

# Evaluation of frequency, characteristics, and risk factors of neurotoxicity in patients on long-term amiodarone by nerve conduction studies

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## ABSTRACT

**Background:** Amiodarone is an iodine-rich drug that is a highly effective and widely used as an antiarrhythmic agent for the treatment of symptomatic supraventricular and ventricular tachyarrhythmias. Amiodarone is associated with many adverse effects that involve different organs. Incidence of neurologic problems like peripheral neuropathy has been reported after long-term usage of amiodarone.

**Aim of the Study:** The aim of the present study is to evaluate the incidence of neurologic problems like peripheral neuropathy in patients on long-term medication with amiodarone.

**Materials and Methods:** We carried a retrospective medical record analysis of cardiac patients treated with amiodarone at Prathima Institute of Medical Sciences, Karimnagar, Telangana, from January 1, 2015 to December 31, 2017. 27 patients on long-term amiodarone therapy with neurologic problems were compared with 15 controls without neurological disease. Patients on whom nerve conduction studies and electromyography were performed after admission were selected. All possible neurologic adverse effects that might be attributable to amiodarone were recorded and tabulated.

**Results:** Neurologic problems included tremor, gait ataxia, peripheral neuropathy, and cognitive impairment. The primary risk factor for amiodarone neurotoxic effects was duration of treatment, not age, drug dose, sex, or indication for therapy.

**Conclusion:** Amiodarone infrequently causes clinically significant neurologic toxic effects. Substantially higher estimates of neurotoxic effects in the early studies may be related to a much higher daily dose during those times.

**Key words:** Amiodarone, arrhythmia, cognitive impairment, naranjo algorithm, peripheral neuropathy

## INTRODUCTION

Amiodarone is a diiodinated benzofuran derivative initially developed in the 1960s as an antianginal agent. It was later used as a cardiac antiarrhythmic agent in the management of supraventricular and ventricular arrhythmias. It belongs to Class III antiarrhythmic agents. Its antiarrhythmic effect is by virtue of prolonging action potential duration in contrast to drugs that act by local anesthesia properties. Amiodarone has properties of all four groups, i.e., it blocks fast sodium channel (Class I), adrenergic receptors (Class II): IK channels (Class III), and "L" calcium channel (Class IV).<sup>[1-3]</sup>

Amiodarone was first synthesized by Labaz laboratories in Belgium as an antianginal agent during a systemic search for potent coronary vasodilators.<sup>[4,5]</sup> Common adverse drug effects include hepatotoxicity, corneal microdeposits, and thyroid dysfunction, and the drug was initially reported to have a strong association to neurotoxicity including reversible peripheral neuropathy.<sup>[6-8]</sup> Muscle weakness and peripheral neuropathy have also been reported in 10% of the patients who were administered the antiarrhythmic agent amiodarone.<sup>[9]</sup>

Drug-induced peripheral neuropathy can begin weeks to months after initiation of treatment with a particular drug and reach a peak at, or after, the end of treatment. In most cases, the pain and paresthesia completely resolve after cessation of treatment. However, in some cases, it is only partially reversible and can be permanent.<sup>[10-12]</sup>

We carried out this study to evaluate the incidence of neurologic problems like peripheral neuropathy in patients on long-term medication with amiodarone by nerve conduction study.

## MATERIALS AND METHODS

We carried a retrospective study on 27 patients who were given long-term amiodarone therapy and compared with 15 controls without neurological problem. After obtaining the Institutional Ethical Committee clearance, the study was done at Prathima Institute of Medical Sciences, Karimnagar, Telangana, from January 1, 2015, to December 31, 2017, using hospital medical records. We limited the primary analysis to the amiodarone-treated patients who were seen in the

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neurologic clinic (for any reason) after long-term amiodarone therapy was initiated.

We compared the clinical characteristics of the patients with amiodarone neurotoxic effects with all patients prescribed amiodarone over the period of the study who did not develop neurologic problems<sup>[13]</sup> for sex, treatment indication, age, treatment duration, and dose. Nerve conduction studies and electromyography findings were noted. Records were reviewed for neurologic problems developing after initiation of long-term amiodarone therapy. Diabetes mellitus, Liver diseases, Uremia, Thyroid disorders, Collagen vascular disorders, Paraproteinemias, Imipramine, Amitriptylin, Hydralazine.

## RESULTS

We recognized 40 amiodarone-treated patients referred to neurodepartment for neurologic adverse events. After reviewing their records, 10 patients were excluded because the neurologic problem developed before the initiation of amiodarone therapy and 3 were excluded because the problem was not neurologic. Among 27 remaining patients, 9 had problems considered to be biologically unlikely as drug effects (5 strokes, 1 meningioma, 1 subdural hematoma, 1 carpal tunnel syndrome, and 1 transient ischemic attack secondary to a documented carotid dissection). The problems of other three patients were considered as possible adverse effects but with other likelier causes (asymmetric AQ2

neuropathy in the setting of systemic vasculitis in two patients and peripheral neuropathy in the setting of carboplatin and paclitaxel therapy in the other patient).

The remaining 15 patients problem was judged to be biologically plausible and likely drug effects: New-onset tremor (6 patients), worsening of preexisting essential tremor,<sup>[3]</sup> peripheral neuropathy,<sup>[3]</sup> tremor with gait ataxia,<sup>[1]</sup> gait ataxia plus mild peripheral neuropathy,<sup>[1]</sup> and cognitive impairment.<sup>[1]</sup> In three cases, these clinical problems were noticed incidentally by neurologists when assessing the patients for other problems. Of these 15 patients (11 male and 4 female), 13 were prescribed amiodarone for atrial arrhythmias and 2 for ventricular arrhythmias.

The mean age of the affected patients at the time they were seen in neurology was 73.13 years (range, 65–82 years) and the mean age when starting amiodarone therapy was 70.1 years (range, 63–80 years), the mean daily dose of amiodarone hydrochloride was 220 mg (range, 100–400 mg), and the average length of time receiving treatment was 30.6 months (range, 2–62 months). In nine cases, administration of the drug was stopped or reduced, and of these, all but two patients improved. Naranjo Adverse Drug Reaction probability algorithm estimates the likely causality of an adverse drug reaction. We followed the algorithm and found that out of 15 biologically plausible drug effects, 9 were categorized as probable and 6 as possible and none were considered either definite or doubtful [Table 1].

**Table 1: The clinical characteristics of the study sample**

Case No.	Age	Sex	Duration of amiodarone treatment in months	Dose in Mg	Indication	Neurologic problem	Neurologic problem stopped or reduced treatment	Outcome	Naranjo criteria for ADR
1	73	M	14	200	AF	Tremor	Stopped	Clinically improved	Probable
2	68	M	38	200	AF	Worsening of preexisting essential tremor	No	NA	Possible
3	74	F	38	100	AF	Peripheral neuropathy	Stopped	Clinically improved	Probable
4	72	M	2	200	AF	Worsening of preexisting essential tremor	Stopped	NA	Probable
5	68	M	29	200	VT	Tremor	Reduced to 100 mg	Clinically improved	Possible
6	73	M	24	200	AF	Peripheral neuropathy	No	Clinically improved	Probable
7	65	M	21	400	AF	Tremor with gait ataxia	Reduced to 100 mg	Not improved	Probable
8	76	M	36	200	AF	Tremor	Stopped	Clinically improved	Possible
9	67	F	62	200	VT	Peripheral neuropathy	No	NA	Probable
10	82	M	22	400	AF	Worsening of preexisting essential tremor	Reduced to 100 mg	Clinically improved	Possible
11	75	M	39	200	AF	Tremor	Stopped	NA	Probable
12	76	F	21	200	AF	Gait ataxia plus mild peripheral neuropathy	No	Clinically improved	Possible
13	73	M	37	200	AF	Tremor	No	Clinically improved	Probable
14	81	M	44	200	AF	Cognitive impairment	Stopped	NA	Probable
15	74	F	32	200	AF	Tremor	No	Clinically improved	Possible

ADR: Adverse drug reaction, AF: Atrial fibrillation, NA: Non-applicable, ND: Not determined, VT: Ventricular tachyarrhythmia

We compared these patients with 15 adults who received amiodarone therapy during our study period and did not have any neurotoxic effects [Table 2]. The mean age, sex, type of arrhythmia, and mean daily dose were almost similar. However, those with neurotoxic effects took amiodarone for significantly longer (mean, 30.6 months vs. 16.8 months).

## DISCUSSION

Amiodarone hydrochloride is a Class III antiarrhythmic drug prescribed commonly for atrial fibrillation and ventricular arrhythmias. The initial experience with this drug suggested substantial potential for neurologic toxic effects, with frequencies in the early reports ranging from 27.5% to as high as 74%, the most common of these neurologic adverse effects have been tremor, ataxia, and peripheral neuropathy.<sup>[6,15]</sup> On the other hand, the frequency of neurologic adverse effects in longer term amiodarone clinical trials has been much lower, at <5%.<sup>[4,13,16]</sup>

It is noted that the incidence of neurological symptoms is directly related to a significant reduction in maintenance doses of amiodarone from 600 mg to 200 mg, while the highest risk factor for adverse drug effects apart from increased dose appears to be the length of drug therapy. As a result of advances in surgical procedures, the use of amiodarone has declined over the years.<sup>[3-5]</sup>

The main risk factor for amiodarone neurotoxic effects in our study was length of time receiving therapy. This is in agreement with previous studies of Vorperian *et al.* and Orr and Ahlskog.<sup>[4,17]</sup>

Age was not a risk factor in our study, in agreement with a previous report, and neither was sex or indication for amiodarone therapy.<sup>[4,6]</sup> With the amiodarone dosing strategy of the current era, the risk of neurologic toxic effects is small; however, it may be suspected among patients with otherwise unexplained tremor, gait ataxia, peripheral neuropathy, or cognitive impairment. Hence, patients who are on long-term amiodarone therapy should be monitored for any neurotoxic effects.

## Future Research

Early detection and subsequent modification of the treatment regimen is one of the most important factors for reducing the

incidence and severity of drug-induced peripheral neuropathy. Better understanding of the underlying pathophysiology of this side effect will be a cornerstone for further improvement of both prevention and treatment of the neuropathy. There is also a need for further randomized, controlled trials to clarify the efficacy of possible neuroprotective agents.

## CONCLUSION

Patients with amiodarone-induced polyneuropathy were older and receiving higher mean daily maintenance dose of amiodarone. Electrophysiological studies detected subclinical polyneuropathy which helped in closely following these patients to detect clinical symptoms and signs of neuropathy. Prospective studies on a larger sample are needed to determine the incidence of neurotoxicity with amiodarone use and its correlation with histopathological studies will help in determining the mechanism of neuropathy and to compare and draw definite conclusions.

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**Table 2. Comparison of patients with amiodarone neurotoxic effects and controls without effects**

Character	Study sample	Controls
Mean age in years	73.13	71.93
Gender		
Male	11	12
Female	4	3
Indication		
AF	13	12
VF	2	3
Mean dose in mg	220	200
Mean duration in months	30.6	16.8

AF: Atrial fibrillation, VT: Ventricular tachyarrhythmia

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