TTU Journal of Biomedical Sciences 2023, ***02***:29-32
(RESEARCH ARTICLE) DOI: 10.53901/tjbs.2023.08.art03

Research article

Amiodarone-Induced Delirium

Aisha Khalid [1,2,*], Jack Tarlinton [2], Tony Kwan [2], Kenneth Khoo [2,3]

[1] *Harvard Medical School, Boston, MA, USA*
[2] *Calvary Public Hospital Bruce, Canberra, ACT, AU*
[3] *Australian National University, Canberra, ACT, AU*

***Corresponding author**:
Aisha Khalid
Harvard Medical School, MA, USA
Email: aisha.khalid000@gmail.com

Article history: Manuscript received August 5, 2023; revised manuscript received August 28, 2023; accepted August 30, 2023.

ABSTRACT

Amiodarone is a complex drug for the treatment of atrial fibrillation (AF) and ventricular tachyarrhythmias (VTs). Amiodarone can cause a lot of side effects, including pulmonary toxicity, exacerbation of arrhythmia, hyper and hypothyroidism, and hepatic failure. Amiodarone can also cause neurological symptoms, such as tremors, poor coordination, balance disturbances, dizziness, myoclonic jerks, myopathy, and peripheral neuropathy. Amiodarone could cause delirium, depression, insomnia, agitation, confusion, and fatigue. In some cases, patients may experience sensory disturbances, such as visual or auditory hallucinations. A case report of a patient developing delirium after starting amiodarone and improved after discontinuing amiodarone. The exact mechanism of this side effect is not fully understood. In the care of patients receiving amiodarone, the patients should be closely monitored for signs of delirium, particularly with higher doses, new onset of symptoms after drug initiation, and longer treatment durations. Prompt recognition and management of amiodarone-induced delirium are essential to prevent complications and ensure optimal patient outcomes.

KEYWORDS Amiodarone, Delirium.

BACKGROUND

The use of amiodarone for treating atrial fibrillation (AF) and preventing ventricular tachyarrhythmias (VTs) in high-risk patients is off-label and without an FDA-sanctioned randomized controlled trial [1]. Whereas in Australia, the Therapeutic Goods Administration (TGA) has approved this drug for severe tachyarrhythmias unresponsive to other therapy [2]. It is common practice to use amiodarone to prevent arrhythmia development after cardiac surgery [3].

Amiodarone has been shown to decrease the incidence of arrhythmic death due to ventricular tachyarrhythmias in heart failure (HF) patients, mainly when used in conjugation with beta-blockers. However, its effect on cardiovascular and overall survival in these patients remains uncertain [4].

Based on the Vaughan-Williams classification, amiodarone is a class III antiarrhythmic, with its principal effect through potassium channel blockade. The reduction of potassium efflux delays the repolarization of the cardiac myocyte and subsequently prolongs the duration of the cardiac action potential. However, amiodarone also exhibits antagonism at the sodium and calcium channels (class I and class IV actions, respectively), which can further modify the characteristic of the action potential and its conduction speed throughout the myocardium. Finally, amiodarone has been shown to have anti-adrenergic properties (a class II action), thus exerting a negative chronotropic effect on the myocardium via the reduction of sympathetic tone. This is particularly beneficial in patients with HF [5].

Amiodarone has a complex pharmacokinetic profile due to its high lipophilicity, large volume of distribution, and extensive metabolism. Amiodarone is metabolized primarily in the liver by the cytochrome P450 (CYP) enzyme system, specifically CYP3A4, and CYP2C8. The major metabolite of amiodarone is desethylamiodarone (DEA), which is also pharmacologically active and has a longer half-life than amiodarone. The elimination half-life of amiodarone ranges from 15 to 142 days, with an average of approximately 58 days. The elimination half-life of DEA is longer, ranging

from 57 to 142 days, with an average of approximately 107 days [6]. Both amiodarone and DEA are highly protein-bound, and their elimination is primarily through hepatic metabolism and biliary excretion [7].

Amiodarone is known to cause various adverse reactions, such as pulmonary toxicity [8], exacerbation of arrhythmia, hyper and hypothyroidism, and hepatic failure. The prevalence of adverse effects from amiodarone is as high as 15% within the first year and 50% for long-term use [1]. Amiodarone can also cause neurological symptoms, such as tremors, poor coordination, balance disturbances, dizziness, myoclonic jerks, myopathy, and peripheral neuropathy. The severity of these symptoms can be related to the drug dose [9]. The drug's structural similarity to thyroxine and its iodine content can result in thyroid abnormalities in approximately 15% of patients, leading to neuropsychiatric symptoms [7].

While adverse psychiatric reactions to amiodarone are not common, they have been reported and may include symptoms such as delirium, depression, insomnia, agitation, confusion, and fatigue. In some cases of amiodarone-induced delirium, patients may experience sensory disturbances, such as visual or auditory hallucinations [10]-[12]. However, isolated cases of perceptual disturbances without delirium have been reported, such as a case of musical hallucinations associated with amiodarone use [6]. Here, we present a case report of a patient experiencing symptoms during amiodarone therapy and how symptoms resolved after cessation of the drug.

CASE PRESENTATION

A mid-60s man underwent a biologic Bentall procedure at a tertiary-level hospital in Melbourne for an ascending aortic aneurysm. The postoperative course was complicated by a left-sided pneumothorax one day after the procedure, which required decompression with a chest tube. He subsequently developed atrial fibrillation with a rapid ventricular response (AF-RVR) and was started on 5 mg oral bisoprolol, a loading dose of 300 mg intravenous amiodarone followed by an oral maintenance dose of 200 mg BD, and apixaban. The patient became delirious on postoperative day 4, exhibiting the symptoms of delirium, including agitation and irritability, inattention and near-complete aphasia, visual hallucinations, and personality changes. A Stroke call was initiated and a CT angiogram and MRI of the brain (DWI phase only) were done and showed normal results. In the workup of delirium, an infective screen was initiated, including inflammatory markers (full blood count and C-reactive protein), electrolytes, comprehensive metabolic profile (calcium, magnesium, phosphate), chest X-ray, urine analysis, and blood cultures, which were unremarkable. An electroencephalogram was done after a neurology review which showed mild theta wave slowing but no epileptiform discharge.

The patient had a history of depression and anxiety with acute psychosis at age 30 due to a relationship breakdown. The psychosis was resolved after treatment with Fluoxetine for 6 months, without the need for long-term antipsychotic medications. This was on a background of suspected developmental delay in childhood of unclear etiology but without significant functional impact on his independence in adulthood. He also had a history of bowel cancer, was treated with resection, and was presumed in remission.

He was discharged home on 200 mg BID amiodarone, 5 mg bisoprolol, and apixaban under the care of his son and referred to a geriatrician for follow-up. However, 4 weeks later, the patient was readmitted to another hospital due to ongoing behavioral changes. The symptoms on admission were similar to those observed during his initial hospitalization and included alternating withdrawal and hyperactivity, wandering behaviors, sleep-wake disturbance, and echolalia. In the emergency department, he was also noted to have speech latency, distractibility, and prolonged staring suggestive of response to internal stimuli.

No acute precipitant was identified during the initial workup, with traumatic, metabolic, and infective causes excluded, which include full blood count (FBE), urine, electrolyte, creatinine (UEC), CMP, CRP, arterial blood gas (ABG), blood and urine culture. Neurological examination revealed no focal abnormalities in tone or motor power, gait, or frontal release signs. After a complete normal CT scan of the brain, an MRI of the brain was done and showed small vessel changes and early-onset changes of amyloid angiopathy, but no other pathology was found. An ECG was performed, which showed sinus rhythm with a prolonged QTc interval of [510 milliseconds].

Given the patient's known prior psychiatric history and the possibility of underlying psychosis, the hospital's inpatient consultation liaison psychiatry service reviewed the patient in person and considered the presentation most consistent with delirium, with no evidence of a primary psychiatric disorder to explain the observed behavioral abnormalities. Due to severe agitation and aggression requiring antipsychotic medications (risperidone) in the setting of a prolonged QT interval, consideration was given to stopping amiodarone. It was ultimately completely discontinued after titrating to 200 mg daily for the first three days. Within 48 hours without amiodarone, the patient began to recognize his surroundings, and in 72 hours, the previously observed behavioral changes had almost entirely resolved. His Montreal Cognitive Assessment (MOCA) score, which was unassessable initially due to the patient's inability to engage, was subsequently normal at 29/30 after cessation of amiodarone. At 6 weeks of follow-up in the clinic, the MOCA score was 30/30.

Given the temporal association of the resolution of behavioral changes to the cessation of amiodarone, the onset of initial delirium with the commencement of amiodarone in his initial hospitalization, and the absence of any other clear triggers, amiodarone-induced delirium was thought to be the most likely cause. In the case of our patient, his background of prior severe depression, co-administration of beta blockers, and evidence of early microvascular ischemia in the brain likely all contributed to potentiating or increasing

the risk of the delirium observed.

DISCUSSION

Amiodarone is a common medication for cardiac arrhythmias. However, it has been associated with developing delirium in a small subset of patients. Delirium is a sudden onset of confusion, disorientation, and changes in attention, which can be caused by various factors, including medications [13].

The mechanism causing delirium by amiodarone needs to be better understood. Still, it is thought to be related to the drug's ability to cross the blood-brain barrier, as shown in a rat model [14]. While there were many in vitro studies on animal tissue [15], the data in humans are lacking. Still, it is postulated that amiodarone will passively cross the blood-brain barrier due to the drug's lipophilicity [14] and affect neurotransmitter systems in the brain as proven in multiple rat models [14]. Specifically, amiodarone has been shown to interact with multiple neurotransmitter receptors, including acetylcholine, gamma-aminobutyric acid (GABA), and N-methyl-D-aspartate (NMDA) receptors by attaching ion channels [15], [16].

Amiodarone's interaction with the cholinergic system is of particular interest as it has been associated with the development of delirium. Studies have shown that amiodarone is a positive allosteric modulator of muscarinic receptors for N-methylscopolamine (NMS) that selectively targets the M5 subtype over the M1 sub-type. By enhancing the binding of N-methylscopolamine (NMS), a selective M5 receptor agonist, amiodarone may influence these intracellular signaling pathways, resulting in altered cellular responses [17]. Amiodarone has been identified as the initial compound demonstrating the ability to augment receptor efficacy without concurrently increasing potency. specifically, at the M5 recepto [18].

Muscarinic receptors are widely distributed throughout the brain and are crucial in regulating numerous physiological and cognitive processes, including learning, memory, attention, and emotion. Therefore, the effect of amiodarone on the brain would likely involve the modulation of these processes, potentially leading to cognitive and behavioral changes. This change in cholinergic activity can lead to cognitive impairment, which is a hallmark of delirium. However, further studies are required to fully understand the implications of amiodarone's modulation of muscarinic receptors and its potential therapeutic uses in neurological and psychiatric disorders.

Given amiodarone's potential for organ injury, toxicity should be considered when first-line medications have failed or are contraindicated. The American College of Cardiology (ACC), American Heart Association (AHA), and Heart Rhythm Society guidelines support this approach [19].

There have been several case reports and studies that have examined the association between amiodarone use and delirium. A single case study reported the onset of symptoms after four days of amiodarone therapy; these symptoms improved upon discontinuing amiodarone, with relapse after a re-challenge four days later [20]. Although the number of cases is limited, a trial of cessation and subsequent re-challenge of a suspect medication is a robust therapeutic maneuver in identifying adverse drug reactions.

One study found that the risk of delirium increased with higher doses of amiodarone, suggesting a possible dose-dependent relationship [9] and longer treatment duration [21]. It is possible to speculate that the commencement of amiodarone in hospitalized patients may have resulted in an increased incidence of undiagnosed cases of altered mental status [7]. The impact of amiodarone on thyroid function may also contribute to the observed mood variability in affected patients. However, there is insufficient data to fully support this hypothesis due to the limited instances of amiodarone-induced catatonic depression where thyroid stimulating hormone (TSH) levels were only mildly elevated [11].

The exact incidence of amiodarone-induced delirium is not well established. It is likely underreported and may be influenced by factors such as patient age, comorbidities, and concurrent medication use [22], [23]. The aging process can result in structural alterations in neural connections and networks, cerebral blood flow (CBF) changes, modifications in the blood-brain barrier (BBB), and fluctuations in cerebrospinal fluid (CSF) dynamics. These age-related factors collectively contribute to an increased vulnerability of the aging brain to delirium [22]-[24].

Research has demonstrated that after discontinuing chronic therapy, a decrease of 50% in the plasma concentration of amiodarone can be observed within three to ten days [22]. This decrease in plasma concentration coincides with the resolution of symptoms in the patient in our study. Managing amiodarone-induced delirium typically involves discontinuing the medication and providing supportive care; this includes environmental measures, monitoring vital signs, and addressing any underlying medical conditions that may have contributed to the delirium.

CONCLUSION

Overall, these studies suggest that amiodarone's effects on neurotransmitter systems in the brain could contribute to developing delirium in some patients. However, further research is needed to understand the underlying pathophysiology. In conclusion, amiodarone can cause delirium, although the exact mechanism is not fully understood. Patients receiving amiodarone should be closely monitored for signs of delirium, particularly with higher doses, new onset of symptoms after drug initiation, and longer treatment durations. Prompt recognition and management of amiodarone-induced delirium are essential to prevent complications and ensure optimal patient outcomes.

CONFLICTS OF INTEREST

None of the authors have conflicts of interest to declare.

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