when doses greater than 400 mg daily are used for more than two months.[4] Toxicity has also occurred at low dosages after a prolonged period of time. A range of pulmonary injury patterns can be produced by amiodarone that may not immediately be recognized as drug-related.[3] This report describes two cases of bronchiolitis obliterans (BO), one with organizing pneumonia (BOOP) secondary to long-term, low dose treatment with amiodarone.

CASE 1

A 77 year-old male was admitted to hospital with a three-week history of gradually increasing chest tightness, a seven kilogram weight loss, anorexia, and malaise. One week prior to admission, he developed shortness of breath and a non-productive cough. After an outpatient chest X-ray revealed a bilateral infiltrate, he was started on two separate courses of antibiotics without improvement. His only other medication was amiodarone 200 mg daily which he had been taking for four years for a benign arrhythmia. He was a life-long non-smoker. On examination, he was tachypneic with occasional bilateral lung crackles and questionable bronchial breathing at the left base. The remainder of the physical examination was unremarkable. The patient's leukocyte count was elevated at 15.3 x 10^9/L, but without eosinophils. The lactate dehydrogenase was slightly increased at 195 U/L. Capilliary blood gases on admission revealed pO_2 of 41 mmHg, pCO_2 of 34 mmHg, HCO_3 of 25 mmol/L, and pH of 7.48 on room air. Pulmonary function tests showed moderate restrictive disease with a low diffusion capacity consistent with parenchymal involvement. To establish the diagnosis, a bronchoscopy and transbronchial biopsy of the right upper lobe were performed. Microscopic examination of the biopsy showed BO associated with areas of desquamation and patchy alveolar damage. Occasional focal aggregates of foamy macrophages were identified. The broncho-alveolar lavage fluid and sputum grew no organisms and cytology found no malignant cells. On the basis of this, the patient was diagnosed as having BOOP thought to be secondary to amiodarone. Amiodarone was discontinued and the patient was started on 60 mg of prednisone daily. He responded quickly to this therapy and the corticosteroid was rapidly reduced due to the occurrence of hyperglycemia. However, the pulmonary symptoms returned necessitating the reinstatement of the former dose of prednisone. Shortly thereafter the patient was discharged home. At the time of his discharge, capillary blood gases were a pO_2 of 64 mmHg, pCO_2 of 41 mmHg, HCO_2 of 27 mmol/L, and pH of 7.43 on room air.

CASE 2

A 56 year-old male, previous 80 pack-year smoker, was admitted to hospital because of a vocal cord lesion. During the six months prior to admission he had become dysphagic and felt a foreign body sensation in his throat. In addition, his voice had changed and he had experienced a significant weight loss. His past medical history included arthritis and four previous myocardial infarctions, including one four years ago after which he developed episodes of ventricular tachyarrythmias and for which he had been prescribed 200 mg of

J. Heipel, B. Sc. Phm, is currently a staff pharmacist at Cambridge Memorial Hospital. At the time of this study she was a Hospital Pharmacy Resident at Victoria Hospital in London, Ontario.
J. Dawdy, MD, is a member of the Department of Medicine at Victoria Hospital in London, Ontario
C.F.P. George, is a member of the Department of Medicine at Victoria Hospital.
C.D. Bayliff, is a Coordinator in the Department of Pharmacy Services at Victoria Hospital.
Acknowledgements: The authors wish to thank Mrs. Jan Butler for her invaluable secretarial assistance.

amiodarone daily. His physical exam on admission was unremarkable except for a grey discolouration of his face. While in hospital, the patient developed an elevated temperature, chills throughout the night, shortness of breath and pain in the right upper and lower chest. Laboratory values were within normal limits except for a low albumin of 21 g/L, low calcium of 1.96 mmol/L, low hemoglobin of 116 g/L, elevated leukocytes of 13.1 x 10^9/L, elevated platelets of 553 x 10^9/L, and mildly increased lactate dehydrogenase of 240 U/L. Capillary blood gases showed a pO^2 of 66 mmHg, pCO_2 of 35 mmHg, HCO_3 of 26 mmol/L and pH of 7.48 on room air. In addition to the mild hypoxemia, an impaired CO diffusion capacity (measured 15.8 mL/min/mmHg vs predicted of 31.7 mL/min/mmHg) consistent with severe restrictive disease was also present. Chest X-ray revealed an interstitial pattern and oxygen, furosemide, and erythromycin were prescribed. Despite these measures, the patient experienced no subjective improvement and a bronchosopy and transbronchial lung biopsy were performed. The pathology report showed diffuse alveolar damage with a focal accumulation of lipid laden macrophages. No vasculitis, malignant cells, or organisms were seen. This interstitial lung disease was diagnosed as BO likely secondary to amiodarone. The patient was subsequently commenced on 60 mg of prednisone daily for an intended duration of four to six weeks and amiodarone was discontinued. An amiodarone serum concentration performed during his stay was therapeutic at 2.1 umol/L (normal range 1.8 to 3.6 umol/L). The patient was discharged to another facility prior to any noted improvement in blood gases. These were pO_2 of 55 mmHg, pCO_2 of 37 mmHg, HCO_3 of 26 mmol/L, and pH of 7.45 on room air.

DISCUSSION

Amiodarone pulmonary toxicity is clinically complex and likely reflects underlying mechanisms of lung injury that result from immunologic processes, indirect inflammation, as well as the direct toxic effects of the drug or its metabolites.[6] Pneumonitis caused by amiodarone has been frequently reported, however in 1985, Epier was the first to differentiate BO and usual interstitial pneumonitis as two distinct infiltrative presentations.[7] It is important to distinguish BO and BOOP from other infiltrative lung diseases because the former follow a more benign course and may be more responsive to steroid therapy. Hence, earlier reports may have failed to distinguish the various types of pulmonary toxicity and, in fact, BO may be underestimated.

Bronchiolitis Obliterans is a lesion that results when injury to small conducting airways is repaired by proliferation of granulation tissue.[7] The clinical presentation is insidious with cough, dyspnea on exertion, weight loss, and bilateral infiltrates.[8] A combination of these symptoms were present in the two cases reported. As well, an organizing pneumonia may occur with BO known as BOOP.

Few other cases of BO due to amiodarone are documented in the literature. Camus et al were the first to report a case of BOOP attributed to amiodarone.[9] Their patient was an 81 year-old male who presented with the classic symptoms while taking amiodarone 200 mg five days per week for more than three years. Upon amiodarone discontinuation, subjective improvement was noted, but one month later, due to recurrent symptoms, the patient was prescribed 40 mg of prednisone daily which resulted in considerable clinical improvement. Eventually the prednisone was discontinued with no disease recurrence.

Reports of pulmonary toxicity associated with amiodarone at low dosages in the literature is mixed. Roca et al studied 61 symptomless patients receiving long-term treatment of 400 mg of amiodarone daily.[10] They found a 4.9% incidence of pulmonary side effects suggesting lower toxicity with the lower amiodarone dose. However, using serial pulmonary function tests in 24 consecutively studied patients, Ulrick et al found a higher incidence pulmonary toxicity to low dose amiodarone.[11] These authors also observed a direct relationship between cumulative drug dose and pulmonary toxicity. Amiodarone toxicity was diagnosed in 33 of 573 patients studied by Dusman et al; however, no patient receiving a mean daily maintenance dose of less than 305 mg of amiodarone developed pulmonary toxicity.[4] Adams et al found in their prospective study of 33 patients treated with amiodarone that pulmonary symptoms did not develop in patients whose dose was less than 400 mg daily.[5] From studies and case reports it appears that dose and duration of therapy are the principle factors in the development of pulmonary toxicity, but that this toxicity can also develop in patients receiving low doses of amiodarone for a long period of time. However, serum concentrations of amiodarone and its metabolites are not predictive or diagnostic of pulmonary b toxicity.[12]

Treatment options for minimizing amiodarone pulmonary toxicity are limited and mostly anecdotal. Most reports recommend discontinuing amiodarone or at least lowering the dose to less than 400 mg daily.[3] In most cases, after discontinuation, the symptoms will begin to improve within a few days with complete resolution requiring several months due to the long half-life of the drug. Prednisone is considered the treatment of choice, with

initial doses of 60 mg or 1 mg/kg daily given until a response or for one to three months.[7] Subsequent doses of 40 mg every one to two days with downward tapering in responsive patients may be administered up to a total of one year. However, it should be noted that in our first patient (Case 1) the rapid reduction of corticosteriods resulted in a recurrence of pulmonary symptoms. This further emphasizes the need for prolonged administration of corticosteroids.

Amiodarone is currently under investigation in the Canadian Amiodarone Myocardial Infarction Arrhythmias Trial (CAMIAT). The investigators hope to show beneficial effects of amiodarone, administered in daily doses of 300 to 400 mg daily, on the two year mortality post myocardial infarction due to cardiac arrhythmias. In light of our two cases and others recorded in the literature, careful assessment of risks of amiodarone therapy needs to be performed. Of note, both our cases manifested pulmonary toxicity secondary to amiodarone at 200 mg daily after more than two years of treatment. This has implications for clinicians because the time interval between initiation of amiodarone and evidence of pulmonary toxicity may be lengthy; therefore, the drug may not be regarded as the causative agent. Also, with the CAMIAT study, the two year observation period may not be long enough for the pulmonary toxicities to present themselves in those patients.

In conclusion, a number of pulmonary toxicities may occur with amiodarone including BO and BOOP even at low dosages and after a considerable length of time.

REFERENCES

1. Marcus FI, Fontaine G, Frank R, et al. Clinical pharmacology and applications of the antiarrhythmic agent, amiodarone. *Am J. Heart* 1981; 101: 480-93.
2. Kudenchuk PJ, Pierson BJ, Green HL, et al. Prospective evaluation of amiodarone pulmonary toxicity. *Chest* 1984; 86:541-8.
3. McNeil KD, Firouz-Abadi A, Oliver W, et al. Amiodarone pulmonary toxicity - three unusual manifestations. *Aust NZ J Med* 1992; 22:14-8.
4. Dusman RE, Stanton MS, Miles WM, et al. Clinical features of amiodarone-induced pulmonary toxicity. *Circulation* 1990; 82:51-9.
5. Adams GD, Kehoe R, Lesch M, et al. Amiodarone-induced pneumonitis assessment of risk factors and possible risk reduction. *Chest* 1988;93:254-63.
6. Martin WJ II, Rosenow EC III. Amiodarone pulmonary toxicity: recognition and pathogenesis. Part I, *Chest* 1988; 93:1067-75.
7. Epler GR, Colby TV, McLoud TC, et al. Bronchiolitis obilterans organizing pneumonia. *N Eng J Med* 1985; 312:152-8.
8. Guerry-Force ML, Miller NL, Wright JL, et al. A comparison of bronchiolitis obliterans organising pneumonia, usual interstitial pneumonia and small airways disease. *Am Rev Respir Dis* 1987; 135:705-12.
9. Camus P, Lombard J. Perrigan M, et al. Bronchiolitis obliterans organising pneumonia in patients taking acebutolol and amiodarone. *Thorax* 1989; 44:711-5.
10. Roca J, Heras M, Rodiguez-Roisin R, et al. Pulmonary complications after long term amiodarone treatment. *Thorax* 1992; 47:372-6.
11. Ulrik CS, Backer V, Aldershville J, et al. Serial pulmonary function tests in patients treated with low-dose amiodarone. *Am Heart J* 1992; 123:1550-4.
12. Martin WJ II, Rosenow EC III. Amiodarone pulmonary toxicity: recognition and pathogenesis. Part II. *Chest* 1988; 93:1242-8.