Sir,

Bilateral optic neuropathy linked with amiodarone

Amiodarone hydrochloride is used in the treatment of tachycardia associated with Wolff–Parkinson–White syndrome. It may only be used for the treatment of other arrhythmias when other drugs are ineffective or contraindicated and should be initiated only under hospital or specialist supervision. Recommended dosage for amiodarone is 200 mg three times daily for 1 week reducing to 200 mg twice daily for another week. Maintenance dose is usually 200 mg or the minimum required to control the arrhythmia.[1] Between 76% and 100% of patients on this medication develop a keratopathy characterised by pigmented curved or whorl-like microdeposits on the lower half of the cornea that do not usually affect visual acuity.[2,3]

Other side effects include photosensitivity, hyper- or hypothyroidism, constipation, hepatitis, tremor, insomnia and headaches. Less commonly it causes pulmonary fibrosis, abnormal skin pigmentation, peripheral neuropathy, proximal muscle weakness and truncal rash, bradycardia, nausea and vomiting, metallic taste, nightmares, benign raised intracranial hypertension, epididymitis, ataxia, vasculitis, alopecia and thrombocytopenia.[1] Ocular side effects are not usually sight-threatening.[1,3]

Visual loss and optic disc changes have been described with amiodarone. Gittinger and Asdourian[2] have reported two cases of optic disc swelling associated with amiodarone and Nazarian and Jay[4] have reported a case of bilateral optic neuropathy associated with amiodarone therapy.

Here we describe the case of a man who developed bilateral optic neuropathy while on amiodarone therapy.

Case report

A 56-year-old man was referred to the outpatient department at the Royal Halifax Infirmary in March 1997. The patient had a history of pulmonary tuberculosis 6 years previously that had been adequately treated with a combination of rifampicin, isoniazid and pyrazinamide (Rifater, Hoechst) in the initial phase and with a combination of rifampicin and isoniazid (Rifanah 300, Hoechst) in the continuation phase. In April of 1996 he was diagnosed with paroxysmal atrial fibrillation and was started on digoxin 0.25 μg daily and aspirin 150 mg daily. He was not hypertensive and his blood pressures were always within normal limits. Echocardiography showed mild to moderate mitral regurgitation with a mildly enlarged left ventricle and a left atrium that was the upper limit of normal size. When reviewed in November 1996 his atrial fibrillation was still uncontrolled. His dose of digoxin was halved to 0.125 μg and he was changed from aspirin to warfarin. He was also put on amiodarone 200 mg daily, which was reduced to 100 mg daily on review 1 month later. This new regime controlled his atrial fibrillation. Apart from digoxin and amiodarone, no other medication was used to treat his atrial fibrillation. A digoxin level was not performed. He was also on salmeterol and beclomethasone inhalers for asthma. He had stopped smoking 30 years previously and admitted to drinking mainly on weekends.

His visual problems started in January 1997 when he noticed loss of vision in the superior field of his left eye. This progressed over the course of 6 weeks until he visited his optometrist. When he was seen in our department, the visual loss had progressed to involve both eyes. Visual acuity was 6/5 in the right eye and 6/6 in the left eye. Blood pressure was 136/94 mmHg and urine testing by dipstick showed no abnormalities. Fundus examination showed a pale swollen right optic disc with a disc haemorrhage and the left disc was atrophic (Fig. 1). It was initially thought that this was a pseudo-Foster–Kennedy syndrome due to ischaemic neuropathy; however, it is unusual in such cases for central vision to be retained, particularly with the degree of disc swelling noted. Urgent imaging was performed that showed no intracranial space-occupying lesion.

Erythrocyte sedimentation rate (ESR) performed then was 77 mm/h, but this patient had had high ESRs in the past dating back to 1982. Also, he had no history of headaches, malaise, anorexia, weight loss or jaw claudication. Humphrey visual field testing showed bilateral gross constriction of fields with small residual central fields in both eyes (Fig. 2). Fluorescein angiography showed no areas of abnormal filling, a normal arterial phase, and diffuse hyperfluorescence of the disc that was evident from the arteriovenous phase with marked late staining of the disc.

The patient was admitted to the ward. He was given 100 mg hydrocortisone intravenously on admission and underwent three alternate-day treatments with 500 mg methylprednisolone intravenously. A temporal artery biopsy was performed. Further investigations included autoantibodies, cholesterol and triglycerides, full blood count, anti-neutrophil cytoplasmic antibodies, VDRL, protein electrophoresis, calcium levels and immunoglobulin levels. A lumbar puncture was performed for cerebrospinal fluid testing. An echocardiogram was also performed to exclude atrial myxoma. His amiodarone was stopped because of the possibility of toxic optic neuropathy.

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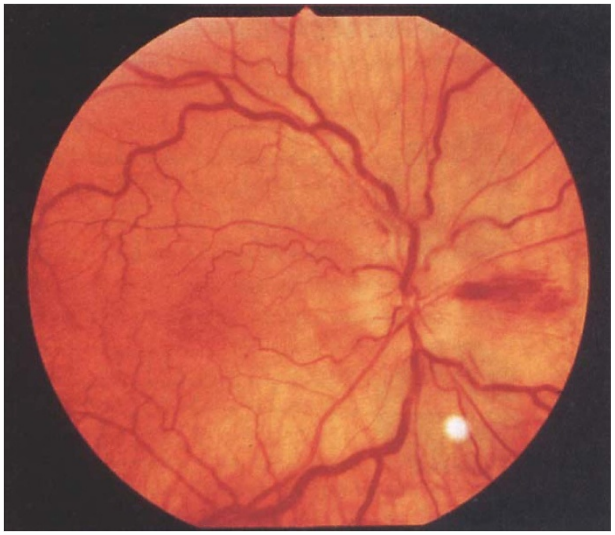

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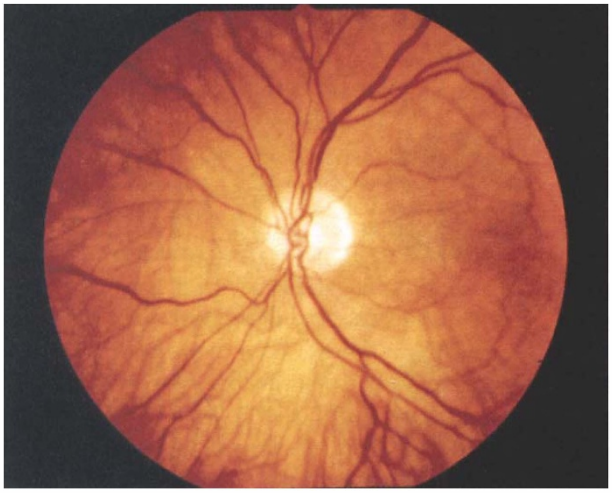

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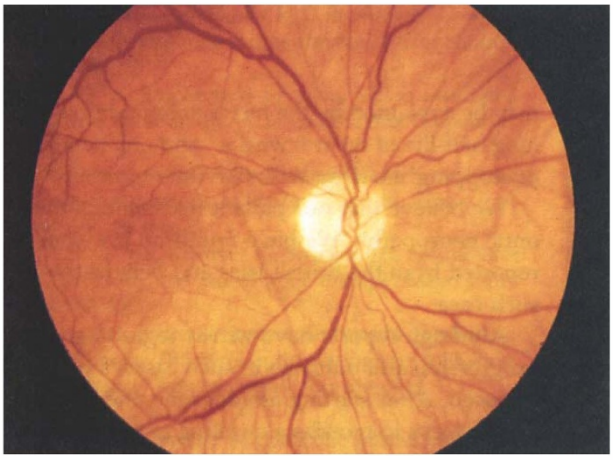

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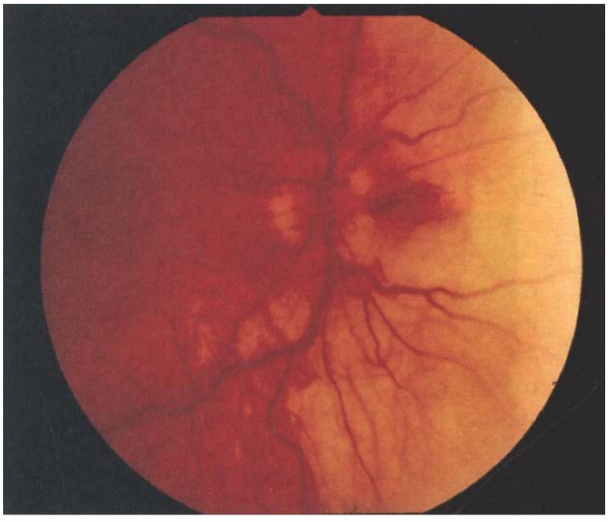

(d)

Fig. 1. *(a), (b) Photographs of left and right optic discs on admission. Note the swollen right optic disc with haemorrhage. (c), (d) Photographs of left and right discs after 3 months.*

All investigations performed were found to be within normal limits. The temporal artery biopsy showed no evidence of giant cell arteritis. He was also tested for Leber's optic neuropathy, but there was no evidence of any of the common Leber's mutations or of any abnormality of mitochondrial DNA. A repeat visual field after 3 weeks showed a worsening of the right field. By then the optic disc swelling had subsided and both optic discs were pale (Fig. 1).

When reviewed in June 1997, his visual acuities were 6/24 in the right eye and 6/5 in the left eye. His visual fields had remained stable (Fig. 2) and fundal examination showed flat atrophic discs (Fig. 1).

Discussion

Amiodarone, like other drugs that produce corneal deposits in a vortex pattern, is a cationic amphiphilic drug. This means it has adjacent hydrophilic and hydrophobic groups on the same molecule,[3,5] which gives it the ability to penetrate lysosomes and bind irreversibly with polar lipids. The resulting complexes accumulate within lysosomes and can be seen on electron microscopy as lamelloid or crystalloid bodies.[5] Amiodarone-induced intracytoplasmic membrane-bound vesicles have been detected in several ocular tissues including corneal epithelium, corneal fibroblasts, corneal endothelium, conjunctival fibrocytes, vascular endothelium, eyelid, lens epithelium, retinal pigment epithelium, Müller cells, extraocular muscles, uveal fibrocytes, scleral fibrocytes, pigment epithelium of iris and ciliary body and retinal ganglion cells.[3,5] Amiodarone is known to cause a peripheral neuropathy. Histopathologically this has consisted of varying degrees of demyelination, axonal loss and the presence of numerous lysosomal inclusions in Schwann cells and other cell types. There is also selective loss of large axons.[5] Lamellar inclusions have been selectively found in the large axons of the optic nerve of an asymptomatic individual taking amiodarone.[5]

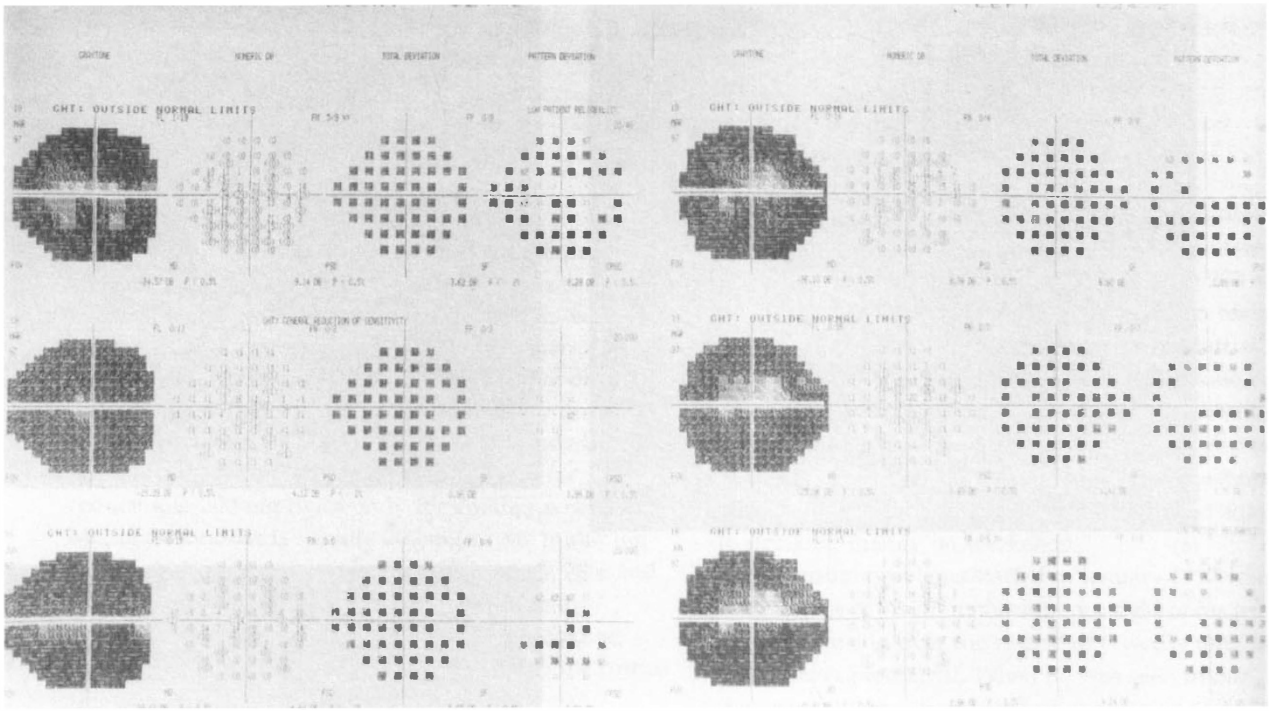

Fig. 2. *Progression of visual fields from admission to follow-up at 3 months.*

It has been reported that there was impairment of colour vision in patients on amiodarone therapy. This impairment was correlated with the severity of amiodarone keratopathy.[6] However, it may be that these colour vision defects are likely to be a result of a mild subacute form of amiodarone-induced optic neuropathy, and it has been suggested that testing of colour vision, visual evoked potentials and visual fields may be helpful in detecting otherwise asymptomatic cases of amiodarone optic neuropathy.[5]

The recommended dosage of amiodarone by mouth is 200 mg three times daily for 1 week reduced to 200 mg twice daily for a further week. Maintenance is usually 200 mg daily or the minimum required to control arrhythmia.[1] However, in the USA, where most of the cases of amiodarone-induced optic neuropathy have been reported, the maintenance dosage can be as high as 1200 mg daily, although cases have been reported with doses of 200 mg daily.[7]

Our patient started to have symptoms within 6 weeks of starting amiodarone treatment. Ocular side effects of amiodarone can be seen relatively quickly; corneal microdeposits have been recognised as early as 10 days after initiation of treatment.[3] It is possible that our patient had bilateral anterior ischaemic optic neuropathy that was unrelated to amiodarone, but the visual fields are not typical of this. Normally this would cause an altitudinal or central visual field defect; in this case there was central sparing of fields. Fluorescein angiography could not distinguish between ischaemic optic neuropathy and amiodarone-induced optic neuropathy.

Although in our patient the deterioration in vision continued even after the cessation of amiodarone therapy, this has been the case in other reports of possible amiodarone-induced optic neuropathy.[4,7] This may be explained by the fact that amiodarone has a very long half-life of several weeks,[1] and any beneficial effects of stopping the drug will take time to occur.[2]

We believe that our patient had amiodarone-induced optic neuropathy. We have found no previous cases reported from the British Isles and believe this is the first such case.

Although reports have varied regarding the progression and outcome in such cases, a pattern may be deduced. After starting amiodarone, there occurs within a few weeks to months a swelling of optic discs[2,4,7,8] that may be unilateral but can progress to be bilateral.[3,7] These discs eventually progress to optic atrophy.[2,4,7,8] Visual field changes may be mild and reversible[2,8] or severe and irreversible.[3,7] Field loss tends to be peripheral and central vision may be decreased slightly.[2,4,7,8]

It is possible that some patients are at higher risk of developing amiodarone-induced optic neuropathy, but at present there is no way of predicting this. We propose that these persons are the same group who are at risk of developing an ischaemic optic neuropathy, because they have small posterior scleral canals and crowded nerve axons at the optic nerve head. Then when amiodarone causes a liposis of the larger axons,[5] there are compressive effects to the other nerve fibres leading to a neuropathy.

The risks of complications due to amiodarone use must be weighed against the benefit of therapy in those patients whose lives are threatened by cardiac arrhythmias. It could be recommended that all patients who receive amiodarone therapy should undergo complete ophthalmological examinations, including evaluation of the fundus, regularly during such therapy. However, the number of patients that such testing would

add to already burdened clinics would be prohibitive. At present no test is available that is able to predict either those patients who are at risk of developing amiodarone-induced optic neuropathy or those patients who develop the pre-symptomatic state on the drug. Therefore, until a reliable screening test is developed, patients should be advised to visit their doctors should any visual symptoms occur, and ophthalmologists seeing patients with swollen optic discs who are using amiodarone should consider the possibility of amiodarone-induced optic neuropathy.

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Sir,

Transient retinal arterial compromise in Graves' orbitopathy

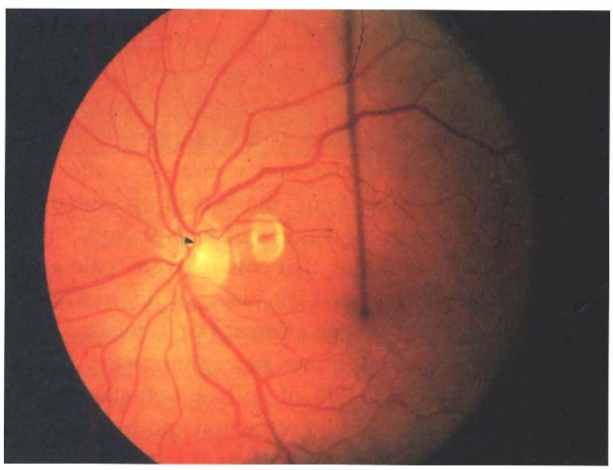
Graves' orbitopathy is a well-recognised autoimmune process, whose pathogenesis is still being elucidated.[1] Severe visual loss may occur because of compressive optic neuropathy or corneal exposure, and diplopia, choroidal folds and transient hypermetropia are also well recognised.[2]

We describe a single patient with Graves' orbitopathy, in whom elevation of intraocular pressure in upgaze occurred to such a marked level that the retinal arterial circulation was temporarily compromised.

Case report

A 70-year-old Caucasian woman was referred from her endocrinologist for management of her left orbital discomfort associated with thyroid orbitopathy 5 months after she had been diagnosed with hyperthyroidism.

Initial examination revealed corrected visual acuity of 6/5 in each eye, with normal pupils. There was obvious chemosis and proptosis of the left eye, measured at 20 mm on the left side compared with 16 mm on the right side using the Luedde system.[3] A left hypotropia was present in the primary position, with defective elevation on adduction and abduction, and 2 mm of left upper eyelid retraction relieved on downgaze.[4] Intraocular pressures were 20 mmHg bilaterally in the primary position, but were measured at 36 mmHg in the right eye and 54 mmHg in the left eye on attempted upgaze, at which point the left retinal arterial system was noted to



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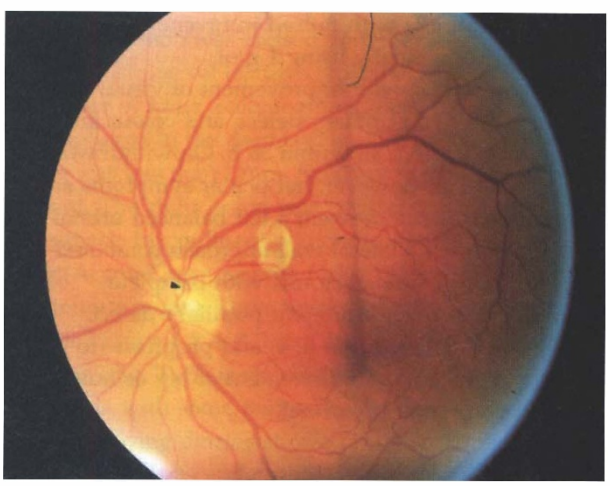

(b)

Fig. 1. *(a) Left fundus showing normal retinal vessels in primary gaze. (b) Same left fundus showing collapsed arterial vessels (arrowhead) at the disc during systole when the patient was attempting upgaze.*