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Amiodarone-induced parkinsonism

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Abstract

Drug-induced parkinsonism (DIP) is the second most common cause of parkinsonism, primarily resulting from medications that block dopamine D2 receptors or reduce dopamine in the basal ganglia. While antipsychotics are most frequently linked to DIP, cases related to other agents like amiodarone are rare. We describe a 79-year-old Filipino woman with sick sinus syndrome who developed parkinsonian symptoms after two months of amiodarone therapy. A high Nanjaro score, lack of response to levodopa, and dramatic improvement following discontinuation of amiodarone all aided the diagnosis of DIP. Supporting features include acute-subacute onset, timing of symptom development and absence of non-motor signs typical of PD. In conclusion, although rare, amiodarone can be associated with parkinsonism, highlighting the importance of clinical suspicion and vigilance, as the motor features of DIP can closely mimic those of PD.

INTRODUCTION

Drug-induced parkinsonism (DIP) is the second most common cause of parkinsonism after idiopathic Parkinson's disease (iPD).[1] Its exact mechanism is unclear, but all causative medications either block post-synaptic dopamine D2 receptors or deplete dopamine in the basal ganglia, resulting in parkinsonism.[2] Typical and atypical antipsychotic medications pose the greatest risk for DIP due to their strong D2 receptor affinity and blockage in the striatum.[3] Subjects exposed to antipsychotics have over three times the risk of DP, with higher risk associated with atypical than typical antipsychotics.[4] However, reports of parkinsonism induced by other compounds, such amiodarone, are rare.

Amiodarone is a class III antiarrhythmic agent commonly used to manage supraventricular and ventricular arrhythmias. It acts as a potassium cardiac channel inhibitor and a non-competitive beta-adrenoceptor antagonist. Due to its chemical similarity to thyroid hormone, amiodarone is linked to various adverse effects, including thyroid problems, liver toxicity, photosensitivity, vision issues, nausea, and constipation.[5] It can also lead to a wide range of neurological symptoms, such as tremors, gait ataxia, cognitive deficits, peripheral neuropathy, myoclonus, and, though infrequently, parkinsonism and myopathy.[6] In a pharmacovigilance study of 20,855 reported adverse drug reactions, only 1.14% of cases (3 out of 261) related to DIP were attributable to amiodarone.[7]

Early identification and intervention are crucial, as DIP is a reversible condition. If not properly managed, DIP can result in falls, nursing home placement, and increased mortality.[8] We report a case of an elderly Filipino woman who developed gradual parkinsonism after two months of amiodarone use, with symptoms improving following discontinuation of the medication.

CASE REPORT

A 79-year-old, Filipino woman with a medical history of sick sinus syndrome was maintained on amiodarone following her cardiac pacemaker insertion. She was maintained on amiodarone 200 mg tablet once daily on a stable dose with no adjustments. Other maintenance medications include edoxaban, nebivolol, metformin and atorvastatin. After a period of 2 months, she gradually developed signs of parkinsonism, starting with postural tremor of both hands. It was initially thought as essential tremors, however, propanolol did not provide any relief. Other signs slowly developed over the succeeding months, such as slowness of movements, imbalance, stooped posture and stiffness of extremities. This

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prompted referral to the movement disorders clinic.

There was notable absence of non-motor symptoms, such as constipation, anosmia, dream enactment suggestive of REM-sleep behavior disorder (RBD), excessive daytime sleepiness, memory problems and urinary symptoms. Non-Motor Symptom Scale (NMSS) score was 0. The patient had no history of hypotension, recent infections, cancer, or toxin exposure. There was no reported use of herbal supplements like Mucuna, and no history of brain trauma or family history of movement disorders. On examination, symmetrical signs of bradykinesia, postural hand tremors and rigidity were observed. Gait impairment and postural instability were also present. UPDRS (United Parkinson's Disease Rating Scale) Part III motor score was 30 (see Table 1). The rest of the systemic and neurologic findings were normal.

MRI of the brain showed microvascular ischemic white matter changes and mild cerebro-cerebellar volume loss. Blood tests were normal, including creatinine, thyroid and liver function tests. Dopamine transporter (DaT) scan and amiodarone plasma level measurements were not locally available.

PD was considered, however, no improvement of symptoms was noted after treatment with levodopa/carbidopa (300 mg/day). No improvements were observed during the levodopa challenge test (LCT) using levodopa/carbidopa 250/25 mg immediate-release tablet. Owing to the persistence of symptoms, DIP secondary to amiodarone was suspected. The Naranjo score was calculated to be 7, indicating a probable adverse drug reaction. Discontinuing amiodarone led to dramatic improvement of symptoms at 3, 6 and 7 months, with complete resolution observed at 10 months follow-up, without the need for any dopaminergic medications (see table 1 and figure 1). Admittedly, the patient was not inclined to perform exercises at home and did not undergo non-pharmacologic interventions such as physical or occupational therapy, dance therapy, or other alternative treatments that might have potentially alleviated her symptoms.

DISCUSSION

A large pharmacovigilance study found no evidence of an association between amiodarone use and the development of parkinsonism.[9] However, this study was limited by the inherent constraints of disproportionality analyses. Discussions may remain ongoing, as DIP is often misdiagnosed as PD[8], and more cases may be reported in the future. Physical examination, including the MDS-UPDRS part 3, may not effectively differentiate DIP from PD.[10] Therefore, clinicians should always consider the possibility that the offending drug may unmask underlying subclinical PD.

The exact mechanisms underlying the development of parkinsonism remain poorly understood. Several of the suggested mechanisms include drug accumulation and direct toxic effect,

Table 1: Evolution of UPDRS Part III motor scores through 7 months of follow-up

UPDRS part 3	Baseline	1 month	3 months	6 months	7 months	10 months
Bradykinesia	21	24	16	11	4	0
Rigidity	1	3	2	0	0	0
Tremor	2	4	1	0	0	0
Posture	1	1	1	1	0	0
Postural instability	3	3	3	3	3	0
Gait	2	2	1	1	1	0
Total score	**30**	**37**	**24**	**16**	**8**	**0**
Events	*Initial consult; started with levodopa/ carbidopa 300 mg daily*	*No response during LCT → Amiodarone discontinued*	*Improvement of symptoms; no dopaminergic treatment given; no non-pharmacologic interventions performed*			*Resolution of symptoms*

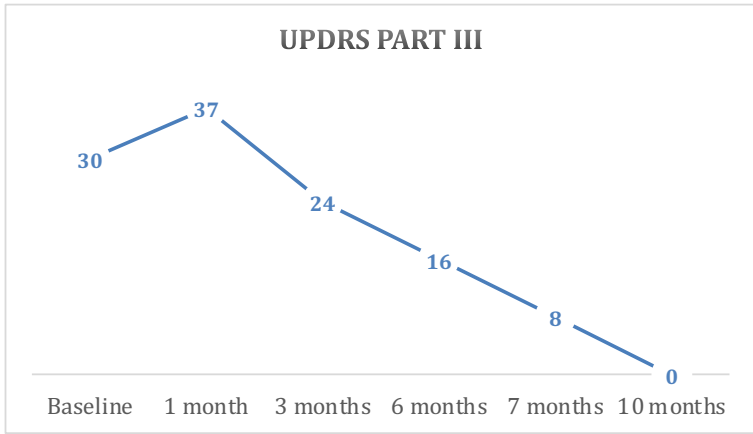

Figure 1. Trend of UPDRS improvement after discontinuation of amiodarone

mitochondrial and lysosomal enzyme dysfunction, and potassium channels inhibition on dopamine striatal release.[9,11-13] Overall, the cumulative incidence of likely amiodarone neurotoxic effects is 2.8%.[6] The mechanism of neurotoxicity is unclear, but amiodarone and its metabolite may cause tissue phospholipid accumulation by inhibiting liposomal phospholipase.[14]

Discontinuing amiodarone served both as a diagnostic and therapeutic measure in our patient. Typical DIP often resolves naturally after stopping the trigger, though this recovery can take several months, especially with high doses.[2] However, in 15% of cases, parkinsonism continues indefinitely even after the offending agent is discontinued.[15] In the case of amiodarone-induced parkinsonism, symptoms may persist well after discontinuation of the drug because amiodarone has a half-life of 26 to 107 days.[5] The recurrence of symptoms upon reintroducing amiodarone would support a diagnosis of DIP; however, the cardiology team advised against it. A case of DIP has been reported to recur upon reintroduction of amiodarone and resolve again when the dose was lowered.[16] Notably, our patient developed parkinsonian signs after two months of low-dose amiodarone (200 mg/day), similar to a case who exhibited parkinsonism after the same dose and a longer interval of two years.[11] Even low doses of amiodarone can inhibit respiratory chain complexes I and II[11], which is one of the suggested mechanisms of parkinsonism. In contrast, a patient developed akinesia within an hour after taking a higher dose of amiodarone (3000 mg) and symptoms resolved four hours after discontinuation.[12] This variability in the timing of symptom onset and resolution underscores the clinical diversity among patients.

Timing is also a key factor. The onset of symptoms in DIP is typically acute to subacute, whereas PD has a more gradual, chronic onset.[17] Our patient had a UPDRS part III score of 30 within 2 months, predominantly bradykinetic symptoms. In DIP, symptoms can develop within days or weeks of starting or increasing the dosage of the neuroleptic therapy, and usually resolve within a few days after stopping the offending drug.[2] Symptoms of DIP are expected to resolve within six months of stopping the offending medication.[18] However, our patient's symptoms resolved after a period of 10 months. This aligns with a case series noting persistent parkinsonism nine months post-discontinuation, suggesting that monitoring for up to a year may be needed.[19]

Our patient's age (79 years old) and female sex also increased her risk of developing DIP. One study showed that adverse drug events are more common in older adults, peaking in the 75-79 age group.[20] Speaking of DIP in particular, one pharmacovigilance study found that 48% of patients were between 60 to 79 years old[7]. Elderly patients are more vulnerable to DIP, likely because of age-related decline in neuronal circuits and striatal dopamine levels.[21] Other factors to consider in older individuals include higher comorbidity rates and medication use. Potential risk factors of female patients to develop DIP include higher doses per kilogram in females, better treatment adherence, and hormonal factors.[7]

Another key feature supporting DIP over idiopathic (or unmasked) PD was the absence of typical non-motor symptoms. A study found that PD patients scored significantly higher on the NMSS compared to DIP patients, with early-distinguishing features including urinary issues, sleep disturbances, concentration problems, and

hyposmia[22]—none of which were present in our patient (NMSS score = 0). Additionally, DIP generally does not improve with levodopa, unlike idiopathic PD.[2] Although it's uncertain whether a higher dose of levodopa/carbidopa might have helped, the lack of response to 250/25 mg during the LCT led to the decision to avoid further dopaminergic therapy.

Several diagnostic tests, such as DaT scan and amiodarone plasma level measurements, could aid in diagnosis. However, these tests are not readily available in countries like the Philippines and can be costly for patients. Unlike those with idiopathic PD, who usually have abnormal DaT scan results, individuals with DIP generally show normal scans.[23] Meanwhile, neurological side effects from amiodarone increase when plasma levels exceed 2.5 mg/L.[24]

In conclusion, amiodarone's rare association with parkinsonism underscores the need for clinical suspicion and vigilance, as motor features of DIP and PD can be identical. The diagnosis of DIP is grounded on the patient's history of exposure to neuroleptics, or other culprit medications, particularly in older individuals. However, in some cases, ancillary testing may be beneficial. Early recognition allows for prompt discontinuation of the offending agents, potentially avoiding the necessity for dopaminergic treatment.

DISCLOSURE

Ethics: This case report has been approved by the institutional review board of Makati Medical Center (MMCIRB2025-02-028). Patient consent was obtained for publication of this case report.

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