Amiodarone-induced neurotoxicity

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Amiodarone is commonly used for the treatment of ventricular arrhythmias and atrial fibrillation.1,5 The adverse effects of amiodarone that have been extensively reported include pulmonary fibrosis, thyroid abnormalities, ocular sequelae, skin discoloration, and elevated hepatic enzymes.1,3,5 Although case reports of amiodarone-induced neurotoxicity have been previously published,6-22 it remains an underrecognized adverse reaction for which clinicians do not routinely monitor.

Case report

A 76-year-old man came to the emergency department with complaints of increasing imbalance over the past 2.5 months after a recent discharge from the hospital. He reported that his balance had worsened over the past week and that he had to use a cane to walk and stabilize his balance. The patient indicated that he could walk without difficulty but “felt drunk” without using a cane. He denied any shortness of breath, chest pain, abdominal pain or tenderness, melena, changes in stool color or bowel habits, and mental status changes.

His medical history included coronary artery disease (with past myocardial infarction and coronary artery bypass surgery), paroxysmal atrial fibrillation (newly diagnosed three months prior during his previous hospitalization), peripheral vascular disease, chronic obstructive pulmonary disease, hypertension, chronic kidney disease (stage 3), and hyperlipidemia. His home medications included enteric-coated aspirin 325 mg orally daily, isosorbide dinitrate 20 mg orally twice daily, amiodarone hydrochloride 400 mg orally three times daily, extended-release metoprolol succinate 142.5 mg (equivalent to metoprolol tartrate 150 mg) orally daily, simvastatin 80 mg orally daily, and warfarin sodium 2.5 mg orally daily. Physical examination of the patient revealed finger-to-nose dysmetria, unsteady gait with leftward prevalence, positive Romberg’s sign, and inability to perform heel-to-toe walk. All radiographic imaging studies and laboratory test values ruled out acute pathologies, bleeding, masses, and ischemia. As there were no physiological findings for the patient’s symptoms and after careful evaluation of the patient’s drug regimen, the patient’s amiodarone was discontinued. His ataxia began to slowly improve. All neurologic symptoms resolved completely five months after discontinuation of amiodarone.

Conclusion. A 76-year-old man developed ataxia after taking amiodarone hydrochloride 400 mg orally three times daily for more than two months; the regimen was the intended loading dosage. The ataxia lessened over the first two weeks after the amiodarone was discontinued and resolved completely within five months after drug discontinuation.

Index terms: Amiodarone; Aspirin; Cardiac drugs; Hydralazine; Isosorbide dinitrate; Metoprolol; Neurotoxicity syndromes; Simvastatin; Toxicity; Warfarin

previous hospitalization), hydralazine hydrochloride 10 mg orally four times daily, extended-release metoprolol succinate 142.5 mg (equivalent to metoprolol tartrate 150 mg) orally daily, simvastatin 80 mg orally daily, and warfarin sodium 2.5 mg orally daily (started during his previous hospitalization). The patient denied taking any nonprescription medications, herbal products, or supplements and reported no drug allergies.

On admission, the patient was afebrile with a blood pressure of 185/70 mm Hg and a heart rate of 58 beats/min. His physical examination was positive for finger-to-nose dysmetria, unsteady gait with leftward prevalence, positive Romberg’s sign, and inability to perform heel-to-toe walk. The patient’s abnormal laboratory test values included the following: aspartate transaminase, 126 units/L (normal, 8–33 units/L); alanine transaminase, 167 units/L (normal, 4–36 units/L); blood urea nitrogen, 38 mg/dL; serum creatinine, 2.4 mg/dL; partial thromboplastin time, 85.3 sec; prothrombin time, >50.0 sec; and international normalized ratio, >5.0. Computed tomography and magnetic resonance imaging of the head and the neck yielded normal findings for the patient’s symptoms.

Other pertinent findings included normal levels of thyroid-stimulating hormone, hemoglobin, hematocrit, potassium, magnesium, cyanocobalamin, and folate. Results of a hepatitis panel, urinalysis, and stroke panel (erythrocyte sedimentation rate, C-reactive protein, homocysteine, anticiardiolipin antibodies, lipoprotein a, lipid panel) were also normal. The patient’s electrocardiogram revealed sinus bradycardia and first-degree atrioventricular block, which was already known for this patient. His transthoracic echocardiogram showed only mild impairment of left ventricular systolic function, with an ejection fraction of 45–50%.

Since there were no physiological findings for the patient’s symptoms based on the radiographic examinations and laboratory test values, the patient’s medication history was verified, and his pillbox was obtained and thoroughly examined. It was determined that the patient was still taking the loading dose of amiodarone hydrochloride of 400 mg orally three times daily for the past 2.5 months, and the patient’s amiodarone was discontinued. The patient’s ataxia slowly improved over the next two weeks, and the patient returned his walker to the clinic at the follow-up visit. Five months after discontinuation of amiodarone, the patient’s neurologic signs and symptoms had resolved completely.

Discussion

The neurologic adverse effects of amiodarone are not as well recognized as the more commonly known adverse effects of pulmonary fibrosis, thyroid abnormalities, ocular sequelae, skin discoloration, and elevated hepatic enzymes. Even though case reports of amiodarone-induced neurotoxicity have been previously published, no specific recommendations exist for routine screening of and monitoring for this adverse effect.1,3-5,15 Widely used amiodarone-monitoring forms, such as those adopted by the American Academy of Family Physicians, the North American Society for Pacing and Electrophysiology, and the Department of Veterans Affairs, do not have specific baseline and monitoring parameters for neurologic symptoms. Furthermore, a recent clinical therapeutics review of amiodarone did not enumerate any baseline or monitoring recommendations for neurologic symptoms similar to those listed for cardiac, hepatic, thyroid, pulmonary, and ophthalmologic adverse effects.4

Although the patient was taking a markedly high maintenance dosage of amiodarone, previous cases of amiodarone-induced ataxia occurred at maintenance amiodarone hydrochloride dosages of 200–800 mg daily.6-10,24,25 The reported frequency of amiodarone-induced neurotoxicity (encompassing tremors, peripheral neuropathy, ataxia, dyskinesia, encephalopathy) widely varies from 0.3% to 74%,1,6-9,24,26 while the frequency of amiodarone-induced ataxia ranges from 3% to 37%,1,6-8,24

The exact mechanism of neurotoxicity is unknown. However, amiodarone has been shown to cross the blood-brain barrier, and amiodarone and its active metabolite, desethylamiodarone, have been measured in the central nervous system.7 Other studies have shown that amiodarone causes the formation of lysosomal phospholipid-containing inclusions in Schwann’s cells, fibroblasts, and perineurial cells as well as drug accumulation in the sural nerve.2,7 The onset of neurologic symptoms may be anywhere from 12 days to 12 months after initiation of amiodarone, and improvement of symptoms has been seen one week to 4 months after drug discontinuation.6,7

According to the Naranjo et al.28 adverse drug reaction probability scale, it was probable that amiodarone caused the patient’s neurotoxicity (score = 6). The score might have been higher if the patient had been rechallenged with amiodarone and if serum amiodarone levels were measured.

In addition to educating the medical team, the clinical pharmacy staff also reviewed the medication error in which the three-month refill of the loading dose of amiodarone was continued. The pharmacy staff was educated on proper amiodarone dosing, and the maximum amount of tablets of amiodarone that patients can receive was limited in the pharmacy database.

This case report highlights the importance of proper monitoring of the adverse effects of amiodarone.
As seen with previous case reports, elderly patients may be more susceptible to adverse neurologic effects; these effects may be dosage related. Clinicians and pharmacists should be cognizant of adverse neurologic effects and be just as diligent in performing baseline and periodic neurologic screenings as they are in cardiac, hepatic, thyroid, pulmonary, and ophthalmologic monitoring.

Conclusion

A 76-year-old man developed ataxia after taking amiodarone hydrochloride 400 mg orally three times daily for more than two months; the regimen was the intended loading dosage. The ataxia lessened over the period was the intended loading dosage. The ataxia lessened over the daily for more than two months; the regimen was the intended loading dosage. The ataxia lessened over the

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