Sir,

Severe systemic toxicity caused by brimonidine drops in an infant with presumed juvenile xanthogranuloma

Systemic absorption of ophthalmic medications is known to occur and can lead to toxicity. Infants especially are highly vulnerable to eye drop toxicity.[1] We report the medical management of an infant, presenting with spontaneous hyphaema and raised intraocular pressure (IOP) due to presumed juvenile xanthogranuloma, leading to severe systemic toxicity caused by brimonidine drops.

Case report

An 8-week-old girl presented as an emergency with a 10 day history of a red right eye. The parents had noted the right eye appeared both darker and larger than the left and a white mark had developed at the bottom of the iris. The infant was born at 41 weeks gestation via a caesarian section for fetal distress. She was a face presentation and developed a bruise on the forehead. The parents were unemployed and lived in a hostel.

Examination revealed a distressed baby. The right cornea was cloudy with a diameter of 11.5 mm. There was a hyphaema of half to three-quarters of the anterior chamber and the intraocular pressure (IOP) was 44 mmHg (Perkins). There was a dull red reflex with no fundal details visible. The left eye was normal.

The infant was admitted for further investigation and treatment. The paediatrician found no other evidence of non-accidental injury and no skin lesions. A full blood count and clotting screen were normal. Ultrasound of the eye and a CT scan of the orbit and brain found no intraocular lesions or calcification, although the right eye was larger than the left. Our working diagnosis was that of juvenile xanthogranuloma.

The treatment started was g. atropine 0.5% b.d., g. levobunolol 0.5% b.d., g. betamethasone 3-hourly and acetazolamide syrup 25 mg b.d. At 3 days the IOP was still elevated at 45 mmHg and at this stage g. dorzolamide 2% b.d. and g. brimonidine 0.2% b.d. were added. At 8 days the IOP was 20 mmHg.

At 2 weeks after presentation the infant was admitted as an emergency under the paediatricians with a history of severe floppy episodes and failure to thrive. The baby became unrousable and hypotonic for several hours at a time. Thorough examination and extensive investigations, including an infection screen, metabolic screen, toxicology, EEG and a head CT scan found no cause. At this point it was thought that symptoms could be due to some of the topical or systemic medication the infant was on for her ocular condition. The β-blocker, atropine and acetazolamide were discontinued with no improvement in her systemic condition. The brimonidine drops were then stopped with an immediate cessation in the infant's floppy episodes. After this the other medications were cautiously re-introduced and there were no further systemic problems.

At 3 weeks after presentation patching was commenced. There was a rebleed at 6 weeks. The steroid drops were increased to g. betamethasone 2-hourly and g. atropine 0.5% b.d., g. timolol 0.25%, g. dorzolamide 2% b.d. and acetazolamide 25 mg b.d. were continued. An examination under anaesthetic at 7 weeks showed the acute haemorrhage to have cleared although the iris was tented up to the cornea and an inferior iris mass was visible (Fig. 1). The corneal diameter was 12 mm, the IOP was 10 mmHg and there was the start of an anterior capsular cataract.

The family failed to attend clinic on a number of occasions. At 6 months after presentation the IOP was controlled and the medications were gradually discontinued, the IOP remaining stable. A sedated examination at 10 months after presentation showed the IOP to be 17 mmHg, the corneal diameter 12 mm and the iris to have come away from the cornea, the iris mass having shrunk.

Currently the infant can follow targets with the right eye and is tolerating patching poorly. The IOP is stable without treatment and there is an anterior lens opacity.

Comment

All eye drops and systemic treatments have the potential to cause side-effects, especially in infants. Beta-blocker drops, atropine drops and carbonic anhydrase inhibitors can all have significant systemic side-effects, some potentially fatal, including drowsiness.[1] Infants, because of their size and immature drug clearance, are highly vulnerable to eye drop toxicity. Our patient had severe floppy episodes in which extensive examination and investigations, including an infection screen (including a lumbar puncture), metabolic screen, toxicological investigations (looking for illicit drug administration), EEG and head CT scan by the paediatricians found no cause. The focus of attention was then on the infant's ophthalmic medication and, by a process of elimination, brimonidine drops were found to be the cause of these floppy episodes.

Brimonidine tartrate is a highly selective α_2-adrenergic receptor agonist indicated for the chronic treatment of glaucoma and ocular hypertension in

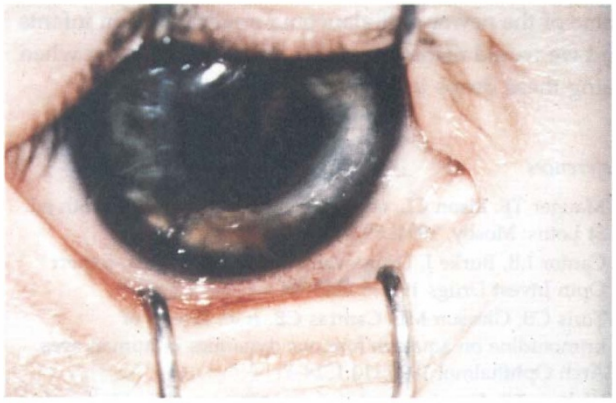

Fig. 1. *Photograph of the right eye showing the iris tented up to the cornea, an inferior iris mass and a streak of organised blood in the anterior chamber.*

adults.[2] Brimonidine lowers IOP through a dual mechanism of action: it reduces aqueous humour production and increases uveoscleral outflow.[3] Significant systemic absorption of brimonidine eye drops occurs in adults, peak plasma concentrations occurring within 1–4 h with a half-life of approximately 2.5 h.[2] Systemic metabolism of brimonidine is primarily by the liver and urinary excretion is the major route of elimination of the drug and its metabolites.[2] Brimonidine, like most drugs, has not been formally tested on children but has, along with other side-effects, caused drowsiness in adults.[4] There have been several unpublished reports of floppy episodes (J.A. Bradbury, Bradford Royal Infirmary, personal communication) and severe life-threatening reactions to brimonidine drops in infants (Allergan, USA, personal communication). The marked sensitivity of infants to brimonidine may be due to their size, immature metabolism and excretion of drugs or an increased receptor sensitivity. To our knowledge this is the first published report of a severe adverse reaction to brimonidine in an infant.

This infant presented with spontaneous hyphaema and raised IOP. The most common cause for hyphaema in any age group is trauma.[5] Non-accidental injury should be excluded in any infant presenting in this way. The most frequently presenting sign in iris juvenile xanthogranuloma is hyphaema, although other causes should be sought.[5] Once the diagnosis of iris juvenile xanthogranuloma is established treatment should be initiated rapidly. Several modes of treatment have been advocated including topical steroids,[5] subconjunctival steroids,[6] systemic steroids[7] and radiotherapy.[8] Not all cases resolve with local or systemic steroids and treatment should be adjusted according to clinical status.[5] If hyphaema and raised IOP is present, as in our case, aggressive antiglaucoma medication with eye drops and oral acetazolamide, if necessary, should be instituted.[5]

In summary, this infant's eye with presumed juvenile xanthogranuloma was controlled medically with topical steroids and with topical and systemic anti-glaucoma medication. However, the child has been left with dense amblyopia and a lens opacity. This case illustrates the potential pitfalls in prescribing adult drops, especially some of the newer anti-glaucoma medications, in infants and we would recommend that great care be taken when using these drops in infants and children.

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Hormone replacement therapy and retinal vein occlusion

The use of sex hormone preparations is a risk factor for cardiovascular and cerebrovascular disease.[1–3] A number of isolated case reports and a recent hospital-based retrospective study of retinal vein occlusions have implicated the oral contraceptive pill (OCP) but not hormone replacement therapy (HRT) as an independent risk factor for retinal vein occlusion.[4] However, as an increasingly large proportion of the population are using HRT, reporting cases of retinal vein occlusion in patients on this therapy may have management implications.[4] We report a case of central retinal vein occlusion in a patient on HRT.

Case report

A 43-year-old woman presented with a 3 day history of reduced visual acuity. There was no previous ophthalmic history. This patient had started HRT comprised of low-dose oestrogen and progesterone 5 weeks prior to presentation to alleviate menopausal symptoms. Of note was that she smoked 20 cigarettes a day, but there was no other significant medical or family history.

On examination visual acuity was 1/60 in the right eye and 6/18 in the left. There was no relative afferent pupillary defect and intraocular pressures were normal. Fundal examination demonstrated in the right eye a swollen optic disc, tortuous retinal vessels and multiple intraretinal haemorrhages consistent with a diagnosis of central retinal vein occlusion. The left eye was normal. Fluorescein angiography did not demonstrate any signs of retinal ischaemia. A comprehensive medical examination revealed no abnormalities and the patient was normotensive (125/80 mmHg). A range of haematological (including a thrombophilia screen),