

# Levetiracetam for the treatment of myoclonic neurotoxicity induced by amiodarone



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## Introduction

Amiodarone is a class III antiarrhythmic prescribed for atrial fibrillation and ventricular arrhythmias commonly associated with adverse events such as pulmonary toxicity, thyroid dysfunction, QT prolongation, corneal opacities, and, rarely, myoclonic neurological toxicity. Those events require weeks to months to be reversed upon drug discontinuation or tapering, impairing the quality of life of these cardiac patients. Some of them are irreversible in nature, but fortunately in the present case we demonstrate an off-label use of the anticonvulsant levetiracetam for the treatment of a particularly rare neurotoxicity side effect presenting as myoclonus.

## Case report

A 60-year-old man with past medical history of ischemic heart failure with reduced ejection fraction and history of ventricular tachycardia with cardiac resynchronization defibrillator system implanted, previously on amiodarone with subsequent neurotoxicity leading to myoclonus, presented to a local emergency department with a 3-week-long period of palpitations, chest pain, and syncope.

The patient stated that in the weeks leading up to his presentation to the hospital he experienced intermittent episodes of palpitations with accompanying chest pain that lasted a few seconds at a time, which gradually became more severe and longer in duration, leading to syncope. He was found to have sustained monomorphic ventricular tachycardia accompanied by hypotension; he was placed on sotalol and was transferred to our hospital for advanced electrophysiology management.

On arrival he was complaining of palpitations. Physical examination showed hypotension and tachycardia and he was found to have recurrent sustained monomorphic ventricular tachycardia. The patient was given lidocaine 100 mg intravenous bolus, followed by a drip at 2 mg/min, which immediately resolved the ventricular tachycardia and was

decreased to 1 mg/min in the following days for a total of 5 days with the ultimate goal of transitioning to oral medication. A transthoracic echocardiogram demonstrated a large apical thrombus later confirmed by cardiac computed tomography with contrast, making the patient ineligible for radiofrequency ablation.

Considering discontinuation of the lidocaine drip, discussion of amiodarone incorporation revealed that 3 years before presentation he was prescribed the antiarrhythmic and 4 months into treatment he developed severe and uncontrollable “muscle jerks” triggered by fine touch prior to going to bed, which limited his quality of life lasting for 9 months. Even after its discontinuation, and owing to its long half-life, this side effect did not resolve until 3 months later.

Neurology was consulted and concluded that the recurrence of neurotoxic symptoms could not be predicted, and posited that if they presented, the symptoms would follow a similar pattern as before, with resolution following cessation of medication. In agreement with the patient’s wishes, a loading dose of amiodarone 400 mg twice a day was initiated and up-titrated on day 3 to 400 mg 3 times a day; unfortunately, he began experiencing sudden involuntary full-body limb-predominant myoclonus triggered by fine touch, which progressed by the hour. On the following day, the patient was found in severe distress, stating he was not able to sleep and that his past traumatic experience was repeating; subsequently, amiodarone was discontinued, and the patient was placed on mexiletine.

In an effort to alleviate the myoclonus, levetiracetam 500 mg twice a day was administered, and symptoms resolved within 24 hours. As his symptoms were alleviated with levetiracetam, the patient was amenable to switching back from mexiletine to amiodarone concurrently with levetiracetam. Unfortunately, myoclonus reappeared, and the decision was made to ultimately discontinue amiodarone and restart mexiletine.

The patient was subsequently discharged on mexiletine and anticoagulation with scheduled follow-up for future consideration of radiofrequency ablation when thrombus resolved.

**KEYWORDS** Adverse reaction; Amiodarone; Drugs side effects; Myoclonus; Neurotoxicity; Ventricular tachycardia; Levetiracetam (Heart Rhythm Case Reports 2020;6:488–490)

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## Discussion

This case delineated a patient with a history of prior amiodarone-induced myoclonus, presenting with sustained

**KEY TEACHING POINTS**

- Amiodarone is a useful antiarrhythmic medication that has a narrow therapeutic index and has been associated with multiple side effects. Reversible side effects might take weeks to months to extinguish after discontinuation of the drug, which affects the patient's quality of life.
- Myoclonus is a movement disorder characterized by involuntary, jerky, sudden muscular movements, which could be cortical, subcortical, spinal, or peripheral; treatment election is based on this classification. Furthermore, drug-induced myoclonus is usually cortical as well.
- In the present case, an off-label use of levetiracetam shortened the amiodarone-induced myoclonus neurotoxicity. Unfortunately, concurrent use of both drugs was not enough to avoid reappearance of symptoms.
- Physicians should proceed cautiously regarding the off-label use of levetiracetam for the treatment of this rare side effect of amiodarone. Further research must be conducted to determine pathophysiology of such side effect.

monomorphic ventricular tachycardia that was once controlled with lidocaine drip. The patient was started on amiodarone with subsequent development of sudden involuntary full-body limb-predominant myoclonus triggered by fine touch; however, the use of levetiracetam was associated with shortening the duration of this rare side effect. The concurrent use of amiodarone and levetiracetam continued to induce myoclonus and it was only after complete discontinuation of amiodarone that the patient returned to baseline.

Amiodarone is a class III antiarrhythmic prescribed for atrial fibrillation and ventricular arrhythmias, commonly associated with adverse events such as pulmonary toxicity, thyroid dysfunction, QT prolongation, and corneal opacities, to name a few.<sup>1-4</sup> Although rarely associated with neurotoxicity, previous studies reported different neurological adverse events with the use of this drug, including ataxia, peripheral neuropathy, tremor, and parkinsonism.<sup>5-8</sup> Interestingly, a 12-year retrospective study of 707 patients exposed to amiodarone did not report the presence of myoclonus.<sup>7</sup>

Although the mechanism of the amiodarone-induced neurotoxicity is still unknown, amiodarone and its active metabolite desethylamiodarone have been measured in the central nervous system, suggesting that this drug is able to cross the blood-brain barrier.<sup>9,10</sup> Moreover, different studies have demonstrated that amiodarone could promote the formation of lysosomal phospholipid-containing inclusions in

Schwann cells, fibroblasts, and perineural cells.<sup>11</sup> The onset of the neurological symptoms ranged from 12 days to 12 months after initiation of amiodarone treatment.<sup>9</sup> Since amiodarone is highly lipophilic and has an extremely long elimination half-life (on the order of 6 months<sup>7,11</sup>), this could be a reasonable explanation for the prolonged recovery after amiodarone discontinuation, as seen in our patient. These symptoms improved after the amiodarone was either discontinued or tapered down in most of the cases.<sup>5,10</sup> Curiously enough, our patient developed myoclonus in a much shorter time frame, after having received 3 days' worth of amiodarone. The pathophysiology behind this phenomenon is unclear.

To our knowledge there are less than a handful of amiodarone-induced myoclonus cases. One recent publication reported an experience involving a 90-year-old man developing action-induced involuntary jerks and gait impairment after 1 year of amiodarone use; the report described the first successful response to levetiracetam at 1 month with full recovery of baseline functionality at 4 months.<sup>5</sup> Levetiracetam has been associated with behavioral changes including psychosis, irritability, hypertension, weakness, and drowsiness, which is why a low-dose levetiracetam was decided for this patient, with the aim to up-titrate to avoid further instability.

According to Naranjo and colleagues,<sup>12</sup> the adverse drug reaction probability scale for amiodarone being responsible for the neurotoxicity was 6, giving a high likelihood that amiodarone caused the patient's neurotoxicity. Of note, it might have been higher if serum amiodarone levels were measured. Drug interactions were evaluated and did not appear to be the culprit of our patient's side effect.

Myoclonus is a movement disorder characterized by involuntary, jerky, sudden muscular movements, which could be cortical, subcortical, spinal, or peripheral; treatment election is based on this classification. In our case the myoclonus was generalized, primarily on distal limbs, and triggered by fine touch and movement, which would fit on the cortical myoclonus classification; drug-induced myoclonus is usually cortical as well.<sup>13</sup> Levetiracetam is a broad-spectrum antiseizure drug that binds to the synaptic vesicle protein SV2A modulating synaptic transmission through alteration of vesicle fusion; it is 1 of the first-line treatments for reflex cortical myoclonus, primarily aiming at augmenting inhibitory processes within the sensorimotor cortex.<sup>14</sup>

After careful consideration, we decided to start high-dose levetiracetam given the previous literature descriptions and the distressing nature of symptoms. Nevertheless, caution is warranted regarding the use of amiodarone and levetiracetam in combination, as it may be associated with an increased risk for the development of psychosis.<sup>15</sup>

Finally, our findings suggested that levetiracetam in this setting was useful to shortening the duration of amiodarone-induced myoclonus that otherwise would have impaired quality of life for months.

## Conclusion

Our experience delineates a case of a patient requiring amiodarone for the management of sustained monomorphic tachycardia in the setting of prior amiodarone-induced myoclonus and the use of levetiracetam in shortening the duration of this rare side effect. Nevertheless, in our experience the concurrent use of amiodarone and levetiracetam continued to induce myoclonus and it was only after complete discontinuation of amiodarone that the patient's baseline was achieved.

Physicians should proceed cautiously regarding the off-label use of levetiracetam for the treatment of this rare side effect of amiodarone; moreover, there is a known association of amiodarone with mild tremors, which should by no means be treated with levetiracetam. Further research must be conducted to determine the pathophysiology of such side effect.

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