REVIEW

Amiodarone-Associated Optic Neuropathy: Clinical Review

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ABSTRACT

Amiodarone, an antiarrhythmic agent, has been associated with visual loss secondary to optic neuropathy. The reported mean duration of amiodarone use before visual loss is about 9 months. Patients receiving amiodarone have a 2-fold increased risk of developing optic neuropathy, especially in males and possibly in patients with longer duration of treatment. Amiodarone-associated optic neuropathy is characterised by an insidious onset, slow progression, bilateral simultaneous visual loss, and protracted disc swelling. After discontinuing amiodarone use, visual acuity and visual field deficits tend to improve or stabilise in most patients, with about 20% of the patients getting worse.

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Amiodarone, a di-iodinated benzofuran derivative, is originally developed for angina pectoris treatment in the 1960s and acts as a potassium channel blocker, which is categorised as a class III agent.¹ It also shares some similar effects and actions with those of antiarrhythmic class I, II, and IV agents. Clinically, amiodarone is prescribed for the management of atrial fibrillation and ventricular tachycardia/fibrillation.¹ The applications of these class III agents, including amiodarone and sotalol, are increasing because those class I agents (sodium channel blocker) were found to be associated with proarrhythmic toxicity.^{1,2} Amiodarone is currently one of the most effective antiarrhythmic drugs in the treatment of ventricular and supraventricular arrhythmias.^{3,4}

Systemic side effect

The clinical use of amiodarone has been restricted by the drug toxicity, with about 50% of long-term users finally discontinuing the drug.^{3,5} Its toxic effects are usually cumulative dose-dependent, but it may occur shortly after drug use.^{6,7} Amiodarone-induced toxicity is ubiquitous, affecting multiple tissues.³ It has been reported to be associated with pulmonary toxicity, thyroid dysfunction, peripheral neuropathy, ataxia, photosensitivity, and gastrointestinal

disturbance.^{5,8,9} Special emphasis is focused on those potentially fatal toxicities related to amiodarone-associated hypersensitivity pneumonitis.^{2,3,5}

Ocular change

Amiodarone-induced ocular change has been first reported in the 1960s. Verticillate keratopathy is the most commonly associated ocular change, occurring in about 70–100% of patients receiving amiodarone.^{10,11} It may induce symptoms of glare, halos, or blurred vision.^{2,11} Patients taking moderate to high dose of amiodarone may experience anterior subcapsular cataract.¹² Maculopathy has also been reported in amiodarone users.¹³ In addition, amiodarone-associated optic neuropathy (AAON) was reported to occur in 1.76% of amiodarone user in 1987, although its causal relationship remains controversial.^{1,14–16}

Histopathology

Ultrastructural changes of amiodarone-induced effect have been studied in an asymptomatic patient receiving amiodarone. Primary lipidosis has been illustrated in the retrobulbar optic nerve.¹⁷ There were lysosome-like intracytoplasmic membranous

lamellar bodies accumulated in the large optic nerve axons, which presumably may decrease or block the axoplasmic flow and result in optic disc swelling.¹⁷

Clinical manifestations

The severity of visual loss is variable in patients with AAON, ranging from mild reversible visual loss to severe permanent blindness. Macaluso et al. has reviewed 73 reported patients with AAON and outlined the clinical characteristics of them.¹⁸ It is characterised by an insidious onset, slow progression, bilateral simultaneous visual loss, and protracted disc swelling.¹⁸ In the 296 AAON patients reviewed by Passman et al., the mean duration of amiodarone use before visual loss was 9 months. Forty-four percent of AAON patients were insidious onset, and nearly one third of them were asymptomatic.¹⁹ Optic disc oedema was present in 85% of cases. Optic nerve swelling tends to persist for several months^{18,20} and resolves more slowly than the 2- to 6-week period seen in typical non-arteritic anterior ischaemic optic neuropathy (NAION). The disc oedema may persist even after discontinuing amiodarone, since its half-life is up to 100 days.²¹ After discontinuing amiodarone, visual acuity and visual field deficits tend to stabilise.¹⁸

Unilateral Involvement versus bilateral involvement

Although most cases with AAON occur bilaterally, several unilateral cases have been reported. Purvin et al. reviewed 22 AAON patients and found 14 cases with bilateral involvement and 8 cases with unilateral involvement. In these eight unilateral cases, the association with amiodarone use was indeterminate in five and presumably coincidental in three.²² Johnson et al. had reviewed 55 reported cases and found 36 cases (65%) present with bilateral optic neuropathy, and 19 (35%) patients initially have unilateral optic disc oedema.⁶ Of the 19 unilateral cases, 7 of them became bilaterally involved eventually. Thus, there were 12 cases (22%) with unilateral involvement in a total of 55.⁶

Causal relationship between amiodarone and AAON

The cause-and-effect relationship between amiodarone and optic neuropathy has been an issue of intense controversy.^{1,14–16} Hayreh suggested that “amiodarone-induced optic neuropathy” is actually non-arteritic anterior ischaemic optic neuropathy (NAION) unrelated to amiodarone.¹⁶ The clinical feature of AAON is quite similar to that of NAION. Those patients taking amiodarone often have cardiovascular risk factors and are also at high risk of developing NAION. In addition, a prospective randomised trial failed to find any cases with bilateral visual loss in a total of 837 subjects treated with a mean daily dose of 3.7 mg/kg of amiodarone for a minimum of 27 months.²³ On the other hand, we have conducted a retrospective population-based cohort study to investigate whether amiodarone use is associated with an increased risk of optic neuropathy.²⁴ In this study, 6175 amiodarone newly treated patients and 24,700 age- and gender-matched controls between 2005 and 2009 from Taiwan National Health Insurance Research Database were analysed. During the observational period, optic neuropathy developed in 17 amiodarone-treated patients (0.3%) and in 30 control patients (0.1%).²⁴ Multivariate Cox regression analysis showed that amiodarone-treated patients had a 2-fold increased risk of optic neuropathy (hazard ratio = 2.09), especially in males and possibly in patients with longer duration of amiodarone treatment.²⁴

Differential diagnosis

When to make a diagnosis of amiodarone-associated optic neuropathy (AAON)?

For an optic neuropathy patient with following clinical characteristics, we should consider the diagnosis of AAON: (1) a clear history of taking amiodarone, (2) insidious onset, (3) slow progression, (4) bilateral visual loss, (5) protracted disc swelling.^{18,20} Moreover, if the patients didn't have a small crowded optic disc (disc at risk) classically seen in NAION, clinicians should be vigilant for the possibility of AAON.²⁵

Amiodaone-associated optic neuropathy (AAON) and non-arteritic anterior ischaemic optic neuropathy (NAION)

Despite the obscure causal relationship, we still try to differentiate clinically between AAON and NAION in each individual case, since the treatment and visual outcome may differ for these two entities. Macaluso et al. described that AAON is characterised by an insidious onset, slow progression, bilateral visual loss, and protracted disc swelling that tends to stabilise within several months of discontinuing the medication.¹⁸ NAION is characterised by acute, unilateral disc swelling with haemorrhage, which commonly resolved over several weeks. Visual loss in NAION usually reach nadir at onset, but may aggravate in some cases. Johnson et al. found that there is a male predominance in AAON patients, with 48 (87%) men and 7 (13%) women.⁶ In Cheng et al.'s study, among the amiodarone-treated patients, male gender was associated with a nearly 3-fold increased risk of optic neuropathy development compared with female gender.²⁴ However, there is no sex predilection in NAION. In addition, optic disc swelling in NAION usually resolved within 2 to 6 weeks. However, disc swelling may persist for 1 to 8 months in AAON, with a median duration of 3 months.⁶ Finally, patients with NAION tend to have small, crowded optic discs, which may not be the case in patients with AAON.²⁵

Treatment

It is important to work with cardiologist prior to discontinue amiodarone because patients taking amiodarone usually have potentially fatal arrhythmia and discontinues amiodarone abruptly might lead to devastating sequela.

It is prudent to consult the cardiologist regarding the feasibility of discontinuing the drug with alternative medication or catheter ablation, and leave the decision regarding the safety of discontinuing amiodarone to them.^{1,26,27}

Visual prognosis

In Macaluso et al.'s study, visual acuity and visual field deficits tend to stabilise after discontinuing of amiodarone, although the optic disc swelling tend to persist for several months.¹⁸ Nagra et al. suggested that with discontinuing amiodarone, slow resolution of optic

disc swelling occurs and visual function improves in some patients.²⁰ Passman et al. have reviewed 296 cases with AAON. They found that following amiodarone discontinuation, 58% of patients had improved visual acuity, 21% were unchanged, and 21% had further visual impairment.¹⁹ Legal blindness (<20/200) was noted in at least one eye in 20% of cases.¹⁹

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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