

Unforeseen consequences: Class III antiarrhythmic amiodarone stimulated increase in prostate-specific antigen



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Introduction

Amiodarone is a commonly used antiarrhythmic medication (AAM). While it is approved only for the treatment of life-threatening ventricular arrhythmias,¹ it is more broadly used for the treatment of refractory atrial arrhythmias, particularly atrial fibrillation (AF). While effective, amiodarone usage carries with it a multitude of mild to potentially significant or even life-threatening side effects coupled with relatively long half-life, which require frequent multi-system monitoring. Amiodarone has numerous noncardiac adverse effects, including involvement of the lung, eye, skin, thyroid, peripheral nervous system, and liver.¹ Thyroid dysfunction has been the most studied endocrine abnormality related to amiodarone. However, other endocrine abnormalities have also been reported with prolonged amiodarone use, including testicular dysfunction and higher serum levels of follicle-stimulating hormone, luteinizing hormone levels,² and syndrome of inappropriate antidiuretic hormone.³ We present a case of prostate-specific antigen (PSA) elevation following amiodarone initiation with reduction in PSA after cessation of amiodarone. This drug-induced effect has not been reported in the literature.

Case report

Our patient, reviewed retrospectively, is a 64-year-old white man with significant history of persistent AF, hypertension, coronary artery disease with prior myocardial infarction and stent placement, ankylosing spondylitis, asthma, gastroesophageal reflux disease, and recurrent lower gastrointestinal bleed secondary to hemorrhoids. He was initially

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KEY TEACHING POINTS

- Amiodarone is principally listed as a Vaughn-Williams class III antiarrhythmic medication (affecting potassium efflux) but exhibits similar properties and effects as the other 3 classes of medications, which makes it an effective antiarrhythmic drug for the treatment of supraventricular and ventricular arrhythmias.
- Amiodarone can affect numerous organ systems (both cardiac and noncardiac structures), including lung, eye, skin, thyroid, peripheral nervous system, and liver. In rare cases, the reproductive organs were affected.
- Prostate-specific antigen is androgen-regulated serine protease produced by both prostate epithelial cells and prostate cancer and is the most commonly used serum marker for prostate cancer. An increase in serum levels may be seen with amiodarone toxicity.

diagnosed with AF in February 2010 and underwent direct current cardioversion (DCCV), which restored sinus rhythm for a brief period of time until June 2010, with the reinitiation of AF. He underwent repeat DCCV and subsequent electrophysiology study and radiofrequency ablation (RFA) for AF in June 2010 and was placed on flecainide for a brief period post ablation. He experienced freedom from AF until subsequent recurrence, leading to a repeat RFA in 2014. He experienced another AF-free period through 2018. In late February 2018, he presented with AF with rapid ventricular response. Following DCCV and third electrophysiology study with RFA, he was initiated on amiodarone to maintain sinus rhythm; the medication was discontinued 2 months following the procedure. Amiodarone was chosen during this time because of the development of coronary artery

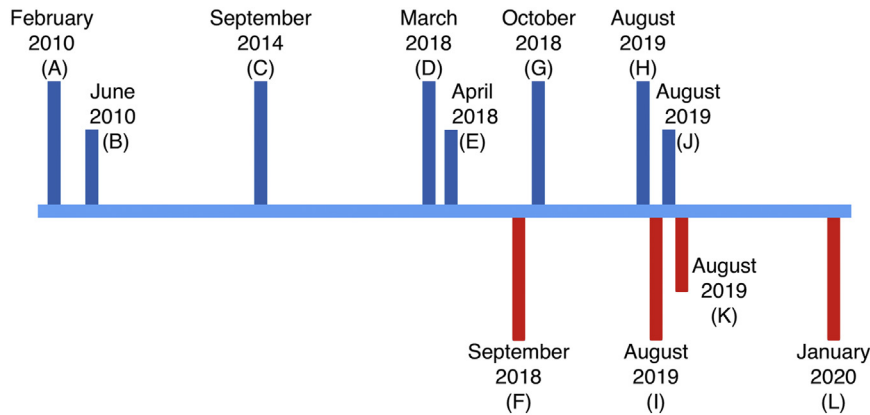


Figure 1 Patient care overview timeline. **A:** Initial diagnosis of atrial fibrillation (AF) in February 2010 and first direct current cardioversion (DCCV). **B:** First recurrence of AF and second DCCV with initiation (and discontinuation) of flecainide in June 2010. **C:** Second recurrence of AF and first radiofrequency ablation (RFA) pulmonary vein isolation in September 2014. **D:** Admission for third recurrence of AF with rapid ventricular response with third DCCV and redo RFA in March 2018. Patient was loaded with amiodarone (400 mg orally 3 times daily for 3 days while inpatient then discharged on 200 mg orally daily). **E:** Discontinuation of amiodarone in April 2018. **F:** Routine prostate-specific antigen (PSA) testing performed, resulting in total PSA 3.5 ng/mL, and patient reported as asymptomatic in September 2018. **G:** Fourth recurrence of AF and fourth DCCV. Amiodarone is reinitiated at 200 mg orally daily in October 2018. **H:** A routine ophthalmology visit for amiodarone toxicity surveillance noting concern for ocular involvement in August 2019. **I:** Routine lab work for amiodarone monitoring notes total PSA 5.4 ng/mL with percent free PSA 8.0% along with abnormal thyroid and liver function and leukopenia in mid-August 2019. **J:** Amiodarone discontinued following lab work results in mid-August 2019. **K:** Repeat lab work demonstrates return to near baseline total PSA 3.8 ng/mL and improved percent free PSA 11.6% 10 days after discontinuation of amiodarone. **L:** Surveillance lab work without change to PSA (total PSA 3.5 ng/mL and percent free PSA 12.3%) in January 2020.

disease in the intervening years and QTc prolongation with sotalol. In October 2018, he was once more found to be in AF, and he underwent a fourth DCCV and reinitiation of amiodarone at 200 mg daily. Prior to initiation of the medication, the patient had undergone a routine total PSA test, which resulted in 3.5 ng/mL (reference range 0.0–4.0 ng/mL). His chronic medications at this time included metoprolol succinate, allopurinol, rivaroxaban, aspirin, pantoprazole, albuterol, montelukast, and simvastatin. The patient continued routine follow-up and was asymptomatic. He was subsequently evaluated by ophthalmology in August 2019 as part of routine screening for amiodarone toxicity. He was noted to have developed mild pigmented whorls,

bilaterally, which were believed to be dystrophic and not believed to be associated with amiodarone toxicity; however, concern was raised for the new ophthalmologic changes. Routine serum laboratory work was obtained, which demonstrated acute leukopenia, elevated thyroid-stimulating hormone, and elevated PSA. The total PSA was 5.4 ng/mL and the percent free PSA (a ratio value of free PSA to total PSA used to check probability of prostate cancer by age in patients with total PSA between 4 and 10 ng/mL) was 8.0%.⁴ Amiodarone was discontinued with subsequent resolution in laboratory work to within normal limits (Figure 1) and returned to prior baseline. Serum amiodarone concentration evaluation was not available prior to or after

Table 1 The Naranjo Algorithm for adverse drug reaction assessment

Question	Yes	No	Unknown
1 Are there previous <i>conclusive</i> reports on this reaction?	+1	0	0
2 Did the adverse event appear after the suspected drug was administered?	+2	-1	0
3 Did the adverse reaction improve when the drug was discontinued or a <i>specific</i> antagonist was administered?	+1	0	0
4 Did the adverse reaction appear when the drug was re-administered?	+2	-1	0
5 Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0
6 Did the reaction reappear when a placebo was given?	-1	+1	0
7 Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
8 Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
9 Did the patient have a similar reaction to the same or similar drugs in <i>any</i> previous exposure?	+1	0	0
10 Was the adverse event confirmed by any objective evidence?	+1	0	0
Total Score: 6			

Each question results in a yes, no, or unknown answer based on the patient history and experience. Each answer carries a point value, which is summated. Based on scoring, the probability of adverse drug reaction is as follows: ≤0 is doubtful, 1–4 is possible, 5–8 is probable, and ≥9 is definite. Our “answers” for our patient are denoted in the bolded numbers, yielding a total score of 6, a probable adverse drug reaction.

discontinuation of amiodarone. Total PSA and percent free PSA 10 days post discontinuation in August 2019 were 3.8 ng/mL and 11.6%, respectively. During this time, he underwent no other medication changes except the discontinuation of amiodarone therapy. Reassessment in January 2020 resulted in a total PSA of 3.5 ng/mL and 12.3% free PSA.

Discussion

Amiodarone, a derivative of an iodinated benzofuran, has multiple and complex electrophysiological effects that make it an effective antiarrhythmic drug for the treatment of supraventricular and ventricular arrhythmias. It is principally listed as a Vaughn-Williams class III antiarrhythmic medication (affecting potassium efflux) but exhibits similar properties and effects as the other 3 classes of medications.¹ Amiodarone has numerous noncardiac adverse effects, including involvement of the lung, eye, skin, thyroid, peripheral nervous system, and liver.¹ Epididymitis has been reported as a rare genitourinary system adverse effect of amiodarone use.^{5,6} Furthermore, as discussed previously, testicular involvement with long-term amiodarone therapy has also been reported.² To date, there have been no cases of prostate involvement with amiodarone usage.

PSA is an androgen-regulated serine protease produced by both prostate epithelial cells and prostate cancer and is the most commonly used serum marker for prostate cancer. The principal utility of PSA is in monitoring patients after definitive cancer therapy.⁷ Disruption of prostatic epithelial cells, for example in benign prostatic hyperplasia, inflammation, infection, or prostatic cancer, may lead to diffusion of the PSA into the surrounding tissue and the blood.⁸

The exact mechanism by which amiodarone affects the prostate gland is not clear and has not been studied. Extensive tissue deposition is a characteristic of amiodarone.⁹ It is possible that amiodarone deposits in the prostate gland similar to other organs like epididymis and testis.¹⁰ Focal fibrosis and lymphocytic infiltration were proposed as a mechanism of sterile epididymitis that is partly similar to the alveolar fibrosis and interstitial inflammation seen on lung biopsy of the patients with chronic amiodarone use.^{5,6,11,12} Similarly, deposition of amiodarone and its metabolite might occur in the prostate gland and this leads to lipidosis and ultrastructural changes seen in other organs, and this may lead to secretion of PSA.⁹

Prostate infection can also increase PSA levels. However, in our patient infectious etiology of prostatitis was ruled out because our patient did not have a urinary tract infection and he was not experiencing symptoms such as fevers, chills frequency, urgency, or dysuria. In addition, reduction in PSA after cessation of amiodarone is another evidence against infectious etiology. He also did not have reported symptoms of benign prostatic hyperplasia and had no evidence of prostate cancer. Furthermore, following administration of amiodarone, he experienced significant leukopenia

and concomitant thyroid dysfunction, both of which resolved following cessation of amiodarone therapy. Lastly, no medication adjustments were made that would alter the levels of PSA, aside from the amiodarone.

Based on one of the widely used causality assessment scales for adverse drug reactions, the Naranjo Scale (Table 1),¹³ the causal associations between amiodarone and PSA elevation are very likely. In our case the Naranjo score would be 6. This demonstrates that PSA levels followed a reasonable temporal sequence after initiation and discontinuation of amiodarone, and it followed a recognized response to amiodarone and was confirmed by improvement on withdrawing amiodarone (Figure 1).

Conclusion

Amiodarone is a common, widely used antiarrhythmic medication for the treatment of atrial and ventricular arrhythmias. Despite being considered one of the more effective antiarrhythmic medications owing to general ease of use, amiodarone usage carries with it a multitude of side effects coupled with relatively long half-life, which require frequent multisystem monitoring. We describe a case of PSA elevation following initiation of amiodarone and resolution following withdrawal without other identifiable etiologies. This demonstration may yield further research into the bioeffects of this iodinated benzofuran derivative and, ultimately, improved patient monitoring and outcomes.

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