www.ajbrui.org

Afr. J. Biomed. Res. Vol.19 (May, 2016); 103- 108

Full Length Research Paper

Travoprost Lowers Intraocular Pressure in Healthy Student Volunteers in a Nigerian Medical School

[1] Olusanya B.A, [2,3] Adedapo A.D.A, [1] Ashaye AO

Departments of [1]Ophthalmology and [2] Pharmacology & Therapeutics
College of Medicine, University of Ibadan. Ibadan, Nigeria
[3]Department of Clinical Pharmacology, University College Hospital, Ibadan. Ibadan, Nigeria.

ABSTRACT

We evaluated the change in diurnal intraocular pressure (IOP) induced by the instillation of single dose travoprost 0.004% and placebo into the eyes of 20 healthy African volunteers in a randomized double masked, placebo controlled, crossover, single centre study. Pulse rate, systolic and diastolic blood pressure, and respiratory rate were also measured. Mean IOP was lower than baseline values up to 72 hours after instillation but the mean IOP was significantly lower in the eyes that received travoprost compared to eyes that received placebo at 6 hours ($p < 0.007$), 12 hours ($p < 0.019$), and 24 hours ($p < 0.001$) after drug administration. Maximum IOP reduction was observed at 12 hours for travoprost and placebo with IOP lowered to 9.2mmHg $\pm$ 0.6mmHg (mean $\pm$ SEM) compared to 11.1mmHg $\pm$ 0.6mmHg for placebo. The maximum reduction of IOP from baseline values was more with travoprost 4.3mmHg $\pm$ 2.5mmHg (31%) versus 3.2mmHg $\pm$ 2.1mmHg (22%) for placebo although not statistically significant. There was minimal intraocular pressure reduction in the fellow eye which did not receive travoprost, but the reduction in IOP was not significantly lower in fellow eyes that received placebo. Systolic and diastolic blood pressure, and respiratory rates were unaffected by travoprost. This study suggests that a single dose of travoprost lowers the IOP more in eyes of indigenous African volunteers compared with placebo. The IOP lowering effect was for up to 72 hours after drug application. No adverse effect was observed in blood pressure and respiratory rates.

Keywords:- Travoprost, Intraocular Pressure, Healthy Volunteers, Africans

*Author for correspondence: *E-mail:* debyee1965@yahoo.co.uk ; *Tel:* +234-803-363-5204
Received: January 2016; Accepted (Revised): April, 2016

INTRODUCTION

Glaucoma is the commonest cause of irreversible blindness in most developing countries of the world (Hiller and Kahn, 1975; Sommer *et al.*, 1991; Wilson *et al.*, 1985; Martin *et al.*, 1985; Tielsch *et al.*, 1991; AGIS, 1998). Glaucoma resulting in bilateral blindness affected 4.5 million and 4.3 million for open angle glaucoma and angle closure glaucoma respectively in 2010 and will rise to 5.9 million and 5.3 million respectively by 2020. Women are disproportionately affected (Quigley and Broman, 2006). Surgery is perhaps the preferred choice of treatment in developing countries but this method is not always acceptable to the patients. In a study in Ibadan, 18% of glaucoma subjects offered surgery accepted to have the procedure done (Bekibele and Oluleye, 1999). Therefore many more affected individuals opt for medical treatment. Pharmacological treatment for glaucoma aims to lower the intraocular pressure (IOP) and thereby reduce the risk of optic nerve damage. There are evidences that show that reduction of IOP prevents development and progression of visual field loss (Kass, 1990; Hattenhaver *et al.*, 1998).

Several drug treatment frequently used in many developing countries for glaucoma include timolol, a topical β-blocker, pilocarpine, a cholinergic-agonist and acetazolamide, a carbonic anhydrase inhibitor. However side effects like cardiovascular and pulmonary disorders for β-blockers, headache, poor vision from miosis and myopia with pilocarpine, and paraesthesia, diuresis and gastrointestinal symptoms with acetazolamide are frequently reported in populations where clinical trials are conducted. Such studies are very few in West African population (Mahon *et al.*, 1979; Zadok *et al.*, 1994). More commonly, several socioeconomic factors make compliance to medical treatment poor (Kwame, 2004). Hence newer drugs such as prostaglandin receptor agonist including latanoprost, travoprost and bimatoprost that have been introduced, raise hopes if the cost were more affordable.

Travoprost is a topical ocular isopropyl ester prodrug that is rapidly hydrolysed by esterases in the cornea to the biologically active drug similar to other prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) analogues. It exerts its action by increasing outflow of aqueous through the uveoscleral outflow and has minimal effect on aqueous production (Netland *et al*., 2001). Travoprost has been found to be at least as effective as β-adrenergic blockers in lowering the IOP in patients with glaucoma, and there are suggestions that it produces lower mean IOP especially in blacks compared to non-blacks (Netland *et al.*, 2001). Travoprost has been found to be more effective than tafluprost in primary open angle glaucoma among Indians (Bachkheti *et al*., 2014). It thus seems to be a promising drug in the management of black glaucoma patients who do not accept to have surgery.

However, as there may be differences in the response to different anti-glaucoma medications in different races as there are to the surgical treatment for glaucoma (AGIS, 1998; Konstas *et al.*, 1997), studies on the effect of travoprost on indigenous African among whom glaucoma is commonest are rare.

The purpose of this study was to evaluate the effect of a single-dose administration on IOP of travoprost 0.004% or placebo in healthy volunteers over 72 hours, to determine the degree of IOP reduction and time of maximum reduction of IOP and duration of IOP lowering effect as a preliminary to a larger study in glaucoma patients. In addition, specific ocular and systemic side effects were observed.

MATERIALS AND METHODS

Study Design: The study was a randomised, double-masked, cross-over, placebo controlled single-centre trial, carried out at the Department of Ophthalmology, University College Hospital, Ibadan, Nigeria. Approval was obtained from the University of Ibadan/University College Hospital ethical review Committee; the principles of good clinical practice and the Helsinki's declaration were adhered to.

Participants selection: Twenty male healthy volunteers who were medical students aged 20 years to 30 years who had IOP less than 22 mmHg and had no ocular disease were enrolled into the study. All subjects read, understood and signed the written consent forms before participating in the study.

Before the study, medical and ocular histories were taken. Visual acuity, refraction, slit lamp evaluation of conjunctival hyperaemia, ophthalmoscopy and IOP measurements were done. Exclusion criteria were any visual field defects, IOP greater than 21 mmHg in either eyes, disc cupping greater in any eye than 0.5, presence of eye inflammation, previous eye injury, administration of a topical eye-drop at least 4 weeks preceding the onset of the study. Presence of any cardiovascular, renal, hepatic, lung diseases or use of steroids within 4 weeks prior to onset of study or any local eye factor that can prevent IOP to be measured.

The eligible subjects were randomly assigned by a computer generated randomization list to receive either Travoprost 0.004% or Placebo at 9.00a.m. on the first day on a randomly chosen eye. This timing was chosen for the convenience of the study participants. The eye drops were administered by the unmasked coordinator. All other participants were masked to the medications on trial. The IOP were measured at 0 hour (Baseline, 9.00 a.m.) 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 24 hours, 48 hours and 72 hours post instillation of test eye drop. All the measurements were performed by two senior resident doctors who were masked to the treatment assignments. Prior to the study their measurements were tested for consistency and agreements (K = 0.82).

Measurement of Intraocular pressure: After a three weeks washout period, a crossover study was carried out. The subjects received a single-dose of the other eye drop. IOP and other clinical evaluations were repeated. Intraocular pressure was measured with Goldmann applanation tonometer. Two measurements were taken in the study eye and averaged. The mean IOP was used at each time point. The IOP in the fellow eye was taken twice and averaged. Maximum IOP reduction was obtained from the difference between the baseline IOP and the lowest IOP.

Systolic and diastolic blood pressure (SBP, DBP), pulse rate and respiratory rates were measured at baseline, and at 1 hour and 4 hours after instillation of test medication.

Volunteers all lived in hostels very close to the study centre and were not admitted to the wards. During the period of study, they observed normal lifestyle. They had standardized meals and drinks. Ocular adverse effects were monitored by soliciting for specific symptoms and by clinical examination throughout the study. An adverse effect was defined as any change in general physical status or ocular health of the patient from baseline occurring during the study.

Statistical analysis: The data was analyzed on a microcomputer using the statistical package (SPSS) for data entry and analysis. The data was summarized using mean, median and standard deviations. The presentation was in frequency tables and line graph. The cross over

design nature of the study was taken into consideration in this method of analysis. At different points, the effect of the treatment was evaluated by analysis of covariance taking the initial IOP as covariate. Paired t-test was used to test the significance of differences in physiological characteristics when patients were on Travoprost compared with placebo. The repeated measures analysis was used to assess the effect of Travoprost on the physiological parameters and intraocular pressure.

RESULTS

Twenty volunteers participated in this study. Ten received travoprost, 10 others received placebo during the first phase. After 3 weeks, these were crossed over. One subject did not complete the second part of the study because he had to travel out of the study venue. The demographic characteristic of the volunteers is shown in Table 1. There were no differences in the demographic characteristic between the two groups of volunteers. The mean age was 24.4 years (SD = 2.2 years), the youngest volunteer was 21 years and the oldest was 28 years.

Table 1:
Summary statistics of the demographic characteristics of the respondents

	Mean	Median	SD	Min	Max
1. Age (yrs.)	24.39	24.00	2.20	21.00	28.00
2. Weight (kg)	64.72	64.50	9.58	53.00	87.00
3. Height	1.74	1.76	0.07114	1.57	1.90
4. BMI	Freq	%			
Under weight	5	(25.0)			
Normal	14	(70.0)			
Over weight	1	(5.0)			
Total	20	(100)			

Table 2a:
Baseline IOP, Pulse, Blood Pressure and Respiratory Rates

Baseline Parameters	Travoprost **n = 20**	Placebo **n = 19**	P - Value
IOP ± SEM	13.54 ± 2.12	14.22 ± 2.10	0.277
Pulse	71.4 ± 10.7	71.3 ± 6.92	0.985
Systolic BP	116.9 ± 14.2	116.0 ± 11.0	0.847
Diastolic BP	77.6 ± 8.9	74.6 ± 7.3	0.305
Respiratory Rates	18.8 ± 4.1	17.1 ± 2.9	0.217
R IOP	13.5 ± 2.5	14.1 ± 2.2	0.439
L IOP	13.7 ± 2.3	14.3 ± 2.0	0.373

Table 2b:
A Comparison of Physiological characteristics of subjects when on Travoprost and Placebo at different time points

Time			Mean	Median	Mode	Std.dev.	t-value	p-value
0	1. Pulse	Travoprost	71.57	11.48	54.00	100.00		
		Placebo	70.70	6.47	60.00	80.00	0.429	0.675
	2. SBP	Travoprost	116.71	15.24	100.00	150.00		
		Placebo	116.14	11.59	100.00	140.00	0.176	0.863
	3. DBP	Travoprost	78.00	9.32	66.00	100.00		
		Placebo	73.86	7.46	60.00	84.00	1.575	0.139
	4. Resp. Rate	Travoprost	19.36	4.06	12.00	29.00		
		Placebo	17.18	2.56	12.00	22.00	1.698	0.120
1hr	1. Pulse	Travoprost	71.33	8.25	60.30	84.00		
	Travoprost	Placebo	72.44	7.30	62.00	86.00	-0.676	0.508
	2. SBP	Travoprost	115.67	11.38	100.00	146.00		
	Travoprost	Placebo	117.39	13.73	105.00	168.00	-0.714	0.485
	3. DBP	Travoprost	78.61	7.50	66.00	95.00		
	Travoprost	Placebo	77.11	6.86	68.00	90.00	0.644	0.528
	4. Resp. Rate	Travoprost	19.45	3.80	14.00	28.00		
	Travoprost	Placebo	18.64	3.59	14.00	26.00	0.820	0.432
4hr	1. Pulse	Travoprost	75.88	10.31	60.00	100		
	Travoprost	Placebo	78.88	10.83	58.00	104.00	-0.868	0.398
	2. SBP	Travoprost	116.35	12.70	100.00	150.00		
	Travoprost	Placebo	115.18	8.84	104.00	140.00	0.413	0.685
	3. DBP	Travoprost	77.88	8.35	60.00	100.00		
	Travoprost	Placebo	75.53	7.98	58.00	90.00	0.832	0.418
	4. Resp. Rate	Travoprost	20.70	5.70	16.00	35.00		
	Travoprost	Placebo	19.40	2.07	16.00	24.00	0.756	0.469

Table 3:
Mean Intraocular Pressure with time for Travoprost and Placebo Treated Eyes

Time(hr)	Travoprost n = 20 IOP (mmHg) ± SD	Placebo n = 19 IOP (mmHg) ± SD	P – value
1	12.39 ± 2.09	13.33 ± 2.28	0.203
2	12.06 ± 2.15	12.83 ± 2.48	0.329
4	11.24 ± 2.54	13.11 ± 2.61	0.039
6	10.81 ± 2.17	13.40 ± 2.75	0.007
8	10.59 ± 2.00	11.00 ± 2.24	0.587
12	9.24 ± 2.39	11.06 ± 1.95	0.019
24	11.33 ± 2.20	14.00 ± 1.97	0.001
48	12.28 ± 2.89	13.06 ± 2.13	0.364
72	13.61 ± 2.79	13.44 ± 1.76	0.831

Table 4:
Maximum IOP Reduction in Eyes treated with Travoprost and Placebo

Treatment	IOP Reduction	P-value	t-test	95%C.I.
IOP Reduction 12 hours				
Travoprost	4.3 ± 0.6	<0.16	1.435	-0.47 to 2.73
Placebo	3.2 ± 0.5			
IOP Reduction 24 hours				
Travoprost	2.1 ± 0.6	<0.024	2.355	0.26 to 3.52
Placebo	0.22 ± 0.6			

DISCUSSION

In this study, single dose of travoprost 0.004% significantly reduced the IOP from the baseline in the eyes of healthy male volunteers compared to those who received placebo. The maximum IOP reduction of 31.0% with travoprost occurring at 12 hours post dosing (9.00 p.m.) shows a much larger reduction in these African eyes than previously reported for studies in Caucasian and Asian subjects, (Bito and Barrody, 1987; Kiuchi *et al*., 1994) although other types of prostaglandin analogues were used. Kiuchi and colleagues found maximum reduction of IOP in their Caucasian population to be 20% while Larsson found an IOP reduction of 20.4% after 12 hours and 24.5% reduction after 24 hours also in his predominantly Caucasian study subjects (Larsson, 2001). Both authors however studied the effect of latanoprost on the eyes of healthy volunteers.

The increased response could be as a result of the differences in the type of prostaglandin receptor agonist used or there may be a response difference due to racial differences. The time of maximal IOP reduction found in this study is in good agreement with that previously reported (Kiuchi *et al*., 1994; Larsson, 2001; Konstas *et al.*, 1997). Travoprost administered in the morning produced a maximum IOP reduction at 12 hours unlike the studies by Kiuchi and Konstas but similar to the results of Larsson, the reduction of IOP persisted till 24 hours and even up to 72 hours, although the reduction at 48 and 72 hours were not significant. Single dose travoprost in this study has a significantly sustained ocular hypotensive effect at least over 24 hours in healthy eyes.

The IOP reducing effect after 72 hours has not been studied presently and such result might be interesting. Daily IOP measurements beyond 72 hours could have been useful to assess when IOP would return to baseline value. Duration of action of the drug on healthy volunteers may be estimated from this.

The reduction of IOP in eyes which received the placebo might be the result of changes in circadian rhythm of IOP reported even in healthy persons (Drance, 1960; Liu *et al.*, 1998; Noel *et al*., 2001), and accentuated in glaucoma patients (Wilensky, 1990). This reduction was up to 19.5% in the placebo group in this study, occurring at 9.00 p.m, while the IOP quickly returned to baseline value by 24 hours (9.00 a.m.). In all the healthy young subjects in this study who were on placebo, diurnal IOP showed a peak measurement at 9.00 a.m. and a trough measured at 9.00 p.m., but these measurements were in sitting positions and without specific physiologic controls.

Instillation of test drops at 9.00 p.m. (baseline) rather than 9.00 a.m. might have produced larger reduction of IOP in these volunteers, because all prostaglandin analogues have been found to lower IOP better when instilled in the evening at least in glaucoma patients. This may also be true for healthy eyes.

The pattern of IOP reduction observed in this study may not reflect the 24 hours IOP pattern in ordinary life situations which is IOP in vertical position during the day and recumbent at night. There are no uniform reports on the circadian rhythm of IOP in healthy individuals. Whereas Noel et al found that IOP follows a 24 hours rhythm with a nocturnal peak value in healthy young Africans, unlike the early morning peak found in subjects with glaucoma (Noel *et al*., 2001). Liu and colleagues found that peak IOP occurred at 5.30 a.m., trough IOP occurred at 9.30 p.m. in healthy volunteers under strict control of experimental conditions (Liu *et al*., 1998). In this study, the effects of the drugs on nocturnal IOP have not been observed. There is a possibility that nocturnal IOP peaks were not detected in this study but the continuous reduction of IOP in the eyes of subjects treated with travoprost suggest that there was a control of the IOP peaks if they occurred. The study situation reflects the data collected in most glaucoma clinics where sitting IOPs during the daytime are considered mostly in patient management.

There was no change in blood pressure, respiratory rate and pulse rate in the 2 groups during the study time. Influences of physical activities and upright posture on

the blood pressure were the same in the 2 groups hence the lack of effects observed may be related to the test drugs.

The biases associated with measurements of IOP were minimised in this study by simulating glaucoma clinic situations as much as possible. Ambulatory diurnal IOPs were measured while subjects were in the sitting positions. There were no hospitalisations.
Measurements were taken by masked observers, an average of 2 readings taken. The effect of corneal thickness of IOP however was not considered in this study. Also the importance of the nocturnal part of the circadian IOP curve could not be ignored. Most of the effect of these biases however have been minimised with the masked crossover design of the study which assure even distribution of biases to the two treatment groups. However, observed effects cannot be generalised to all healthy population as only young males were studied. Results obtained in this study also cannot be generalised to glaucomatous eyes, who generally have higher presenting IOP and who are much older than the study population. The IOP in healthy volunteers before instillation was low, though they experienced conjuctival hyperaemia as adverse drug reaction following instillation of travoprost (Ashaye *et al*., 2007). It is expected that IOP reduction will be more in African subjects with glaucoma who have higher IOPs and the next study should evaluate the effect of prostaglandin analogues on glaucoma subjects in indigenous African population.

In conclusion, a single drop application of travoprost 0.004% reduced diurnal IOP in the eyes of healthy African volunteers. Maximal IOP lowering effect occurred at 12 hours after dosing. The amount of reduction in IOP at 12 hours was more in these African subjects than previously reported in healthy Caucasian volunteers.

Acknowledgement:
The volunteers who were University of Ibadan medical students, and Doctors O. Komolafe, O. Olawoye for measuring the intraocular pressure.

REFERENCES

AGIS Investigators (1998): The Advanced GlaucomaIntervention Study (AGIS): 4. Comparison of treatment outcomes within race. Seven-year results. Ophthalmology, 105:1146-1164.

Ashaye A.O, Adedapo A.D.A, Olusanya B.A, Adeoti C.O. (2007): Conjuctival hyperaemia and other ocular adverse effects on healthy African subjects after single dosing with 0.004% Travoprost. Afr J Med Med Sci, 36:37-42.

Bachkheti N, Chalia D, Sehgal V.K, Walia S. (2014): Efficacy and safety of travoprost 0.004% compared with tafluprost 0.0015% in patients with primary open-angle glaucoma. IJBCP, 3(6):958-963.

Bekibele C.O, Oluleye T.S. (1999): Acceptability of surgery for the primary treatment of chronic open angle glaucoma. A prelim report. Nig. of Ophthalmol, 7(1): 5-9.

Bito L.Z, Barrody R.A (1987): The ocular pharmacokinetics of eicosanoids and their derivatives. I. Comparison of ocular eiconoid penetration and distribution following the topical application of PGF2 alpha, PGF2 alpha-I-methyl ester, and PGF2 alpha-l-isopropyl ester. Exp. Eye Res, 44: 217-226

Drance S.M. (1960): The significance of the diurnal tension variations in normal and glaucomatous eyes. Arch Ophthalmol, 60: 494-501.

Hattenhaver M.G, Johnson D.H, Ing H.H. et al., (1998): The probability of blindness from open-angle glaucoma. Ophthalmology, 105:2099-2104.

Hiller R, Kahn H.A. (1975): Blindness from glaucoma. Am J. Ophthalmol, 80:62-69.

Kass M.A. (1990): Timolol treatment prevents or delays glaucomatous visual field loss in individuals with ocular hypertension: a five year randomised double-masked, clinical trial. Trans Am J. Ophthalmol Soc, 87:592-618.

Kiuchi Y, Takamatsu M, Mishima H.K. (1994): PhXA41, a prostaglandin F-analogue reduces the intraocular pressure (IOP) in human volunteers during day and night. Invest Ophthalmol Vis Sci**,** 35:(Suppl): 2178.

Konstas A.G.P, Dimitrios A.M, Stewart W.C. (1997): Diurnal intraocular pressure in untreated exfoliation and primary open-angle glaucoma. Arch Ophthalmol, 115: 182-185.

Kwame O.B. (2004): Unaffordable drug prices: the major cause of non-compliance with medication in Ghana. J. Pharm Pharmaceut Sci., 7(3):350-352.

Larsson L. (2001): Intraocular pressure over 24 hours after a single-dose administration of latanoprost 0.005% in healthy volunteers. A randomised, double-masked placebo controlled cross-over single centre study. Acta Ophthalmological Scaninavica, 79(6):567-571.

Liu J.H, Kripke D.F, Hoffman R.E, Twa M.D, Loving R.T, Rex K.M, Gupta N, Weinreb R.N. (1998): Nocturnal elevation of IOP in young adults. Invest Ophthal Vis Sci., 39(13) 2702 – 2712.

Martin M.J, Sommer A, Gold E.B, Diamond E.L. (1985): Race and primary open-angle glaucoma. Am J. Ophthalmol, 99:383-387.

Mc Mahon C.D, Shaffer R.N, Hoskins H.D. et al., (1979): Adverse effect experienced by patients taken timolol. Am J. Ophthalmol, 88:736-738.

Netland P.A, Landry T, Sullivan E.K. et al., (2001): Travoprost compared with latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension. Am J. Ophthamol, 132(4): 472-484.

Netland P.A, Robertson S.M, Sullivan E.K, Silver L, Bergamini M.V, et al., (2003): Response to travoprost in black and non-black patients with open-angle glaucoma or ocular hypertension. Adv Ther., 20(3): 149-163

Noel C, Kabo A.M, Romanet J.P, Montmayeur A, Buguet A (2001): Twenty-four hour time course of IOP in healthy and glaucomatous Africans: relation to sleep pattern. Ophthalmology, 108(1): 139-144.

Quigley H.A, Broman A.T. (2006): The number of people living with glaucoma worldwide in 2010 and 2020. Br J Ophtalmology, 90:262-267.

Sommer A, Tielsch JM, Katz J et al., (1991): Racial differences in the cause-specific prevalence of blindness in East Baltimore. N. Engl J. Med., 325:1412-1417.

Tielsch J.M, Sommer A, Katz J, Royall R.M, Quigley H.A, Javitt J (1991): Racial variations in the prevalence of open-angle glaucoma. The Baltimore Eye Study. JAMA, 266:369-374.

Wilensky JT (1990): Diurnal variations in intraocular pressure. Trans Am Ophthalmol Soc,. 89:757 – 700.

Wilson R, Richardson T.M, Hertzmark R, Grant W.M. (1985): Race as a risk factor for progressive glaucomatous damage. Am J Ophthalmol, 17:653-659.

Zadok D, Geyer O, Zadok J et al., (1994): Combined timolol and pilocarpine alone and timolol alone in the treatement of glaucoma. Am J. Ophthalmol, 117:728-731.