Cent. Eur. J. Med. • 9(3) • 2014 • 437-442
DOI: 10.2478/s11536-013-0306-y

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Central European Journal of **Medicine**

Amiodarone neurotoxicity: the other side of the medal

Case Report

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Received 8 August 2013; Accepted 30 November 2013

Abstract: The efficacy of amiodarone is tempered by its toxicity, with 50% of long-term users discontinuing the drug. The non-cardiac side effects of amiodarone may involve central and peripheral nervous system. We studied two patients treated with amiodarone for 46 and 15 months respectively. Both patients exhibited progressive distal extremity weakness, impaired perception, loss of deep reflexes. Electrophysiology identified a widespread, sensorimotor polyneuropathy with features of axonal loss and demyelination. Visual evoked potentials (VEPs) showed prolonged P_{100} latency bilaterally in absence of visual symptoms or brain magnetic resonance imaging (MRI) abnormalities. Extensive laboratory examinations excluded known causes of peripheral neuropathies. At 21 months after amiodarone withdrawal, P100 latency of case 1 VEPs returned to normal, whereas polyneuropathy continued to progress. In the second patient neuropathy has worsened similarly over 2 years whereas P_{100} latency of VEPs recovered to normal within 7 months after withdrawal of amiodarone. These findings may suggest different mechanisms of toxicity, which could be due to amiodarone pharmacokinetic and its metabolite effects on the peripheral nerves, as opposed to the optic nerve. We emphasize that use of amiodarone needs monitoring of patients at risk of development side effects.

Keywords: *Amiodarone-induced neuropathy • Antiarrhythmic drugs • Optic neuropathy • Visual evoked potentials • Demyelination*

1. Introduction

Side effects of anti-arrhythmic drugs may affect thyroid, lung, liver, eyes, central, and peripheral nervous system [1-11]. Amiodarone hydrochloride, the most commonly prescribed anti-arrhythmic drug, is an iodinated benzofuran derivative prescribed at recommended dose of 200 mg daily; its direct action is to prolong repolarization and refractoriness in cardiac tissues, including the sinus, the atrium,the atrioventricular nodes, and the Purkinje system [1,5,6]. Amiodarone's clinical efficacy has been tempered by its ubiquitous toxicity, with almost 50% of long-term users discontinuing the drug [1,2,5-7]. Amiodarone toxicity might be function of cumulative dose administered, but it can occur shortly after drug initiation [1,2,5-7]. We present two patients chronically exposed to oral amiodarone; both developed a progressing peripheral neuropathy associated with asymptomatic bilateral optic neuropathy. The optic neuropathy was reversible months after amiodarone withdrawal, whereas the polyneuropathy gradually deteriorated both clinically and electrophysiologically, suggesting different mechanisms of toxicity in peripheral nerves as compared with the optic nerve.

1.1. Case Report

Case1. A 67-year old man with previous history of intermittent tachycardia experienced gradual progression of distal paraesthesias and weakness in the lower extremities. He denied any autonomic symptoms such as nausea, vomiting, diarrhea, or constipation. His past medical history was significant for hypertension and cardiac arrhythmias, with intermittent paroxysmal supraventricular tachycardia that rarely went into atrial fibrillation. His medications included amiodarone 200 mg daily six days a week for 36 months and hydrochlorothiazide 6.25

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mg once daily. On referral to our hospital, the patient showed normal cranial nerves and coordination, postural hand tremor, deep areflexia, grade 2/5 on Medical Research Council (MRC) scale asymmetric weakness of finger extensors, anterior tibial, peroneal, intrinsic feet muscles. Other symptoms included gait unsteadiness, a positive Romberg's test after eye closure, reduced vibration and position sense in the toes, diminished pinprick and temperature in stocking/glove distribution. The patient denied having any visual symptoms.Brain and spinal cord imagings (MRI) were negative. Electrophysiological studies showed low amplitude of tibial, peroneal compound muscle action potentials (CMAP) ranging from1.0 to 2.0 mV (normal>5,0), slowed motor conduction velocity (38–41m/sec, normal>50), delayed F-waves (58–60m/sec, normal<45), lowered amplitude of sural responses (SAP) down to 3.0 uV (normal>6). Needle electromyography (EMG) showed denervation. Overall, the electrophysiological results identified a widespread sensorimotor polyneuropathy with signs of demyelination associated with axonal damage in absence of definite conduction blocks (CB) [12]. Visual field, acuity, ophthalmoscopy, and fluorescein angiography were normal, whereas visual evoked potentials (VEPs) showed bilaterally prolonged P_{100} latency (120–130 msec, normal<110) (Figure 1). Brainstem auditory evoked responses (BAERs) and electroencephalography were normal. Negative laboratory results included a complete blood count, erythrocyte sedimentation rate (SR), creatine kinase (CK), thyrosine-based hormones, antithyroglobulin, thyroperoxidase antibodies, B12, folate copper level, HIV1-2, anti-nuclear, anti-nuclear (ANA) and extractable nuclear antibody (ENA), rheumatoid factor, complement C3,C4, search for IgG and IgM anti-GM1 antibodies. Spinal fluid (CFS)examination showed normal protein content (40 mg/dl, normal <45), without cells and detectable IgG oligoclonal bands. Amiodarone was halted after 46 months of treatment. Intravenous immunoglobulins (IVIg) were given and repeated (0.4 g/kg daily for 5 consecutive days) without clear improvement in sensation or in muscle strength. After 10 weeks, he received a second course of IVIg, with similar results. There was no response to a trial of oral prednisone (1 mg/Kg body weight), which was gradually tapered over 2 months. During the following 5 years, the weakness progressed asymmetrically with strength graded within 1/5–2/5 (MRC) distally in his upper and lower limbs. Serial electrophysiology confirmed features of demyelination and axonal loss as indicated by dispersed motor responses, slowed conduction velocity ranging within 30 and 35 m/sec, absent F waves in the peroneal and tibial nerves [12]. Conversely, the P_{100} latency of VEPs returned gradually to normal values within 21 months after amiodarone withdrawal.

Case 2. This 58 year-old man was referred because of complaint of numbness in his feet for about 1 year, without any pain or motor symptoms in his hands. He denied autonomic or visual symptoms. His past medical history was significant for hypertension and a primary cardiomyopathy, with arrhythmias and paroxysmal supraventricular tachycardia episodes. He had been using amiodarone (200 mg daily) 5 days a week for 15 months and irregularly diuretics. On first examination, cranial nerves and mental state were normal. His muscle strength in the upper limbs was normal, whereas in the lower extremities, the strength was graded 3/5

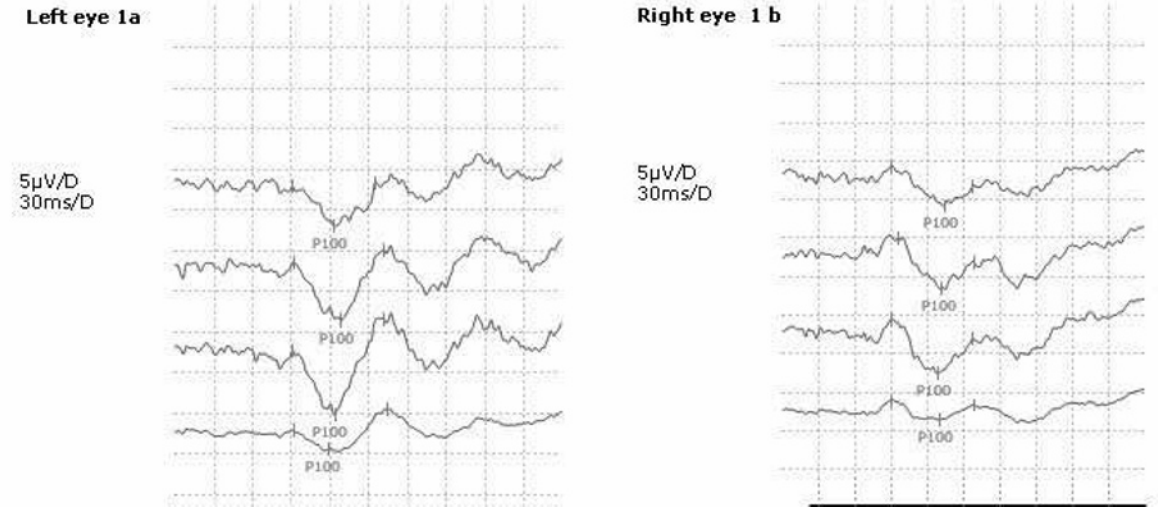

Figure 1. Pattern of visual evoked potentials (VEPs) by monocular stimulation of the left (1a) and right (1b) eye in case 1, treated with amiodarone 200 mg daily for 46 months. The P_{100} component of the pattern VEPs had bilateral prolonged latency as to controls (normal less than 110 msec). The visual acuity was 20/20 in both eyes without ophthalmoscopic and fluorescein angiographic abnormalities. The P_{100} latency recovered to normal 21 months after amiodarone withdrawal.

proximally and 2/5 distally (MRC). Deep reflexes were decreased but symmetrical, including the ankles. He had decreased pinprick sensation in a stocking distribution and diminished temperature up to the knees. Vibration was intact in his upper extremities and reduced at the ankles. The limb coordination on testing was normal, but the patient had mild difficulty with standing. On first referral, the nerve conduction study showed slowed motor velocities in the ulnar, median, peroneal and tibial nerves (38.0–42.0 m/s); the sensory conduction velocity in the surals was 40.0 m/s, with SAP amplitude of 1,5–1,8 uV and excessive temporal dispersion [12]. VEPs showed prolonged P_{100} latency bilaterally (120–125 msec).Visual fields and acuity were normal as BAERs.MRI of brain and spinal cord did not show abnormalities. An extensive blood work-up, including SR, oral glucose tolerance test, vitamin B12, folate levels, Sjogren serology, serum and urine protein electrophoresis, anti-ganglioside antibody assays, CSF was negative or normal. His CK was mildly elevated on repeated samples (450–580 IU/L, normal <190). After 13 months of amiodarone therapy, a subclinical hyperthyroidism was shown by low TSH levels (0.10 uIU/ml; normal 0.45-4.50) and elevated T4 Free/Direct and T3. Patient denied specific treatment for his polyneuropathy, including a trial of IVIg or steroids. Amiodarone was halted at 15 months. Thereafter, the motor symptoms especially showed a gradual worsening; at 24 months since the first evaluation, the strength was scored 1/5 in his hands and in peroneal and tibial distributions. On electrophysiology, abnormalities were suggestive of demyelination in motor nerves, as indicated by prolonged distal motor latencies, slowed conduction velocities, absent tibial, and peroneal F-waves [12]. A needle EMG showed chronic partial denervation and reinnervation at multiple sites. Seven months after amiodarone withdrawal, the P_{100} latency of VEPs had recovered bilaterally to less than 110 msec.

2. Discussion

The two patients presented in our study had clinical and electrophysiological features of a sensorimotor polyneuropathy associated with abnormal VEPs. The abnormalities of VEPs were consistent with an optic neuropathy (ON) [5,6,8-11]. In both cases, the past medical history was significant for hypertension as well as for intermittent paroxysmal supraventricular tachycardia and atrial fibrillation. The patients remained free of visual symptoms during the disease course; moreover, a key feature was the reversal to normal of the VEP abnormalities months after amiodarone withdrawal. An anterior ischemic optic neuropathy was ruled out, as it usually occurs unilaterally at onset, with visual loss, stepwise progression, eventual subsequent not completely reversible contralateral eye involvement [9,10]. The peripheral neuropathy of our cases (Table 1) progressed during period of years in an asymmetric fashion, showing in motor and sensory nerves a full range of electrophysiological changes suggestive of demyelination, as prolonged distal motor latencies, conduction slowing, and prominent temporal dispersion in absence of clear-cut CBs [12]. The reduction of distal CMAP amplitudes observed during the disease progression was related to axonal loss [12]. The cranial nerves were unaffected and there were no clinical signs or MRI abnormalities pointing to central nervous system (CNS) disturbances. IVIg and oral steroids had no effect in one patient; the other patient denied treatment. Negative family, personal history and extensive laboratory screenings ruled out all known causes of peripheral neuropathies, namely nutritional disorders or other toxic neuropathy. A sural biopsy was denied. When the Naranjo algorithm was applied to our patients, it indicated a highly probable relationship between the adverse effects and amiodarone use, ranging the Adverse Drug Reaction (ADR) Probability Score between 6 and 7 for both conditions,the optic and the peripheral neuropathy [13]. None of the subjects was exposed to other antiarrhythmic agents.

Neurotoxic side effects of amiodarone occurred with a cumulative incidence of 2.8%, 1.6% of all patients of Orr et al [6] who reported a peripheral neuropathy; 3 patients out of 11 cases referred for neurologic assessment, were treated from 2 weeks to 79 months. In a collaborative study, 3% of cases receiving antiarrhythmic drugs, including amiodarone, showed clinical polyneuropathy, while 25% presented electrophysiological findings in keeping with a diagnosis of polyneuropathy [7]. Burakgazi et al [14] reported a unique case of neuropathy affecting small nerve fibers induced by flecainide, another commonly used antiarrhythmic agent; the neuropathy was confirmed by skin biopsy with improvement associated with increased of intraepidermal fiber density 16 months after flecainide withdrawal. Three patients of Fraser et al [1] during long-term high-dose therapy developed predominantly sensory neuropathy; high concentrations of amiodarone and its N-desethyl metabolite were found in lysosomes especially in tissues rich of macrophages. That is similar to Kang et al [2] patient who developed 17 months after receiving oral amiodarone, neuropathy and hepatitis; both conditions improved after drug cessation. In humans exposed to amiodarone, nerve conduction abnormalities vary from a predominant axonopathy, with reduced amplitudes of evoked responses, to prominent conduction slowing

suggesting demyelination, to a mixed picture [1,2,7]. Inhibition of Complex 1 of respiratory chain and altered folate metabolism were proposed as one possible mechanism for toxicity [15]. Santoro et al [16] described electrophysiologically acute demyelination with CB at day 3 after amiodarone endoneurial injection into rat tibial nerves, suggesting a direct toxic effect on motor axons related to different drug concentrations, due to variable efficacy and vulnerability of blood-nerve barrier leading to different concentration in the nerves. In amiodarone-associated peripheral neuropathy, demyelination and mild axonal loss were detected by Jacobs et al [3] and by Costa-Jussa' et al [4] whilst the temporal sequence of changes, although not clear, was suggestive of Schwann cell abnormalities preceding the myelin breakdown, similarly to that shown by perhexiline maleate. Examination of sural nerve specimens showed early formation of phospholipid-containing lamellated inclusions in cytoplasm of Schwann cells of myelinated and unmyelinated axons related to strong inhibition of lysosomal phospholipase functions [2-4]. Interestingly, distribution of cells containing drug-induced inclusions demonstrated that amiodarone was excluded from areas of nervous system that lack a blood-brain or blood-nerve barrier [3,4]. In experimental animals, amiodarone was found to induce necrosis and denervation atrophy in the muscles, thus explaining the clinical observation of delay in motor recovery [3,4]. Ocular side-effects of amiodarone are well known [5,8-11]; the most common is the keratopathy manifested as corneal epithelial deposits, which has been reported in 33%–100% of patients taking amiodarone. These deposits do not cause visual loss nor do they result in permanent damage to corneal tissues; they usually disappear with cessation of amiodarone [5,6]. The ON in patients on amiodarone therapy is a recognized, although infrequently observed, phenomenon [1,8-11]. Although the degree to which the eyes are affected is quite variable, there is a higher rate of bilateral involvement, which may cause serious and permanent effects on vision [8-10]. The optic disk swelling and visual loss may require several months to stabilize after amiodarone discontinuation [8-10]; patients rarely exhibit abnormal VEPs as the only feature of an associated ON, such as in the cases reported here. Ultrastructural findings of the optic nerve in patients with amiodarone-associated ON are similar to those seen in patients with amiodarone-induced peripheral neuropathy [3,4,8-11]; cytoplasmic lipid inclusions similar to those observed in humans were reproduced experimentally in many ocular cell types of rats exposed to amiodarone [3,4]. A patient treated with amiodarone without visual symptoms who was enucleated for a melanoma demonstrated lamellated inclusion bodies in the retrobulbar optic nerve large axons, unaccompanied by demyelination or axonal loss; the lamellated inclusions could simply have a mechanical effect on the axoplasmic flow along the optic axons [11].

The syndrome of simultaneous bilateral optic and peripheral neuropathy is known to occur in nutritional and metabolic disorders such as B12 and folate pathway disorders, and with unclear precise incidence in acute and in chronic polyneuropathies [17-19]. The optic nerve can be affected in chronic demyelinating polyneuropathies (CIDP), due to the particular susceptibility to immune-mediated damage of both the peripheral and the optic nerves, which share rather similar proteins functioning as antigens capable of inducing self-reactive T-cell responses [17]. Indeed,it has been shown that myelin P1 expressed in peripheral nerves is identical to the central myelin basic protein; in addition, myelin-associated–glycoprotein is common to CNS and to peripheral nerves [17-19]. Subclinical visual pathway abnormalities in CIDP patients with and without detectable CNS lesions on MRI were reported by Stojkovic et al [17], who pointed out a lack of concordance between VEP and MRI abnormalities in some patients: of the 8 cases with altered VEPs only 4 had neuroradiological abnormalities. The discrepancy between negative MRI results and altered VEPs in CIDP similarly to what happens in multiple sclerosis could be the consequence of transient demyelinating lesions due to blood brain barrier damage that are eventually reversed by treatments [17]. It is of interest to note that in our two patients, the abnormalities in peripheral nerves persisted on consecutive electrophysiological studies, despite treatments in one case and of amiodarone withdrawal in both, whereas the bilateral visual pathway involvement fully recovered functionally. The histopathologic differences could be due to myelination by oligodendrocytes of central nerves or differences in the time course of ocular versus peripheral neuropathy findings [9]. Although the significance of the association of peripheral neuropathy and of asymptomatic ON with the amiodarone use in our cases remains ultimately unclear, we want to alert clinicians that the use of amiodarone requires a targeted monitoring of patients because of the risk of developing side effects [1,7,9]. The main risk of amiodarone neurotoxicity seems to relate to the length of receiving therapy; but symptoms may occur as little as 200 mg per day with duration of only a month, suggesting inter-individual variability of amiodarone metabolism and possibly a multi-faceted combination of toxic and indirect immunologically mediated effects [1,2,5-10].

Table 1. Summary of relevant features of the present cases with amiodarone–associated peripheral and optic neuropathy

Patients	Age at first onset(y) gender	Main symptoms at first onset	Duration amiodarone treatment prior symptom onset (mo)	Main neurological signs at first referral	Total duration amiodarone treatment (mo)	Amiodarone daily dose (mg)	Electrophysiology (NCS/VEPs) on follow up	Concurrent systemic side effects	Neuropathy treatment after amiodarone withdrawal	Disease evolution on follow up
Case 1	67 y/ M	Distal LE numbness, paraesthesias, postural tremor, gait unsteadiness	32-36	Asymmetric, distal UE,LE weakness; pinprick, vibration, temperature loss, sensory ataxic gait, areflexia	46	200, 6 days a week	P_{100} latency of VEPs recovered at 21 mo. Asymmetric sensorimotor axonal/ demyelinating polyneuropathy persistent at 24,36,60 mo	None	Repeated IVIg courses, oral steroids	Chronic progression, worsened signs at 60 mo
Case 2	58 y/ M	Distal LE burning paraesthesias, cramps, gait unsteadiness	3-4	Asymmetric, distal LE weakness; pinprick, vibration, temperature loss, mild ataxia, stepping gait, hyporeflexia	15	200, 5 days a week	P_{100} latency of VEPs recovered at 7 mo Asymmetric sensorimotor axonal/ demyelinating polyneuropathy, persistent at 21,24 mo	Thyroid dysfunction, mildly increased CK	None	Chronic progression, worsened signs at 24 mo

CK, creatine kinase; M, male; mo, months; y, years; UE, upper extremities; LE, lower extremities; IV, intravenous ; IVIg, intravenous immunoglobulin; NCS, nerve conduction study; VEPs, visual evoked potentials

Declaration of interest

The authors have no conflict of interest or sources of funding.

The authors alone are responsible for the content and writing of the paper

References

[1] Fraser AG, McQueen INF, Watt AH, Stephens MR. Peripheral neuropathy during longterm high-dose amiodarone therapy. J Neurol Neurosurg Psychiatry 1985;48:576-578

[2] Kang HM, Kang YS, Kim SH, Seong JK ,Kang DJ, Lee HY, Lee BS. Amiodarone-induced hepatitis and polyneuropathy. Korean J Intern Med 2007;22:225-229

[3] Jacobs JM, Costa-Jussà FR.The pathology of amiodarone neurotoxicity. II. Peripheral neuropathy in man. Brain 1985;108:753-769

[4] Costa-Jussa' FR, Jacobs JM. The pathology of amiodarone neurotoxicity.I Experimental studies with reference to changes in other tissues. Brain 1985;108:735-752

[5] Mackenzie C, Syed J, Pollak TP, Koren G. Falling between the cracks: a case of amiodarone toxicity. CMAJ 2007;183:1393-1397

[6] Orr E C, Ahlskog E. Frequency, characteristics and risk factors of amiodarone neurotoxicity. Arch Neurol 2009;66:865-869

[7] The collaborative Group for the study of Polyneuropathy Antiarrhytmic drugs and polyneuropathy J Neurol Neurosurg Psychiatry 1994;57:340-343

[8] Purvin V, Kawasaki A, Borruat FX. Optic neuropathy in patients using amiodarone. Arch Ophthalmol 2006;124:696-701

[9] Passman, RS, Bennet CL, Purpura JM, Kapur R, Johnson LN, Raisch DW, West DP, Edwards BJ, Belknap SM, Liebling DB, Fisher MJ,Samaras AT, Jones LGA, Tulas KME, McKoy J. Amiodarone-associated optic neuropathy a critical review.A J Med 2012;125: 447-453

[10] Johnson LN, Krohel GB, Thomas ER. The clinical spectrum of amiodarone-associated optic neuropathy. J Natl Med Assoc 2004;96:1477-1491

[11] Mansour AM, Puklin JE, O'Grady R. Optic nerve ultrastructure following amiodarone therapy. J Clin Neurophthalmol 1988;8:231-237

[12] Van den Bergh PY, Hadden RD, Bouche P, Cornblath DR, Hahn A, Illa I, Koski CL, Léger JM, Nobile-Orazio E, Pollard J, Sommer C, van Doorn PA, van Schaik IN; European Federation of Neurological Societies; Peripheral Nerve Society.Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society – First Revision. Eur J Neurol.2010;17:356-363

[13] Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239-245

[14] Burakgazi AZ, Polydefkis M, HöKe A. Skin biopsy proven of flecainide-induced neuropathy .Muscle Nerve 2011;45:144-146

[15] Serviddio G, Bellanti F, Guidetti AM, Gnoni GV, Capitanio N, Tamborra R, Romano AD, Quinto M, Blonda M, Vendemiale G, Altomare E. Mitochondrial oxidative stress and respiratory chain dysfunction account for liver toxicity during amiodarone but not dronedarone administration Free Radic Biol Med. 2011;51:2234-2242

[16] Santoro L, Barbieri F, Nucciotti R, Battaglia F, Crispi F, Ragno M, Greco P, Caruso G. Amiodarone-induced experimental acute neuropathy in rats. Muscle Nerve 1992;15:788-795

[17] Stojkovic T, de Seze J, Hurtevent JF, Arndt C, Beaume A, Hache JC, Vermersch P. Visual evoked potentials study in chronic idiopathic inflammatory demyelinating polyneuropathy. Clin Neurophysiol. 2000;111:2285-2291

[18] Tsai DC, Lin PK, Lin KP, Kao KP, Liu JH. Optic neuropathy in a patient with chronic inflammatory demyelinating polyneuropathy. Eye (Lond) 2010;14:911-912

[19] Allen D, Riordan-Eva P, Paterson RW, Hadden RDM. Subacute peripheral and optic neuropathy with no evidence of a toxic or nutritional cause. Clin Neurol Neurosug 2013;115:1389-1393