

**AFRICAN JOURNAL OF
MEDICINE
and medical sciences**

VOLUME 36 NUMBER 1

MARCH 2007



**Editor-in-Chief
YETUNDE A. AKEN'OVA**

**Assistant Editors-in-Chief
A. O. OGUNNIYI
O. D. OLALEYE**

ISSN 1116-4077

Conjunctival hyperaemia and other ocular adverse effects on healthy African subjects after single dosing with 0.004% Travoprost

AO Ashaye*, ADA Adedapo**, BA Olusanya*, and CO Adeoti***
Departments of Ophthalmology, Pharmacology**, College of Medicine,
University of Ibadan, Ibadan and College of Medicine***, Ladoke Akintola
University of Technology, Osogbo, Nigeria.*

Summary

Conjunctival hyperaemia and ocular adverse effects induced by a single dose of 0.004% travoprost in healthy subjects were evaluated. A randomized, double-blind cross-over placebo controlled study was done. Conjunctival hyperaemia was evaluated clinically at 12, 24, 36 and 72 hours after dosing and volunteers reported all ocular adverse effects. 15 out of 20 subjects (70%) dosed with travoprost compared with 2 out of 20 (10%) dosed with placebo developed clinically moderate hyperaemia. However, significant difference in hyperaemia in the two groups occurred only at 24 hours ($P < 0.048$). The hyperaemia cleared by 72 hours. Travoprost may cause significantly short-term conjunctival hyperaemia even after a single dose in the eyes of healthy African subjects.

Keywords: *Adverse effects, Travoprost, clinical trial, healthy African volunteers*

Résumé

L'hyperémie conjonctivale et les effets adverse oculaire induit par une dose de 0.004% de travoprost chez les sujets sans étaient évaluées par une étude contrôlée, sans biais, masquée et avec un placebo. L'hyperémie conjonctivale était évaluée cliniquement à 12, 24, 36 et 72 heures après médication et les volontaires apportaient tous les effets adverses oculaire. Quinze sur vingt (70%) sujets recevaient le Travoprost comparé à deux sur vingt (10%) ayant eu un placebo avaient l'hyperémie modérée ; Cependant une différence significative en hyperémie chez les deux groupes apparaît seulement à 24 heures ($P=0.048$) et éliminée au 72 heures. Travoprost peut cause l'hyperémie conjonctivale significative à court terme après une dose dans les yeux des sujets Africain sain.

Correspondence: Dr. A.O. Ashaye, Department of Ophthalmology, College of Medicine, University of Ibadan, Ibadan, Nigeria. E-mail: adeyinkaashaye@yahoo.com

Introduction

Chronic glaucoma is the second leading cause of blindness in several regions in West Africa [1]. Treatment options for chronic glaucoma are aimed at lowering the intraocular pressure by surgery or medications.

Racial differences have been reported in response to surgical treatment of glaucoma [2], and there are suggestions that response to medical treatment may differ in different races [3,4]. Few reports on medical treatment for chronic glaucoma are available on indigenous Africans, the population that is probably mostly affected by chronic glaucoma [5].

The prostaglandin receptor agonists (Latanoprost, Travoprost and Bimatoprost) have been found to reduce intraocular pressure at least as effectively as Timolol maleate, a non-selective beta-adrenergic antagonists [6-8]. The latter had been the first line drugs used for the medical treatment of glaucoma even in developing countries. Whereas unwanted systemic side effects on the eye and cardiopulmonary system are reported with Timolol [6-9] in populations where clinical trials are conducted, there is paucity of such trials in indigenous African population. The prostaglandin receptor agonists seem to be devoid of such serious side effects. Conjunctival hyperaemia has been the adverse effect commonly reported, more so with travoprost [6-10]

Reports on the intraocular pressure (IOP) reduction effect or the adverse effects of these glaucoma drugs in the literature were studies conducted on Caucasians, Asians and African – Americans [3,4]. Travoprost (Travatan; Alcon, USA) which is one of the drugs released into the developing world market is one of the prostaglandin receptor agonist found to be effective in lowering elevated intraocular pressure associated with glaucoma [4]. This eyedrop has been found to lower intraocular pressure considerably in eyes of African – Americans [4] but produces more hyperaemia than the other prostaglandin analogues. The once daily application of this drug and its effectiveness in lowering IOP makes it attractive for medical lowering of IOP in glaucoma but the hyperaemia it causes may limit its

acceptance to glaucoma patients. The purpose of this study was to evaluate the degree of conjunctival hyperaemia and other ocular adverse effects after a single dose instillation of travoprost 0.004% in healthy subjects as part of a preliminary study to a randomized clinical trial of the effect of the drug on African glaucoma subjects.

Materials and methods

This was a prospective, randomized, double-masked crossover placebo controlled single centre trial. Details of which have been described in an earlier report (in print). Approval for the study was obtained from the Ibadan College of Medicine's ethical review committee, the principles of good clinical practice and the Helsinki's declaration were adhered to.

Subjects included in this study were male medical students aged 18 years and over. They were willing to comply with the protocol, had provided a signature on the informed consent document, and were in good physical and ocular health. 20 healthy volunteers were randomly assigned to receive one drop of travoprost 0.004% or placebo in a masked fashion.

Subjects were excluded from this study if they had a history of ocular hypertension or glaucoma; any abnormality preventing reliable applanation tonometry in the study eye; any concurrent infections or noninfectious conjunctivitis, keratitis, or uveitis in either eye, any significant systemic or ocular disease, any history of allergy or hypersensitivity to the test drug.

At the first visit, subjects read and signed an approved informed consent before any procedures were performed. Subjects had an ocular and systemic history taken. An ocular system questionnaire was completed to evaluate redness, dryness, photophobia, tearing, burning, crusting, itching, foreign body sensation, irritation. Visual acuity, funduscopy and physical examination was performed and documented.

Subjects who qualified for the study were randomly assigned to be given either one drop of travoprost 0.004% or placebo to be instilled in one randomly selected eye. At this preliminary visit and each subsequent visit, the subjects had slit-lamp biomicroscopy and Goldmann applanation tonometry. Each subject was examined by a masked observer. Subjects were dosed by an unmasked dosing study coordinator and had eye examination with pen-torch and slit-lamp biomicroscopy for inflammatory cells

and flare performed at the end of 6 hours, 12 hours, 24 hours, 48 hours and 72 hours post instillation of eyedrops. The instillation of fluorescein and measurement of intraocular pressure were made after all procedures were completed. After a three weeks washout period, the participants were invited to receive a single dose of the other eyedrops to the opposite eye. Subjects returned for the repeat evaluation

The subjects, other physicians except the unmasked dosing coordinator were masked to the medications in this trial. The conjunctival hyperaemia, were graded clinically at the slit lamp (Table 1), as described by Stewart [10] but modified and was also evaluated by comparing study eye with non-study eyes. The number of subjects who developed at least grade 2 conjunctival hyperaemia were counted. The presence and absence of inflammatory cells and flare, superficial punctate keratopathy were noted. These and other side effects were noted by an independent masked observer. An ocular adverse effect was defined as any change in the ocular health of the patient from baseline occurring during the study. These adverse effects were either observed or solicited for by the investigator at each visit.

The data was analyzed using Epi-Info version 6. Chi square test was used to analyze the differences between variables.

Results

Twenty male subjects were enrolled, all completed the first phase of study. All subjects were Africans. Nineteen subjects completed the second phase of the study. The only subject who discontinued early had to be out of town unexpectedly.

Table 1: Conjunctival hyperaemia grades and corresponding clinical signs.

Grade	Classification	Clinical signs
0	None	No visible vessel dilatation
1	Minimal	Barely noticeable regional vessel dilatation
2	Moderate	Fairly obvious generalized vessel dilatation giving moderate reddish hue
3	Severe	Very obvious generalized vessel dilatation giving deep reddish hue

The mean age of subjects was $24.4 \pm \text{SD } 2.2$ years. Travoprost produced significantly more moderate hyperaemia than placebo from baseline only at 24 hours. There was no significant difference in conjunctival hyperaemia at 12 and 36 hours. (Table 2). Travoprost demonstrated significantly more hyperaemia in the study eye compared to the non-study eye at 24 and 36 hours only. There was no difference in hyperaemia between the study and non-study eyes at 12 and 72 hours (Table 3).

Table 2: Grade 2 conjunctival hyperaemia in eyes treated travoprost and Placebo

At least Grade 2 Conjunctival Hyperaemia	Travoprost	Placebo	Yates Correction	*P value
0 to 12 Hours				
Yes	5	1		
No	15	19	1.76	0.182
> 12 Hours to 24 Hours				
Yes	7	1	3.91	0.048
No	13	19		
> 24 Hours to 36 Hours				
Yes	2	0	0.53	0.47
No	18	20		

*Fisher's Exact Test

Table 3: Conjunctival hyperaemia in study and non-study eyes after instillation of Travoprost

At least Grade 2 Conjunctival Hyperaemia	Travoprost	Placebo	Yates Correction	*P value
0 to 12 Hours				
Yes	5	1		
No	15	19	1.76	0.182
> 12 Hours to 24 Hours				
Yes	12	3	6.83	0.008
No	8	17		
> 24 Hours to 36 Hours				
Yes	9	2	4.51	0.03
No	11	18		
> 36 hours to 72 hours				
Yes	4	1	0.91	0.34
No	16	19		

*Fisher's Exact Test

Fourteen (14) (70%) of study subjects who received travoprost compared to 2(10%) of subjects who received the placebo developed at least grade 2 hyperaemia, that is, moderate conjunctival hyperaemia by the end of 72 hours after dosing out of which 1(5%) who received travoprost had severe hyperaemia. No subject had hyperaemia at the start of the study, and none of the subjects who received the placebo developed severe hyperaemia.

Adverse effects noticed or reported are listed in Table 4. Both groups reported various adverse effects such as redness, stinging, foreign body sensation, itching, headaches and shortness of breath and headaches. The most frequent side effects reported by more subjects dosed with Travoprost were hyperaemia, foreign body sensation, itching and stinging sensation. Of the reported adverse effects, conjunctival hyperaemia and foreign body sensation were significantly associated with travoprost. Three subjects complained of shortness of breath or mild chest pain which they had previously not experienced before the start of the study. Only one subject complained of temporary visual blurring.

No subject developed anterior chamber inflammatory cells and flare throughout the 72 hours of study. None had superficial punctate keratopathy. No subject was discontinued from this trial for an adverse event and no subject discontinued because of conjunctival hyperaemia.

Discussions

This study evaluated the ocular adverse effect after instillation of a single dose of travoprost in healthy African subjects. The finding of moderate conjunctival hyperaemia and the duration were consistent with previous reports on the adverse events reported with travoprost [4,10] but a higher prevalence of conjunctival hyperaemia than previously reported was observed in this study. In other studies the prevalence of conjunctival hyperaemia has been found to be up to 50% in eyes treated with travoprost 0.004% for two days [4,9,10] but in this study 70% of eyes developed noticeable redness after a single instillation of the eyedrop.

The reasons for conjunctival hyperaemia after instillation of a prostaglandin receptor agonist is a subject for speculation. The release of a vasodilator, nitric oxide is thought to be the cause of localized vessel dilation associated with prostaglandins [11]. However, the mechanism by which the release of nitric oxide occurs is not known exactly. Perhaps such

Table 4: Reported Ocular Adverse Effects in Travoprost and Placebo Treated Eyes

Adverse Reaction	Travoprost		Placebo		Yate's Correction	'P value
	n	(%)	n	(%)		
Conjunctival hyperaemia	15	(75.0)	4	(21.1)	9.29	0.002
Stinging	4	(20.0)	3	(15.8)		
Ocular dryness	3	(15.0)	2	(10.5)		
Foreign body sensation	6	(30.0)	1	(5.3)	2.54	0.05
Visual blurring	1	(5.0)	0	(0)		
Ocular itching	5	(25.0)	2	(10.5)	0.22	0.64
Shortness of breath/chestpain	3	(15.0)	1	(5.3)		
Headaches	2	(10.0)	2	(10.5)		
Skin darkening	0	(0)	0	(0)		

Fisher's Exact Test

mechanism is exaggerated in African eyes leading to increased inflammation of the conjunctiva and all prostaglandin analogues have been found to produce this. It is known that response to inflammatory agents is generally more in Africans [12,13].

On the other hand in vivo study of inflammatory potential and toxicity profile of prostaglandin analogues on conjunctival derived epithelial cells showed that none of the different analogues appeared to induced direct stimulation of the inflammatory pathways [14]. The authors suggested that preservative like benzalkonium chloride may be the major factor responsible for long-term ocular surface reactions in patients receiving prostaglandins on long term basis.

Other studies have found that benzalkonium chloride induces cell growth arrest and death even at low concentration and this may explain the toxicity effect of long term topical treatments with preservative containing drugs [15]. Although the test drugs both contain benzalkonium chloride but at higher concentration in the travoprost than the placebo, their use on a short term in these volunteers produced hyperaemia. It is possible that the pathogenesis of long term hyperaemia is the same as for short term hyperaemia and one might be finding an exaggerated response in Africans. Longer studies and the use of a placebo free of preservative in the next study should clarify these issues.

Corneal complications e.g. erosions have been similarly suggested to be the cause of conjunctival hyperaemia [7]. But no patient developed corneal punctate erosion nor anterior chamber cells during the period of study.

This study did not evaluate long-term effects of travoprost. The long-term use of travoprost is expected to be associated with more hyperaemia than single dose instillation but it has been reported that conjunctival hyperaemia with two day use of other types of prostaglandins, latanoprost, increases only in the first week of use, then reduces and stabilizes by 6 months when hyperaemia diminishes [16]. If travoprost were to have the same effect of less conjunctival hyperaemia with use, then the amount of hyperaemia found in this study may not correlate to long term effects of travoprost in African eyes. The single dose application of travoprost and duration of study will not allow observation of the reduction of hyperaemia effect.

Other reported effects such as stinging, foreign body sensation, itching were more prevalent in this study group than previously reported. None of these prevented the volunteers from continuing to participate to the end of study.

Clinical grading might have been subjective but the grading was done by a single observer who was masked to the drug received by volunteers thus eliminating variation in assessment and to some extent bias. However, it is unlikely that the observer may not recognize those who received travoprost because of the more hyperaemia it caused. Photographic documentation of the anterior segment could have been a more objective assessment; this requires a special camera attached to a slit lamp which was not available to the authors at the time of the study. Also, the subjects studied being medical students may over-report the adverse effects but there seem to be a consistency between reported conjunctival hyperaemia and what was observed clinically.

The study on healthy subjects, though limited in number due to cost provides some information on the effect of travoprost on the study population, the result may be different in diseased eye. This study did not evaluate ocular adverse effects in subjects with glaucoma itself. This may differ and is hoped to be the next area of study. Further, any adverse effects in subjects who also have other causes of red eye (for example, allergy, blepharitis, dry eye) were not evaluated in this trial.

More research is needed to determine the long-term clinical adverse effects associated with prostaglandins in Africans being treated for glaucoma. This study suggests that single dose travoprost causes more noticeable conjunctival hyperaemia in healthy African subjects at 12 hours than eyes dosed with placebo. The conjunctival hyperaemia resolved by 72 hours after instillation no adverse effect prevented any volunteer from discontinuing from the study.

Acknowledgements

All volunteers who were University of Ibadan medical students.

References

1. Thylefors B, Negrel AD, Pararajase-garam R and Dadzie KY; Globaldata on blindness 1995, 73: 115-121.
2. AGIS Investigators, The Advanced. Glaucoma Intervention Study (AGIS): 4. Comparison of treatment outcomes within race. Seven-year results. *Ophthalmology* 1998;105:1146-1164.
3. Hedman K and Larsson LI; The effect of latanoprost compared with timolol in African – American, Asian, Caucasian and Mexican Open angle glaucoma or ocular hypertensive patients. *Surv. Ophthalmol* 2002; 47:577-589.
4. Netland PA, Landry T, Sullivan K, *et al.* Travoprost compared with Latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension. *Am J. Ophthalmol* 2001; 132(4): 472-484.
5. Olurin O; Primary glaucoma in Nigeria. *East African Med. J.* 1972; 49:725-734.
6. United States Latanoprost Study Group. Camras CB; Comparison of latanoprost and timolol in patients with ocular hypertension and glaucoma: a six-month, masked multi-centre trial in the United States. *Ophthalmology* 1996, 103:138-147.
7. Alm A and Stjernschantz J; Effects on intra-ocular pressure and side effects of 0.005% latanoprost applied once daily, evening or morning. A comparison with timolol. Scandinavian latanoprost study group. *Ophthalmology* 1995; 102: 1743 – 1752.
8. Aquino MV and Lat-Luna M; The effects of latanoprost vs timolol on intraocular pressure in patients with glaucoma and ocular hypertension. *Asian J. Ophthalmol.* 1999; 1: 3-7.
9. Inan UU, Ermis SS, Orman A, *et al.*; The comparative cardiovascular pulmonary, ocular blood flow and ocular hypotensive effects of topical travoprost, bimatoprost, brimonidine and betaxolol. *J. Ocul Pharmacol Ther.* 2004; 20(4): 293-310.
10. Stewart WC, Kolker AE, Stewart JNN, Leech J and Jackson AL; Conjunctival hyperaemia in healthy subjects after short term dosing with latanoprost, bimatoprost and travoprost. *Am J. Ophthalmol* 2003; 135(3): 314-320.
11. Resul B and Stjernschantz J; Structure-activity relationships of prostaglandin analogues as ocular hypotensive agent. *Current Opinion in Therapeutic Patients.* 1993; 781 – 795.
12. Onadera T, Crimbel HV and Debroff BM; Effects of cycloplegia and iris pigmentation on post-operative inflammation. *Ophthalmic Surg.* 1999; 24(11): 746 – 752.
13. Broadway D, Grierson I and Hitching R; Racial differences in the results of glaucoma filtration surgery: are racial differences in the conjunctival cell profile important? *Br. J. Ophthalmol* 1994; 78(6): 466 – 475.
14. Guenoun JM, Baudouin C, Rat P, *et al.*; In vitro study of inflammatory potential and toxicity profile of latanoprost, travoprost and bimatoprost in conjunctival derived epithelial cells. *Invest Ophthalmol Vis. Sc.* 2005; 46(7): 2444-2450y.
15. De Sain Jean M, Brignole F, Bringaier AF, *et al.*; Effects of benzalkonium chloride on growth and survival of conjunctival cells. *Invest Ophthalmol Vis. Sc.* 1999; 40(3): 619-630
16. United States Latanoprost Study Group. Canirus CB; Comparison of latanoprost and timolol in patients with ocular hypertension and glaucoma in a six-month, masked, multicentre

- trial in the United States. *Ophthalmology* 1996;103:138-147.
17. Stewart WC, Stewart JA, Jenkins JN and Jackson AL: Corneal punctate staining with latanoprost bimatoprost and travoprost in healthy subjects. *J. Glaucoma* 2003; 2(6): 475 – 479.

Received: 13/06/06

Accepted: 07/03/07