Journal of the South East Asia Glaucoma Interest Group

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Asian Journal of OPHTHALMOLOGY

***Fusarium* Keratitis in Hong Kong**

Retinal Nerve Fibre Layer Measurements

Hormone Replacement Therapy and Dry Eye

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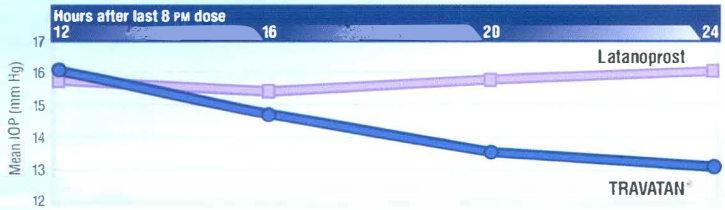
Scientific Communications

Endurance

TRAVATAN® Solution is still going strong 24 hours post dose.[1*]



TRAVATAN®

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TRAVATAN® (travoprost 0.004%) Ophthalmic Solution Sterile DESCRIPTION Travoprost is a highly selective, potent agonist for the FP prostanoid receptor. Its chemical name is isopropyl (Z)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(1*E*,3*R*)-3-hydroxy-4-[(α,α,α-trifluoro-*m*-tolyl)oxy]-1-butenyl]cyclopentyl]-5-heptenoate. Its molecular formula is $C_{26}H_{35}F_3O_6$. Travoprost is a clear, colorless to pale yellow oil, which is very soluble in acetonitrile, methanol, octanol, and chloroform. It is practically insoluble in water. TRAVATAN® 0.004% Ophthalmic Solution is supplied as a sterile, buffered aqueous solution of travoprost with a pH of approximately 6.0 and an osmolality of approximately 290 mOsmol/kg. Each mL of TRAVATAN® 0.004% contains 40 µg travoprost. Preservative: benzalkonium chloride 0.015%. Inactive Ingredients: polyoxyl 40 hydrogenated castor oil, tromethamine, boric acid, mannitol, edetate disodium, sodium hydroxide and/or hydrochloric acid (to adjust pH) and purified water. **CLINICAL PHARMACOLOGY** Mechanism of Action Travoprost free acid is a highly selective, potent agonist for the FP prostanoid receptor. FP receptor agonists are reported to reduce intraocular pressure by increasing uveoscleral outflow. Pharmacokinetics/Pharmacodynamics Absorption: Travoprost is absorbed through the cornea. Studies in rabbits have shown peak concentrations in aqueous humor were reached one to two hours following topical administration. In humans, peak plasma concentrations of travoprost free acid were low (25 pg/mL or less) and occurred within 30 minutes following topical administration. Elimination from plasma was rapid resulting in concentrations below the limit of quantitation (< 10 pg/mL) by one hour. Metabolism: Travoprost, an isopropyl ester prodrug, is rapidly hydrolyzed by esterases in the cornea to the biologically active free acid. Systemically, travoprost free acid is rapidly and extensively metabolized to inactive metabolites. Biotransformations include beta-oxidation of the α(carboxylic acid) chain to give the 1,2-dinor and 1,2,3,4-tetranor analogs, oxidation of the 15-hydroxyl moiety, as well as reduction of the 13,14 double bond. Excretion: In rats, 95% of a subcutaneous radiolabeled dose was eliminated within 24 hours. The major route of elimination was via the bile (61%) with the remainder excreted by the kidneys. **INDICATIONS AND USAGE** TRAVATAN® Ophthalmic Solution is indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. **CLINICAL STUDIES** TRAVATAN® 0.004% Ophthalmic Solution dosed once-daily in patients with open-angle glaucoma or ocular hypertension produced significant reductions in intraocular pressure (IOP) when used either as primary therapy or adjunctively to TIMOPTIC® (timolol maleate ophthalmic solution) 0.5% BID. As primary therapy, TRAVATAN® 0.004%, dosed QD, reduced IOP 7 to 9 mmHg. Stable diurnal IOP reductions were achieved as early as 2 weeks after initiation of therapy and were maintained over the 6 to 12 month treatment periods in three (3) well-controlled studies. The IOP reductions with TRAVATAN® (travoprost 0.004%) Ophthalmic Solution were superior to those obtained with TIMOPTIC® and equal or better than those obtained with XALATAN® (latanoprost ophthalmic solution) 0.005% QD. TRAVATAN® 0.004% demonstrated an earlier stabilization of IOP reduction and better IOP control throughout the day compared to XALATAN® 0.005%. TRAVATAN® 0.004% was significantly more effective (up to 1.4 mmHg) than XALATAN® 0.005% in reducing IOP in black patients. A responder analysis (IOP reduction ≥30% or mean IOP ≤17 mmHg) demonstrated that TRAVATAN® 0.004% had a significantly higher responder rate (56%) compared to XALATAN® 0.005% (50%) and which were both significantly greater than TIMOPTIC® (40%). In a 6-month well-controlled study, TRAVATAN® 0.004% dosed QD adjunctively to TIMOPTIC® 0.5% BID provided additional clinically significant IOP reductions (6 to 7 mmHg). **CONTRAINDICATIONS** Known hypersensitivity to travoprost, benzalkonium chloride or any other ingredients in this product. TRAVATAN® may interfere with the maintenance of pregnancy and should not be used by women during pregnancy or by women attempting to become pregnant. **WARNINGS** TRAVATAN® may gradually change eye color, increasing the amount of brown pigmentation in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. The long term effects on the melanocytes and any consequences thereof are currently unknown. The change in iris color occurs slowly and may not be noticeable for months to years. These changes may be permanent. Periorbital and/or eyelid skin darkening has been reported in association with the use of TRAVATAN®. TRAVATAN® may gradually change eyelashes in the treated eye; these changes include: increased length, thickness, pigmentation, and/or number of lashes. Patients who receive treatment in only one eye may experience increased brown pigmentation of the iris, periorbital and/or eyelid tissue, and eyelashes in the treated eye. They may also experience disparity between the eyes in length, thickness, and/or number of eyelashes. These changes in pigmentation and lash growth may be permanent. **PRECAUTIONS General** There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the epithelial surface (see Information for Patients). Patients may slowly develop increased brown pigmentation of the iris. This change may not be noticeable for months to years (see Warnings). This change in eye color has predominantly been seen in patients with mixed colored irides, i.e., blue-brown, grey-brown, yellow-brown and green-brown; however, it has also been observed in patients with brown eyes. Based upon information from the literature, the color change is believed to be due to increased melanin content in the stromal melanocytes of the iris. Typically the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may become more brownish. No further increase in brown iris pigment has been observed after discontinuation of treatment, but the resultant color change may be permanent. TRAVATAN® should be used with caution in patients with active intraocular inflammation (iritis/uveitis). Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin $F_{2\alpha}$ analogues. These reports have mainly occurred in aphakic patients, pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. TRAVATAN® (travoprost 0.004%) Ophthalmic Solution should be used with caution in these patients. Patients should remove contact lenses prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of TRAVATAN®. **Information for Patients** Patients should be advised concerning all the information contained in the Warnings and Precautions sections. Patients should also be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions. Patients also should be advised that if they develop an intercurrent ocular condition (e.g., trauma, or infections) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multi-dose container. Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and lid reactions, they should immediately seek their physician's advice. Patients should also be advised that TRAVATAN® contains benzalkonium chloride which may be absorbed by contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of TRAVATAN®. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart. **Carcinogenesis, Mutagenesis, Impairment of Fertility** Travoprost was not mutagenic in bacteria, in one mouse lymphoma assay, in the mouse micronucleus tests and in the rat chromosome aberration assay. In another mouse lymphoma assay, higher concentrations of travoprost were slightly mutagenic only in the presence of activation enzymes. In life and early post-mortem evaluations of carcinogenicity studies in rats and mice suggest no evidence of a carcinogenic potential. Travoprost did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 µg/kg/day (250 times the recommended human dose). The mean number of corpora lutea was slightly reduced at that dose, and the post-implantation losses were increased, but was not affected at 3 µg/kg/day (75 times the maximum recommended human dose). **Pregnancy: Teratogenic Effects Pregnancy Category: C** In reproduction studies conducted in pregnant rats and mice, travoprost reduced fetal viability when administered during gestation at doses as low as 1.0 µg/kg/day (25 times the maximum recommended human dose) with the lowest no effect level at 0.3 µg/kg/day (7.5 times the maximum recommended human dose). The incidence of skeletal malformations was increased in fetuses of rat dams receiving travoprost by subcutaneous injection at 10 µg/kg/day (250 times the maximum recommended human dose), but not at 3 µg/kg/day (75 times the maximum recommended human dose). No fetal abnormalities were observed in mice at 1.0 µg/kg/day (25 times the maximum recommended human dose). No adequate and well-controlled studies have been performed in pregnant women. TRAVATAN® may interfere with the maintenance of pregnancy and should not be used by women during pregnancy or by women attempting to become pregnant. **Nursing Mothers** A study in lactating rats demonstrated that radiolabeled travoprost and/or its metabolites were excreted in milk. It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRAVATAN® is administered to a nursing woman. **Pediatric Use** Safety and effectiveness in pediatric patients have not been established. **Geriatric Use** No overall differences in safety or effectiveness have been observed between elderly and other adult patients. **ADVERSE REACTIONS (see Warnings and Precautions)** The most common ocular adverse event observed in controlled clinical studies with TRAVATAN® (travoprost 0.004%) Ophthalmic Solution was ocular hyperemia which was reported in 35 to 50% of patients. 95% of the ocular hyperemia observed with TRAVATAN® (travoprost 0.004%) Ophthalmic Solution was mild in intensity and subsided over time without treatment. Approximately 3% of patients discontinued therapy due to conjunctival hyperemia. Ocular adverse events reported at an incidence of 5 to 10% included decreased visual acuity, eye discomfort, foreign body sensation, pain, and pruritus. Ocular adverse events reported at an incidence of 1 to 4% included, abnormal vision, blepharitis, blurred vision, cataract, cells, conjunctivitis, dry eye, eye disorder, flare, iris discoloration, keratitis, lid margin crusting, photophobia, subconjunctival hemorrhage, and tearing. Nonocular adverse events reported at a rate of 1 to 5% were accidental injury, angina pectoris, anxiety, arthritis, back pain, bradycardia, bronchitis, chest pain, cold syndrome, depression, dyspepsia, gastrointestinal disorder, headache, hypercholesterolemia, hypertension, hypotension, infection, pain, prostate disorder, sinusitis, urinary incontinence, and urinary tract infection. **OVERDOSAGE** A single-dose intravenous study in rats was conducted to elucidate maximal acute hazard. The dose employed was 250,000-times the proposed daily clinical exposure and over 5000-times the possible exposure from the entire contents of one product container. No treatment related pharmacotoxic signs were present in the animals receiving Travoprost. If overdosage with TRAVATAN® occurs, treatment should be symptomatic. **DOSAGE AND ADMINISTRATION** The recommended dosage is one drop in the affected eye(s) once-daily in the evening. The dosage of TRAVATAN® should not exceed once-daily since it has been shown that more frequent administration may decrease the intraocular pressure lowering effect. Reduction of intraocular pressure starts approximately 2 hours after administration and the maximum effect is reached after 12 hours. TRAVATAN® may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart. **HOW SUPPLIED** TRAVATAN® (travoprost 0.004%) Ophthalmic Solution is a sterile, isotonic, buffered, preserved, aqueous solution supplied in Alcon's oval DROP-TAINER® package system inside a sealed foil pouch. This package system is comprised of a plastic oval shaped dispenser bottle, a dropper tip and tamper evident neck-band which shrinks to conform around the closure and neck area of the package. 0.004%: 2.5 mL **fill Storage** Store between 2° to 25° C (36° to 77° F). Refrigeration is not required. **Rx Only (USA) CAUTION:** Federal (USA) law prohibits dispensing without prescription.

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* A washout period of 4 weeks was followed by 2 weeks of TRAVATAN® Solution (n=16) or latanoprost monotherapy (n=18). At day 14, the final dose was administered at 8 pm and IOP measurements were taken. Baseline values for the two treatment groups were not significantly different. The standard deviations for the TRAVATAN® group were 3.9 mm Hg (12 hours), 2.9 mm Hg (16 hours), 3.2 mm Hg (20 hours), and 2.1 mm Hg (24 hours). For the latanoprost group, the standard deviations were 3.8 mm Hg (12 hours), 3.0 mm Hg (16 hours), 3.2 mm Hg (20 hours), and 3.1 mm Hg (24 hours). The difference between the two groups at 24 hours post dose was statistically significant (p=0.0117).

Reference: 1. Dubiner HB, Sircy MD, Landry T, et al. Comparison of the diurnal ocular hypotensive efficacy of travoprost and latanoprost over a 24-hour period in patients with elevated intraocular pressure. Clin Ther. 2004;26:84-91.

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SEAGIG
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As new technologies and therapeutic interventions are continually being developed, ophthalmology has become a field of rapid change, particularly in the Asia-Pacific region, where disease patterns and health care delivery differ greatly from those seen in the West. *Asian Journal of OPHTHALMOLOGY* was established in 1998 and became the official journal of SEAGIG in 2003, with the aim of disseminating information relevant to ophthalmology and glaucoma throughout Asia and to interested groups worldwide. The objectives of *Asian Journal of OPHTHALMOLOGY* are as follows:

- to provide a platform for the publication of information with a focus on ophthalmology in Asia
- to disseminate information that will improve the care of patients with all types of ophthalmological disorders, with a special focus on glaucoma
- to increase the understanding of such disorders through reporting of educational activities
- to publish the results of research programmes to expand knowledge about the causes, prevention, and treatment of ophthalmological disorders
- to work closely with Asian and international researchers to achieve these aims
- to provide a forum for young and relatively inexperienced researchers to present their research results as Original Articles via an international platform
- to maintain and promote relationships with any organisation with similar goals.

Although the focus of *Asian Journal of OPHTHALMOLOGY* is on glaucoma, other topics relevant to the region will not be ignored, and submissions on all aspects of ophthalmology are welcome.

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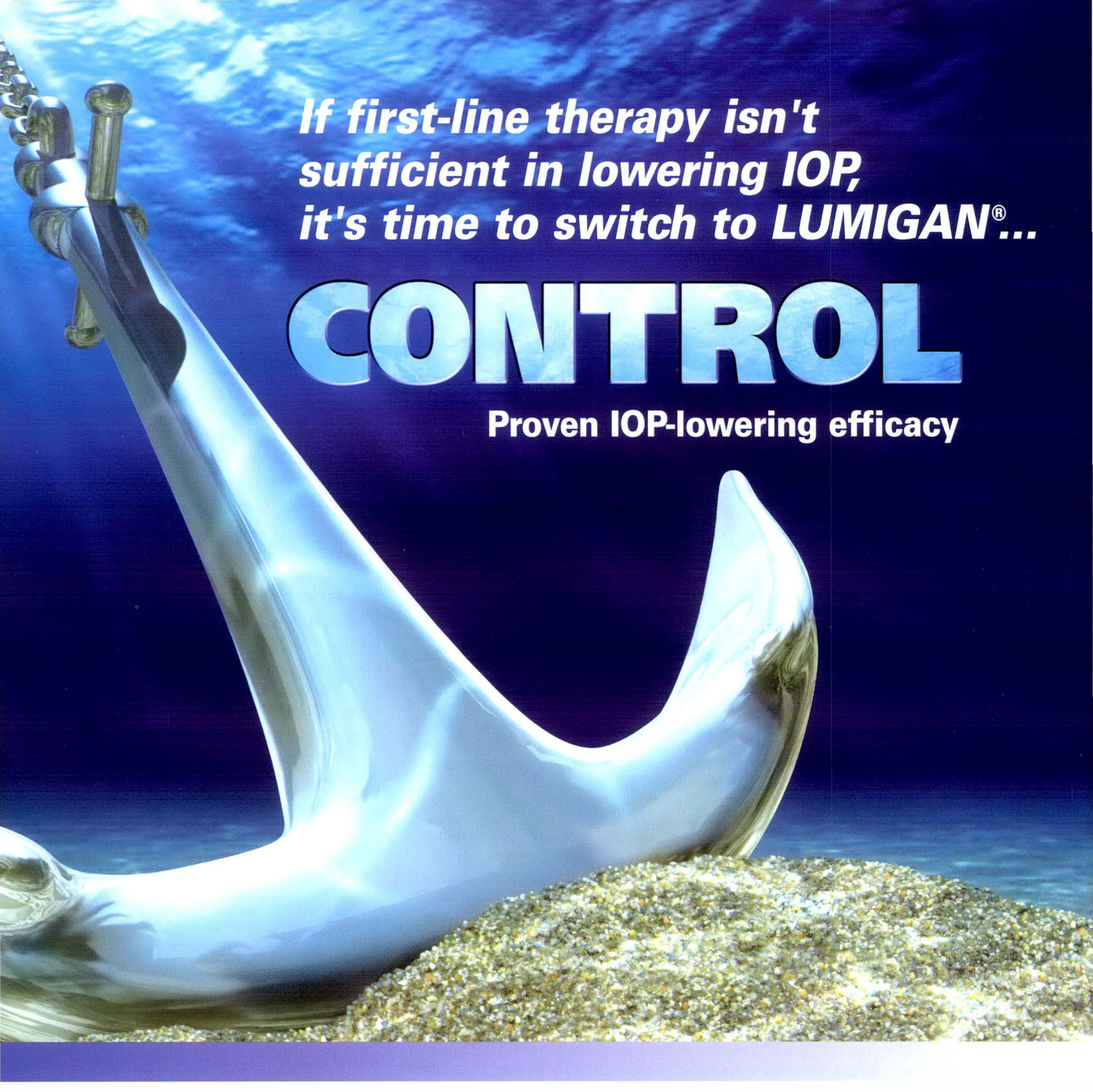

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The most frequently reported adverse events occurring in approximately 15% to 45% of patients dosed once daily, in descending order of incidence, were conjunctival hyperemia, growth of eyelashes, and ocular pruritus.

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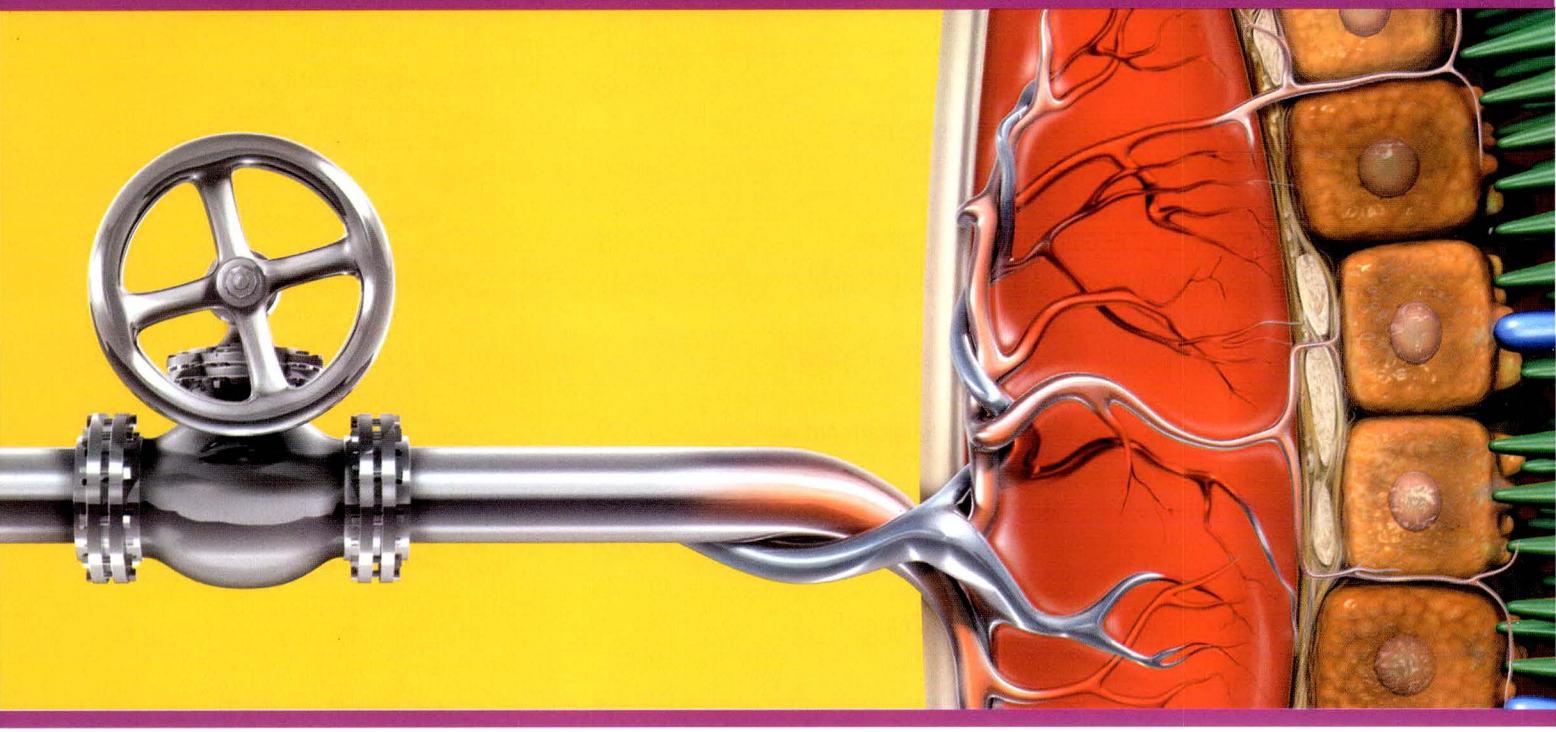
NOW, ONE THERAPY CAN TREAT ALL NEOVASCULAR AMD*... AT ITS SOURCE



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* Age-related macular degeneration. † Vascular endothelial growth factor. ‡ Defined as <15 letters lost over 2 years.

References: 1. Data on file. Pfizer Inc, New York, NY. 2. Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR, for the VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group. Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med.* 2004;351:2805-2816.

MACUGEN ABBREVIATED PACKAGE INSERT TRADE NAME: Macugen **PRESENTATION:** Macugen injection is supplied in a single use 1 mL glass syringe containing pegaptanib sodium 0.3 mg in a 90 µL deliverable volume. **INDICATIONS:** Treatment of neovascular (wet) age-related macular degeneration. **DOSAGE:** 0.3 mg administered once every six weeks by intravitreous injection into the eye to be treated. Macugen should be inspected visually for particulate matter and discoloration prior to administration. The injection procedure should be carried out under controlled aseptic conditions. Adequate anesthesia and a broad-spectrum microbicide should be given prior to the injection. **CONTRAINDICATIONS:** Patients with ocular or periocular infections. **WARNINGS & PRECAUTIONS:** FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY. Intravitreous injections have been associated with endophthalmitis. Proper aseptic injection technique should always be utilized when administering Macugen. Patients should be monitored during the week following the injection to permit early treatment, should an infection occur. Intraocular pressure as well as the perfusion of the optic nerve head should be monitored and managed appropriately. **INTERACTIONS:** Pegaptanib is metabolized by nucleases and is generally not affected by the cytochrome P450 system. **PREGNANCY AND LACTATION:** Pregnancy Category B. Pegaptanib crosses the placenta in mice. There are no studies in pregnant women. The potential risk to humans is unknown. Macugen should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. It is not known whether pegaptanib is excreted in human milk, caution should be exercised when Macugen is administered to a nursing woman. **SIDE EFFECTS:** Anterior chamber inflammation, blurred vision, cataract, conjunctival hemorrhage, corneal edema, eye discharge, eye irritation, eye pain, hypertension, increased intraocular pressure (IOP), ocular discomfort, punctate keratitis, reduced visual acuity, visual disturbance, vitreous floaters, and vitreous opacities. Injection procedure related side effects include endophthalmitis, retinal detachment, iatrogenic traumatic cataract. **STORAGE:** Store in refrigerator at 2°C to 8°C. Do not freeze or shake vigorously. Reference: USPI (Dec 2004). **FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.**

MAC06003P

Fusarium Keratitis in Contact Lens Wearers

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Infectious keratitis is a well-known complication of contact lens wear. The risk of infection from contact lens wear is still present even though the optical qualities and comfort of contact lenses have improved. It has been reported that the incidence rates for bacterial keratitis range from approximately 2.0/10,000 per year for rigid contact lens and 2.2 to 4.1/10,000 per year for daily-wear soft contact lens to 13.3 to 20.9/10,000 per year for extended-wear soft contact lenses.[1] The rate of fungal keratitis varies according to geographical location and ranges from 2% of keratitis cases in New York to 35% in Florida. Fungal keratitis is also more commonly seen in countries with tropical climates. A study in Florida found that contact lens–related fungal keratitis has been increasing over the years, with contact lenses replacing trauma as the most common cause since 2005.[2]

The outbreak of *Fusarium* keratitis in late 2005 in Singapore, Malaysia, and Hong Kong led to the withdrawal of ReNu MoistureLoc multipurpose contact lens solution (Bausch & Lomb, Rochester, USA) in February 2006. This was followed by halting of shipments in the USA in April 2006 and a worldwide recall of ReNu MoistureLoc in May 2006. After months of testing, the company determined that ReNu MoistureLoc's unique disinfectant and moisture-retention agents, in combination with poor hygiene habits could, in some cases, create a thin film that sheltered the fungus from the solution's steriliser.[3] An analysis by various ophthalmologists and the Centers for Disease Control and Prevention concluded that ReNu MoistureLoc was the only cleaner implicated, noting that the spike in infections rapidly subsided after its worldwide recall.

Various studies have shown that the bactericidal activity of polyhexamethylene biguanide (PHMB) as a preservative is reduced after several days of lens storage.[4,5] Another study showed that there was a loss of fungicidal activity in alexidine- and PHMB-based disinfecting solutions. Approximately 30% to 60% of the PHMB (used in ReNu Multiplus) and alexidine (used in ReNu MoistureLoc) were depleted after 6 hours in storage with a contact lens.[6]

In this issue of the Journal, Law et al report on the Hong Kong experience of the recent worldwide outbreak of *Fusarium* keratitis. While this group of patients has a better overall visual outcome compared with that seen in Singapore and the USA, it serves to remind us of the potential risk to vision that contact lens users face.

References

1. Liesegang TJ. Contact lens-related microbial keratitis: part I. Epidemiology. Cornea. 1997;16:125-31.
2. Iyer SA, Tuli SS, Wagoner RC. Fungal keratitis: emerging trends and treatment outcomes. Eye Contact Lens. 2006;32:267-71.
3. Levy B, Heiler D, Norton S. Report on testing from an investigation of *Fusarium* keratitis in contact lens wearers. Eye Contact Lens. 2006;32:256-61.
4. Rosenthal RA, McDonald MM, Schlitzer RL, Abshire R, Stone R. Loss of bactericidal activity from contact lens storage solutions. CLAO J. 1997;23:57-62.
5. Dannelly HK, Waworuntu RV. Effectiveness of contact lens disinfectants after lens storage. Eye Contact Lens. 2004;30:163-5.
6. Rosenthal RA, Dassanayake NL, Schlitzer RL, Schlech BA, Meadows DL, Stone RP. Biocide uptake in contact lenses and loss of fungicidal activity during storage of contact lenses. Eye Contact Lens. 2006;32:262-6.
7. Law RW, Tang EW, Li RT, Lai JS. Outbreak of *Fusarium* keratitis — Hong Kong experience. Asian J Ophthalmol. 2007;9:162-6.

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Outbreak of *Fusarium* Keratitis — Hong Kong Experience

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Aim: *To describe a regional outbreak of* Fusarium *keratitis among contact lens wearers in Hong Kong.*
Methods: *In this retrospective hospital-based study, all cases of fungal keratitis among contact lens wearers receiving treatment in 1 of the 7 hospital clusters in Hong Kong (United Christian Hospital and Tseung Kwan O Hospital) from May 2005 to September 2006 were reviewed. Additional clinical information was obtained through telephone interviews conducted by the same trained interviewer.*
Results: *Fourteen patients (16 affected eyes) were identified as contact lens wearers with culture positive* Fusarium *keratitis during the study period. The mean age was 31.3 years (SD, 9.4 years; range, 18 to 49 years) with female predominance (male to female ratio, 3:11). Eleven of 12 patients (92%) reported using ReNu MoistureLoc multipurpose contact lens solution prior to the onset of infection. The onset of symptoms ranged from 1 to 7 days (average, 2.5 days). Five patients (36%) were treated with topical antibiotics without the need for specific antifungal therapy. Nine patients (64%) were treated with topical antifungal therapy. No patients required therapeutic penetrating keratoplasty. Fourteen eyes (87.5%) resolved with vision 20/40 or better and no eyes had vision 20/60 or worse. No recurrence of fungal lesions was noted.*
Conclusions: *These findings showed that the majority of the affected patients were using ReNu solution prior to infection. Early commencement of either intensive topical broad-spectrum antibiotics or antifungal treatment was associated with improved visual outcome.*

Key words: *Contact lenses, Contact lens solutions,* Fusarium, *Infection, Keratitis*

Asian J Ophthalmol. 2007;9:162-6

Introduction

There was a worldwide outbreak of *Fusarium* keratitis among contact lens users in the USA and Singapore starting in March 2005.[1-4] Circumstantial evidence suggesting an association between *Fusarium* keratitis and the use of Bausch & Lomb ReNu MoistureLoc multipurpose contact lens solution (Rochester, USA) has been reported.[1] Epidemiological study also supports the association between *Fusarium* keratitis and reusing the contact lens solution already in the lens case for lens storage.[1] Although the mechanism for the association remains unclear, Bausch & Lomb permanently withdrew ReNu MoistureLoc solution from the worldwide market on 15 May 2006.[5]

The Centre for Health Protection (CHP) of the Department of Health of Hong Kong reported *Fusarium* keratitis in 33 contact lens wearers in May 2006.[6] Interviews conducted by the CHP revealed that 90.6% of the culture-positive patients (29/32) had used ReNu MoistureLoc solution. Among the 7 hospital clusters in Hong Kong, the Kowloon East cluster represents the largest number of cases of *Fusarium* keratitis (11/33) from May 2005 to May 2006. Despite the publicity of the outbreak and the announcement of product withdrawal from Bausch & Lomb in February 2006, there were still 3 more cases of contact lens–associated *Fusarium* keratitis being treated from June to August 2006. This report is of 14 cases of soft contact lens–associated *Fusarium* keratitis in the Kowloon East cluster (which represents 1.33 million population[7] under the catchment areas of the United Christian Hospital and Tseung Kwan O Hospital) in Hong Kong from May 2005 to September 2006.

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Methods

Patients

Patients who wore contact lenses and had a confirmed cultured positive diagnosis of fungal keratitis who received treatment at the United Christian Hospital and Tseung Kwan O Hospital from 1 May 2005 to 10 September 2006 were included in this case series. A contact lens wearer was defined as an individual who had a history of non-therapeutic soft contact lens wear 1 month

before infection. Patients with a history of ocular trauma, defined as trauma resulting from exposure to soil or organic or vegetable matter, were excluded. A confirmed case was a patient who had a positive culture for *Fusarium* from a corneal specimen (e.g., corneal scrape or biopsy). A possible case was defined as those patients not fulfilling the confirmed case criteria but where *Fusarium* species was cultured from their contact lenses or lens cases.

Methods

Corneal scrapings were obtained aseptically from the base and edges of each ulcer with a disposable microblade. All eyes were anaesthetised topically with preservative-free amethocaine eye drops for local anaesthesia. Gram-stained smears of corneal samples were examined by microscopy. Inoculation of various culture media (blood and chocolate agars, and thioglycolate broth for bacteria, Sabouraud's agar for fungi) was carried out at the time of the procedure. Culture plates were examined using routine laboratory techniques to isolate and identify bacteria and fungi of presumed pathological significance.

Demographic data, duration and symptoms, initial slit-lamp examination findings, any prior treatment received, and visual acuity at initial examination and at the last visit were obtained from the medical records. A standard questionnaire was designed to obtain further clinical information, including contact lens type, solutions, and hygiene practices. The questionnaires were completed through telephone interview after obtaining verbal assent from the patients. One trained interviewer conducted the interviews. Participation in all interviews was voluntary.

All statistical analyses were performed using the Statistical Package for the Social Sciences Version 11.5. The results are presented in terms of mean, standard deviation, and range.

Results

Fourteen patients were identified as contact lens wearers with *Fusarium* keratitis from May 2005 to September 2006 (Table 1). One patient with positive corneal scraping culture for *Fusarium* was excluded because the patient was not a contact lens user and had a recent history of the affected eye being in contact with bird's faeces prior to the onset of symptoms. There were 10 confirmed cases and 4 possible cases (Table 2). Two patients (14%) had bilateral infection.

The patients' mean age was 31.3 years (SD, 9.4 years; range, 18 to 49 years). There were 3 men (21.4%) and 11 women (78.6%). The number of cases increased steadily from July 2005 and 2 incidence peaks were noted; the greatest one was from July to September 2005, with a smaller one from June to August 2006 (Figure 1).

The response rate to telephone interview was 86%. Twelve of 14 patients completed the questionnaire. Two patients could not be reached by telephone because of invalid phone numbers. Among the respondents, 11 of 12 patients (92%) reported using the same

Table 1. Characteristics of patients with *Fusarium* keratitis from 1 May 2005 to 1 September 2006.

Characteristic	Number of patients (%) [n = 14]
Age (years)	
<20	1 (7)
20-40	11 (79)
>40	2 (14)
Sex	
Men	3 (21)
Women	11 (79)
Diabetes or immunosuppression	1 (7)
Affected eye(s)	
Right	6 (43)
Left	6 (43)
Bilateral	2 (14)
Contact lens type	
Daily	1 (7)
Every 14 days	6 (43)
Monthly	5 (36)
1-year conventional	1 (7)
Other	1 (7)
Contact lens wear duration*	
<10 hours/day	1 (7)
10-15 hours/day	12 (86)
>15 hours/day	1 (7)
Overnight use	3 (21)
Occasional wear only, not daily basis	1 (7)
Contact lens solution*	
ReNu solution	11 (79)
Complete solution	1 (7)
Characteristics of lesion†‡	
Number of lesions	
Solitary	6 (38)
Multifocal	8 (50)
Site of lesion	
Axial	5 (31)
Para-axial	2 (13)
Superior	4 (25)
Diffuse	1 (6)
Treatment	
Resolved with antibiotics alone	5 (36)
Resolved with topical antifungal (with or without antibiotics)	9 (64)
Corneal transplant	0 (0)
Best-corrected visual acuity at presentation†‡	
20/30 or better	5 (31)
20/40 to 20/60	6 (38)
20/80 or worse	4 (25)
Best-corrected visual acuity at last follow-up visit†‡	
20/25 or better	5 (31)
20/30 to 20/40	9 (56)
20/45 to 20/60	1 (6)
20/80 or worse	0 (0)

* Figures do not add up to 100% as 4 patients could not be contacted by telephone.
† Figures do not add up to 100% due to lack of photographic or diagramatic documentation in the medical records.
‡ Representing 16 affected eyes.

Table 2. Results of corneal scraping, contact lens, and case cultures.

Patient number	Sex/age (years)	Eye	Corneal scraping	Contact lens	Contact lens cases	Confirmed/possible case
1	F/35	Right	Positive	NA	NA	Confirmed
2	F/26	Left	Negative	Positive	NA	Possible
3	F/49	Left	Positive	NA	NA	Confirmed
4	F/26	Left	Negative	Positive	NA	Possible
5	F/21	Right	Positive	NA	NA	Confirmed
6	F/27	Left	Positive	NA	NA	Confirmed
7	F/18	Left	Negative	Positive	NA	Possible
8	M/30	Both	Positive	NA	NA	Confirmed
9	F/28	Both	Positive	Positive	NA	Confirmed
10	F/28	Right	Positive	NA	NA	Confirmed
11	F/48	Right	Positive	Positive	NA	Confirmed
12	M/24	Left	Negative	Positive	Positive	Possible
13	F/39	Right	Positive	Positive	NA	Confirmed
14	M/39	Right	Positive	Positive	NA	Confirmed

Abbreviation: NA = not available.

brand of multipurpose contact lens cleaning solution (ReNu MoistureLoc multipurpose contact lens solution) prior to the onset of infection.

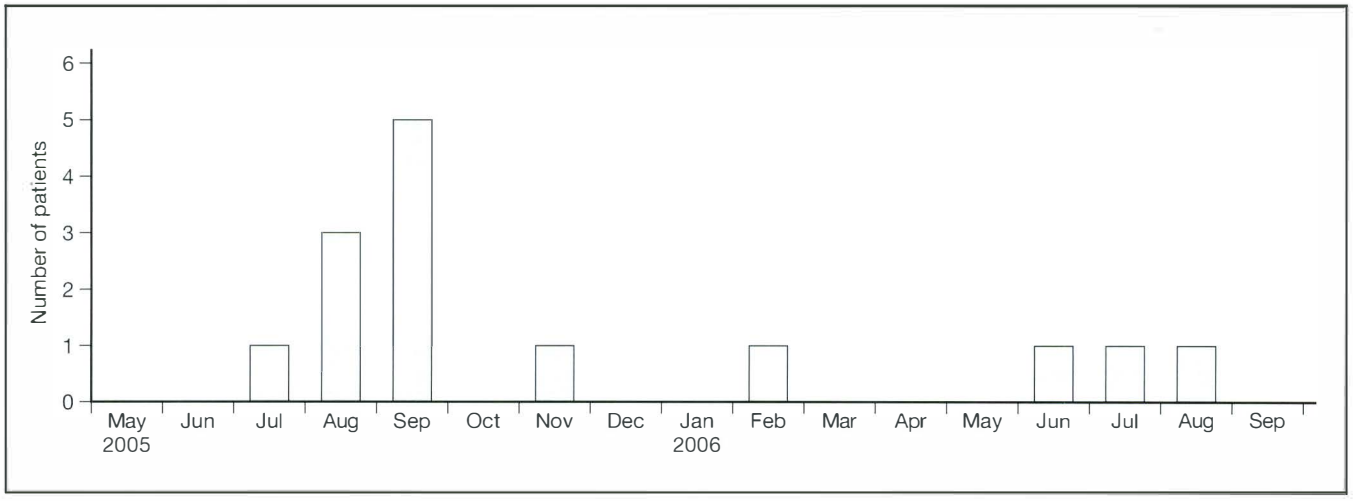
The onset of symptoms ranged from 1 to 7 days (average, 2.5 days). Only 1 patient (7%) had been treated with corticosteroid eye drops prior to presentation at the hospital. The best-corrected visual acuity (BCVA) in the affected eye was 20/30 or better in 5 patients (31%), 20/40 to 20/60 in 6 patients (38%), and 20/80 or worse in 4 patients (25%) [Table 1]. Five of 16 eyes (31%) had axial infiltrates and another 6 eyes (37.5%) had para-axial or superior corneal infiltrates. Thirteen of 14 patients (93%) required inpatient management of their infection. The average hospital stay was 7.4 days (range, 2 to 14 days). No readmission was required.

Five patients (36%) were treated with topical antibacterial medications (typically with fortified ceftazidime 50 mg/mL and tobramycin 15 mg/mL as first-line treatment for severe contact lens–related corneal infections). The infection resolved completely without the need for specific antifungal therapy. Among these 5 patients, 2 were confirmed cases and 3 were possible cases. Nine patients (64%) were treated with antifungal medications, either topical natamycin 5% (n = 6) or topical amphotericin B 0.15% (n = 3). None of the patients required therapeutic penetrating keratoplasty during the acute phase of infection or during follow-up. The final BCVA ranged from 20/20 to 20/50. Fourteen eyes (87.5%) resolved with vision 20/40 or better and none had vision 20/60 or worse. No recurrence of fungal lesions has occurred to date.

Discussion

This article reports a regional outbreak of *Fusarium* keratitis associated with the use of ReNu MoistureLoc multipurpose contact lens solution among contact lens wearers in Hong Kong. The peak incidence occurred in September 2005, which corresponds with the timing of the outbreak reported in the USA and Singapore.[1,2] Prior to this outbreak, the reported local incidence of microbial keratitis was only 3.4 per 10,000 contact lens wearers, with 1

Figure 1. Onset of *Fusarium* keratitis from May 2005 to September 2006.



fungal infection for every 17 bacterial infections.[8,9] This sudden increase in incidence of *Fusarium* keratitis drew immediate global attention and created international concern amoung related health-care professionals.

Before the outbreak, Houang et al recommended the use of multipurpose solutions by contact lens wearers in Hong Kong to achieve the lowest expected rates of infection, mainly due to the potential effect against *Acanthamoeba*.[9] ReNu MoistureLoc cleanser was introduced as a multipurpose contact lens cleaning solution in late 2004 by Bausch & Lomb. In this worldwide outbreak, it has been postulated that the increase in incidence of *Fusarium* keratitis was associated with ReNu MoistureLoc solution.[1,2] These findings are consistent with those of the studies in the USA and Singapore, which showed that the majority of the affected patients were using ReNu solution prior to infection.

Two incidence peaks were noted from July to September 2005 and June to August 2006, which corresponds with the summer months and increased rainfall in Hong Kong. These authors postulate that the tropical climate and increased humidity may promote fungal growth resulting in an increase in the number of infections.

Other interesting results in this study were the female predominance and the fact that all affected patients were soft contact lens wearers. The contact lens hygiene practices were not significantly different between the sexes. However, this difference may be explained by the fact that the contact lens market in Hong Kong is dominated by soft lenses,[10] and most of the non-therapeutic contact lens users are women.

Three more patients (2 confirmed cases and 1 possible case) were reported after the withdrawal of ReNu solution from the Hong Kong market in February 2006. These patients reported that they had continued to use ReNu contact lens solution despite advice to discontinue use of the product.

The overall visual outcome (87.5% with final BCVA 20/40 or better) in this case series was good compared with those of Singapore and the USA.[1,2] None of the patients required penetrating keratoplasty during the course of the infection. The mean duration of symptoms before presentation was 2.5 days. There was no predilection for the site of corneal infiltrates. We believe the success of treatment was associated with early commencement of intensive topical antibiotic or antifungal treatment.

Five patients (36%; 2 confirmed cases and 3 possible cases) responded to intensive topical antibiotics (ceftazidime and tobramycin) alone and achieved complete resolution of the infection without the need for specific antifungal therapy. Topical fluoroquinolones have been shown to have activity against *Fusarium* species.[11] It is interesting to find that topical broad-spectrum antibiotics alone were effective for some of the patients.

Topical natamycin 5% is the most commonly used first-line treatment for confirmed *Fusarium* keratitis in the study centre. In this series, topical amphotericin B 0.15% was given to 3 patients as first-line treatment instead of natamycin. Two patients received topical amphotericin B treatment in September 2005 because of a lack of natamycin eye drops in Hong Kong during the peak period. Another patient was pregnant at the time of onset of infection, and amphotericin B was thought to be less teratogenic (US FDA Pregnancy Category B) than natamycin (US FDA Pregnancy Category C).*

There are several limitations in this study. First, recall bias may have limited the accuracy of patients' responses as the interviews were conducted weeks or months after the infections occurred. Second, not all contact lens cases and solutions of every patient were collected for microbiological testing; as a result, only limited information could be obtained from this area. Third, these data only represent part of the population in Hong Kong living in certain districts; the findings should not be over-interpreted.

In conclusion, these findings show that the majority of the affected patients were using ReNu MoistureLoc multipurpose contact lens solution prior to infection. Prompt diagnosis and early medical treatment may improve the final visual outcome of these patients. Intensive topical broad-spectrum antibiotics alone are effective and adequate for selected patients.

References

1. Chang DC, Grant GB, O'Donnell K, et al. Multistate outbreak of *Fusarium* keratitis associated with use of a contact lens solution. JAMA. 2006; 296:953-63.
2. Khor WB, Aung T, Saw SM, et al. An outbreak of *Fusarium* keratitis associated with contact lens wear in Singapore. JAMA. 2006;295: 2867-73.
3. Centers for Disease Control and Prevention (CDC). Update: *Fusarium* keratitis — United States, 2005-2006. MMWR Morb Mortal Wkly Rep. 2006;55:563-4.
4. Centers for Disease Control and Prevention (CDC). *Fusarium* keratitis

* These definitions are those used by the United States Food and Drug Administration (FDA).
Category B: Either animal-reproduction studies have not demonstrated a foetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the 1st trimester (and there is no evidence of a risk in later trimesters).
Category C: Either studies in animals have revealed adverse effects on the foetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the foetus.

— multiple states, 2006. MMWR Morb Mortal Wkly Rep. 2006;55: 400-1.
5. Bausch & Lomb voluntarily recalls MoistureLoc® worldwide [Newsroom]. Rochester: Bausch & Lomb; 15 May 2006. www.bausch.com/en_US/corporate/corpcomm/news/2006_5_15_recall.aspx
6. Update on cases of fungal corneal infections. Hong Kong: Centre for Health Protection; 16 May 2006. www.chp.gov.hk/
7. Population by District Council District 2001. Hong Kong: Census and Statistics Department, The Government of the HKSAR; 2001.
8. Lam DS, Houang E, Fan DS, et al. Incidence and risk factors for microbial keratitis in Hong Kong: comparison with Europe and North America. Eye. 2002;16:608-18.
9. Houang E, Lam D, Fan D, Seal D. Microbial keratitis in Hong Kong: relationship to climate, environment and contact-lens disinfection. Trans R Soc Trop Med Hyg. 2001;95:361-7.
10. Cheung SW, Cho P, Edwards MH. Contact lens practice in Hong Kong in the new millennium. Clin Exp Optom. 2002;85:358-64.
11. Alfonso E, Miller D. Impact of 4th generation fluoroquinolones on growth rate and detection time of fungal pathogens. Proceedings of the Association for Research in Vision and Ophthalmology Annual Meeting; 3 May 2005; Fort Lauderdale, USA.

Intraobserver Reproducibility of Retinal Nerve Fibre Layer Measurements using Scanning Laser Polarimetry with Variable Corneal Compensation in Glaucoma Suspects

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Aim: *To evaluate quantitatively the intraobserver reproducibility of retinal nerve fibre layer measurements using scanning laser polarimetry with variable corneal compensation in glaucoma suspects.*

Methods: *Twenty six eyes of 26 glaucoma suspects were enrolled in the study. Complete ophthalmologic examination and automated perimetry were performed for all patients. Retinal nerve fibre layer measurements were done using scanning laser polarimetry with variable corneal compensation by an experienced operator. The test was repeated immediately by the same operator. Reproducibility of the retinal nerve fibre layer measurements was assessed using the coefficient of variation.*

Results: *Patients were aged from 24 to 70 years (mean, 55.9 years; SD, 11.5 years). There were 20 women and 6 men. Eighteen patients had ocular hypertension and 8 patients had large cup-disc ratios. No patients had glaucomatous field defects. The mean coefficients of variation for measurements of temporal superior nasal inferior temporal average, superior average, inferior average, temporal superior nasal inferior temporal SD, and nerve fibre indicator were 0.77, 0.95, 0.91, 0.81, and 0.98, respectively. The mean coefficient of variation of scanning laser polarimetry for the 5 main parameters was 88.4.*

Conclusion: *Scanning laser polarimetry showed a good test-retest correlation and acceptable intraobserver reproducibility. Nerve fibre indicator may be the most reproducible scanning laser polarimetry parameter for glaucoma suspects.*

Key words: *Glaucoma, Reproducibility of results, Scanning laser polarimetry*

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Introduction

There is increasing evidence that a structural retinal nerve fibre layer (RNFL) defect precedes the functional loss due to glaucomatous optic neuropathy in most patients.[1-4] By the time a visual field defect is present on automated achromatic perimetry, as many as 40% of the retinal ganglion cells may already be lost.[3] To detect RNFL thinning in vivo, objective and quantitative measurements can be obtained by scanning laser polarimetry (SLP), in which polarised laser light passing through tissues with physical properties of form birefringence undergoes retardation, linearly related to thickness in a primate model.[5] The most recent generation of scanning laser polarimeters with variable corneal compensation (GDx-VCC) provides a customised compensation of anterior segment birefringence.[6-10]

It is essential to be sure that this new technique designed to quantify structural alterations is capable of making accurate, reliable, and reproducible measurements. Although a reproducible measurement for GDx has been shown in healthy people and patients with glaucoma,[11-13] there are few reports measuring its reproducibility in glaucoma suspects.[14] This study was conducted to quantitatively assess the reproducibility of the GDx-VCC parameters in glaucoma suspects.

Methods

Patients

Twenty six glaucoma suspects from the glaucoma clinic at the Farabi Eye Hospital, Tehran, Iran, were enrolled in the study. There were 20 women and 6 men. All patients underwent a complete

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ophthalmologic examination. Corneal thickness was measured by ultrasound and achromatic visual field testing was done using the Swedish interactive threshold algorithm standard strategy (Humphrey field analyzer program 24-2; Zeiss Humphrey System, San Leandro, USA).

Patients were classified into 2 groups of ocular hypertension (intraocular pressure [IOP] consistently >24 mmHg with no other signs of glaucoma) and isolated large cup/disc ratio (>0.6 with no other signs of glaucoma). No glaucomatous field defect was noted in any patients.

Patients with corneal disease, advanced cataract, peripapillary/retinal atrophy, high myopia, clinically relevant floater, keratorefractive surgery, best-corrected visual acuity worse than 20/40 in either eye, previous intraocular surgery, secondary causes of elevated IOP, anatomically narrow angles, other diseases that cause visual field loss, background diabetic retinopathy, or optic disc abnormalities that produce visual field loss or obscure the interpretation of the optic disc were excluded from the study.

Measurements

A single experienced examiner scanned each of the patients using GDx-VCC (Laser Diagnostic Technologies, San Diego, USA). Two separate tests were performed on each patient approximately 10 minutes apart. The quality of all images represented as Q by the software was >8. Ellipse around the inner margin of the peripapillary scleral ring was modified by the operator if necessary.

Data were analysed using the Statistical Package for the Social Sciences. Coefficient of variation and Cronbach's α reliability were calculated for each of 16 GDx parameters.

Results

Eighteen patients had ocular hypertension (group 1) and 8 had large cup-disc ratios (group 2). The mean age was 55.9 years (SD, 11.5 years; range, 24 to 70 years). The mean IOP was 27.1 mm Hg (SD, 3.2 mm Hg) and 14.3 mm Hg (SD, 2.1 mm Hg) for the ocular hypertension and large cup-disc ratio groups, respectively. The mean central corneal thickness was not significantly different between the 2 groups (group 1: mean, 531.5 μm; SD, 35.2 μm; range, 453-610 μm; group 2: mean, 522.4 μm; SD, 30.5 μm; range, 446-606 μm). The results of the tests are shown in Table 1.

Table 2 shows the coefficient of variation (COV) between the results of the 2 tests for 10 GDx parameters. The mean COV for measurements of the temporal superior nasal inferior temporal (TSNIT) average, superior average, inferior average, TSNIT-SD, and nerve fibre indicator (NFI) were 0.77, 0.95, 0.91, 0.81, and 0.98, respectively. The mean COV of GDx for the 5 main parameters was 88.4. Cronbach's α reliability for each of the GDx parameters is shown in Table 2.

Table 1. Mean results of 10 parameters of the 52 tests performed in glaucoma suspects (2 for each patient).

	Test 1 Mean (SD)	Test 2 Mean (SD)
Temporal superior nasal inferior temporal average	52.00 (7.30)	53.19 (8.54)
Superior average	62.25 (9.54)	62.44 (9.88)
Inferior average	59.83 (10.11)	60.37 (11.17)
Temporal superior nasal inferior temporal SD	20.78 (4.65)	20.93 (5.51)
Nerve fibre indicator	23.15 (15.89)	23.35 (16.79)
Symmetry	0.96 (0.12)	0.96 (0.09)
Superior/nasal	2.29 (0.58)	2.34 (0.55)
Maximum modulation	2.51 (0.87)	2.40 (0.89)
Ellipse SD	20.79 (4.65)	20.93 (5.51)
Ellipse average	52.35 (7.20)	52.15 (7.44)

Table 2. Coefficient of variation and Cronbach's α reliability for 10 parameters in glaucoma suspects.

	Coefficient of variation	Cronbach's α
Temporal superior nasal inferior temporal average	0.77	0.86
Superior average	0.95	0.97
Inferior average	0.91	0.95
Temporal superior nasal inferior temporal SD	0.81	0.88
Nerve fibre indicator	0.98	0.98
Symmetry	0.76	0.83
Superior/nasal	0.86	0.92
Maximum modulation	0.76	0.86
Ellipse SD	0.81	0.88
Ellipse average	0.94	0.97

Discussion

In the detection of glaucoma, IOP measurement has relatively poor discriminating power. Approximately 32% to 53% of patients with glaucoma have an IOP within the normal range (<21 mm Hg) at first presentation.[15,16] It is difficult to differentiate physiological optic disc variation from pathological cupping, particularly in early glaucoma.[17] The main weakness of screening using automated perimetry is the subjective nature of the test and the high variability of the results.[18] In addition, histological studies have found that as many as half of all ganglion cells can be lost before a visual field defect can be detected.[3]

The GDx-VCC is a scanning laser polarimeter that measures RNFL thickness using polarised light. The advantage of the GDx-VCC over previous models is the ability of the instrument to measure and individually compensate for anterior segment birefringence, thereby eliminating measurement inaccuracies in RNFL thickness.[9] Objective RNFL data are provided that are compared with an extensive normative database. The GDx software

has been tested in many clinical trials. GDx variables are calculated by 2 methods — using a total of 1500 pixels per quadrant peripheral to an ellipse of 1.75 disc diameters or using pixels within the 10 pixel-wide elliptical band that is automatically positioned concentric with the disc margin outline and 1.75 disc diameters from the centre of the optic disc.[6,9]

The aim of this study was to evaluate the intraobserver reproducibility of GDx-VCC quantitatively. As the main aim of this device is to diagnose early glaucoma, the study group comprised glaucoma suspects. Each patient underwent the test twice. A high correlation existed between the parameters obtained by the first and second tests. The mean COV of GDx for the 5 main parameters was 88.4. NFI, which is one of the most important factors, had a COV of 0.98.

The reproducibility of RNFL measurements has been assessed previously using both GDx and optical coherence tomography (OCT), in healthy and glaucomatous eyes.[12,13] Schuman et al reported high intraoperator reproducibility of peripapillary RNFL thickness using OCT, which is consistent with the properties of the RNFL.[19] The mean COV range reported was 4.3% to 6.9%.[14,19]

Lleo-Perez et al evaluated quantitatively the intraobserver reproducibility of measurements of the RNFL in healthy people (n = 30) and patients with ocular hypertension (n = 30) using GDx-VCC and OCT.[14] In both groups, the authors found fair correlations between the 2 methods in all ratio and thickness parameters. The authors could not detect any significant differences between healthy and ocular hypertensive eyes, although in healthy eyes the correlations improved slightly. This study showed a better test-retest correlation with GDx. Blumenthal and Frenkel also showed a good interdevice reproducibility of RNFL thickness measurements obtained with the commercially available GDx-VCC.[20] Item reliability (Cronbach's α) for their 5 GDx parameters were: TSNIT-average, 0.97; superior average, 1.00; inferior average, 0.84; TSNIT-SD, 0.99; and NFI, 0.99.

Comparisons in the reproducibility of the RNFL thickness measurements between different nerve fibre analysers have been studied by several authors, and GDx yielded the most reliable results.[14] Bagga et al showed that GDx-VCC parameters had greater correlation with visual function than OCT.[6] Data obtained by GDx showed the lowest COV, followed by those obtained by Heidelberg retinal tomography and OCT.[21]

Measurement bias using GDx has been studied previously. The presence of vitreous opacity, dense posterior subcapsular cataract, peripapillary atrophy, posterior staphyloma, and high axial myopia can affect GDx measurements.[22] In this study, none of the patients had these conditions. Performing the second test immediately after the first one eliminates confounding factors such as changes in environment, pupil size, media clarity, and disease status, and resulted in a high COV.

NFI is a special retardation parameter in GDx-VCC that indicates the likelihood that glaucoma is present. NFI has a close relationship with RNFL thickness and visual field status in glaucoma. In healthy eyes and eyes with initial glaucoma, this parameter is reported to be less reproducible.[13,14] Although some studies have reported that NFI has the worst COV of all the major parameters,[14] other studies have found the opposite.[20,23] In this study, NFI showed the highest reproducibility.

In summary, interdevice, interexaminer, intrasession, intersession, and intraobserver reproducibility as well as short- and long-term variability are all important for any new diagnostic technology. This study showed that GDx-VCC had a good test-retest correlation and acceptable intraobserver reproducibility. It was a highly reproducible test for RNFL analysis in glaucoma suspects. NFI might be the most reproducible major GDx parameter in glaucoma suspects. Further studies with a larger number of patients and in different situations are needed to establish this hypothesis.

References

1. Kass MA, Heuer DK, Higginbotham EJ, et al. The ocular hypertension treatment study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120:701-13.
2. Pederson JE, Anderson DR. The mode of progressive disc cupping in ocular hypertension and glaucoma. Arch Ophthalmol. 1980;98: 490-5.
3. Quigley HA, Addicks EM, Green WR. Optic nerve damage in human glaucoma. III. Quantitative correlation of nerve fiber loss and visual field defect in glaucoma, ischemic neuropathy, papilledema, and toxic neuropathy. Arch Ophthalmol. 1982;100:135-46.
4. Sommer A, Katz J, Quigley HA, et al. Clinically detectable nerve fiber atrophy precedes the onset of glaucomatous field loss. Arch Ophthalmol. 1991:109:77-83.
5. Weinreb RN, Dreher AW, Coleman A, Quigley H, Shaw B, Reiter K. Histopathologic validation of Fourier-ellipsometry measurements of retinal nerve fiber layer thickness. Arch Ophthalmol. 1990;108: 557-60.
6. Bagga H, Greenfield DS, Feuer W, Knighton RW. Scanning laser polarimetry with variable corneal compensation and optical coherence tomography in normal and glaucomatous eyes. Am J Ophthalmol. 2003; 135:521-9.
7. Greenfield DS, Knighton RW, Huang XR. Effect of corneal polarization axis on assessment of retinal nerve fiber layer thickness by scanning laser polarimetry. Am J Ophthalmol. 2000;129:715-22.
8. Knighton RW, Huang XR. Linear birefringence of the central human cornea. Invest Ophthalmol Vis Sci. 2002;43:82-6.
9. Weinreb RN, Bowd C, Zangwill LM. Glaucoma detection using scanning laser polarimetry with variable corneal polarization compensation. Arch Ophthalmol. 2003;121:218-24.
10. Weinreb RN, Bowd C, Greenfield DS, Zangwill LM. Measurement of the magnitude and axis of corneal polarization with scanning laser polarimetry. Arch Ophthalmol. 2002;120:901-6.
11. Iacono P, Da Pozzo S, Fuser M, Marchesan R, Ravalico G. Intersession reproducibility of retinal nerve fiber layer thickness measurements by

GDx-VCC in healthy and glaucomatous eyes. Ophthalmologica. 2006; 220:266-71.
12. Kook MS, Sung K, Park RH, Kim KR, Kim ST, Kang W. Reproducibility of scanning laser polarimetry (GDx) of peripapillary retinal nerve fiber layer thickness in normal subjects. Graefes Arch Clin Exp Ophthalmol. 2001;239:118-21.
13. Rhee DJ, Greenfield DS, Chen PP, Schiffman J. Reproducibility of retinal nerve fiber layer thickness measurements using scanning laser polarimetry in pseudophakic eyes. Ophthalmic Surg Lasers. 2002;33: 117-22.
14. Lleó-Pérez A, Ortuño-Soto A, Rahhal MS, Martinez-Soriano F, Sanchis-Gimeno JA. Intraobserver reproducibility of retinal nerve fiber layer measurements using scanning laser polarimetry and optical coherence tomography in normal and ocular hypertensive subjects. Eur J Ophthalmol. 2004;14:523-30.
15. Sommer A, Tielsch JM, Katz J, et al. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. Arch Ophthalmol. 1991;109:1090-5.
16. Anderson DR, Drance SM, Schulzer M; Collaborative Normal-Tension Glaucoma Study Group. Natural history of normal tension glaucoma. Ophthalmology. 2001;108:247-53.
17. Quigley HA, Katz J, Derick RJ, Gilbert D, Sommer A. An evaluation of optic disc and nerve fibre layer examinations in monitoring progression of early glaucoma damage. Ophthalmology. 1992;99:19-28.
18. Keltner JL, Johnson CA, Quigg JM, Cello KE, Kass MA, Gordon MO. Confirmation of visual field abnormalities in the ocular hypertension treatment study. Ocular Hypertension Treatment Study Group. Arch Ophthalmol. 2000;118:1187-94.
19. Schuman JS, Pedut-Kloizman T, Hertzmark E, et al. Reproducibility of nerve fiber layer thickness measurements using optical coherence tomography. Ophthalmology. 1996;103:1889-98.
20. Blumenthal EZ, Frenkel S. Inter-device reproducibility of the scanning laser polarimeter with variable cornea compensation. Eye. 2005;19: 308-11.
21. Klemm M, Rumberger E, Walter A, Richard G. Reproducibility of measuring retinal nerve fiber density. Comparison of optical coherence tomography with the nerve fiber analyzer and the Heidelberg retinal tomography device. Ophthalmologe. 2002;99:345-51.
22. Hoh ST, Greenfield DS, Liebmann JM, et al. Factors affecting image acquisition during scanning laser polarimetry. Ophthalmic Surg Lasers. 1998;29:545-51.
23. Zangwill L, Berry CA, Garden VS, Weinreb RN. Reproducibility of retardation measurements with the nerve fiber analyzer II. J Glaucoma. 1997; 6:384-9.

The Effect of Hormone Replacement Therapy on Development of Dry Eye in Postmenopausal Women

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Aim: *To evaluate the effect of hormone replacement therapy on development of dry eye in postmenopausal women.*
Methods: *In this prospective comparative case series, 120 eyes of 60 postmenopausal women who were taking hormone replacement therapy (group 1) and 168 eyes of 84 postmenopausal women who were not taking hormone replacement therapy (group 2) were compared. The tear function was examined using Schirmer's test, tear film break-up time, and fluorescein and rose bengal corneal staining. Patients' symptoms were noted and scored according to the ocular surface disease index. Students* t *test was used for statistical analysis and Pearson correlation test was used to assess the correlation.*
Results: *The average duration of hormone replacement therapy was 39.80 months (SD, 9.51 months). The average Schirmer's test result was 12.71 mm (SD, 2.51 mm) and 12.35 mm (SD, 5.29 mm) for groups 1 and 2, respectively. The average tear film break-up time was 13.53 seconds (SD, 3.48 seconds) and 9.45 seconds (SD, 4.51 seconds) for groups 1 and 2, respectively ($p < 0.05$). One patient (6%) in group 1 and 4 patients (19.04%) in group 2 had grade 4 and 5 disease based on corneal staining. The average blood oestradiol levels were 139.00 pmol/L (SD, 123.31 pmol/L) and 134.53 pmol/L (SD, 145.75 pmol/L) in groups 1 and 2, respectively. The ocular surface disease index scores were 69.4 (SD, 12.5) and 83.3 (SD, 11.4) in groups 1 and 2, respectively ($p < 0.05$).*
Conclusion: *These data suggest that postmenopausal women who have never used hormone replacement therapy are at an increased risk for dry eye compared with postmenopausal women who are taking hormone replacement therapy.*

Key words: *Dry eye syndromes, Estrogens, Hormone replacement therapy, Menopause*

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Introduction

The preocular tear film plays a critical role in maintaining ocular surface integrity, defending against microbial challenge and preserving visual acuity.[1,2] These functions, in turn, are extremely dependent upon the composition and stability of the tear film structure, which includes an underlying mucin foundation, a middle aqueous component, and an overlying lipid layer.[1,2] Perturbation, deficiency, or absence of the tear film may dramatically impact the eye; if unmanaged with artificial tear substitutes or tear film conservation therapy, tear film disorders may lead to desiccation of the corneal epithelium, ulceration and perforation of the cornea, an increased incidence of infectious disease, and potentially serious visual impairment and blindness.[3,4] Treatment for dry eye syndrome is generally costly and inadequate, and many patients are unable to find satisfactory relief from their symptoms.[5] The majority of people with dry eye syndromes are women.[6] In fact, female sex has been recognised as a risk factor for the development of dry eye.[7] Moreover, evaporative dry eye may often occur during menopause. Of interest, sex-related differences in the incidence of dry eye syndromes have been observed in elderly people (65 to 84 years) — a finding that may be due to the dramatic decline in androgen levels in both sexes during ageing.[8] Hormone replacement therapy (HRT) for postmenopausal women has a role in the treatment of a variety of menopausal symptoms[9] and may confer other health benefits.[10] However, studies have noted that oestrogen may have adverse effects on the ocular surface.[11,12] This study examined the effect of HRT on the development of dry eye.

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Methods

Patients

120 eyes of 60 postmenopausal women who were taking HRT and 168 eyes of 84 postmenopausal women who were not taking HRT

were enrolled in this study. All participants were attending the gynaecology clinic at the Izmir Training and Research Hospital, Izmir, Turkey, for menopausal symptoms. Postmenopausal patients with symptoms of dry eye were referred to the cornea department for assessment of the relationship of HRT and dry eye.

The research followed the tenets of the Training and Planning Committee of the Izmir Training and Research Hospital. Informed consent was obtained from all patients after explanation of the nature and possible consequences of the study.

Methods

History of dry eye was obtained by interviewer-administered questionnaire. The Ocular Surface Disease Index (OSDI)[13] was administered to assess the patients' symptoms. The recently introduced OSDI 135 is a 12-item questionnaire designed to provide a rapid assessment of the symptoms of ocular irritation in dry eye. 144 patients with OSDI score ≥52.1 were considered to have dry eye and were included in the study.

Exclusion criteria included use of anticoagulants, corticosteroids, or vitamins A, E, or β-carotene supplements. Women who had had previous eye surgery, dry eye before menopause or initiation of HRT, or history of cancer, myocardial infarction, stroke, liver disease, renal disease, peptic ulcer, or oophorectomy were excluded. Patients with concomitant ocular diseases such as Sjögren's syndrome, ocular rosacea, or diabetes mellitus that might lead to an increased risk of dry eye were excluded.

All the women were postmenopausal with a follicle-stimulating hormone level >30 IU/L and an oestradiol level <184.5 pmol/L and had been amenorrhoeic for at least 1 year. The women were divided into 2 groups; group 1 comprised women who were taking HRT and group 2 comprised women who were not taking HRT. The HRT consisted of oestrogen <2 mg per day.

The participants' demographic information and medical history were noted, as well as duration of HRT use and menopause, and blood oestrogen levels. The tear function was examined using Schirmer's test, tear film break-up time (TFBUT), and fluorescein and rose Bengal corneal staining, and symptoms of dry eye according to the OSDI were noted. Comparison between groups 1 and 2 was made for patients with grade 4 and 5 dry eye according to the OSDI.

Students *t* test was used to compare values for statistical analysis. Statistical significance was accepted as $p \leq 0.05$. Pearson correlation test was performed to assess the correlation between the blood-oestradiol levels and tear function for each group.

Results

144 postmenopausal women had dry eye symptoms. There were 60 women (41%) in group 1 and 84 (58%) in group 2. The average age of the women in groups 1 and 2 was 53.40 years (SD, 7.18 years) and 57.52 years (SD, 7.45 years), respectively. There was no significant difference between the 2 groups. There was no significant difference between the ages of the patients and tear function over the relatively short age range tested. The average menopause period was 106.00 months (SD, 68.66 months) in group 1 and 107.48 months (SD, 84.53 months) in group 2. There was no significant difference between the 2 groups. The average duration of use of HRT was 39.80 months (SD, 9.51 months) [Table 1].

Table 1. Age, menopause duration, and blood-oestrogen levels of postmenopausal women in relation to hormone replacement therapy use.

	Group 1	Group 2
Age (SD) [years]	53.40 (7.18)	57.52 (7.45)
Menopause duration (SD) [months]	106.00 (68.66)	107.48 (84.53)
Oestrogen levels (SD) [pmol/L]	139.00 (123.31)	134.53 (145.75)

Table 2. Average Schirmer's test results of postmenopausal women taking hormone replacement therapy.

	Number of eyes	Schirmer's score (SD) [mm]
Group 1	120	12.71 (2.51)
Group 2	168	12.35 (5.29)
Total	288	12.50 (4.33)

Table 3. Average tear film break-up time of postmenopausal women taking hormone replacement therapy.

	Number of eyes	Tear film break-up time (SD) [seconds]
Group 1	120	13.53 (3.48)
Group 2	168	9.45 (4.51)
Total	288	11.15 (4.56)

The average Schirmer's test result was 12.71 mm (SD, 2.51 mm) in group 1 and 12.35 mm (SD, 5.29 mm) in group 2. There was no significant difference between the 2 groups (Table 2). The average TFBUT was 13.53 seconds (SD, 3.48 seconds) in group 1 and 9.45 seconds (SD, 4.51 seconds) in group 2 ($p = 0.014$) [Table 3].

The average blood-oestradiol level was 139.00 pmol/L (SD, 123.31 pmol/L) in group 1 and 134.53 pmol/L (SD, 145.75 pmol/L) in group 2. There was no significant difference between the 2 groups. Serum oestradiol levels decreased with age in women who were not taking exogenous oestrogen. There was a negative correlation between the serum oestradiol levels and age. Test levels did not change with the use of HRT. There was a significant positive correlation between the TFBUT result and oestradiol levels in group 1 ($r = 0.78$), but no significant correlation was found between the Schirmer's test results and oestradiol levels. In group 2, there was no significant correlation between the blood oestradiol levels and TFBUT, but there was a significant correlation between Schirmer's

test results and blood oestradiol levels (r = 0.001). One patient (6%) in group 1 and 4 patients (19%) in group 2 had grade 4 and 5 disease based on corneal staining (p = 0.035).

The mean OSDI scores were 69.4 (SD, 12.5) in group 1 and 83.3 (SD, 11.4) in group 2 (p < 0.001).

Discussion

Despite the common occurrence of dry eye, basic epidemiological data are limited. Clinical observations suggest, and most epidemiological studies support,[14] that dry eye is more common in women, a finding that would be consistent with either a detrimental effect of oestrogen or a beneficial role of androgen,[15,16] or both. Indeed, it may be the balance of androgen and oestrogen that is important in determining risk for dry eye. Epidemiological studies have directly assessed the potential relationship of exogenous oestrogen with dry eye. Two studies reported that there was no statistically significant relationship of HRT with the presence of self-reported dry eye symptoms.[14,17] However, one study concluded that there was a significantly elevated risk for dry eye among women who took exogenous oestrogen.[18]

This study suggests that postmenopausal women who have never used HRT are at an increased risk compared with those who are receiving HRT in the form of oestrogen alone. Although there was no significant difference between the Schirmer's test results and HRT use, there was a significant difference between the 2 groups for TFBUT, corneal staining (p < 0.05), and OSDI score.

Basic research suggests that sex hormone levels may influence both the lacrimal and meibomian glands.[16,18] Laboratory and preliminary clinical studies suggest that, whereas androgens have a beneficial influence on lacrimal and meibomian gland function,[17,19] oestrogen may play a role in exacerbating dry eye.[16,19-21] Meibomian gland function may also play a role in the complex relationship between sex hormone levels and tear function. A previous report suggested that meibomian gland function might be influenced by androgen levels and this could affect evaporation.[22] Tear volume and tear osmolarity would be altered by changes in evaporation, although tear turnover and Schirmer's test would not be affected.[22]

In this study, there was no significant correlation between oestrogen levels and TFBUT, Schirmer's test, and corneal staining in group 2. There was a significant correlation between TFBUT and corneal staining and oestrogen levels, but no correlation between Schirmer's test and oestrogen levels in group 1. Mathers et al reported that serum oestradiol levels did not correlate as highly with tear function as did testosterone and prolactin.[23] These authors also reported that there was a negative correlation between serum oestradiol levels and tear function for perimenopausal women. Schaumberg et al reported that women who take HRT, especially oestrogen alone, are at increased risk for dry eye.[19]

The action of oestradiol could be explained by stimulation of nitric oxide synthase and its vasodilatory effect, which may act on blood vessels as well as the lacrimal ducts. However, lacrimal gland tissue does not have identifiable oestrogen receptors; there are prolactin receptors in lacrimal gland acini and prolactin is synthesised by the lacrimal glands.[24,25] Prolactin levels fall with the increased oestrogen stimulation and also decrease slowly with age.[18] However, this study found that HRT was associated with slightly increased oestrogen levels. It may be that the threshold level of oestrogen necessary to increase serum prolactin may be above that achieved with HRT. This paradoxical result may be explained by the type of oestrogen assay used in this study, which measured only serum oestradiol. The serum oestradiol value would reflect endogenous oestrogen production before menopause, but in postmenopausal women this value would not reflect either endogenous or exogenous oestrogens.

Although significant differences were found between HRT use and TFBUT, corneal staining, and OSDI score, there was no significant difference between Schirmer's test and HRT use. Although this study was limited by the sample size, given the findings of the relationship between HRT and dry eye, further studies of the effects of sex steroid hormones on dry eye are recommended. Postmenopausal women who have never used HRT are at an increased risk for dry eye compared with those who are receiving oestrogen. Physicians should be apprised of this potential complication of menopause.

References

1. Dartt DA. Physiology of tear production. In: Lemp MA, Marquardt R, editors. The dry eye. Berlin: Springer-Verlag; 1992. p. 65-99.
2. Dartt DA, Sullivan DA. Wetting of the ocular surface. In: Albert DM, Jakobiec FA, editors. Principles and practice of ophthalmology. Philadelphia: WB Saunders Co; 1998.
3. Lemp MA. Report of the National Eye Institute/Industry Workshop on clinical trials in dry eyes. CLAO J. 1995;21:221-32.
4. Driver PJ, Lemp MA. Meibomian gland dysfunction. Surv Ophthalmol. 1996;40:343-67.
5. Nelson JD, Helms H, Fiscella R, Southwell Y, Hirsch JD. A new look at dry eye disease and its treatment. Adv Ther. 2000;17:84-93.
6. Caffery BE, Richter D, Simpson T, Fonn D, Doughty M, Gordon K. CANDEES: the Canadian Dry Eye Epidemiology Study. Adv Exp Med Biol. 1998;438:805-6.
7. Caffery BE, Richter D, Simpson T, Fonn D, Doughty M, Gordon K. The prevalence of dry eye in contact lens wearers: part 2 of the Canadian Dry Eye Epidemiology Study (CANDEES). Invest Ophthalmol Vis Sci. 1996;37 (Suppl 1):S72-73.
8. Schein OD, Tielsch JM, Munoz B, Bandeen-Roche K, West S. Relation between signs and symptoms of dry eye in the elderly. A population-based perspective. Ophthalmology. 1997;104:1395-401.
9. Belchetz PE. Hormonal treatment of postmenopausal women. N Engl J Med. 1994;330:1062-71.

10. Grodstein F, Stampfer MJ, Colditz GA, et al. Postmenopausal hormone therapy and mortality. N Engl J Med. 1997;336:1769-75.
11. Hulley S, Grady D, Bush T, et al; for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA. 1998;280:605-13.
12. Taskinen MR. Oestrogen replacement therapy and coronary heart disease. Ann Med. 1998;30:443-51.
13. Walt JG, Rowe MM, Stern KL. Evaluating the functional impact of dry eye: the Ocular Surface Disease Index. Drug Inf J. 1997;31:1436.
14. Moss SE, Klein R, Klein BE. Prevalence of and risk factors for dry eye syndrome. Arch Ophthalmol. 2000;118:1264-8.
15. Sullivan DA. Gender and dry eye. In: Research to prevent blindness science writers seminar. New York: Research to Prevent Blindness; 1997. p. 57-60.
16. Sullivan DA, Wickham LA, Rocha EM, et al. Androgens and dry eye in Sjögren's syndrome. Ann NY Acad Sci. 1999;876:312-24.
17. McCarty CA, Bansal AK, Livingston PM, Stanislavsky YL, Taylor HR. The epidemiology of the dry eye in Melbourne, Australia. Ophthalmology. 1998;105:1114-9.
18. Sullivan DA, Wickham LA, Rocha EM, Kelleher RS, da Silveira LA, Toda I. Influence of gender, sex steroid hormones, and hypothalamic-pituitary axis on the structure and function of the lacrimal gland. Adv Exp Med Biol. 1998;438:11-42.
19. Schaumberg DA, Buring EJ, Sullivan DA, Dana MR. Hormone replacement therapy and dry eye syndrome. JAMA. 2001;286:2114-9
20. Sato EH, Sullivan DA. Comparative influence of steroid hormones and immunosuppressive agents on autoimmune expression in lacrimal glands of a female mouse model of Sjögren's syndrome. Invest Ophthalmol Vis Sci. 1994;35:2632-42.
21. Nagler RM, Pollack S. Sjögren's syndrome induced by estrogen therapy. Semin Arthritis Rheum. 2000;30:209-14.
22. Sullivan DA, Edwards JA. Androgen stimulation of lacrimal gland function in mouse models of Sjögren's syndrome. J Steroid Biochem Mol Biol. 1997;60:237-45.
23. Mathers WD, Stovall D, Lane JA, Zimmerman MB, Johnson S. Menopause and tear function: the influence of prolactin and sex hormones on human tear production. Cornea. 1998;17:353-8
24. Mircheff AK, Warren DW, Wood RL, Tortoriello PJ, Kaswan RL. Prolactin localization, binding, and effects on peroxidase release in rat exorbital lacrimal gland. Invest Ophthalmol Vis Sci. 1992;33:641-50.
25. Wood RL, Zhang J, Huang ZM, et al. Prolactin and prolactin receptors in the lacrimal gland. Exp Eye Res. 1999;69:213-26.

Ophthalmic Electrodiagnosis in Christchurch, New Zealand

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This paper reviews the clinical value of ophthalmic electrodiagnosis in Christchurch Hospital, New Zealand, during the past 4 decades. Electroretinography is most useful when clinical diagnosis is uncertain, particularly during infancy. This is especially true for differentiating the early stages of congenital retinal dystrophy and nystagmus where clinical examination has failed to confirm the diagnosis. Electro-oculography is the most sensitive indicator of retinal toxicity from desferrioxamine, an iron-chelation therapy used for the treatment of iron overload caused by blood transfusion–dependent anaemia. An accurate differential diagnosis of optic neuritis is essential, as there are important implications for the development of multiple sclerosis. Therefore, one of the most important clinical applications of visual evoked potentials remains the detection of healed optic neuritis. In this review, the clinical value of ophthalmic electrophysiology as a useful tool in the practice of ophthalmology is discussed. Ophthalmic electrodiagnosis will continue to be used at Christchurch Hospital, as the knowledge of electrophysiology of the eye can be applied when examining ophthalmic disorders.

Key words: *Electrodiagnosis, Electrophysiology*

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Ophthalmic Electrodiagnosis

In principle, ophthalmic electrodiagnosis resembles electrocardiography where the electrical activity of the retina and optic pathway can be recorded at points that are remote from the site of origin of the waveform. However, the small electrical potential changes in the visual system have to be evoked by applying repetitive flashes of light or reversing chequerboard pattern stimuli.

The electrical activity of the retina and optic nerve is closely related to its function and thus may be altered by disease. The detection and analysis of this kind of electrical activity, under certain conditions, is the basis of electrodiagnosis. In general, there are 3 types of evoked response that are useful in the ophthalmic clinic;[1] electro-oculography (EOG) and flash or pattern electroretinography (ERG) both arise from the retina, and the visual evoked potential (VEP) arises from the occipital cortex of the brain. By means of EOG, ERG, and VEP, the location of pathological process in the course of the visual pathway can be found. Such electrodiagnostic testing has now become routine in many eye clinics around the world, as it is becoming recognised that this can provide important information about the function of the retina and the visual pathway. The results of this type of test have the great advantage of being purely objective. However, the size of these potentials is very small, although the technique of averaging has made it possible to detect responses down to less than 2 μV.

This paper reviews the clinical value of ophthalmic electrodiagnosis in Christchurch Hospital, New Zealand, with respect to our clinical experience during the past 4 decades. The process of evaluation that provides evidence of the clinical diagnostic effectiveness of electrodiagnostic testing in eye clinics helps to justify the need to establish an ophthalmic electrodiagnostic clinic in the hospital.

Ophthalmic electrodiagnostic tests provide information on retinal and optic nerve function. These tests include the EOG, ERG, VEP, and pattern electroretinography (PERG).

Electro-oculography

EOG measures the standing potential of the eye by an indirect method. Electrodes are placed on the skin close to the inner and outer canthi (the angle of the eyelids) of each eye. The patient is positioned looking into a ganzfeld sphere and asked to move both eyes together from side to side by following a set of small red lights. Measurements are made every 2 minutes. For the first 12 minutes the test is performed in the dark and, for the following 12 minutes, the patient is exposed to the uniform bright field within

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the ganzfeld sphere. The ratio of the maximum standing potential in the light environment to the minimum standing potential in the dark environment is known as the Arden ratio. If the retina is functioning normally, this ratio should exceed 1.8.

Electroretinography

The ERG signal induced by a flash originates from the entire retina. The ERG can be measured with a gold foil electrode, which is hooked over the lower lid. The eye is anaesthetised using 1 topical ophthetic drop. One drop of tropicamide is administered to dilate the pupil. The cone and rod responses are differentiated by making the measurement with the eyes light adapted (photopic) and dark adapted (scotopic). The cone response is also tested with a flicker ERG, which employs a flash with a repetition rate of 30 Hz. Rods are not able to respond to flashes as rapid as this. The ERG signal consists of a negative 'a wave' followed by a larger signal positive 'b wave'. The a wave is associated with the eye receptors (i.e., cones and rods) while the b wave is thought to arise from the Muller cells/bipolar cells.

Visual Evoked Potential

For the VEP test, the electrodes are glued to the scalp. The positive electrode is positioned on the midline, 2 cm above the inion (a small bony protuberance on the back of the head). The negative electrode is placed on the midline on top of the head. A common earth electrode is clipped onto an earlobe. For pattern VEP, the patient is seated 90 cm from the monitor screen. The patient is instructed to look at the red light emitting diode on the monitor screen, which is used to provide a reversing checkerboard pattern stimulus. The amplitude of the signal is very small, of the order of 10 μV, arising from the occipital cortex. A normal VEP waveform indicates normal optic nerve function.

Pattern Electroretinography

PERG is performed using a new commercial electrodiagnostic system, the Nicolet Bravo (Nicolet Biomedical Inc, Madison, USA). PERG is a retinal response evoked by viewing reversing chequerboard pattern stimuli presented to both eyes and recorded by gold foil electrodes hooked over the lower lids. The eyes are anaesthetised using 1 topical Ophthetic drop. The PERG is recorded without dilatation of the pupils to preserve accommodation. PERG responses may be altered in dysfunction of the macula or the inner retina (ganglion cells) selectively, which does not significantly affect the conventional full-field ERG. However, PERG has a very small signal (between 2 and 7 μV) and has been shown to be very sensitive to retinal damage from glaucoma and macular degeneration.[2]

Clinical Findings

ERG has been found to be most useful when clinical diagnosis is uncertain, particularly in infancy. This is especially true for differentiating the early stages of congenital retinal dystrophy and nystagmus where clinical examination has failed to confirm the diagnosis. Electrodiagnosis helps clinicians to provide a more accurate prognosis for a child, which means they can offer better advice on future education and career opportunities. In addition, genetic counselling can be arranged and low-vision aids introduced at an early age. In this respect, the analysis of the ERG into rod- and cone-mediated responses helps to establish the diagnosis of a number of disorders in infants suspected of having poor vision due to nystagmoid (involuntary) movements of the eyes. For example, in patients with Leber's congenital amaurosis (congenital retinal dystrophy or congenital blindness), both the photopic and scotopic ERGs and the cone response to flicker stimulation are found to be extinguished.

In a retrospective study involving 113 children who were investigated at the Electrodiagnostic Clinic, Christchurch Hospital, Christchurch, New Zealand, during a 5-year period (Table 1), 53 children were referred for investigation of disease of the retina (hereditary), 23 for optic nerve problems and brain damage, and 37 for general disorders including functional visual loss, refractive errors, and squint.[3] Eighteen of 23 children who were referred for optic nerve problems were found to have serious disorders of the visual pathways, as indicated by the non-measurable or delayed response in the VEP. Interestingly, 21 of the 113 children referred to the clinic were found to have functional visual loss. These patients complained of visual loss but subsequent examinations revealed that their ocular findings, EOG, ERG, and VEP were normal. The age of this group ranged from 7 to 15 years, with the average being 11.3 years. Electrodiagnostic investigations in infants and preschool age children is often carried out under chloral hydrate sedation and is the method of choice at the Paediatric Department, Christchurch Hospital.[3,4]

The earliest symptom of vitamin A deficiency is night blindness. A case report documented changes in the EOG and ERG of a patient with night blindness following vitamin A deficiency due to malabsorption syndrome.[5] In this investigation, a 46-year-old man complained of difficulty seeing in the dark for the previous few months. He also had chronic pancreatitis and a history of carcinoma of the testes 7 years previously. Ophthalmological examination found visual acuity of 6/5 in each eye and no abnormalities in either retina. The diagnosis made by the referring ophthalmologist was vitamin A deficiency or carcinoma-associated retinopathy. Humphrey visual field analysis revealed normal fields in both eyes. However, his EOG Arden ratios were subnormal (right eye, 1.3; left

Table 1. Classification of ophthalmic disorders in 113 children investigated by electrodiagnosis (electro-oculography/electroretinography/visual evoked potentials) over 5 years.

Ophthalmic disorder	Electro-oculography/ electroretinography	Visual evoked potentials	Number of patients (n = 113)
Disease of the retina (hereditary) – 47%			
Congenital nystagmus	Normal		12
Retinitis pigmentosa	Abnormal		3
Family history of retinitis pigmentosa	Normal		7
Retinal pigmentation	Normal		5
Leber's congenital amaurosis	Abnormal		3
Cone/retinal dystrophy	Abnormal		7
Rod monochromat	Abnormal		2
Stargardt's disease	Abnormal		2
Vitelliform macular dystrophy	Abnormal		1
Miscellaneous	Normal		11
Optic nerve problems – 20%			
Optic atrophy		Abnormal	5
Cortical blindness		Abnormal	4
Brain damage		Abnormal	4
Craniopharyngioma		Abnormal	2
Other neurological conditions		Abnormal	3
Miscellaneous		Normal	5
General disorders – 33%			
Functional visual loss	Normal	Normal	21
Others*	Normal	Normal	16

* Others include refractive errors.

eye, 1.2) and extinguished scotopic ERG recorded from both eyes suggested a bilateral rod-type retinal dysfunction. The cone ERG response from each eye was normal. In the light of these abnormal electrodiagnostic findings and clinically normal retinas, vitamin A deficiency was suspected. Following high-dose vitamin A treatment, the patient fully recovered and the night blindness completely disappeared. Consistent with this clinical recovery, the EOG and scotopic ERG also returned to normal values, suggesting a return of normal rod function in each eye. The results obtained from this investigation confirm the clinical value of electrodiagnosis to help establish a diagnosis of night blindness as a result of vitamin A deficiency, especially in the absence of clinical findings and a widespread electrophysiological dysfunction.[5]

Electrophysiological abnormalities have not been extensively examined in acutely methanol-poisoned patients. McKellar et al were the first to report widespread electrophysiological dysfunction caused by acute methanol ingestion in a young man.[6] At presentation, the scotopic ERG was subnormal with diminished a and b waveforms and the cone response to 30 Hz flicker stimulation was reduced. The VEP P100 waveform was normal in latency but decreased in amplitude. The results of electrophysiological testing suggest that methanol affects the photoreceptors (rods and cones), Muller cells, and the retrolaminar portion of the optic nerve.

In line with the clinical use of electrodiagnostic testing as a monitor of retinal and optic nerve toxicity, EOG has been found to be the most sensitive indicator of retinal toxicity of desferrioxamine, an iron-chelation therapy used in the haematology clinic for the treatment of iron overload caused by blood transfusion–dependent anaemia.[7] A 61-year-old woman had been taking desferrioxamine for autoimmune haemolytic anaemia. Prior to starting treatment, her baseline ophthalmic examination and EOG (right and left, >1.8) were normal. After 2 years, she noticed a grey scotoma in her right eye and funduscopy revealed evidence of non-specific mottling of the retinal pigment epithelium of both retinas. The EOG was flat and subnormal (right, 1.1; left, 1.5). After desferrioxamine treatment was stopped, her vision returned to normal and the EOG returned to the normal range (right, 2.1; left, 2.1). Subsequently, she underwent splenectomy.

It has been widely accepted that the most important clinical application of VEP remains the detection of healed optic neuritis.[8] In such cases, there is a characteristic delay in the VEP latency, which persists after the acute attack and when complete healing appears to have occurred. Eighteen patients with a clinical diagnosis of unilateral acute optic neuritis underwent repeated VEP tests during a 5-year period to document any VEP latencies that returned to normal.[9] In general, the delayed VEP latencies remained constant during the period of investigation. However, 2 patients demonstrated a return to normal latencies, although this was only temporary. Their latencies become prolonged again within 2 years. These results provide evidence that the delayed P100 latency observed in patients with optic neuritis can return to the normal range in a small percentage of patients. However, this improvement may spontaneously deteriorate as a result of further episodes of subacute demyelination.[9]

Of special interest is the clinical application of PERG using the new Nicolet Bravo system. This system provides an additional electrodiagnostic test to offer to ophthalmology patients. Prior to the introduction of the new system, PERG was only used as a research tool.[10,11]

Conclusions

This experience confirms the clinical value of ophthalmic electrodiagnosis for the diagnosis and prognosis of ocular conditions and promotes clinician confidence in the electrodiagnostic unit.

References

1. Evans DL, Goode DH. A flexible automated data acquisition system for ophthalmic electrophysiology. Australas Phys Eng Sci Med. 1992; 15:124-30.
2. Berninger TA, Arden GB. The pattern electroretinogram. Eye. 1988;2 (6 Suppl):257-83.
3. Hidajat RR, Goode DH. The clinical value of ophthalmic electrodiagnosis in children. Australas Phys Eng Sci Med. 2001;24:1-5.
4. Wright KW, Eriksen KJ, Shors TJ, Ary JP. Recording pattern visual evoked potentials under chloral hydrate sedation. Arch Ophthalmol. 1986;104:718-21.
5. Hidajat R, McLay J, Borthwick J. The electrophysiological effects of vitamin A deficiency due to malabsorption syndrome [abstract]. Australas Phys Eng Sci Med. 2001;24:260.
6. McKellar MJ, Hidajat RR, Elder MJ. Acute ocular methanol toxicity: clinical and electrophysiological features. Aust NZ J Ophthalmol. 1997; 25:225-30.
7. Hidajat RR, McLay JL, Goode DH, Spearing RL. EOG as a monitor of desferrioxamine retinal toxicity. Doc Ophthalmol. 2004;109: 273-8.
8. Galloway NR. Evoked responses and the eye. Trans Ophthalmol Soc UK. 1986;105:273-86.
9. Hidajat RR, Goode DH. Normalisation of visual evoked potentials after optic neuritis. Doc Ophthalmol. 2003;106:305-9.
10. Hidajat RR, McLay JL, Elder MJ, Goode DH, Morton JP, Burley CD. A comparison of two patient-friendly ERG electrodes. Australas Phys Eng Sci Med. 2003;26:30-4.
11. Hidajat RR, McLay JL, Burley CD, Elder MJ, Morton JP, Goode DH. Influence of axial length of normal eyes on PERG. Doc Ophthalmol. 2003;107:195-200.

Total Retinal Detachment in an Eye and Proliferative Retinopathy in the Fellow Eye in a Patient with Incontinentia Pigmenti

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Ocular involvement of incontinentia pigmenti is rare in Asian patients. This report is of a 17-year-old Chinese girl who was diagnosed with incontinentia pigmenti in infancy. She has ocular, skin, and dental manifestations of incontinentia pigmenti. At the last follow-up, her vision in the right eye was no light perception and her best-corrected vision in the left eye was 6/6. Fluorescein fundus angiography of the left eye showed leakage within the macula and ischaemic areas in the peripheral retina for which laser photocoagulation was done. She continues to be followed up.

Key words: *Cataract, Incontinentia pigmenti, Retinal detachment, Vitreoretinopathy, proliferative*

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Introduction

Incontinentia pigmenti (Bloch-Sulzberger syndrome) is a rare X-linked dominant multi-system disorder that tends to be fatal for male foetuses in utero; nearly all affected patients are therefore females.[1] X chromosome inactivation in females during early embryogenesis results in a mosaic population of cells, which explains the linear and patchy manifestations of incontinentia pigmenti.[2] The disease first manifests with characteristic skin lesions at birth. Incontinentia pigmenti can also affect the eyes, teeth, and central nervous system.

In a 10-year study of 26 patients in Singapore, only 1 patient had ocular involvement (4%), which was associated with neurological involvement.[2] However, ocular manifestations were reported in 20%[3] to 35%[4] of patients in Western countries. In view of the rare occurrence of ocular manifestations of this disease in Asia, this report describes a female patient with incontinentia pigmenti with skin, dental, and ocular manifestations.

Case Report

A 17-year-old Chinese girl was diagnosed as having incontinentia pigmenti when she was 2 months old. She was referred to the eye clinic at the University of Malaya Medical Centre, Kuala Lumpur, Malaysia, in March 1994 for ophthalmic assessment and follow-up. At initial presentation, her best-corrected visual acuity (BCVA) was light perception in the right eye and 6/18 in the left eye. Esotropia was noted in the right eye. Early cataract changes with poor red reflex were seen in the right eye. The anterior segment was normal in the left eye. Dilated fundus examination showed exudative retinal detachments in both eyes, located inferiorly in the right eye and inferonasally in the left eye. However, both posterior poles were flat.

She was followed up at 6-monthly intervals. In April 1995, total retinal detachment was noted in the right eye with no light perception. However, the retinal detachment was stable with a thin fibrous band in the left eye and the BCVA was 6/9. In December 1998, the cataract in the right eye became dense and fundus view was not possible. Ultrasonography (B scan) showed total retinal detachment in the right eye. The left fundus remained the same, apart from increasing tortuousity of the inferior arcades. In October 2002, intragel vitreous haemorrhage was noted in the left eye, which completely resolved with conservative management over a period of 2 months and she regained 6/6 vision.

Follow-up examination in April 2005 showed that the right eye was blind, with esotropia of 30° and mature cataract. The BCVA in the left eye was 6/6. Fundus examination of the left eye showed a small preretinal haemorrhage (2 disc diameters) temporal to the optic disc, with areas of new vessels inferior and temporal to it (Figure 1a). Superotemporal and superonasal arcades at the optic

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Figure 1. Fundus photo of the left eye with (a) small preretinal haemorrhage temporal to the optic disc with areas of new vessels (arrows) inferior and temporal to the haemorrhage; and (b) fibrous band and ghost vessel (arrow) running parallel.

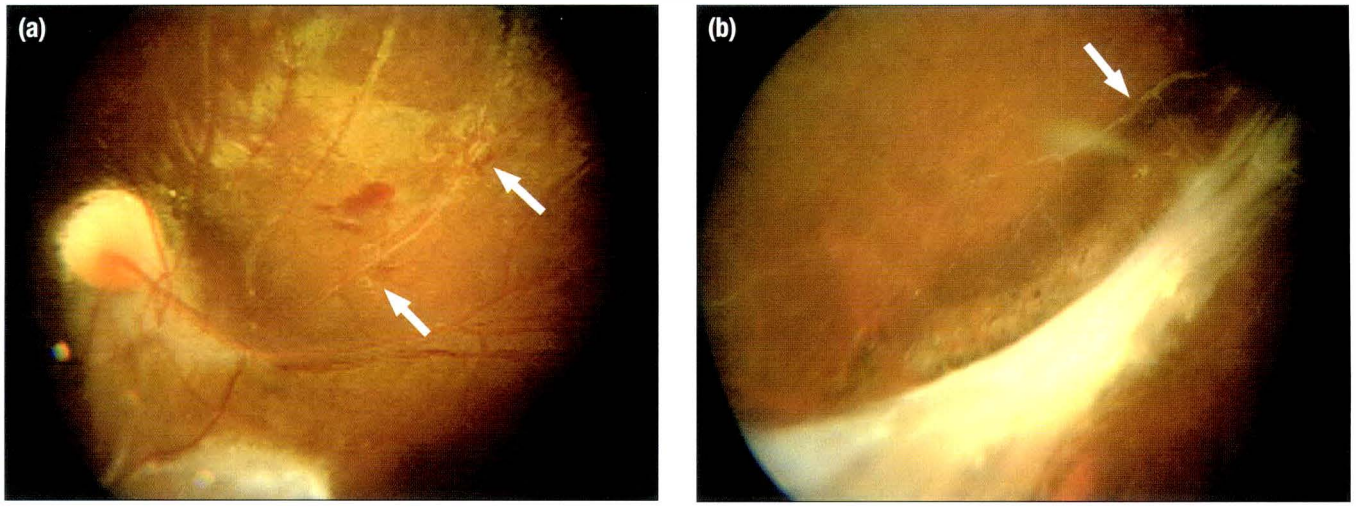
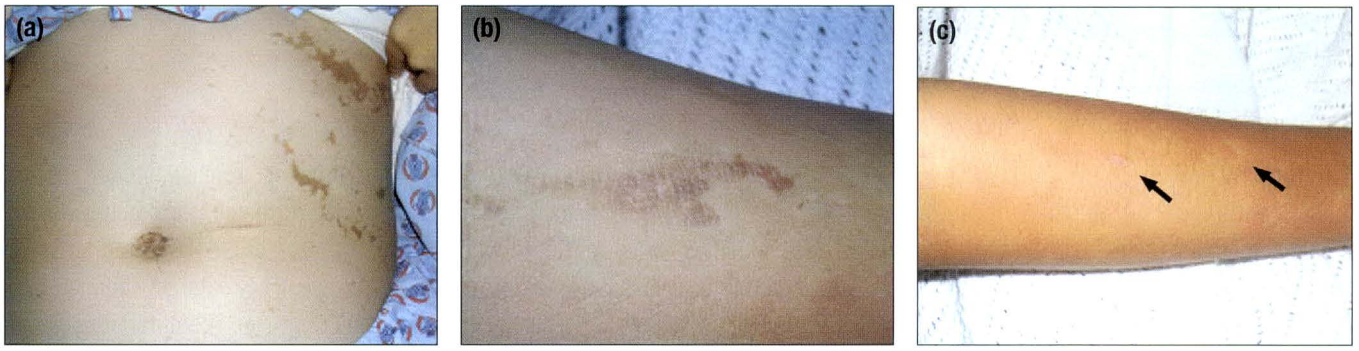


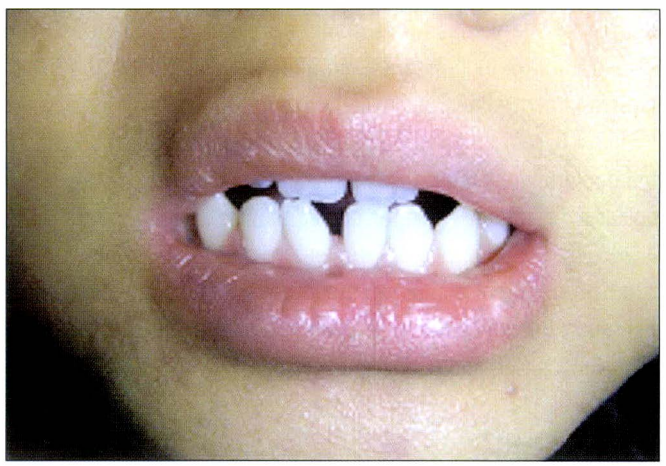
Figure 2. Hyperpigmented skin lesion on (a) the left side of the trunk; (b) the left arm; and (c) the left forearm.



disc were inferiorly displaced and distorted by cicatricial changes; abnormal distribution of retinal arcades was noted in the periphery. An inferior fibrous band arising from the optic disc and extending inferonasally up to the equator was noted, with a ghost vessel running parallel to it (Figure 1b). Foveal reflex could not be seen. Typical skin lesions were seen on the left side of the trunk (Figure 2a), on the left arm (Figure 2b), and on the left forearm (Figure 2c). Dental lesions included hypodontia and round and peg-shaped teeth (Figure 3).

Fluorescein fundus angiography of the left eye was done in June 2005. The early arterial phase showed the abnormal distribution of retinal vessels (Figure 4a). The venous phase showed leakage in the macular area at the site of the new vessels (Figure 4b) and vascular drop-out adjacent to the inferior fibrous band, along the course of the ghost vessel (Figure 4c). Pan-retinal photocoagulation was offered in view of the retinal ischaemia with neovascularisation. 2000 Argon laser shots were given in the eye clinic (via slit-lamp delivery) in 2 sessions with an interval of 1 week (Figure 5). She continues follow-up and the BCVA of 6/6 is maintained in the left eye.

Figure 3. Hypodontia with round and pegged teeth.



Discussion

The main pathology of incontinentia pigmenti includes loss of melanin from basal cells in the epidermis and its collection in the dermis as free pigment or aggregation of melanophages. Usually, the diagnosis is made clinically on the basis of a history of sequential skin lesions and other associated systemic features.

Figure 4. Fundus fluorescein angiography of the left eye showing (a) abnormal distribution of retinal vessels in the arterial phase; (b) leakage in the macular area in the venous phase; and (c) vascular drop-out adjacent to the fibrous band.

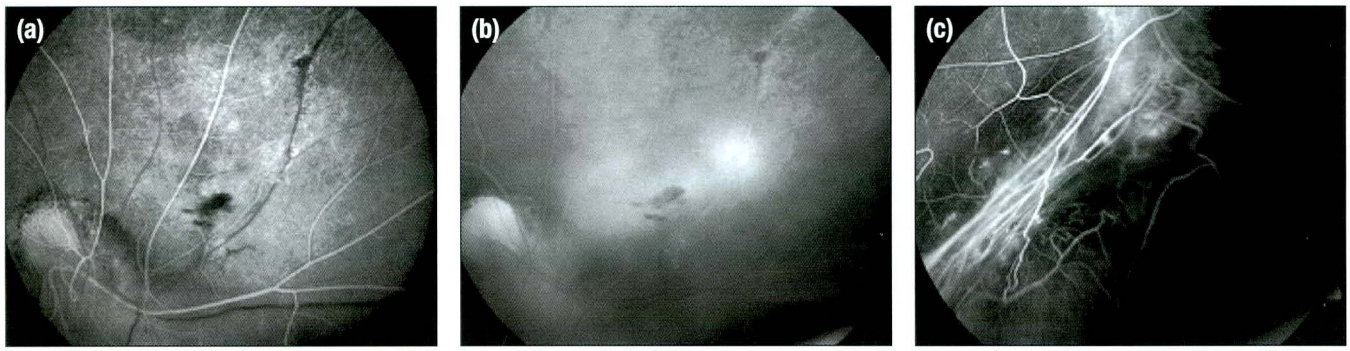
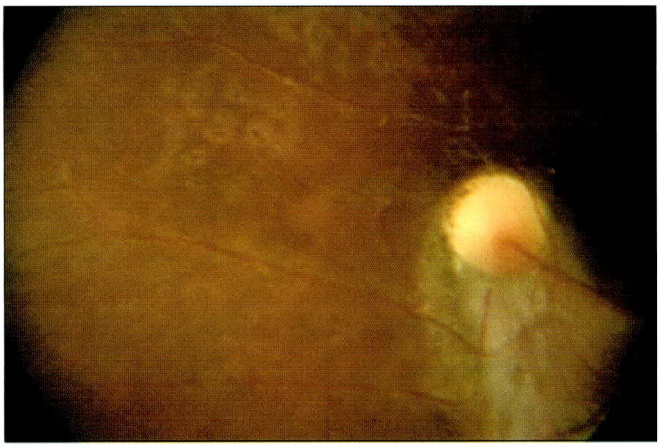


Figure 5. Fundus photo of the left eye showing laser scars.



Retinal changes include tortuous irregular vessels with arborising arteriovenous anastomoses at the junction of the vascular and avascular retina, peripheral avascular zone, aneurismal-like dilation and neovascular changes, exudates, vitreous haemorrhage, preretinal fibrovascular proliferation, retinal detachment, retinal pigment epithelium mottling/granularity/hypopigmentation/coloboma, and foveal hypoplasia.[5] Non-retinal associations include strabismus and cataract.[4]

This patient had total retinal detachment and mature cataract and esotropia in the right eye. Despite the marked peripheral retinal ischaemia, neovascularisation, macular abnormalities and tractional retinal detachment, she maintained good central vision in the left eye. However, long-term follow-up is required to detect subsequent complications in the left eye. The retinal findings in the left eye seen in this patient were similar to that reported by Berinstein and Trese.[6]

Four stages of skin changes occur, mostly on the body along the sides of the trunk.[7] Stage 1 involves linear vesicles, pustules, and bullae with erythema along the lines of Blaschko; this stage is usually present at birth. Stage 2 involves warty keratotic papules and plaques, and occurs between the ages of 2 and 8 weeks. Stage 3 involves hyperpigmented lesions along the lines of Blaschko and occurs between the ages of 12 and 40 weeks. Stage 4 involves hypopigmented streaks and/or patches and cutaneous atrophy; this stage is present from infancy through to adulthood. This patient had typical stage 3 and stage 4 skin lesions on all limbs and on the trunk.

Dental changes include delayed eruption of teeth, hypodontia, microdontia, and abnormally shaped teeth, which may be round, conical, or peg shaped.[8] Hypodontia with round and peg-shaped teeth was clearly noted in this patient.

Central nervous system abnormalities include cerebral ischaemia, oedema, and subsequent atrophy, as well as haemorrhagic necrosis and hydrocephalus, leading to severe mental retardation, spastic paresis, and seizures.[4] This patient had no neurological involvement and her neurological function was normal.

The frequency of ocular manifestations of this disease in patients reported from Asian countries is rare (4%)[2] compared with that in Western countries (>20%).[3] This patient had bilateral ocular involvement, skin manifestations, and dental manifestations with no central nervous system manifestations. Even though her right eye is blind, she has maintained good vision in the left eye despite having marked retinal abnormalities.

References

1. Cho SY, Lee CK, Drummond BK. Surviving male with incontinentia pigmenti: a case report. Int J Paediatr Dent. 2004;14:69-72.
2. Chan YC, Giam YC. A retrospective study of incontinentia pigmenti seen at the National Skin Centre, Singapore over a 10-year period. Ann Acad Med Singapore. 2001;30:409-13.
3. Hadj-Rabia S, Froidevaux D, Bodak N, et al. Clinical study of 40 cases of incontinentia pigmenti. Arch Dermatol. 2003;139:1183-70.
4. Carney RG. Incontinentia pigmenti — a world statistical analysis. Arch Dermatol. 1976;112:535-42.
5. Goldberg MF, Custis PH. Retinal and other manifestations of incontinentia pigmenti (Bloch-Sulzberger syndrome). Ophthalmology. 1993;100:1645-54.
6. Berinstein DM, Trese MT. Anomalous foveal vascular pattern in a case of incontinentia pigmenti. Retina. 1999;19:564-6.
7. Phan TA, Wargon O, Turner AM. Incontinentia pigmenti case series: clinical spectrum of incontinentia pigmenti in 53 female patients and their relatives. Clin Exp Dermatol. 2005;30:474-80.
8. Doruk C, Bicakci AA, Babacan H. Orthodontic and orthopedic treatment of a patient with incontinentia pigmenti. Angle Orthod. 2003;73:763-8.

Controversies in the Antifungal Management of *Candida albicans* Panophthalmitis

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This report is of a patient with Candida albicans *panopthalmitis, probably prompted by a decompensated underlying diabetes mellitus. The clinical course was prolonged (more than 16 weeks), although favourable after treatment with antifungal agents with a predictable activity in this condition and proven susceptibility to* Candida albicans. *This report will discuss the treatment of* Candida albicans *panophthalmitis and review the literature.*

Key words: *Amphotericin B, Antifungal agents,* Candida albicans, *Caspofungin, Fluconazole, Panophthalmitis, Voriconazole*

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Introduction

Candida albicans panophthalmitis is a severe function-threatening infection. This condition usually occurs in immunocompromised patients and there are multiple supporting factors, including diabetes mellitus, primary or secondary immunodeficiency, indwelling central catheter lines, total parenteral nutrition, intravenous drug use, fungal endocarditis, bacteraemia, and underlying malignancies and their treatment.[1-4] Based on prospective observational surveys of patients with candidaemia, 4% to 28% of them may develop a severe ocular localisation.[4]

Case Report

A 53-year-old man who had had poorly controlled insulin-dependent diabetes mellitus for 13 years was admitted through the emergency department of the S Orsola-Malpighi Hospital, Bologna, Italy, in 2005 with sudden visual loss in his right eye. He had previously undergone ophthalmoscopic assessment every 6 months due to the diabetes mellitus.

A diagnosis of *C albicans* panophthalmitis was made following ophthalmological, computed tomography (CT), and fluorangiographic assessment, and confirmed by culture of the anterior eye segment fluid. A *C albicans* strain was cultured that was sensitive to all antifungal polyene and imidazole derivatives (echinocandins were not tested). Vitritis, choroiditis, and retinitis were diagnosed by ophthalmological examination. There was no orbital swelling and no other local complications were present except for limited oedema involving the orbital region. Intravenous fluconazole 800 mg loading dose, followed by 600 mg/day, was immediately started, with topical steroidal-atropine treatment. The patient had previously had a myocardial infarction and underwent double coronary bypass surgery, but endocarditis was excluded by ultrasonography. Repeat blood cultures did not yield any bacterial or fungal pathogen.

The patient developed complete amblyopia in his right eye, and the ophthalmologic, CT, and fluorangiographic assessment showed deterioration (Figure 1). Liposomal amphotericin B 3 mg/kg/day was started and fluconazole was stopped. After 14 days of liposomal amphotericin B therapy, a remarkable reduction of exudates was achieved. However, liposomal amphotericin B had to be stopped after a further 7 days due to renal insufficiency (peak serum creatinine, 186.5 μmol/L [normal range, 53-106 μmol/L], serum urea nitrogen, 47.1 mmol/L [normal range 3.6-17.8 mmol/L]). Subsequently, intravenous caspofungin 70 mg/day loading dose, followed by 50 mg/day, was introduced. After 38 days of caspofungin therapy, active infectious foci were still present at fluorangiography, and visual acuity only recovered to 2/10. The renal impairment resolved after 2 weeks. Finally, intravenous voriconazole 400 mg/day was started and continued for 23 days. The patient achieved a complete and steady resolution of exudates, as shown by ophthalmoscopic and fluorangiographic assessment, and his visual acuity increased to 6/10. CT

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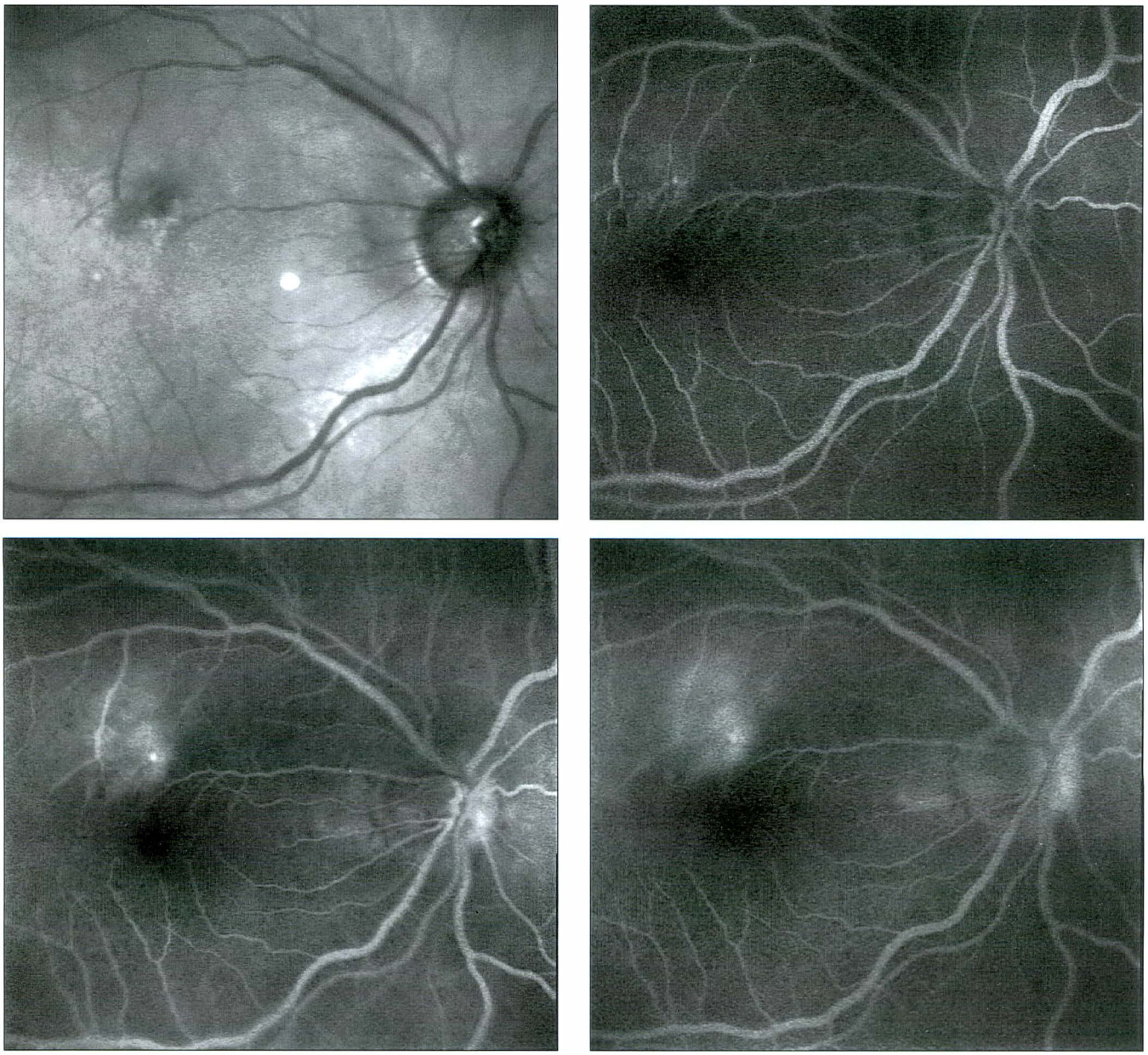
Figure 1. Fluorangiography of the right eye. Exudative *Candida albicans* lesions are still evident after 10 days of full-dose intravenous fluconazole administration.



scan was not repeated due to the evident clinical improvement. Oral voriconazole 400 mg/day was continued for 3 weeks post-discharge. The patient has been followed up for 9 months, and has had no recurrence of infection. However, vitrectomy was necessary to avoid further complications.

Discussion

The rationale for antifungal therapy of *C albicans* panophthalmitis is limited by the unfavourable kinetics of several potentially active antimycotic compounds, and the absence of randomised controlled clinical trials and universally recognised recommendations and guidelines. Most information comes from in vitro and animal studies, small patient series, and anecdotal reports.[2-6] Maximal antifungal doses appropriate for other forms of invasive candidiasis should be reserved for fungal panophthalmitis. As antimycotic agents are often used concurrently, it is difficult to distinguish the role played by each single administered compound,[1-3,5] as shown in this report, in which active antifungal drugs were given sequentially.

While fluconazole has favourable cerebrospinal fluid and brain penetration that extends to the ocular structures, its activity may be limited by its fungistatic activity and the emergence and selection of some non-*albicans Candida* spp. strains such as *C glabrata* and *C krusei*,[6,7] although a sensitive *C albicans* strain was cultured in this patient. This experience may add to the evidence for not using

fluconazole as initial therapy for *C albicans* panophthalmitis if other drugs such as liposomal amphotericin B are available.

Despite their unpredictable tissue penetration, lipophilic amphotericin B and its liposomal derivatives remain the standard treatment for *C albicans* panophthalmitis, and can be administered systemically or via the intraocular route. However, clinical failures have been reported.[5-8]

The endovitreal penetration of caspofungin is still under investigation, although animal models and clinical trials have been published.[5,7] However, isolated unpredictable intraocular concentrations have been detected, which were sometimes associated with clinical failure.[1]

Finally, voriconazole, given either systemically or topically, leads to satisfactory results from an in vitro,[9] pharmacokinetic/pharmacodynamic,[8] and clinical point of view.[5] This recently available antifungal drug is expected to play a key role in the treatment of panophthalmitis (paralleling its activity in the central nervous system).[10] The availability of a bioequivalent oral formulation makes long-term treatment with voriconazole feasible on an outpatient basis.

The patient described here developed a severe but sensitive *C albicans* panophthalmitis and received all 4 available antimycotic agents effective against *C albicans*. However, he experienced disease progression during fluconazole treatment and possibly during long-term caspofungin administration. The initial favourable response to liposomal amphotericin B was hampered by kidney function abnormalities, which have been noticed even after a short course of this drug.[11] After the first course of fluconazole, cultures did not yield any fungal growth, so further therapeutic changes were made on the basis of the clinical progression and prior treatment selection. The other possible limitation of this treatment is that intravitreal amphotericin B was not selected due to lack of experience with this administration technique. Finally, voriconazole proved to be safe and effective, leading to a complete cure and good recovery of visual acuity, although the therapeutic contribution of voriconazole cannot be clearly distinguished from that of the previously administered drugs.

Further, controlled studies are needed to provide therapeutic guidelines for *C albicans* panophthalmitis, which represents an increasing and difficult-to-treat condition in patients with risk factors. Appropriate cost-effectiveness analyses are also needed, due to the high cost of systemic antifungal agents.

References

1. Gauthier GM, Nork TM, Prince R, Andes D. Subtherapeutic ocular penetration of caspofungin and associated treatment failure in *Candida albicans* endophthalmitis. Clin Infect Dis. 2005;41:e27-8.
2. Carstocea B, Armegioiu M, Buliga S, Georgieva V, Mihalcea O. Fungal endogenous endophthalmitis — case report. Oftalmologia. 2005;49:25-9.
3. Takebayashi H, Mizota A, Tanaka M. Relation between stage of endogenous fungal endophthalmitis and prognosis. Graefes Arch Clin Exp Ophthalmol. 2006;244:816-20.
4. Brooks RG. Prospective study of *Candida* endophthalmitis in hospitalized patients with candidemia. Arch Intern Med. 1989;149:2226-8.
5. Breit SM, Hariprasad SM, Mieler WF, Shah GK, Mills MD, Grand MG. Management of endogenous fungal endophthalmitis with voriconazole and caspofungin. Am J Ophthalmol. 2005;139:135-40.
6. Charlier C, Hart E, Lefort A, et al. Fluconazole for the management of invasive candidiasis: where do we stand after 15 years? J Antimicrob Chemother. 2006;57:384-410.
7. Sarria JC, Bradley JC, Habash R, Mitchell KT, Kimbrough RC, Vidal AM. *Candida glabrata* endophthalmitis treated successfully with caspofungin. Clin Infect Dis. 2005;40:e46-8.
8. Hariprasad SM, Mieler WF, Holz ER, et al. Determination of vitreous, acqueous, and plasma concentration of orally administered voriconazole in humans. Arch Ophthalmol. 2004;122:42-7.
9. Marangon FB, Miller D, Giaconi JA, Alfonso EC. In vitro investigation of voriconazole susceptibility for keratitis and endophthalmitis fungal pathogens. Am J Ophthalmol. 2004;137:820-5.
10. Sabbatani S, Manfredi R, Pavoni M, Consales A, Chiodo F. Voriconazole proves effective in long-term treatment of a cerebral cryptococcoma in a chronic nephropathic HIV-negative patient, after fluconazole failure. Mycopathologia. 2004;158:165-71.
11. Sabbatani S, Manfredi R, Marinacci G, Pavoni M, Nafissi M, Chiodo F. Liposomal amphotericin B and HIV-associated visceral leishmaniasis: concerns about nephrotoxicity and administration schedule. Clin Drug Invest. 2005;25:85-7.

Acute Postoperative Multidrug-resistant *Pseudomonas aeruginosa* Endophthalmitis Treated with Intravitreal Piperacillin/Tazobactam

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A 67-year-old lady with keratoconus and cataract underwent uneventful phacoemulsification, posterior chamber intraocular lens implantation and penetrating keratoplasty in her left eye. On the first postoperative day, she developed symptoms and signs of endophthalmitis for which a vitreous biopsy was performed, followed by intravitreal injections of vancomycin and ceftazidime. Vitreous culture revealed multidrug-resistant Pseudomonas aeruginosa *sensitive to piperacillin/tazobactam and imipenem. In 2 days, her vision deteriorated to light perception with a large corneal infiltrate and fulminant endophthalmitis. A therapeutic penetrating keratoplasty, intraocular lens explantation, open sky vitrectomy, and intravitreal injection of piperacillin/tazobactam was performed to salvage the eye. The antibiotic injection was repeated, and dexamethasone was given, after 4 days. The infection was controlled, the graft remained clear, and she regained a best-corrected visual acuity of 20/40 after 6 months.*

Key words: *Drug resistance, multiple, Endophthalmitis, Piperacillin-tazobactam combination product*, Pseudomonas aeruginosa

Asian J Ophthalmol. 2007;9:185-7

Introduction

The increasing prevalence of multidrug-resistant *Pseudomonas aeruginosa*[1] and poor visual outcome despite prompt treatment with appropriate intravitreal antibiotics poses a challenge in the treatment of endophthalmitis.[2] Although the efficacy of piperacillin/tazobactam has been studied in experimental *P aeruginosa* endophthalmitis,[3] there have been no previous reports of its use in clinical endophthalmitis. This report describes a patient with acute postoperative multidrug-resistant *P aeruginosa* endophthalmitis, in whom the vision was salvaged by intravitreal piperacillin/tazobactam.

Case Report

A 67-year-old woman with keratoconus and cataract underwent an uneventful phacoemulsification, posterior chamber intraocular lens (IOL) implantation, and penetrating keratoplasty (PK) in the left eye. There were no surgical complications. She had undergone a similar procedure in the right eye with satisfactory results 1 year previously. She had used contact lenses for 30 years.

On the first postoperative day, she complained of severe pain and cloudy vision in the left eye. The visual acuity was 20/200, with corneal oedema, 3+ cells and flare in the anterior chamber, small hypopyon, and exudative membrane covering the IOL. The fundus view was hazy with red glow, exudates in the vitreous, and the disc was hazily seen. The intraocular pressure (IOP) was 14 mm Hg and 30 mm Hg in the right and left eyes, respectively. A clinical diagnosis of acute postoperative endophthalmitis in the left eye was made.

An ultrasound B-scan showed anterior vitreous echoes of moderate amplitude and the retina was attached. She underwent a vitreous biopsy followed by intravitreal injections of vancomycin 1 mg in 0.1 mL and ceftazidime 2.25 mg in 0.1 mL. Postoperatively, she was given ciprofloxacin eye drops hourly, prednisolone acetate eye drops hourly, atropine eye drops 3 times daily, timolol 0.5% twice daily, oral diamox 250 mg 3 times daily, oral prednisolone 60 mg once daily, and oral ranitidine 150 mg twice daily.

Within 24 hours, the vitreous culture grew *P aeruginosa*, which was resistant to all antibiotics except piperacillin/tazobactam and

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imipenem. Within 48 hours, her visual acuity had reduced to light perception, the cornea developed a ring infiltrate that progressed rapidly to involve the entire cornea, the hypopyon increased to 7 mm, and there was no fundus view. Ultrasonography showed medium to high reflective echoes throughout the vitreous cavity, with attached retina and thickened choroid (Figure 1). The patient was informed about the rapid worsening of the endophthalmitis and, in an attempt to salvage the eye, a therapeutic PK, IOL explantation, open-sky vitrectomy, and intravitreal piperacillin/tazobactam was planned. The experimental nature of intravitreal piperacillin/tazobactam was discussed with the patient and an informed consent was obtained. As the whole cornea was involved, a corneo-scleral graft was performed (Figure 2). An intravitreal injection of piperacillin/tazobactam 250 µg in 0.1 mL of solute was given at the end of the surgery.

On the first postoperative day after the therapeutic PK, her vision was light perception with accurate projection. The corneal graft showed Descemet's folds, the anterior chamber was formed, and the IOP was 4 mm Hg. Vitreous haemorrhage and residual vitreous exudates obscured the fundus view. B-scan ultrasonography showed moderate amplitude echoes in the vitreous cavity, annular choroidal detachment, and an attached retina. She was given imipenem eye drops 0.5% hourly, prednisolone acetate eye drops hourly, and atropine eye drops 3 times daily. She was also given a course of intravenous piperacillin/tazobactam 3.375 g 4 times daily for 7 days; oral prednisolone and ranitidine were continued. The corneal clarity improved over the next few days. However, there was still no view of the fundus due to residual vitreous exudates. A serial ultrasound scan was performed daily to monitor the choroidal detachment and status of the retina. After 4 days, on resolution of the choroidal detachment, a repeat intravitreal injection

Figure 1. Ultrasound showing moderate to high reflective echoes in the vitreous cavity. There is no posterior vitreous detachment, the retina is attached, and the choroid is diffusely thickened.

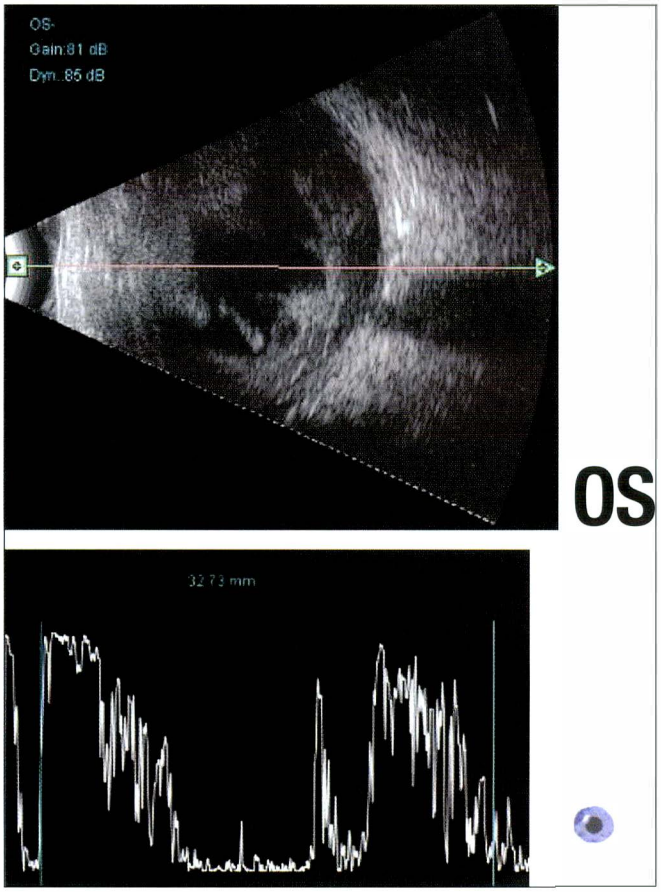


Figure 2. Clear graft with intact sutures, widely dilated pupil, and aphakia.

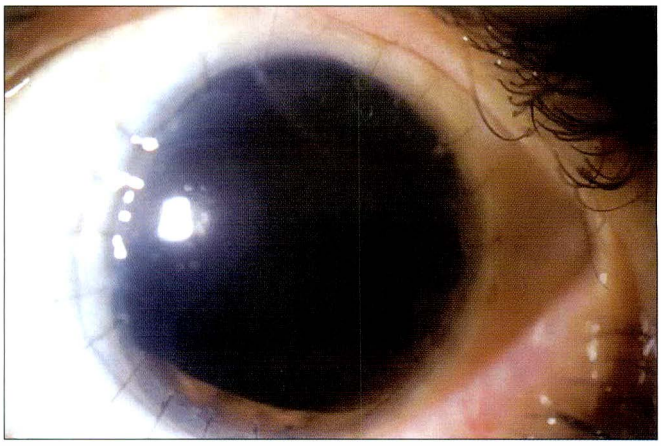


Figure 3. Electroretinogram of both eyes. (a) Rod response for both eyes; (b) maximal combined response for both eyes; and (c) cone response for both eyes.

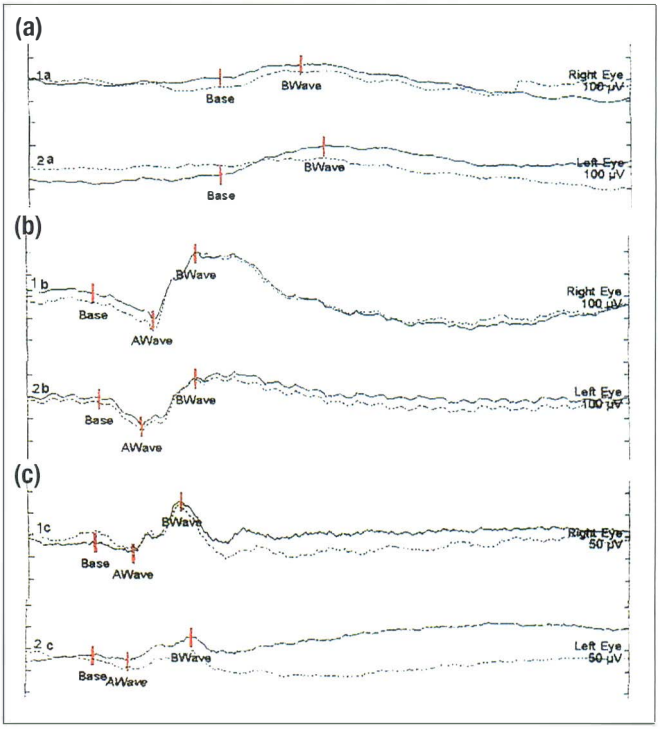


Table 1. Amplitude and latency of B-wave responses.

	B-wave rod response		B-wave maximal response		B-wave cone response	
	Latency (ms)	Amplitude (μV)	Latency (ms)	Amplitude (μV)	Latency (ms)	Amplitude (μV)
Right eye	70.6	58.5	36.2	301.0	31.0	119.0
Left eye	78.0	132.0	36.0	216.0	34.8	55.7
Normal values (SD) [age 40-60 years]	65.4 (1.7)	145.5 (9.0)	37.8 (1.5)	333.0 (29.7)	30.5 (0.6)	191.0 (42.4)

of piperacillin/tazobactam 250 μg in 0.1 mL solute, along with dexamethasone 400 μg in 0.1 mL solute, was given.

The graft clarity gradually improved (Figure 2), the media became clearer with progressive visual improvement and normal fundus details. After 6 months, she regained a best-corrected visual acuity of 20/40 N6 in the left eye with aphakic correction. Contact lens correction is planned for her next follow-up consultation. An electroretinogram showed 50% reduction in B wave amplitude of cone response in the left eye compared with the right eye. The other responses had amplitudes equal to or more than the right eye (Figure 3, Table 1).

Discussion

Endophthalmitis is a devastating complication of intraocular surgery and appropriate intravitreal antibiotics are the primary treatment modality.[4] Although amikacin and ceftazidime are the most commonly used intravitreal antibiotics against gram-negative endophthalmitis, there has been increasing evidence of resistance to these drugs.[5] Piperacillin/tazobactam is currently successful against most gram-negative infections, but there are no reports of its use for the treatment of clinical endophthalmitis.[6] Intravitreal piperacillin/tazobactam has been found to be effective in experimental *P aeruginosa* endophthalmitis;[3,7] a non-toxic dose has been studied in rabbit eyes.[8] Although there are no published clinical trials, piperacillin/tazobactam was used for this patient to salvage the eye. While piperacillin/tazobactam shows promise for multidrug-resistant endophthalmitis, further clinical trials are required to confirm its safety.

References

1. Pop-Vicas AE, D'Agata EM. The rising influx of multidrug-resistant gram-negative bacilli into a tertiary care hospital. Clin Infect Dis. 2005;40:1792-8.
2. Eifrig CW, Scott IU, Flynn HW, Miller D. Endophthalmitis caused by *Pseudomonas aeruginosa*. Ophthalmology. 2003;110:1714-7.
3. Ozkiris A, Evereklioglu C, Esel D, Akgun H, Goktas S, Erkilic K. The efficacy of piperacillin/tazobactam in experimental *Pseudomonas aeruginosa* endophthalmitis: a histopathological and microbiological evaluation. Curr Eye Res. 2005;30:13-9.
4. Results of the Endophthalmitis Vitrectomy Study. A randomized trial of immediate vitrectomy and intravenous antibiotice for the treatment of postoperative baterial endophthalmitis Vitrectomy Study Group. Arch Ophthalmol. 1995;113:1479-96.
5. Anand AR, Therese KL, Madhavan HN. Spectrum of aetiological agents of postoperative endophthalmitis and antibiotic susceptibility of bacterial isolates. Indian J Ophthalmol. 2000;48: 123-8.
6. Young M, Plosker GL. Piperacillin/tazobactam: a pharmacoeconomic review of its use in moderate to severe bacterial infections. Pharmacoeconomics. 2001;19:1135-75.
7. Ozkiris A, Evereklioglu C, Akgun H, Esel D, Caner F, Erkilic K. A comparison of intravitreal piperacillin/tazobactam with ceftazidime in experimental *Pseudomonas aeruginosa* endophthalmitis. Exp Eye Res. 2005;80:361-7.
8. Ozkiris A, Evereklioglu C, Kontas O, Oner AO, Erkilic K. Determination of nontoxic concentrations of piperacillin/tazobactam for intravitreal application. An electroretinographic, histopathologic and morphometric analysis. Ophthalmic Res. 2004;36:139-44.

Plexiform Neurofibroma Simulating Recurrent Chalazion

Dear Editor,

A chalazion is the most common localised lipogranulomatous inflammation of the eyelids and the meibomian glands. Although it seems easy to clinically diagnose chalazion, a number of benign, premalignant, or even malignant lesions may simulate chalazion.[1] Plexiform neurofibroma (PN) is considered to be almost pathognomonic of neurofibromatosis type-1 (NF-1),[2] and has been reported to masquerade as chalazion in a patient with NF-1.[3] We recently treated a patient with PN simulating chalazion, who did not have systemic features of NF-1.

An 18-year-old woman presented with a 2-month history of a lump at the lateral end of the right upper eyelid. At examination, there was a palpable nodule, which was consistent with a diagnosis of chalazion. She underwent incision and curettage of the lesion, and the swelling disappeared. However, samples were not sent for histopathological testing.

The patient presented again 1 year later with a similar swelling at the same site, consistent with a diagnosis of chalazion (Figure 1). An excisional biopsy was performed and histological examination revealed it to be PN (Figure 2). Systemic examination of the patient failed to reveal any evidence of NF-1, and screening of family members for NF-1 was inconclusive.

PN commonly involves the trigeminal or upper cervical nerves and occurs less commonly on the eyelids than the trunk. Pathologically, PN represents diffuse involvement of a nerve segment and its branches with tortuous expansion; its gross appearance has been described as a 'bag of worms'. PN in patients with NF-1 has the potential to develop into malignant peripheral nerve sheath tumours, but the most serious problem is the development of glaucoma in the affected eye in 50% of patients.[3]

Figure 1. Right upper eyelid showing the nodule.

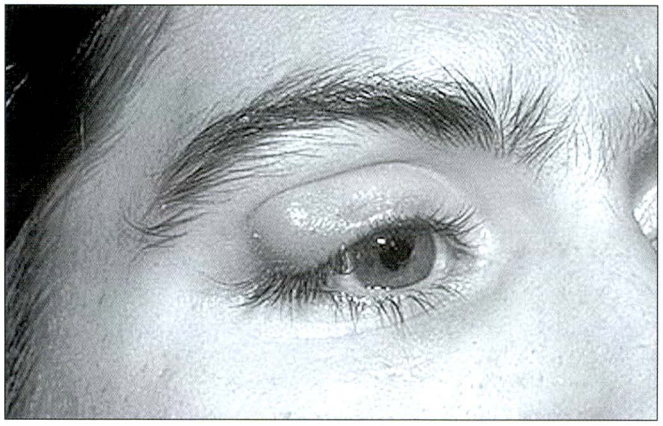
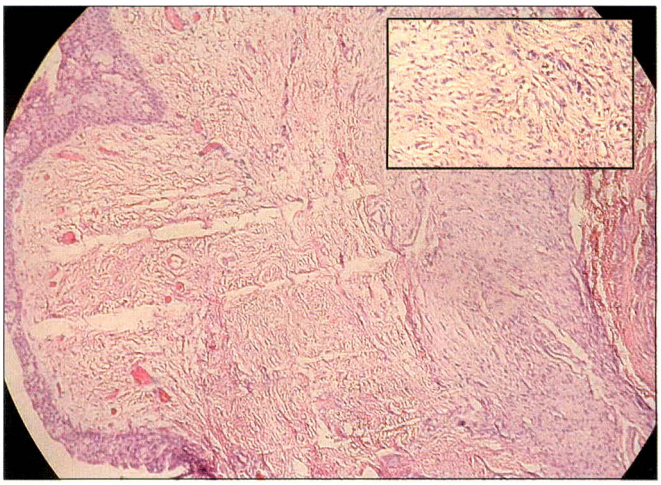


Figure 2. Histological slide showing spindle cells, some of which have wavy nuclei with a bland chromatin pattern with many interspersed histiocytes (original magnification, x 100; inset, x 400).



Various lesions may masquerade as chalazion and appropriate diagnosis may be delayed without histological examination. Histopathological examination of chalazion is generally recommended for patients with atypical symptoms, recurrence, older age, unilateral therapy-resistant keratoconjunctivitis, and regional lymph node involvement.[4]

We would like to emphasise the importance of histological sampling for recurrent or persistent chalazion. In this case, considerable delay in establishing the diagnosis could have been avoided.

References

1. Ozdal PC, Codere F, Callejo S, Caissie AL, Burnier MN. Accuracy of the clinical diagnosis of chalazion. Eye. 2004;18:135-8.
2. Sippel KC. Ocular findings in neurofibromatosis type 1. Int Ophthalmol Clin. 2001;41:25-40.
3. Tey A, Kearns PP, Barr AD. Plexiform neurofibroma masquerading as a persistent chalazion — a case report. Eye. 2006;20:946-8.
4. Domarus DV, Hinzpeter EN, Naumann GO. The clinical misdiagnosis of chalazion. Klin Monatsbl Augenheilkd. 1976;168:175-81.

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Comment

Chalazia are the most common benign and inflammatory mass lesions of the eyelids. Often evolving from an acute hordeolum internum, a chalazion is a non-infective inflammatory lipogranuloma arising from stasis and extravasation of the meibomian gland secretions. The authors highlight another non-inflammatory benign tumour, a neurofibroma, presenting as a 'recurrent chalazion'. Kersten et al demonstrated that a good clinical examination may result in 98% accuracy for the histopathological diagnosis of benign lesions and 90% accuracy for malignant lesions.[1] An astute clinician should therefore be able to diagnose the most common typical lesions, benign or malignant. Of course, this is only possible when the clinician is aware of the typical presentations of common benign lesions and, whenever an atypical presentation is encountered or malignant lesion suspected, to ensure a tissue diagnosis. In fact, most academic centres ensure that all excised lesions, even if typical and benign appearing, are sent for histopathological analysis. Not infrequently, unusual benign conditions such as xanthogranuloma and hair follicle tumours are diagnosed on this basis. The principal role of an ophthalmologist therefore lies in distinguishing a malignant lesion from a benign one, which may not only preserve vision but life as well, if the appropriate diagnostic and therapeutic interventions are instituted.

Neurofibromas are benign tumours of neural origin that may be solitary and localised, multifocal, or plexiform. Neurofibromas are characterised by a proliferation of Schwann's cells, peripheral nerve axons, endoneural fibroblasts, and perineural cells.[2] Isolated solitary neurofibromas usually present in middle age and are unassociated with neurofibromatosis in 90% of patients. Plexiform neurofibromas, on the other hand, are more often associated with neurofibromatosis type I (NF-1). However, strict criteria (≥2 of the following: café-au-lait spots, ≥6; neurofibromas, ≥2 solitary or ≥1 plexiform type; axillary and inguinal freckles, optic nerve glioma, ≥1; Lisch nodules, ≥2; characteristic osseous lesion; and first-degree relative with NF-1) should be applied to diagnose NF-I.[3]

The authors should be congratulated for highlighting the possibility of such a masquerade of the lesion to all clinicians to maintain a high level of suspicion for patients with unusual presentation.

References

1. Kersten RC, Ewing-Chow D, Kulwin DR, Gallon M. Accuracy of clinical diagnosis of cutaneous eyelid lesions. Ophthalmology. 1997;104:479-84.
2. Erlandson RA, Woodruff JM. Peripheral nerve sheath tumours — an electron microsopic study of 43 cases. Cancer. 1982;49;273-87.
3. Neurofibromatosis. Conference statement. National Institutes of Health Consensus Development Conference. Arch Neurol. 1988;45:575-8.

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Welcome from the World Glaucoma Congress

From the World Glaucoma Association

Prof Ivan Goldberg, President of the World Glaucoma Association (WGA), welcomed delegates to the World Glaucoma Congress. In planning for the meeting to be as successful as the Inaugural World Glaucoma Congress held in Vienna in 2005, the organising committee added significantly to its attractions for attendees to make it an unforgettable experience, both professionally and personally.

As well as sessions, workshops, and courses by leading glaucoma experts from around the globe, allowing comprehensive ophthalmologists an opportunity to update their glaucoma knowledge, understanding, and skills, the conference included parallel research and advanced glaucoma treatment programs, basic and clinical science sessions, topic discussion symposia, and video surgery sessions.

SEAGIG members were heavily involved in the scientific programme, chairing and presenting symposia and sessions, courses, and oral and poster presentations. SEAGIG also organised a course: *Safe and effective glaucoma drainage device implantation*, chaired by Prof Ivan Goldberg, with presentations by Prof Paul Chew, Dr Seng Kheong Fang, Dr Paul Healey, Dr Ho Ching Lin, Dr Clement Tham, and Dr Manuel Agulto.

The intention was for delegates to return home enriched and upskilled across the spectrum of glaucoma management, enabling a real difference in care for patients with glaucoma.

From the Organising Committee

What began as a mission to treat this group of diseases according to a set of published modalities a decade or 2 ago is now looked at with new eyes. Prof Paul Chew, President of the Local Organizing Committee welcomed delegates on behalf of the Glaucoma Surgeons Singapore. Prof Chew emphasised that there are great disparities in response to the same treatment regimen administered for any glaucomatous condition.

There is increasingly compelling evidence that one disease does not succumb to the simple formula of a single rigid definition. In Europe, primary open angle glaucoma is usually treated with eye drops, yet in Singapore, the same disease needs to be treated with drainage devices. Perhaps the most significant question is: Why are patients responding differently just because they come from a different country or region? This is a new challenge for an old adversary and the congress highlighted the disease variances in Asia.

Members of the SEAGIG Board

Standing from left to right: Prof Ivan Goldberg, Prof Ravi Thomas, Dr Ningli Wang, Dr Seng Kheong Fang, Dr Ki Ho Park, Dr Da Wen Lu, Dr Clement Tham.

Sitting from left to right: Dr Ramanjit Sihota, Dr Ikke Sumantri, Dr Paul Healey, Prof Prin Rojanapongpun, Dr Manuel Agulto, Prof Paul Chew

IGS and WGS Merger

During the congress, the merger of the World Glaucoma Congress (WGS) and the International Glaucoma Symposium (IGS) was announced, with the first combined meeting to be held as the World Glaucoma Congress in Boston, USA, in September 2009.

The Association of International Glaucoma Societies became the World Glaucoma Association on 22 July 2007. Similarly, the Association of International Glaucoma Patient Organisations became the World Glaucoma Patient Association.

From the Guest of Honour

Dr Vivian Balakrishnan, Minister for Community Development, Youth and Sports, and Second Minister for Information, Communications and the Arts was Guest of Honour on behalf of the Singapore Government. Dr Balakrishnan emphasised that blindness from glaucoma has always been an especially dreaded condition, but is even more so today in an information and knowledge-based society where so much depends on visual inputs. Practising ophthalmologists are at the cutting edge of this challenge: patients see or go blind in their hands.

Advances in healthcare arise from basic research and at the boundaries between disciplines. Surgical techniques are likely to change because of discoveries in the laboratory, or advances in material sciences, precision engineering, or nanotechnology. That is why investment in research must continue. Related to this is the need for international collaboration, and the exchange of data and ideas, which is why the World Glaucoma Congress is so important.

Prevention is better than cure — in glaucoma, this means identification of the population at risk, and earlier detection and treatment. Efforts spent in this phase of the disease will save many more eyes than surgery later on. Community health outreach and appropriate screening programmes are therefore essential.

Glaucoma is the primary cause of irreversible blindness, with an estimated 4.5 million people worldwide blind from primary open angle glaucoma alone. Most of these patients are blind because the disease was not detected early enough. In a study conducted in the Tanjong Pagar district in Singapore, glaucoma was the leading cause of blindness, with primary angle closure glaucoma being the most visually destructive form of the disease. The key to this challenge is early detection and prompt treatment.

It is fitting that the World Glaucoma Patient Association was also represented at the congress, as the patients' welfare is the ultimate index of success.

WORLD OPHTHALMOLOGY CONGRESS 2008

Hong Kong, 28 June to 2 July 2008

In this exciting era of medical and technological breakthroughs, there have been a number of great advancements in ophthalmology over the past decade. Clinicians must keep abreast of these latest developments to serve patients at the best level. The World Ophthalmology Congress will enable participants to immerse themselves in exchange of ideas and knowledge-sharing opportunities, and network with people in the field to facilitate collaborations. These will result in improved treatments and, in turn, benefit millions of individuals with eye diseases.

There is overwhelming support from many of the members of the International Federation of Ophthalmological Societies (IFOS). These internationally respected organisations and leaders are recruiting outstanding session chairs who will ensure the best speakers from around the world for the 32 subspecialty topics.

The world leaders in industry in ophthalmology have fully committed and there will be outstanding technical exhibits.

Hong Kong has been given the privilege of hosting this prestigious meeting. In this dynamic city, you can experience the unique blend of East and West, and enjoy the distinctive shopping and culinary delights. Hong Kong's amazing skyline and breathtaking harbour view will also impress you.

Important Dates

Early-bird registration opens	1 February 2007
Abstract submission opens	1 July 2007
Hotel reservation opens (for speakers and officials)	1 August 2007
Hotel reservation opens (for all delegates)	1 September 2007
Early-bird registration deadline	31 January 2008
Abstract submission deadline	31 December 2007
Advance registration deadline	31 May 2008
Opening ceremony	29 June 2008
Congress banquet	29 June 2008

For further details, e-mail: **info@woc2008hongkong.org** or visit the website at: **www.woc2008hongkong.org/**

IMAGE Modules 7 and 8 Released

The South East Asia Glaucoma Interest Group (SEAGIG) is pleased to announce the release of the fourth 2 modules of the educational resource from the Initiative for Management, Awareness and Glaucoma Education (IMAGE) project. Intended for use by ophthalmologists for their own educational advancement, as well as to facilitate educational programmes, the slides have been prepared by SEAGIG/IMAGE members to be clinically relevant to glaucoma care in the region and to have educational value relevant to the region.

The *Laser Treatment* module covers some of the laser therapies available for open angle glaucoma and angle closure glaucoma. These guidelines are intended to help clinicians choose the most appropriate treatment for their patients and also provide useful tips on pre- and postoperative care.

Each of the laser procedures (laser trabeculoplasty [Figure 1], iridotomy, iridoplasty, and cyclophotocoagulation) will be covered in detail, including an explanation of the procedure, when it is appropriate and why it is used, and general guidelines for managing the procedure.

The *Surgery* module outlines some of the common surgical options available to treat open angle, angle closure, and childhood glaucomas. Upon finishing this module, clinicians should have a better understanding of when surgery is the most appropriate treatment choice and how to augment surgical procedures with pre- and postoperative care to optimise patient outcomes.

After beginning with an overview of when surgery is the most appropriate treatment for glaucoma and the indications for surgery, this module provides a more detailed look at some commonly performed surgical procedures, including trabeculectomy (Figure 2), bleb revision, and iridectomy. Surgical 'pearls' explaining each step of the procedure are included to give clinicians additional guidance on technique.

Figure 1.

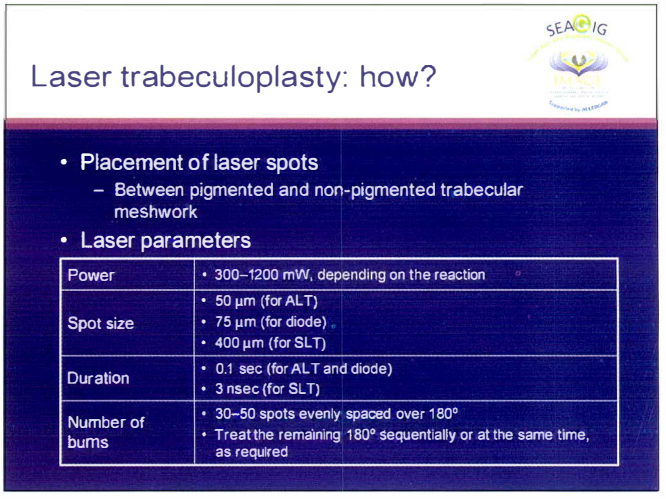
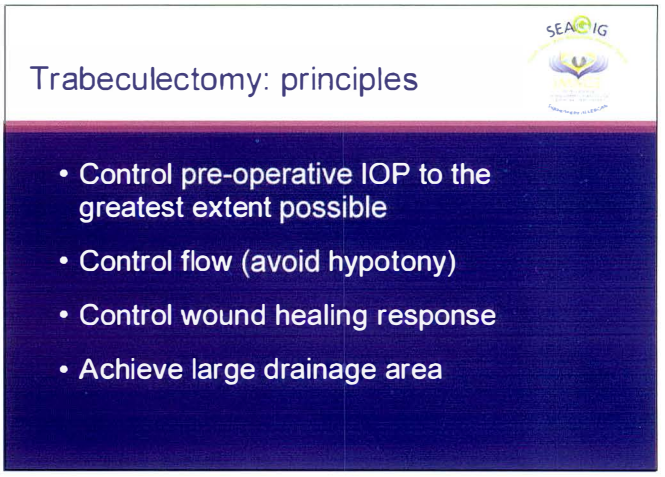


Figure 2.



Acknowledgement

With gratitude to the members of the SEAGIG-IMAGE Project Working Group.

IMAGE Modules Released

To date, the South East Asia Glaucoma Interest Group (SEAGIG) has launched the following Initiative for Management, Awareness and Glaucoma Education (IMAGE) modules

- *Glaucoma Assessment* — providing an overview of the objectives and components of an initial assessment
- *Optic Disc Assessment/RNFL Overview* — highlighting the key role that optic nerve examination plays in the diagnosis and follow-up of patients with glaucoma
- *Automated Perimetry* — intended as a practical guide to automated perimetry and its role in the diagnosis of glaucoma
- *Setting IOP Targets* — covering the rationale for setting target intraocular pressure
- *Medical Treatment* — providing an overview of the medical therapies available for the treatment of glaucoma
- *Laser Treatment* — covering some of the laser therapies available for open angle glaucoma and angle closure glaucoma
- *Surgery* — outlining some of the common surgical options available to treat open angle, angle closure, and childhood glaucomas.

Asian Oceanic Glaucoma Society 2007

AOGS 2007 BANGKOK

Bangkok, Thailand, 2-4 December 2007

The Asian Oceanic Glaucoma Society meeting will take place in Bangkok, Thailand, from 2 to 4 December 2007. The venue is the Central World Convention Center.

The main topics to be covered include:

- Angle closure glaucoma
- Glaucoma drainage devices
- Imaging in glaucoma
- Laser trabeculoplasty
- Neuroprotection
- Nanotechnology
- Normal tension glaucoma
- Congenital glaucoma
- Antivascular endothelial growth factor
- Glaucoma and associated diseases

Important dates

Abstract submission deadline	1 September 2007
Notification of abstract acceptance	15 October 2007
Early-bird registration deadline	30 September 2007
Pre-congress registration deadline	31 October 2007

For further details, contact the website at: **www.aogs2007.org**

5th Congress of the South East Asia Glaucoma Interest Group: SEAGIG 2008

Seoul, Korea, 25-27 September 2008

SEAGIG 2008 Seoul, Korea

The 5th Congress of the South East Asia Glaucoma Interest Group (SEAGIG 2008) will take place in Seoul, Korea, from 25-27 September 2008. SEAGIG was established to facilitate contact between glaucoma specialists in the region, to encourage collaborative research and service projects, to increase the opportunities for exchange of skills and knowledge in this rapidly advancing field, and to assist comprehensive ophthalmological colleagues and other eye care workers (whether medically trained or not) to keep up to date with advances in all aspects of glaucoma diagnosis and management.

The conference organising committee plans to introduce an educational and scientific programme that will cover cutting-edge basic and clinical research topics in the field of glaucoma. You are invited to make the scientific programme more dynamic and stimulating by submitting abstracts and registering for the conference.

Important Dates

Abstract submission deadline	6 June 2008
Early registration	30 June 2008
Abstract acceptance notice	11 July 2008

For further details, contact the website at: **www.seagig2008seoul.org**

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References:
1. Higginbotham EJ, Feldman R, Stiles M, Dubiner H, for the Fixed Combination Investigative Group. Latanoprost and timolol combination therapy vs monotherapy: one-year randomized trial. *Arch Ophthalmol.* 2002;120:915-922. 2. Data on file. Pfizer Inc, New York, NY.

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