Additive effect of unoprostone and latanoprost in patients with elevated intraocular pressure

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Aims: To assess the additive effect of unoprostone and latanoprost in patients with primary open angle glaucoma (POAG) or ocular hypertension (OHT).

Methods: 32 patients with POAG or OHT were randomised to receive either latanoprost once daily or unoprostone twice daily for 4 weeks. After 4 weeks, all patients received both latanoprost and unoprostone for another 4 weeks. The IOP was measured at 9 am and 5 pm on the baseline, day 28, and day 56 visits, and at 9 am on day 14 and day 42 visits. The medications were given to the patients in an open label fashion. The observer was masked to the treatment given. The mean of the measurements was calculated. Safety parameters were also recorded. The additive effect of the medications was assessed by the reduction in intraocular pressure (IOP) when both medications were used, compared with when one medication was used.

Results: 28 patients completed both treatment periods and had IOP data available for evaluation. After 1 month of treatment, latanoprost significantly reduced IOP [mean by 6.1 (SEM 0.8) mm Hg (p < 0.001) and unoprostone by 4.9 (1.0) mm Hg (p < 0.001) from the baseline of 24.4 (0.6) mm Hg and 24.4 (1.1) mm Hg respectively (p = 0.18)]. When latanoprost once daily was given to patients treated with unoprostone, there was additional IOP lowering of 1.9 (0.6) mm Hg (p = 0.012). However, adding unoprostone to those being treated with latanoprost produced an IOP change of +0.4 (0.5) mm Hg (p = 0.42). Ocular symptoms and findings were mild and equally distributed between treatment groups, and after combined therapy. Hyperaemia and ocular irritation were the most frequently reported events. Over a third of patients experienced ocular irritation with the combination of medications.

Conclusions: Latanoprost once daily causes additional IOP lowering in eyes which were being treated with unoprostone twice a day. However, there was no additional IOP lowering when unoprostone was added to eyes which were being treated with latanoprost. Both drugs were well tolerated together with few ocular adverse events.

T he therapeutic regimens for glaucoma have changed dramatically in the past few years. Newer glaucoma therapies such as the prostaglandin analogues, latanoprost and unoprostone, have few side effects and convenient dose schedules. Latanoprost, a prostaglandin F₂α analogue, has proved to be an effective ocular hypotensive drug. Its main mechanism for reducing intraocular pressure (IOP) is an increase in the uveoscleral outflow. Latanoprost 0.005% applied once daily reduced IOP as effectively as the β adrenergic receptor antagonist timolol in patients with primary open angle glaucoma (POAG) or ocular hypertension (OHT). Unoprostone isopropylate is a docosanoid derived from a metabolite of a primary prostaglandin, 13,14-dihydro-15-ketoprostaglandin. It was found to have a significant ocular hypotensive effect, and was as effective as timolol in reducing IOP in POAG. It is thought to act by increasing uveoscleral outflow, similar to latanoprost. However, a study by Taniguchi et al suggested that unoprostone may increase conventional trabecular outflow.

There is no published literature on the additive effect of latanoprost with unoprostone for treatment of primary open angle glaucoma and ocular hypertension. In view of the possibility that they may have differing mechanisms of action, it would be interesting to know if the two drugs exert greater IOP lowering effect when used together. This is especially so in patients who are intolerant or have contraindications to β blocker therapy and a prostaglandin analogue may need to be used. It would also be useful to determine the side effects in patients based on the combined response to these drugs. This study was thus designed to assess the additive ocular hypotensive effect and side effects of using unoprostone and latanoprost together in patients with elevated IOP.

MATERIALS AND METHODS
This two centre study was prospectively carried out at the Singapore National Eye Centre and the National University Hospital, Singapore. After obtaining approval from the ethics committees of each centre and by the Ministry of Health of Singapore, a signed informed consent was obtained from all patients before study enrolment. The study was performed according to the Declaration of Helsinki and the Singapore guidelines on good clinical practice.

Patients 21 years of age or older with primary open angle glaucoma or ocular hypertension were eligible. All patients recruited had IOP > 21 mm Hg at the prestudy visit and were previously untreated. POAG was defined as glaucomatous optic neuropathy with a compatible visual field defect and open angles on gonioscopy, while OHT patients had normal optic discs and visual fields and open angles. Glaucomatous optic neuropathy was defined as a cup:disc ratio of ≥ 0.6, or the presence of notching. A threshold examination of the central 24° of visual field (24-2 program) showing a glaucoma hemifield test (GHT) “outside normal limits,” and a cluster of three contiguous points on the pattern deviation plot depressed at p < 0.5% level (compared with age matched normal subjects) not crossing the horizontal meridian, was considered compatible with glaucoma. Test reliability was determined by the instrument’s algorithm.
Patients requiring bilateral treatment had to fulfil all eligibility criteria for both eyes to be included. However, if only one eye fulfilled the inclusion criteria, that eye was included as the study eye and the fellow eye could be treated with the allocated study therapy provided that no exclusion criteria were met.

Exclusion criteria were gonioscopic appearance of angle closure, secondary glaucoma such as uveitis, neovascular glaucoma or post-trauma, previous intraocular surgery, previous trauma to the eye with damage of the anterior chamber angle, the fellow eye on treatment with another IOP reducing drug, previous treatment with glaucoma therapy, previous corneal infection or corneal abnormalities, uveitis or dry eyes, current contact lens wear, oral drugs known to affect the IOP, and known allergy to benzalkonium chloride. Also, a history of cerebrovascular, hepatic, or metabolic disease (except diabetes mellitus) was considered a reason for exclusion. Currently, pregnant or nursing women, or women considering pregnancy were also excluded, as well as patients with a history of non-compliance or patients who participated in another therapeutic drug study within 1 month.

There were two treatment periods of 4 weeks each. At the prestudy visit, medical and ocular history was taken. Visual acuity and refraction, slit lamp examination, ophthalmoscopy, and measurement of the IOP were performed. Gonioscopy and perimetry were also carried out. Patients were included after these eligibility assessments.

On the baseline day, the patients were randomised (by block randomisation) to two parallel study groups: one group was assigned to treatment with latanoprost 0.005% in the evening and the other group received unoprostone 0.12% twice daily, for a duration of 4 weeks. After 4 weeks, all patients were given 0.12% unoprostone twice daily (in the morning and evening) and latanoprost 0.005% in the evening, for another 4 weeks. All types of medication were dispensed open label as the commercially available preparation, latanoprost (Xalatan, Pharmacia Corporation, Uppsala, Sweden) and unoprostone (Rescula, Ciba Vision Ophthalmics, Bulach, Switzerland).

Patients were instructed to instil unoprostone at approximately 8 am and 8 pm each day and latanoprost at 8 pm. When on both medications, the evening unoprostone and latanoprost doses were administered 10 minutes apart. On visit days to the clinic (days 14, 28, 42, and 56), those on unoprostone administered the eye drops in the mornings at 7 am before the clinic visit. Patients were informed to adhere strictly to the timing of the drops and the time of administration of drops was recorded.

During each study period there were three scheduled visits; at day 0, day 14, and day 28. The IOP was measured at 9 am and 5 pm on the baseline, day 28, and day 56 visits, and at 9 am on day 14 and day 42 visits. The IOP was measured with a Goldmann applanation tonometer. Three measurements were performed in each eye, and the mean of the three measurements was used in the statistical analyses. The observer was masked to the treatment given. Best corrected Snellen visual acuity and refractive error, systemic blood pressure, and pulse rate were determined at each visit, and a slit lamp examination was performed. The presence of cells and flare in the anterior chamber was investigated during slit lamp examination. Flare was graded as none, moderate, or severe, and cells present in a slit of 2 mm width were graded as none (1–2 cells), mild (3–5 cells), moderate (6–20 cells), or severe (>20 cells).

Adverse events were monitored carefully throughout the study. An adverse event was defined as any undesirable event occurring in a subject regardless of whether it was considered related to the drug being investigated. A serious adverse event was defined as an event that was potentially fatal, life threatening, permanently disabling, requiring hospitalisation, or requiring intervention to prevent permanent impairment or damage.

Statistical evaluation

For each patient, the IOP value was calculated at baseline and day 28 of each period as the mean of all measurements made on the study eye(s) on that day (mean diurnal IOP). If the patient had only one study eye, the average was based on the measurements made in that eye only. For patients with bilateral disease, data from one eye chosen at random in each individual were selected for analysis. In the event that the patient was missing one or more measurements, the average was based on the non-missing measurements.

The primary objective of the study was to test if latanoprost was additive to unoprostone, and vice versa. The null hypothesis was defined as IOP reduction on day 28 (monotherapy) being equal to the IOP reduction on day 56 (combined therapy), in both cases compared with the IOP on day 0. The alternative hypothesis was that the combination therapy further reduced IOP by 3 mmHg compared with treatment with only one drug. The further reduction was presumed to represent the additive effect of the second drug since the effect of the first drug is assumed to be stable after 28 days of treatment. It is anticipated that the between treatment groups SD is 3 mm Hg. The trial size of 32 will be sufficient to detect a difference in IOP between day 42 and day 28 of 3.0 mm Hg, with a two sided test size of 5% and power 90%.

All statistical tests were conducted at the 5% level using SPSS software version 8.0 (Statistical Package for Social Sciences, Chicago, IL, USA).

RESULTS

Of the 32 patients randomised to the study, 15 were randomised to start with latanoprost and 17 started with unoprostone. Two patients starting on unoprostone withdrew after day 14 because of side effects.

At day 28, the remaining 30 patients had the other medication added and were on both medications. Two additional patients withdrew before the day 42 visit. Both subjects (one on unoprostone and the other on latanoprost) could not tolerate the side effects.

Unless otherwise stated, the following analyses will take into account 15 subjects on day 28 and 14 subjects on day 56 in each of the groups.

Table 1 refers to the baseline demographic characteristics. There were no significant differences between the two groups with respect to sex, race, and age. As for other factors such as laterality of eyes involved, type of glaucoma, medical history, use of concomitant treatment, ocular symptoms and findings, and vital signs at the prestudy visit, the two treatment groups were comparable.

Change in intraocular pressure during the study periods

Table 2 summarises the change in IOP in the two groups in each study period.

At the end of period 1 (day 28), the mean decrease in IOP was 6.1 (0.8) mm Hg (p=0.0001) for latanoprost treated patients, and 4.9 (1.0) mm Hg (p<0.0001) for unoprostone treated patients. The mean difference in IOP drop between the two groups was 1.2 (1.3) mm Hg in favour of latanoprost (p = 0.35). Every patient had IOP lowering with the medications in this study period (100% response).

At the end of period 2 (day 56), mean decrease in IOP in the latanoprost-unoprostone group was +0.4 (0.5) mm Hg (p=0.42). However, for the unoprostone-latanoprost group, the mean change in IOP during period 2 was 1.9 (0.6) mm Hg (p=0.012). This difference in IOP change of 2.3 (0.8) mm Hg between the two groups in period 2 was significant (p=0.009).

Adjusting for day 28 IOP this difference increases to 2.5 (0.9) (p = 0.009, 95% CI 0.7 to 4.3).
Only 43% of patients on latanoprost had IOP lowering when unoprostone was added. In contrast, 86% of patients on unoprostone experienced lowering of IOP when latanoprost was added to unoprostone treatment.

Adverse events
The adverse events experienced by the subjects by period are summarised in Table 3.

There were a few patients with systemic adverse events during the study. In the first period, one patient experienced palpitations while on unoprostone, stopped the medication on day 14, and withdrew from the study. During the second study period, there was one patient who had body itch after having latanoprost added to her treatment. Another subject experienced fatigue and giddiness, but neither complaint was of sufficient severity to stop treatment. In all cases, the systemic symptoms resolved after cessation of treatment.

There were three subjects who withdrew from the study because of ocular side effects. One subject stopped the trial medication (in this case unoprostone) on day 14, as she developed eye redness and pain after applying the drops. This resolved on stopping the medication. The other two subjects withdrew on day 42 as they experienced intolerable eye irritation after having the second medication added.

Ocular adverse effects were generally mild in nature and similar in the two groups. The commonest adverse events were ocular irritation and redness. Over a third of patients experienced ocular irritation with the combination of medications. There was only one subject who had mild anterior chamber inflammation, while on unoprostone only. Interestingly, there was no case of ocular inflammation found in the second study period when subjects were on two medications.

DISCUSSION
Many glaucoma patients are treated with more than one ocular hypotensive medication. This is especially so after the introduction of newer medications with fewer side effects and convenient dose schedules, such as the prostaglandin analogues. Determination of additive effects on IOP of such glaucoma medications will help define optimum treatment regimens for patients. It has been previously reported that latanoprost has an additive IOP lowering effect when used with timolol, pilocarpine, dipivefrin, dorzolamide, acetazolamide, and the combination of timolol and dorzolamide. The question of whether two of the new prostaglandin analogues, latanoprost and unoprostone, are additive when used together is interesting. Theoretically, this is possible if the two medications have differing mechanisms of action on aqueous outflow.

Our study found that when latanoprost once daily was added to patients being treated with unoprostone twice daily, ocular irritation and redness. Over a third of patients experienced ocular irritation with the combination of medications. There was only one subject who had mild anterior chamber inflammation, while on unoprostone only. Interestingly, there was no case of ocular inflammation found in the second study period when subjects were on two medications.

**Table 1** Demographic characteristics of study groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Latanoprost-unoprostone</th>
<th>Unoprostone-latanoprost</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Age:</td>
<td>58.0</td>
<td>60.8</td>
</tr>
<tr>
<td>Mean</td>
<td>14.0</td>
<td>14.1</td>
</tr>
<tr>
<td>SD</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Sex:</td>
<td>Male 4</td>
<td>8</td>
</tr>
<tr>
<td>Female 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race:</td>
<td>Chinese 9</td>
<td>14</td>
</tr>
<tr>
<td>Malay 1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Indian 3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Others 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of glaucoma:</td>
<td>POAG 10</td>
<td>12</td>
</tr>
<tr>
<td>OHT 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laterality:</td>
<td>Unilateral 1</td>
<td>4</td>
</tr>
<tr>
<td>Bilateral 14</td>
<td></td>
<td>13</td>
</tr>
</tbody>
</table>

**Table 2** IOP profile in the two groups

<table>
<thead>
<tr>
<th>Day</th>
<th>Latanoprost-unoprostone</th>
<th>Unoprostone-latanoprost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td>24.4 (0.6)</td>
<td>24.4 (1.1)</td>
</tr>
<tr>
<td>Day 14</td>
<td>17.4 (0.7)</td>
<td>19.4 (1.2)</td>
</tr>
<tr>
<td>Day 28</td>
<td>17.8 (0.4)</td>
<td>19.6 (0.9)</td>
</tr>
<tr>
<td>Day 42</td>
<td>18.5 (0.6)</td>
<td>18.8 (1.1)</td>
</tr>
<tr>
<td>Day 56</td>
<td>18.2 (0.6)</td>
<td>18.0 (1.2)</td>
</tr>
<tr>
<td>Change in IOP (mean [SE])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days 28 and 0</td>
<td>-6.1 [0.8 [p &lt;0.001]]</td>
<td>-4.9 [1.0 [p &lt;0.001]]</td>
</tr>
<tr>
<td>Days 56 and 28</td>
<td>+0.4 [0.5 [p = 0.42]]</td>
<td>-1.9 [0.6 [p = 0.012]]</td>
</tr>
</tbody>
</table>

**Table 3** Adverse events experienced by patients

<table>
<thead>
<tr>
<th>Period 1</th>
<th>Latanoprost</th>
<th>Unoprostone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye irritation</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Eyelid swelling</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Dry eye</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Eye redness/conjunctiva hyperaemia</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Cornea PEEs</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Uveitis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Palpitations</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Period 2</td>
<td>Latanoprost + unoprostone</td>
<td>Unoprostone + latanoprost</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Tearing</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Eye itch</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Conjunctiva redness/hyperaemia</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Body itch</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Giddiness</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
there was an additional IOP lowering of 1.9 (0.6) mm Hg (p = 0.012) indicating that there was additive effect. However, adding unoprostone to those being treated with latanoprost produced a negligible effect on IOP (change of +0.4 (0.5) mm Hg, p = 0.42). The findings are in agreement with those of Stewart and colleagues who also found no significant reduction in the mean diurnal curve of the IOP compared with placebo when adding unoprostone to latanoprost, although there was some variance in response that appeared to be based on the baseline IOP of latanoprost treated eyes.16

Several reasons may account for the difference in effect found in our study. A plausible explanation is that unoprostone is less effective in reducing IOP at lower IOP levels. This was the case at the beginning of study period 2 when the mean baseline IOP of latanoprost-unoprostone treated patients was 17.8 (0.4) mm Hg, which was in the physiological range. A previous report found that unoprostone reduces IOP by about 10% in normal tension glaucoma.26 Latanoprost, on the other hand, has been previously shown to be effective at so called “low” IOPs in patients with this form of glaucoma, and produces an IOP reduction of approximately 20%.27 28 In this study, the mean baseline IOP of unoprostone-latanoprost patients at the start of study period 2 was 19.6 (0.9) mm Hg. Although this was also within the physiological range, it was within the efficacy range of latanoprost.

Another possible reason to explain the lack of additive effect when unoprostone was added to latanoprost is that there were many patients who did not show IOP lowering with unoprostone in the second study period. Only 43% of patients on latanoprost had IOP lowering when unoprostone was added. In contrast, 86% of patients on unoprostone experienced lowering of IOP when latanoprost was added to unoprostone treatment. In the first study period, all patients (100%) in both groups had IOP lowering with the study medications. It is possible that both latanoprost and unoprostone are competing for the same prostaglandin receptor sites, and latanoprost is more highly competitive or more potent than unoprostone. Thus, when latanoprost is added to unoprostone therapy, there is additional effect, but not vice versa.

Finally, the additional IOP lowering attributed to the addition of latanoprost may actually be due to the delayed response of unoprostone. This is possible if unoprostone had not achieved maximum IOP lowering at the end of 4 weeks of treatment (the first study period), and it only reached its maximum response later. The time required for maximum IOP lowering effect for unoprostone is not known. However, a previous study has shown that after 2 weeks of treatment, latanoprost had almost reached maximum response, compared with 1 and 6 months of treatment.29 Thus, 1 month of treatment should have been sufficient to produce a maximum response in both study groups.

The other significant finding in this study is that latanoprost and unoprostone can be used together without clinically unacceptable systemic or ocular side effects. Overall, both drugs were well tolerated individually and together. The side effects found in the second study period when the two drugs were used together were infrequent and generally mild in nature. The most common complaint was ocular irritation (10 subjects) but only two subjects found it serious enough to stop treatment. There were a few cases of conjunctival hyperemia. Because prostaglandins are known to be released in the inflammatory response,29 31 cells and flare in the anterior chamber were regularly monitored during both study periods. However, there was no case of uveitis found during combined therapy. The only systemic adverse effects found during combined therapy were vague complaints of giddiness and fatigue in one case and body itch in another. We were not able to be sure that these systemic adverse events were caused by the medications, as the patients were not rechallenged with the same eye drops after completion of the study.

The main limitation of this study was that it was single masked to the observer only. A placebo was also not used for the morning dose in the latanoprost group. Accordingly, the side effects found when the second medication was added must be interpreted with caution because of the open label dosing and lack of placebo in the trial.

In conclusion, this study has shown that latanoprost once daily causes additional IOP lowering in eyes which were being treated with unoprostone twice a day. However, there was no additional IOP lowering when unoprostone was added to eyes which were being treated with latanoprost. Both drugs were well tolerated together with few systemic or ocular adverse events. It would be interesting to discover the pathway and molecular basis through which these medications interact and function. Long term studies would be useful to determine if these additive effects are sustainable and if the two drugs can be used continuously without clinically unacceptable side effects.

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Proprietary interest: Nil

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Authors’ affiliations

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Additive effect of unoprostone and latanoprost in patients with elevated intraocular pressure

24 Stewart WC, Sharpe ED, Stewart JA, et al. Additive efficacy of unoprostone isopropyl 0.12% (Rescula) to latanoprost 0.005%. Am J Ophthalmol 2001; 131: 339–44.
Surgically induced diffuse scleritis: comparison of incidence in phacoemulsification and conventional extracapsular cataract extraction

Surgically induced diffuse scleritis (SIDS) is a recognised but less well reported cause of pain and reduced vision following cataract surgery.

We have previously reported on complications of conventional extracapsular cataract extraction in which SIDS was the second most common. Recently, we conducted an audit of patients who underwent phacoemulsification cataract extraction to compare the incidence of SIDS in these patients relative to that found in the ECCE group.

Methods and results

From a computerised departmental database, 666 consecutive patients who had undergone phacoemulsification cataract surgery with intraocular lens (IOL) implantation under a single consultant firm were identified. The case notes were examined and all postoperative complications occurring in both groups and in the National Cataract Surgery Survey (NCSS) 1997–8 are listed in Table 1.

Comment

Ten (1.5%) of the patients who underwent phacoemulsification cataract extraction (including one whose procedure was combined with trabeculectomy) were diagnosed with SIDS. This was approximately half the proportion, (21 = 3.1%) of the ECCE group, but was the second commonest complication in both groups of patients. However, it does not feature in the list of postoperative complications reported in the National Cataract Surgery Survey 1997–8. SIDS has previously been described as an undiagnosed clinical entity and it may be failure to recognise it which explains its absence from the national statistics.

Patients who had undergone previous ipsilateral iris surgery (trabeculectomy, Scheie’s procedure, or YAG iridotomy) appeared to be at increased risk, although this only attained statistical significance in the phacoemulsification surgery group (p = 0.01). General anaesthesia was associated with higher statistical risk for ECCE patients only (p = 0.009). It is unclear why this should have been the case. Intraoperative complications did not increase the risk of developing SIDS, and there was no association with concurrent ocular or systemic disease. The mean age of the SIDS patients in the ECCE group was approximately 11 years younger than that in the phaco group (62.5 v 73.6).

It is our practice to take a thorough history from the postoperative patient. Severe pain, especially that waking the patient from sleep, is a common feature. Examination of the patient both on the slit lamp and in daylight is conducted, the latter to recognise the characteristic violaceous injection of the scleral vasculature. B-scan ultrasonography is performed to measure scleral thickness. Relative thickening compared to the contralateral eye or absolute thickness greater than 1.8 mm supports the diagnosis. Affected patients usually show a favourable response to a combination therapy with oral non-steroidal anti-inflammatory agents, topical steroids, and a topical cycloplegic. SIDS should be considered in the differential diagnosis of a painful red eye postoperatively. Prompt diagnosis and appropriate therapy lead to early resolution of SIDS and improved visual outcome.

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Total exudative detachment as a first presentation of von Hippel Lindau disease

Von Hippel Lindau disease is a rare condition characterised by retinal and central nervous system haemangioblastomas. It is also associated with renal cell carcinoma, phaeochromocytoma, and renal, pancreatic, and epididymal cysts.

The disease usually presents with neurological symptoms and/or visual disturbance; angiomats if seen in the retina can often be treated in an attempt to prevent progression to retinal detachment.

We report a young girl with von Hippel Lindau disease whose initial presentation was with a total exudative retinal detachment.

Case report

A 14-year-old girl presented to the eye casualty department with no perception of light in her left eye. She gave a 2 month history of gradual, painless loss of vision, but had delayed previously mentioning her symptoms. Past ocular history was unremarkable; an optometrist visit a year previously was normal. She was otherwise well.

Slit lamp examination on the left revealed a quiet anterior segment, with retinal folds visible aborting the posterior lens capsule (Fig 1A). The right eye was entirely normal. An ultrasound B-scan showed a left total funnel retinal detachment (Fig 1B). Computed tomograph scan demonstrated normal orbits.

The patient’s identical twin was also present and was examined: both her eyes were normal.

At this stage the family history proved helpful. The patient’s father had recently been diagnosed with renal cell carcinoma and pituitary vascular tumours.

The paternal line had a cluster of various carcinomas, including three relatives with cerebellar tumours. Further investigation revealed at least one of these to be histologically
confirmed haemangioblastoma. The possibility of von Hippel Lindau disease was raised and the patient’s father was screened; the diagnosis was confirmed with polymerase chain reaction analysis; showing a frame shift mutation (single base pair deletion [G]) in codon 195 (exon 3) of the von Hippel Lindau gene. Subsequent extended family screening has revealed the same mutation in the patient and nine other living relatives (Fig 2), including the patient’s identical twin. Five of these relatives have clinical manifestations of the disease, and in one case an asymptomatic stage 1 renal cell carcinoma was diagnosed and successfully resected.

Miss AB’s left eye has subsequently developed pupil block glaucoma which is currently well controlled medically. It remains blind with a rigid total retinal detachment. The cause of this detachment is most likely to be an optic nerve or retinal haemangioblastoma; however, no causal lesion was identified on ultrasound or computed tomography (CT). The few retinal vessels that can be seen (Fig 1A) do not show any abnormality. Her other eye remains normal and screening for signs of the disease elsewhere has proved negative.

Comment
This case highlights the importance of considering von Hippel Lindau disease as a diagnosis when confronted with a patient with an unexplained exudative retinal detachment.

Von Hippel Lindau disease has an autosomal dominant inheritance pattern with an incidence of one in 36 000; with a 70% prevalence of ocular haemangioblastomas. Von Hippel Lindau gene mutation carriers have a 35% probability of visual loss by age 50.

Ocular angiomias occur commonly in the superotemporal mid-peripheral retina, less commonly on the optic disc (8%), and at the posterior pole (1%).

If left untreated, lesions can cause vitreous haemorrhage, macular oedema, epiretinal membrane formation, and exudative or tractional retinal detachment. This last complication is well demonstrated in our patient’s case, with a 2 month delay between onset of symptoms and first presentation.

Treatment comprises laser photocoagulation of angiomas less than one disc diameter. Cryotherapy, or vitreoretinal surgery with trans-scleral drainage and endolaser may be indicated in larger lesions, especially if vitreous traction is present. Early treatment necessarily offers a better prognosis.

This case underscores the value of taking a good family history in order to detect hereditary diseases, which can then be confirmed with genetic molecular analysis. The importance of identification and subsequent screening of von Hippel Lindau gene mutation carriers (both affected and unaffected) is exemplified in our patient’s family—with the potential benefit of early diagnosis and treatment of asymptomatic retinal and cerebellar haemangioblastomas, as well as potentially fatal tumours. The screening should be maintained regularly, as the protean manifestations of von Hippel Lindau disease may occur de novo at any age.

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a consequence there was a relative hold up to the filling of the sigmoid sinus. The AVM therefore now drained anteriorly via a collateral circulation into the cavernous sinus. The later phases of the angiogram revealed that there was relatively little downward venous outflow from the cavernous sinus and the majority of this venous outflow was therefore shunted via the superior ophthalmic vein which was markedly dilated as a consequence. The patient’s symptoms of unilateral proptosis and venous engorgement were therefore a manifestation of increased blood flow through collateral shunts that had developed as a consequence of a stricture in the principal drainage channel of the existing AVM, which itself had not changed significantly in size.

Figure 2 Anterior segment photographs showing the dilated episcleral vessels in the left eye.

Figure 3 Cerebral angiogram dated 1994. A moderately sized arteriovenous malformation is shown fed by branches of the left middle cerebral and anterior cerebral arteries. It is drained by a large superficial vein which continues into the superior sagittal sinus.

Comment

Arteriovenous malformations (AVM) are lesions which consist of racemose networks of arterial and venous channels which communicate directly rather than through a normal capillary bed. These communications are of two types: fistulous and plexiform. In the fistulous type an arterial channel empties directly into a venous channel, while in the plexiform type one or more arterial channels feed a vascular conglomerate that comprises multiple arteriovenous communications from which one or more venous channels emerge as draining veins. The fistulous types are usually supplied by meningeal branches of the external carotid artery and therefore they are also known as dural AVMs. The plexiform type, in contrast, are supplied by branches of the cerebral or cerebellar arteries and hence are also known as pial AVMs. The AVM most commonly encountered by the ophthalmologist is the acquired caroticocavernous sinus fistula, a dural AVM whose characteristic neuro-ophthalmic presentation results from the arterialisation of the orbital venous system. Proptosis and orbital venous engorgement secondary to direct arterialisation of the venous system has also been reported in dural AVMs involving the torcular herophili and the Galenic system. The more common plexiform (pial) AVMs typically present with complications that arise from the massive venous runoff that is generated by the associated arteriovenous shunts—namely, intracranial haemorrhage, seizures, and recurrent headache.

Symptomatic orbital drainage of plexiform (pial) AVMs is rare and when it does occur the AVM is usually in an anterior location.

We describe a patient with a posteriorly located plexiform (pial) AVM who presented with proptosis and venous engorgement of the left globe as a result of the venous outflow of the AVM being shunted anteriorly through newly opened collateral channels. Unilateral proptosis associated with anterior shunting has previously been described in a child with bilateral sigmoid sinus hypoplasia, but has never been described in a patient with a posteriorly located plexiform AVM. Our case is also extremely unusual in that we have angiographic evidence which shows that these collateral channels developed as a result of an acquired stenosis at the junction of the transverse and sigmoid sinus, previously its dominant route of venous drainage. The aetiology of this focal stenosis is unknown. It is unlikely to be a consequence of the stereotactic radiosurgery as the site of the stenosis is remote to the previously treated area. It is more likely that the stenosis represents a response to the chronic endothelial damage that is known to accompany the hyperdynamic circulation of AVMs.

This case serves to illustrate that not all adults who present with proptosis and venous engorgement of the globe have a caroticocavernous sinus fistula and other anomalies of venous drainage must occasionally be considered.

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studies have been performed on the role of acetylcholine receptors caused by circulat-
mal fatiguability of muscles due to deficiency of excessive lassitude or listlessness given by

The child was subsequently subjected to an edrophonium test (0.15 mg /kg body weight intravenously), which was unequivocally positive with complete resolution of the ptosis and ophthalmoplegia (Fig 2). A repetitive stimulation of the left median nerve demonstrated a significant decremental response (22%). Subsequently, a serum analysis of anti-acetylcholine receptor binding, blocking, and modulating antibodies was performed. Normal titres of anti-acetylcholine receptor binding antibodies (5.8 nmol/l; normal is less than 0.8 nmol/l) were present which confirmed the diagnosis of childhood myasthenia gravis. A contrast enhanced CT scan of the thorax was normal. The child was started on tablet neostigmine 3 mg once daily along with oral prednisolone (0.5 mg/kg body weight) and followed up regularly. Marked improvement of the ptosis and ophthalmoplegia was observed which persisted at 1 year of follow up. Systemic steroids were gradually tapered off after 6 months.

Comment
Our patient was diagnosed to have juvenile myasthenia gravis, which comprises approximately 1% of all cases of myasthenia gravis. It

References

Childhood myasthenia gravis in an infant
Myasthenia gravis is defined as an acquired autoimmune disorder where there is abnormal fatiguability of muscles due to deficiency of acetylcholine receptors caused by circulating antibodies directed against them. Ocular myasthenia is a form of myasthenia gravis clinically involving only the levator palpebrae superioris, the orbicularis oculi, and the extraocular muscles. Ptosis and ophthalmoplegia, both unilateral and bilateral, constitute the only signs in about 20% cases while in about 70% cases, ocular symptoms mark the onset of generalised myasthenia gravis.

Case report
We examined a 10 month old male child who presented to us with complaints of ptosis and ophthalmoplegia of the right eye for a month before presentation. The child was born normally at full term to a healthy young mother with an uneventful perinatal and postnatal period. The milestones of the child were recorded as normal. The child had an older sister aged 3 years who gave no history of similar complaints. There was no history of fever, vomiting, pain, trauma, seizures, difficulty in swallowing or chewing, or any history of excessive lassitude or listlessness given by the parents with regard to the child.

General physical examination revealed a child with normal physical and mental development. Systemic examination revealed no presence of heart block or any other cardiovascular abnormality. Neurological examination revealed no motor weakness, incoordina-
tion, ataxia, or areflexia. On ocular examination, the patient had moderate ptosis of the right upper lid with absence of any voluntary movement of the right eyeball. Ocular movements of the left eye appear to be normal. The child was attentive to both visual and auditory stimuli and frequently changed his head posture to look in the direction of origin of the visual or auditory stimuli. The pupillary reactions were normal in both eyes. In the primary gaze position, the visual axes of both eyes were parallel (Fig 1). The child was examined twice after a period of sleep and similar findings were recorded again.

Examination of the anterior and posterior segment of both eyes under general anaesthesia was unremarkable. The forced duction test was negative. Based on the above findings, a tentative diagnosis of an intracranial space occupying lesion was made. However, a contrast enhanced computed tomograph (CT) scan of the head and orbit revealed no abnormalities. Cerebrospinal fluid examination was also normal.

The child was subsequently subjected to an edrophonium test (0.15 mg /kg body weight intravenously), which was unequivocally positive with complete resolution of the ptosis and ophthalmoplegia (Fig 2). A repetitive stimulation of the left median nerve demonstrated a significant decremental response (22%). Subsequently, a serum analysis of anti-acetylcholine receptor binding, blocking, and modulating antibodies was performed. Normal titres of anti-acetylcholine receptor binding antibodies (5.8 nmol/l; normal is less than 0.8 nmol/l) were present which confirmed the diagnosis of childhood myasthenia gravis. A contrast enhanced CT scan of the thorax was normal. The child was started on tablet neostigmine 3 mg once daily along with oral prednisolone (0.5 mg/kg body weight) and followed up regularly. Marked improvement of the ptosis and ophthalmoplegia was observed which persisted at 1 year of follow up. Systemic steroids were gradually tapered off after 6 months. We noted marked improvement of the ptosis and ophthalmoplegia. The patient was subsequently subjected to an edrophonium test (0.15 mg /kg body weight intravenously), which was unequivocally positive with complete resolution of the ptosis and ophthalmoplegia (Fig 2). A repetitive stimulation of the left median nerve demonstrated a significant decremental response (22%). Subsequently, a serum analysis of anti-acetylcholine receptor binding, blocking, and modulating antibodies was performed. Normal titres of anti-acetylcholine receptor binding antibodies (5.8 nmol/l; normal is less than 0.8 nmol/l) were present which confirmed the diagnosis of childhood myasthenia gravis. A contrast enhanced CT scan of the thorax was normal. The child was started on tablet neostigmine 3 mg once daily along with oral prednisolone (0.5 mg/kg body weight) and followed up regularly. Marked improvement of the ptosis and ophthalmoplegia was observed which persisted at 1 year of follow up. Systemic steroids were gradually tapered off after 6 months.

Comment
Our patient was diagnosed to have juvenile myasthenia gravis, which comprises approximately 1% of all cases of myasthenia gravis.
is considered to be a variant of adult myasthenia with similar clinical and autoimmune mechanism of production. In contrast with congenital myasthenia gravis which occurs more commonly in children less than 2 years of age, has a familial mode of occurrence, and is not responsive to steroid therapy, juvenile myasthenia gravis presents usually after 5 years of age, shows no familial occurrence, and is characterised by a definite autoimmune mechanism. Though cases of juvenile myasthenia gravis with age of onset at 2 years or less have been reported, to the best of our knowledge our patient is the youngest patient with the above diagnosis reported so far. We would like to reiterate that investigations to rule out myasthenia gravis should be performed in all patients with acquired ptosis and ophthalmoplegia, irrespective of age.

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References
Several procedures were undertaken to prevent the occurrence of a phototoxic lesion in the second eye. These included the use of ultraviolet filters on the microscope, although air can also be used in the anterior chamber to deflect the light from the retina as can light barriers on the cornea or in the microscope. The time and power of coaxial illumination from the microscope was minimised by turning the microscope off when in use and keeping the patient’s eye downgaze so that the operating microscope’s axis was aligned off the patient’s visual axis so that any phototoxic lesion would be extrafoveal and not cause a homonymous scotoma. Since animal studies have demonstrated a benefit of altering core ocular temperature, the patient’s body temperature was kept low to reduce the temperature within the eye. Alternatively, irrigation solutions may be cooled relative to room temperature to help reduce intraocular temperature. It has been shown that an increase in inspired oxygen markedly enhances retinal phototoxicity and so a low inspired oxygen concentration was used for the patient during the procedure. The patient discontinued hydroxychloroquine treatment following the surgery to her left eye but ophthalmologists should be aware of the possibility of phototoxic retinal lesions in patients taking phototoxic pharmaco- logical agents particularly for underlying potential phototoxic sensitising systemic conditions. Consideration should be given to stopping treatment before surgery and taking appropriate surgical precautions.

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Bilateral uveitis after intravesical BCG immunotherapy for bladder carcinoma

Intravesical bacille Calmette-Guérin (BCG) is indicated for the treatment and prophylaxis of carcinoma in situ of the urinary bladder. It has been associated with arthritis. HLA-B27 has been positive in all cases with uveitis. We describe a patient who is HLA-B27 negative with isolated bilateral uveitis after intravesical BCG therapy.

Case report
A 70 year old man presented to the eye casualty department after a 4 day history of bilateral red, painful, and photophobic eyes. He had no systemic complaints. He had no ophthalmic history of note. He had a medical history of hypertension, gout, and recurrent papillary transitional cell carcinoma of the bladder. Eight weeks previously he had been seen by a urologist for haematuria and increased frequency. A diagnosis of recurrent papillary cell carcinoma was made by cystoscopy and biopsy. A 6 week course of weekly intravesical BCG therapy was commenced. His medications on presentation were Amlodipine (nifedipine) 10mg and aspirin. He was allergic to penicillin and aspirin.

On ocular examination his visual acuities were 6/12 right eye and 6/6 left eye. A diagnosis was made of bilateral acute anterior uveitis. He had 2+ cells and posterior synechiae bilaterally. No keratic precipitates were seen. He had a right sided epiretinal membrane.

Laboratory studies showed an erythrocyte sedimentation rate of 66 with the rest of haematological studies normal. Biochemistry showed a raised sodium, urea, and creatinine, which were longstanding. Tests for anti-nuclear antibodies and rheumatoid factor were negative. Angiotensin converting enzyme was normal and Treponema pallidum antibodies were not detected. HLA-B27 was negative. Chest and pelvis radiographs were normal. His uveitis was found to be secondary to a treated cataract and mydriatics. There was no recurrence of his uveitis over the subsequent follow up period of 3 months.

Comment
There have been no reported cases of intraocular BCG causing isolated uveitis in a patient that is HLA-B27 negative. There have been 26 reported cases of reactive arthritis secondary to intravesical BCG. About 8% of these cases were associated with uveitis. All the reported cases of combined arthritis and uveitis were HLA-B27 positive. In the BCG related arthritis the mean time of presentation was 10.5 days after the last BCG therapy. Our patient started having ocular symptoms 10 days after his last BCG therapy.

In a review of 1278 patients treated with intravesical BCG for bladder cancer, 95% had no complications. There were no reported cases of uveitis. Arthritis and arthralgia accounted for 0.5% of the complications. There has been one reported case of endophthalmitis from Mycobacterium bovis/bacillus Calmette-Guerin after intravesical bacillus Calmette-Guerin injections for bladder cancer. Am J Ophthalmol 1999;128:648–50.

Childhood blindness
The latest issue of Community Eye Health (No 40) discusses new issues in childhood blindness, with an editorial by Clare Gilbert, senior lecturer at the International Centre for Eye Health. For further information please contact: Journal of Community Eye Health, International Centre for Eye Health, Institute of Ophthalmology, 11–43 Bath Street, London EC1V 9EL, UK; tel: +44 (0)20 7608 6910; fax: +44 (0)20 7250 3207; email: eyecare@ucl.ac.uk; website: www.jceh.co.uk. Annual subscription (4 issues) UK £25/US $40. Free to workers in developing countries.

International Centre for Eye Health
The International Centre for Eye Health has published a new edition of the Standard List of
Medical Research, Equipment, Instruments and Optical Supplies (2001) for eye care services in developing countries. It is compiled by the Task Force of the International Agency for the Prevention of Blindness. Further details: Sue Stevens, International Centre for Eye Health, 11–43 Bath Street, London EC1V 9EL, UK (tel: +44 (0)20 7608 6910; email: eyeresource@ucl.ac.uk).

Second Sight

Second Sight, a UK based charity whose aims are to eliminate the backlog of cataract blind in India by the year 2020 and to establish strong links between Indian and British ophthalmologists, is regularly sending volunteers to India. Details can be found at the charity website (www.secondsight.org.uk) or by contacting Dr Lucy Mathen (lucymathen@yahoo.com).

Specific Eye Conditions (SPECS)

SPECS (Specific Eye Conditions) is a not-for-profit organisation which acts as an umbrella organisation for support groups of any condition or syndrome with an integral eye disorder. SPECS represents over fifty different organisations related to eye disorders ranging from conditions that are relatively common to very rare syndromes. We also include groups who offer support of a more general nature to visually impaired and blind people. Support groups meet regularly in the Boardroom at Moorfields Eye Hospital to offer support to each other, share experiences and explore new ways of working together. The website www.eyeconditions.org.uk acts as a portal giving direct access to support groups own sites. The SPECS web page is a valuable resource for professionals and may also be of interest to people with a visual impairment or who are blind. For further details about SPECS contact: Kay Parkinson, SPECS Development Officer (tel: +44 (0)1803 524238; email: k@eyeconditions.org.uk; www.eyeconditions.org.uk).

The British Retinitis Pigmentosa Society

The British Retinitis Pigmentosa Society (BRPS) was formed in 1975 to bring together people with retinitis pigmentosa and their families. The principle aims of BRPS are to raise funds to support the programme of medical research into an eventual cure for this hereditary disease, and through the BRPS welfare service, help members and their families copy with the everyday concerns caused by retinitis pigmentosa. The BRPS welfare service is the telephone helpline (+44 (0)1280 860 363), which is a novel resource for any queries or worries relating to the problems retinitis pigmentosa can bring. This service is especially valuable for those recently diagnosed with retinitis pigmentosa, and all calls are taken in the strictest confidence. Many people with retinitis pigmentosa have found the Society helpful, providing encouragement, and support through the Helpline, the welfare network and the BRPS branches throughout the UK. (tel: +44 (0)1280 821 334; email: lynda@brps.demon.co.uk; web site: www.brps.demon.co.uk).

3rd Interdisciplinary Symposium on the Treatment of Autoimmune Disorders

The 3rd Interdisciplinary Symposium on the Treatment of Autoimmune Disorders will be held in Leipzig, Germany on the 6–8 June 2002. Topics to be covered include: basic aspects of autoimmune diseases, experimental therapeutic concepts, and clinical studies providing novel concepts or novel focus on established therapies. There will also be the presentation of the Nils-Illa-Richter Award (application deadline is April 2002, further details on the web site). Further details: Prof. Dr. med. Michael Sticherline, Department of Dermatology, University of Leipzig (email: sticm@medizin.uni-leipzig.de; website: www/autoimmun.org); Fördergesellschaft zur Therapie von Autoimmunerkrankungen e.V. (email: autoimmun.org@gmx.de)

International Society for Behçet’s Disease

The 10th International Congress on Behçet’s Disease will be held in Berlin 27–29 June 2002. Further details: Professor Ch Zouboulis (email: zoubbere@zedat.fu-berlin.de).

Singapore National Eye Centre 5th International Meeting

The Singapore National Eye Centre 5th International Meeting will be held on 3–5 August 2002 in Singapore. Further details: Ms Amy Lim, Organising Secretariat, Singapore National Eye Centre, 11 Third Hospital Avenue, Singapore 168751 (tel: (65) 322 8374; fax: (65) 227 7290; email: Amy_Lim@sneic.com.sg).

BEAVRS Meeting

The next BEAVRS meeting will be held in the Dalmahoy Hotel near Edinburgh on 31 October to 1 November 2002. Further details: Susan Campbell, Medical Secretary, Gartnavel General Hospital (email: susan.j.campbell.wg@northglasgow.scot.nhs.uk).

CORRECTIONS

We regret that an error occurred in a paper that appeared in the May 2001 issue of theBJO by Lauande-Pimentel et al (Discrimination between normal and glaucomatous eyes with visual field and scanning laser polarimetry measurements, 2001; 85:586–91).

After revision of the paper the authors found that the published cut-off point of the structural linear discriminant formula (LDF) was incorrect. The original formula described by Lauande-Pimentel et al is: LDF = -3.131 + (0.994 * ellipse modulation)− (0.017 * the number)− (0.086 * average thickness) + (0.111 * ellipse average)−

The correct suggested cut-off point, defined as abnormal, is <-0.43 instead of <-0.547. The use of such formula, with the suggested cut-off point, resulted in an enhancement in the sensitivity (sensitivity = 90.4%, specificity = 82.4%) of the scanning laser polarimeter to detect glaucomatous changes.

An error occurred in the article: Additive effect of unoprostone and latanoprost in patients with elevated intraocular pressure Br J Ophthalmol 2002;86:75–9. The authors should have been listed as Tin Aung, Paul T K Chew, Francis T S Oen, Yong-Huak Chan, Lennard H Thean, Leonard Yip, Boon-Ang Lim, Jade Soh, and Steve K L Seah.

An error occurred in the article: Fluoxetine oral administration increases intraocular pressure. Br J Ophthalmol 1996;80:678. The authors should have been listed as C Costagliola, I. Mastrophasqua, I. Stendoza, N Testa.