PEER REVIEWED

Amiodarone Ocular Toxicity, Emphasizing Optic Neuropathy

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Abstract

Amiodarone is one of the most effective antiarrhythmic drugs, but its use is limited by toxicity affecting many organs including the eyes. Corneal verticillata is the most common ocular finding associated with amiodarone therapy. A less common but potentially sight-threatening complication is optic neuropathy. Amiodarone-induced optic neuropathy shares many clinical features with non-arteritic ischemic optic neuropathy making clinical diagnosis difficult. However, several important distinctions exist including an insidious onset, bilateral involvement, male predilection and delayed resolution of disc edema. This case report highlights the unique features of amiodarone-associated optic neuropathy and presents appropriate diagnostic and management strategies.

Key Words: *amiodarone, ocular toxicity, optic neuropathy, optic disc edema, whorl keratopathy, corneal verticillata, non-arteritic ischemic optic neuropathy*

Background

Amiodarone is the most common antiarrhythmic drug prescribed for treatment of atrial fibrillation. Its efficacy has been challenged by its ubiquitous organ toxicity resulting in nearly 50% of long-term users discontinuing the drug.[1] Ocular toxicity most commonly presents as corneal deposits referred to as whorl keratopathy or corneal verticillata, which occur in the majority of amiodarone users.[1,2] Whorl keratopathy is typically asymptomatic with reported glare and halos occurring in less than 5% of patients.[1] This report is aimed toward third- and fourth-year optometric students and optometrists.

The rare occurrence of optic neuropathy can be debilitating to vision. Various studies have reported the incidence of amiodarone optic neuropathy to be as high as 2.0%; however, the exact incidence is unknown.[3,4] Most cases of amiodarone-associated optic neuropathy occur within a year of treatment initiation.[1,5] Characteristics include gradual onset, bilateral involvement and slow resolution. Amiodarone-induced optic neuropathy remains a controversial diagnosis because it shares many clinical features with non-arteritic ischemic optic neuropathy (NAION), the most common optic nerve disorder causing sudden onset vision loss in elderly patients.[4] Patients on amiodarone therapy often have the same risk factors as patients who experience NAION, making it difficult to separate the two diagnoses.[1,6] However, several distinguishing clinical features highlighted in this case suggest amiodarone-associated optic neuropathy is a distinct clinical entity.

Case Description

A 70-year-old Caucasian male complained of intermittent left upper visual field disturbances for two days. He described it as a window shade moving up and down that he initially noticed upon awakening. He also experienced soreness during extreme eye movements.

The patient's medical history was remarkable for hypertension, which was controlled with three medications: lisinopril QPM, terazosin QPM and metoprolol BID. In-office blood pressure was 135 mmHg/81 mmHg. He was also taking atorvastatin daily to control hypercholesterolemia. Due to history of a myocardial infarction, he was prescribed aspirin, clopidogrel and warfarin. His medical history was also remarkable for atrial fibrillation, treated with amiodarone for the past nine months. His dosage of amiodarone was 200 mg BID with an initial higher loading dose. Drug allergies included sulfa drugs and tamsulosin. He had a 40-year history of heavy alcohol and tobacco use, both of which he stopped three years prior.

Best-corrected Snellen visual acuity was 20/20 in each eye with no change in manifest refraction. There were no gross defects or constriction identified on confrontation visual fields or extent of fields. Extraocular motilities were full without pain or diplopia. Pupils were equal, round and reactive with no afferent pupillary defect (APD).

Anterior segment findings were remarkable for gray lines extending into whorl-like patterns on the inferior corneal epithelium in both eyes, which were not noted at his last eye examination six months ago. The patient also had mild nuclear sclerotic cataracts. Goldmann applanation tonometry intraocular pressures were 10 mmHg OD and 12 mmHg OS.

Both optic nerve heads appeared crowded with heaping rim tissue **(Figure 1)**. The left optic nerve appeared to have blurred margins inferiorly with an overlying disc hemorrhage superior-nasally. Cup-to-disc ratios were 0.05 OD and 0.1 OS, which was consistent with the previous eye examination. Other retinal findings, including macula, vasculature and periphery, were normal in both eyes.

Figure 1. Fundus photography taken at the patient's first visit. **(A)** Right optic nerve head exhibits an indistinct inferior disc margin. **(B)** Left optic nerve head has a small cup-to-disc ratio, blurring of the inferior disc margin and a Drance hemorrhage (arrow). No apparent hyperemia or pallor is observed in either eye. Click to enlarge

Visual field testing was ordered prior to dilation and revealed mild to moderately reduced superior-temporal defects extending from the blind spot in the left visual field. Optical coherence tomography (OCT) **(Figure 2)** confirmed elevated rim tissue in both eyes, especially inferiorly in the left eye. Posterior pole analysis showed retinal nerve fiber layer (RNFL) thickening into the arcuate bundles but not extending into the fovea. Ganglion cell layer and inner plexiform layer analysis of the fovea and perifovea revealed normal thickness values **(Figure 3)**.

Figure 2. (A-C) A dense vertical OCT of the left optic nerve head shows elevated rim tissue inferiorly. In the infrared image, the hyporeflectivity of the edematous inferior peripapillary RNFL can be seen. **(D)** OCT circumpapillary RNFL also shows thickening, especially inferiorly OS, compared to the normative database. Click to enlarge

Figure 3. (A) Posterior pole analysis and retinal layer segmentation demonstrate thickening of the circumpapillary RNFL, especially inferior-temporally, in both eyes.
(B-C) The ganglion cell-inner plexiform layer complex surrounding the fovea, when segmented, appears normal. Click to enlarge

Differential diagnoses included amiodarone-induced optic neuropathy, NAION and arteritic anterior ischemic optic neuropathy. The latter, a sequela of giant cell arteritis, was suspected secondary to the

patient's age, visual disturbance and presentation of optic disc edema. In response to questions, the patient denied jaw claudication, headaches, scalp tenderness or diplopia. Erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) testing was ordered that day. Results were 27 mm/H and 7.5 mh/L, respectively, which may be normal for this patient considering his age and vascular conditions such as hypertension, hypercholesteremia, and atrial fibrillation. Due to a low suspicion of giant cell arteritis, a temporal artery ultrasound or biopsy was not pursued. A carotid ultrasound, electrocardiogram and complete blood count, recently ordered by cardiology, were recorded as normal. Concerns of amiodarone-induced optic neuropathy were discussed with the patient's cardiologist, who recommended discontinuation of amiodarone and initiation of sotalol.

At the patient's one-month follow-up visit, visual field testing showed severe superior and inferior arcuate defects in both eyes, with central visual acuity of 20/20 OD and OS remaining intact. The patient noted issues with light and dark adaptation along with flashes of light. Both optic nerve heads were edematous 360° with indistinct margins and multiple Drance and peripapillary hemorrhages. Due to the worsening of bilateral optic disc edema, brain imaging was necessary to rule out a mass or lesion. Magnetic resonance imaging (MRI) **(Figure 4)** showed non-specific vasculitis throughout the brain, which prompted a referral to neurology. To detect any underlying conditions that could cause vasculitis, neurology ordered c-ANCA, p-ANCA, aytpical p-ANCA, anti-myeloperoxidase and anti-proteinase 3 tests, all of which were negative. ESR and CRP were repeated due to the worsening disc edema and visual field, but levels remained stable.

Figure 4. T2-weighted MRI images reveal approximately 40 subcortical white matter lesions (<1cm) throughout both cerebral hemispheres. MRA of head and neck are normal. No signs of acute infarction, aneurysm or stenosis are observed. Click to enlarge

At his three-month follow-up visit, the patient felt his symptoms had improved significantly, but examination findings showed persistent disc hemorrhages and stable visual field defects **(Figure 5)**. The disc swelling had resolved, but thinning of the RNFL was present **(Figure 6)**.

Figure 5. (A-B) A 24-2 visual field test at the three-month follow-up visit demonstrates deep superior and inferior arcuate defects in both eyes, with central islands remaining OU. **(C)** A progression report for the left eye shows an initial early arcuate defect developing into deep bi-arcuate defects that persist from the three- to six-month follow-up visits. Click to enlarge

By his six-month follow-up appointment, the patient reported his visual field had stabilized with mild inferior dimming. His central vision remained intact. Visual field testing showed stable, deep superior and inferior arcuate defects in each eye. Although the persistent disc hemorrhages had resolved, OCT showed further thinning of the circumpapillary RNFL since the three-month follow-up visit. The insidious onset of bilateral disc edema, along with the findings from imaging and lab testing, led to the diagnosis of optic neuropathy influenced by amiodarone. The patient was educated on the likely permanent visual field defects and advised to return in six months or as needed. He was also informed about low vision rehabilitation to help him cope with peripheral vision loss.

Figure 6. OCT circumpapillary RNFL progression reports show resolution of disc edema in both eyes by the three-month follow-up visit, but progressive atrophy compared to the normative database. Disc hemorrhages are still present at the three-month follow-up visit. Click to enlarge

Educational Guidelines

Key concepts

1. Gaining expertise in amiodarone's ocular side effects
2. Critical thinking in differentiating various optic nerve neuropathies
3. Managing patients with ocular toxicity from amiodarone use

Learning objectives

1. Gaining basic knowledge of the drug amiodarone
2. Understanding the adverse ocular effects of amiodarone
3. Extracting case history with exhaustive inquiry
4. Performing comprehensive vision and ocular examination with detailed evaluation of the optic disc
5. Identifying the stages of optic disc edema using the Frisen scale
6. Utilizing various tools, tests and technology to diagnose and assess progression
7. Differentiating various optic neuropathies based on patient presentation and history
8. Understanding management options and visual prognosis of amiodarone-associated optic neuropathy
9. Ensuring full patient care by collaborating with various specialists

Discussion points

1. Basic knowledge and concepts related to the case

a. Identify characteristics and prevalence of amiodarone toxicity
b. Describe the clinical presentation of amiodarone optic neuropathy
c. Identify clinical features of amiodarone optic neuropathy that distinguish it from ischemic optic neuropathy
d. Describe diagnostic tools and appropriate ancillary testing that aid in diagnosis

2. Differential diagnosis

a. What are differential diagnoses based on the patient's symptoms?
b. What are differential diagnoses for unilateral vs. bilateral optic disc edema?
c. What is the appropriate work-up to exclude differential diagnoses?

3. Critical thinking

a. Should amiodarone be discontinued when neuropathy is identified? How do you make that decision as a healthcare provider?
b. What is the appropriate follow-up for patients currently taking amiodarone with no signs of neuropathy?
c. What is the visual prognosis of amiodarone toxicity?
d. Were brain imaging and blood work necessary in this patient's case?
e. Is amiodarone-induced optic neuropathy a diagnosis of exclusion?
f. What are the differences between non-arteritic ischemic optic neuropathy and amiodarone-induced optic neuropathy?

Literature Review

Amiodarone

Amiodarone is approved by the Food and Drug Administration (FDA) for the treatment of refractory ventricular arrhythmias,[7,8] but it is often prescribed for atrial arrhythmias such as atrial fibrillation or flutter. An initial higher dose (800 to 1600 mg daily) is needed to achieve therapeutic plasma levels because, with a bioavailability of approximately 30%, the drug is poorly absorbed. Maintenance dose (100 to 400

mg daily) varies depending on multiple factors, including heart rate.[9] Amiodarone's primary mechanism of action is to block potassium channels, but it also weakly blocks sodium and calcium channels as well as beta and alpha adrenergic receptors. Direct effects on the myocardium cause a delayed repolarization and an increased duration of action potential.[10] The half-life of amiodarone is long yet variable. It has been reported in the literature ranging from 13 days to 180 days.[1,4,5,8–10] Elimination occurs mostly by hepatic metabolism.[9] Geriatric patients have a slower drug clearance and may be more sensitive to adverse effects.[10]

Long-term oral therapy can lead to accumulation in tissue and adverse effects including pulmonary disease, thyroid dysfunction, cardiac toxicity, skin reactions, gastrointestinal and genitourinary problems, neurological dysfunction, ocular toxicity and drug interactions.[7–9]

Clinical manifestations

Whorl keratopathy, also known as corneal verticillata, is the most common ophthalmologic finding in amiodarone patients, with a prevalence of 70-100% with long-term therapy.[9,11] These corneal microdeposits appear in a brown or gray swirl-like or whisker-like pattern at the junction of the middle and lower thirds of the corneal epithelium. Lacrimal gland secretion of amiodarone results in accumulation of these microdeposits on the corneal surface.[11] The keratopathy can be classified into three stages[9] **(Table 1)**, although stepwise classification serves minimal practical value.[11] Clinically, this keratopathy is indistinguishable from that caused by chloroquine derivatives or Fabry disease.[9] The microdeposits do not typically reduce visual acuity, but some patients may experience halos around lights, especially at night, and photophobia.[9,11] These symptoms can also be attributable to age-related lens changes and other sequelae.[9] These ocular adverse effects are typically dose- and duration-dependent, as shown by a meta-analysis of 1,465 patients that found an incidence of 1.5% with low-dose intake compared to 0.1% incidence with placebo.[7] The keratopathy disappears within 3-20 months of discontinuation of the medication.[9,11] Cataracts from amiodarone use have also been noted. These punctate, yellowish-white lens opacities are located in the anterior subcapsule within the pupillary margin in a vertical pattern of about 2 mm in diameter.[9] A study performed by Ingram et al. of more than 100 patients found lid irritation to be the most common ocular symptom associated with amiodarone. This is most likely from photosensitivity of the eyelid skin,[11] which occurs in 10-15% of patients.[10] There are rare reports of dry eyes, macular degeneration,[10] multiple chalazia[9] and thyroid eye disease.[12]

Table 1. Click to enlarge

Amiodarone has also been associated with visual disturbances secondary to optic neuropathy. The exact annual incidence of amiodarone-associated optic neuropathy is unknown. Various reports estimate an incidence of 0.36% to 2.0% in amiodarone users, but specific parameters are often not specified.[3,4] A few reports detected a male predilection for amiodarone-associated optic neuropathy.[1,5,6] Gender differences in body mass, fat distribution enzymatic activity and hormonal stimuli[1] may account for a slightly faster drug clearance in females.[5]

A few key features can aid in diagnosing amiodarone-associated optic neuropathy as well as differentiating it from other pathologies. The optic neuropathy associated with amiodarone is described as having an insidious onset, slow progression and protracted disc swelling.[4] Most cases that present with these clinical features are simultaneously bilateral, but can be asymmetric.[4,6] A small percentage of cases that were reported to present unilaterally were either eventually bilateral,[6] not attributable to amiodarone,[13] or symptomatically unilateral but bilaterally edematous.[1] Visual acuity at presentation ranges significantly from 20/15 to light perception.[1,4] Visual field can be normal, but most patients present with altitudinal defects, arcuate defects or a generalized depression.[13] A case series review by Johnson

et al. found that only 9% of cases of amiodarone optic neuropathy had normal visual fields at presentation, and almost half of patients presented with either altitudinal or arcuate defects. Visual field loss is also typically permanent.[6]

A review of eighty cases of amiodarone-induced optic neuropathy by Passman et al. found that the average interval between starting amiodarone and onset of visual disturbances was approximately nine months, with a median of six months and a range of 1-84 months. After discontinuing the medication, 58% of 61 patients experienced improvement in visual acuity, 21% had unchanged visual acuity, and 21% had worsening of visual acuity. Permanent <20/200 visual acuity in at least one eye resulted in 20% of cases.[1] Even with discontinuation of amiodarone intake, optic atrophy can develop after resolution of disc swelling.[9]

Cheng et al. performed a retrospective population-based cohort study involving 6,175 amiodarone-treated patients and 24,700 age- and gender-matched controls to determine whether amiodarone use was associated with an increased risk of optic neuropathy. Optic neuropathy developed in 17 amiodarone-treated patients (0.3%) and 30 control patients (0.1%). Analysis of this data, with adjustments for age, gender and comorbidities, showed a two-fold increased risk of optic neuropathy. Longer exposure to amiodarone also increased the risk of optic neuropathy, but average daily dose did not demonstrate a correlation.[5] However, this study did not evaluate the features of optic neuropathy (i.e., bilateral or unilateral, type of vision loss, duration of disc edema). Therefore, appropriate classification and cause is difficult to properly assess. Another limitation of the study is that the patients treated with amiodarone had a higher proportion of medical comorbidities than the controls. A correspondence by Mindel et al. reports that these incidence rates may be biased estimates due to these limitations.[14]

Pathophysiology

The pathophysiology of amiodarone neuropathy is not completely understood. It is believed that the drug's lipophilic nature, high volume of distribution, and high tissue affinity result in ultrastructural changes in the optic nerve head.[5,6] In-vitro studies indicate that low-dose amiodarone causes inhibition of lysosomal sphingomyelinase activity and high-dose amiodarone leads to intracellular lipid accumulation and probable phospholipidosis.[5,9] Histopathology after amiodarone use shows lysosome-like intracytoplasmic membranous lamellar bodies.[1,15] These lamellar inclusion bodies have been found in nearly all ocular tissues, including retrobulbar optic nerve large-diameter axons, extraocular muscle fibers, cornea, conjunctiva, scleral, lens, iris, ciliary body, choroid, retinal pigment epithelium, ganglion cells and endothelium of ocular blood vessels.[9] It is theorized that these inclusions mechanically or biochemically inhibit axoplasmic flow, resulting in optic disc edema. The resulting optic nerve head edema can persist as long as axonal transport is inhibited, which results in delayed resolution of optic nerve swelling.[1,5,9,15] These bodies are also seen in peripheral nerves that have been affected by amiodarone-associated peripheral neuropathy. The peripheral nerves have shown signs of demyelination and large axon loss, which is absent in the retrobulbar optic nerve axons, possibly due to different types of myelination or other etiology.[1,16] Amiodarone can also cause vasodilation, possibly leading to oxidative damage and optic neuropathy.[5]

Differential diagnosis

Table 2. Click to enlarge

The most obvious differential diagnosis for amiodarone-induced optic neuropathy is NAION. NAION is the most common cause of vision loss from optic nerve disease in individuals older than 50 years with an incidence of 0.3%.[5] The incidence of NAION in patients with cardiac dysrhythmia is higher than this

because many patients taking amiodarone often have severe vascular disease.[5,17] Amiodarone-associated optic neuropathy is indistinguishable from NAION with regard to optic disc appearance, but the two clinical entities differ in multiple aspects **(Table 2)**. NAION initially presents unilaterally, while amiodarone-associated optic neuropathy often presents bilaterally simultaneously as expected with systemic toxicity.[3,4,14] Vision loss is sudden and complete at onset of NAION, unlike the insidious onset with protracted disc swelling in amiodarone-associated optic neuropathy. NAION also typically resolves in a few weeks[18] compared to months. NAION generally occurs in patients with a small optic nerve cup-to-disc ratio or crowded disc, but this has not been an identifiable risk factor in cases of amiodarone-associated optic neuropathy. Amiodarone-associated optic neuropathy has a predilection toward men, whereas NAION has no gender predilection.[1,5,6]

Along with NAION, there are other conditions that are important to consider given the clinical presentation of optic disc edema. Although amiodarone-associated optic neuropathy typically presents bilaterally, it may present asymmetrically, which warrants thorough investigation to rule out other potential causes of unilateral disc edema. Differential diagnoses include neoplastic, inflammatory, infectious, metabolic, demyelinating, hereditary and vascular etiologies. Neoplastic causes such as optic nerve glioma or optic nerve sheath meningioma can be ruled out based on neuroimaging. Inflammatory etiologies such as sarcoidosis or systemic lupus erythematosus will likely present with other signs of intraocular or systemic inflammation. Infectious causes such as syphilis, Lyme disease, or cat-scratch disease are best identified through bloodwork.[19] The most common demyelinating cause is optic neuritis secondary to multiple sclerosis. Optic neuritis can result in optic disc edema; however, onset is usually unilateral, acute and painful and typically occurs in younger patients.[20]

Differential diagnoses for bilateral optic disc edema include an intracranial mass, malignant hypertension, systemic medications, toxic/nutritional neuropathy, meningitis and pseudotumor cerebri. A space-occupying lesion must always be considered in cases of bilateral disc swelling;[19] however, no lesions were identified in this case based on neuroimaging. The patient in this case report presented with a blood pressure of 135 mmHg/81 mmHg, which ruled out malignant hypertension. Aside from amiodarone, other systemic drugs have been found to be associated with optic disc edema, including tuberculostatic drugs, antimicrobial agents, antiepileptic drugs, disulfiram, halogenated hydroquinolones, antimetabolites, tamoxifen and phosphodiesterase type 5 inhibitors. Toxins, such as metals, organic solvents, methanol and carbon dioxide, as well as nutritional deficits, such as vitamin B, folic acid and proteins with sulfur-containing amino acids can also cause optic neuropathy.[21]

Pseudotumor cerebri, or idiopathic intracranial hypertension (IIH), presents with bilateral disc swelling. In contrast to amiodarone optic neuropathy, IIH often presents with headaches, nausea or transient vision loss, and patients are typically young, overweight females of childbearing age. IIH is a diagnosis of exclusion and must be ruled out with neuroimaging including MRI and magnetic resonance venography. Diagnosis is confirmed with lumbar puncture showing elevated opening pressure. Finally, to avoid unnecessary neuroimaging, causes of pseudopapilledema should not be overlooked. Optic disc drusen can present with unilateral or bilateral disc edema; however, appropriate ancillary testing such as OCT, fundus autofluorescence or B-Scan ultrasonography can help differentiate pseudo from true optic disc edema.[19]

Diagnostic tools

A comprehensive examination including pupil dilation is necessary for accurate diagnosis, and several ancillary tests are crucial when amiodarone optic neuropathy is suspected.

Table 3. Click to enlarge

Pupil testing should be performed prior to instillation of dilation drops. A relative afferent pupillary defect (RAPD or APD) indicates unilateral or asymmetric disease of the retina or optic nerve.[22] It is estimated that at least 25% of RNFL loss is required to induce an APD.[23] The swinging flashlight test can detect an APD, but in the case of bilateral symmetric optic neuropathy, an APD may be absent.[22] Clinical grading of an APD is explained in **Table 3**. This grading system is comparable to the neutral density filter grading system, in which neutral density filters in increasing amounts are placed in front of the non-APD eye until an equal pupillary response is achieved.[24]

Color vision testing can be beneficial when optic nerve disease is suspected because the degree of dyschromatopsia may be greater than the degree of visual acuity loss. Dyschromatopsia was previously thought to be related to the degree of whorl keratopathy in amiodarone users. Research suggests that blue color vision deficiency is a manifestation of amiodarone optic neuropathy. In a case series by Johnson, Krohel and Thomas, acquired color vision loss was found in 40% of patients with amiodarone optic neuropathy.[6] Pseudoisochromatic color plates often miss mild cases of acquired dyschromatopsia, but they are commonly used as a gross test of color vision. To distinguish acquired from congenital abnormalities, arrangement tests should be used. The Farnsworth Panel D-15 test, along with the more sensitive Lanthony desaturated 15-hue test, entails the patient arranging 15 colored discs in order of hue and intensity under standard lighting conditions. The lengthier, more detailed Farnsworth-Munsell 100-hue test requires arranging 85 discs compared to its shorter version of 21 chips.[25]

Red color desaturation may occur in cases of optic neuropathy. A red-capped bottle can be presented to each eye separately for observation of saturation differences, such as a faded or washed-out red. Cone isolation contrast sensitivity testing, such as ColorDx by Konan, uses a newer, more precise technology to detect early degradation in functional vision.[26] Contrast sensitivity and electrophysiological tests may also show abnormalities, but, like color vision testing, are not diagnostic.[27]

Table 4. Click to enlarge

While the characteristics of a swollen optic nerve head and its pathophysiology of obstructed axoplasmic transport are well-understood, diagnosis is not always simple. The Frisen scale[28] **(Table 4)** describes anterior optic nerve edema based on retinal swelling, excluding variable vascular components such as hemorrhages, hyperemia, venous stasis and cotton-wool spots. Stage 0 of the Frisen scale is defined as a fairly normal disc, allowing for variation of normal. Smaller discs may have more margin blurring in one quadrant as overflow is expected. Stage 1 describes excessive blurring of the nasal optic disc margin with a subtle grayish halo. Stage 2 demonstrates elevation of the nasal border and blurring of the entire temporal margin. Here, the halo encompasses the entire disc, and concentric or radiating retinochoroidal folds may be present. In stage 3, the temporal border is also elevated, which obscures major blood vessels. Here, the halo has finger-like extensions. These changes are more pronounced in Stage 4 with disappearance or compression of the optic cup or total obscuration of a central retinal artery or vein. Stage 5 is defined as a dome-shaped protrusion of the optic nerve head.[28]

Visual field testing is an important tool in both the diagnosis and management of amiodarone optic neuropathy. Many patients present with visual field disturbances that gradually worsen over time and become permanent. Visual field defects often present as altitudinal or arcuate defects[6] or a general depression.[13] Thus, visual field testing is a crucial diagnostic and management tool for predicting visual prognosis and facilitating appropriate patient education.

The number of published studies in which OCT was used to monitor the behavior of disc edema in patients with amiodarone-associated optic neuropathy is limited. As stated earlier, the disc swelling is typically bilateral, insidious and prolonged compared to the swelling in NAION.[4] A study by Akbari et al.

evaluated peripapillary RNFL thickness and macular thickness, specifically ganglion cell-inner plexiform layer (GCIPL) thickness, in NAION patients. At initial presentation, peripapillary RNFL and outer macula thickness were elevated. This edema began to decrease by the one-month follow-up, but the GCIPL of the macula began to show thinning until about six months. This is likely due to neuronal loss,[29] with areas of damage commonly correlating with visual field loss.[30] This may be similar in amiodarone-associated optic neuropathy, although swelling may be present for a longer duration. OCT can be used to observe retinal edema, followed by axonal thinning and atrophy.[31]

Less threatening conditions should also be considered, especially in the absence of disc hemorrhages. Optic disc drusen sometimes display a bumpy appearance on funduscopy, exhibit hyper-autofluorescence on fundus autofluorescence, and reveal a hyper-reflective border with posterior shadowing on cross-sectional OCT. A narrow scleral channel or hyperopic disc can have a crowded appearance that is not considered edematous.[32]

Some, but not many, studies utilizing optical coherence tomography angiography (OCTA) in patients with amiodarone-associated optic neuropathy have been published. Evaluations of optic disc blood flow in NAION eyes portray significant non-perfusion, which correlates with the degree of mean deviation of visual field loss. Fluorescein angiography may exhibit similar results but is a more invasive technique.[30]

Optic disc edema with unknown etiology may warrant brain imaging and additional laboratory or serological testing. Bilateral presentations may be secondary to increased intracranial pressure, malignant hypertension, brain mass or lesion, infection, inflammation or toxicity. Unilateral optic disc edema can result from optic neuritis, ischemia or compression, but these can also occur bilaterally.[33]

Management

Patients using amiodarone who report visual disturbances should be promptly examined, and additional testing should be ordered as indicated above. Amiodarone-associated optic neuropathy is a diagnosis of exclusion. Imaging to rule out a cerebral mass or other etiologies is needed, especially in the case of visual disturbances and absence of disc edema.[6,27] Patients taking amiodarone have serious cardiovascular illnesses, making it difficult to associate neuropathies with amiodarone rather than a manifestation of systemic disease. If optic neuropathy due to amiodarone usage is highly suspected, consultation with the patient's cardiologist is necessary to discuss discontinuation and substitution with another antiarrhythmic drug. Abrupt cessation of amiodarone without a therapeutic alternative can lead to a potentially fatal arrhythmia.[7,8,10,13] Once diagnosed, patients should also be aware of the visual prognosis and lengthy timeline of resolution.

Many case reports highlight similar presentations, in which bilateral optic neuropathy occurred after a patient was placed on amiodarone and optic nerve swelling persisted for a few months. In such cases, after discussion with cardiology, amiodarone dosage was decreased or stopped, with resulting resolution of optic nerve swelling and hemorrhages.[9,13,34]

The presence of whorl keratopathy is not an indication to discontinue amiodarone because visual symptoms are rare and not sight-threatening.[9] Corneal refractive laser surgery is contraindicated in patients using amiodarone as it may affect laser accuracy and postoperative healing.[10,35]

Patients with amiodarone-associated optic neuropathy may present to eyecare professionals for irritation of the eyelids, which can be caused by a variety of mechanisms. Consideration of skin photosensitivity should be on the list of differentials in patients taking amiodarone.[11] Ultraviolet radiation protection, cool compresses, and soothing creams may alleviate this drug-induced photosensitivity similar to a sunburn. A corticosteroid cream may be needed for significant inflammation, and an antibacterial cream may be necessary to prevent skin infection if the skin blisters and breaks.[10,36]

There has not been consensus on a follow-up protocol for patients taking amiodarone. Amiodarone manufacturers recommend routine screenings, but do not specify time intervals. The Heart Rhythm Society suggests a baseline evaluation for patients with pre-existing visual impairment.[1] Many physicians recommend an annual comprehensive examination, with an expedited appointment with onset of any visual symptoms.[4,5,10] Johnson et al. recommend a few evaluations within the first year of starting amiodarone as ocular toxicity occurs at an average time point of nine months. Because onset is insidious, periodic evaluation is needed rather than at longer intervals.[6] Beneficial testing at baseline and follow-up may include OCT of the optic nerve head, visual field testing and color vision testing. If ocular toxicity is suspected, physicians should report examination findings, drug dose, drug duration, concomitant drugs and follow-up findings to the FDA's MedWatch program to increase publicity of a potentially serious drug reaction.[1]

Discussion

Due to a $22.8 million judgment against Wyeth-Ayerst Pharmaceuticals in 1997,[2] the FDA added optic neuropathy as a caution in the amiodarone package insert, but not in a black box warning as a serious or life-threatening risk.[1,2,37] Other drugs, including ethambutol, have long been accepted as a cause of optic neuropathy with an incidence of <1%. Similar to amiodarone, there are no evidence-based studies to demonstrate true causation.[1]

Many question the existence of amiodarone-associated optic neuropathy.[1,3,5,17,38,39] A trial by Mindel et al. that involved 1,600 patients and compared amiodarone to placebo did not find any cases of bilateral vision loss.[3] However, results were based solely on patients who answered "yes" to the query of optic neuritis. A comprehensive eye examination was not performed on these patients, and analysis included only patients who had bilateral vision loss, not mildly reduced visual acuity or visual field defects.[1]

Direct causation between amiodarone usage and optic neuropathy remains unproven, and many consider the clinical findings to be a variant of NAION.[5,38,39] Patients share similar features and systemic risk factors, such as hypertension, diabetes mellitus and older age, which complicates the ability to distinguish the two conditions.[1,6] Challenges exist to establishing the relationship between amiodarone and optic neuropathy. Additional research is needed as numerous historical reports have not included pertinent information such as funduscopic features, visual field findings, time course and clinical outcomes. This task is challenging because using a placebo medication on a patient with a life-threatening condition is not ethical. A study comparing incidence of optic neuropathy in patients taking amiodarone vs. another antiarrhythmic medication may be warranted. Sotalal's efficacy is comparable, but amiodarone has the least recurrence of atrial fibrillation.[10]

Conclusion

Amiodarone, although an extremely effective antiarrhythmic drug, can have numerous adverse systemic and ocular effects, some of which are rare but serious. Controversy persists as to whether prolonged, bilateral optic neuropathy occurs secondary to amiodarone use or the plethora of vascular issues exacerbated by amiodarone. Presentation of vision or visual field loss varies significantly and generally has a slow onset, progression and resolution. To distinguish amiodarone-induced optic neuropathy from NAION, differences in laterality and duration of disc edema should be considered. Early recognition is important as the long half-life of amiodarone can lead to severe damage even after cessation of the drug. Active inquiry regarding visual manifestations, thorough clinical evaluation and deliberate ancillary testing can prompt an early diagnosis and facilitate appropriate management. In collaboration with cardiology, attempts should be made to discontinue amiodarone if amiodarone-associated optic neuropathy is highly suspected.

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