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Evaluation of the Intraocular Pressure-Reducing Effect of Latanoprost as Monotherapy in Open-Angle Glaucoma

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A B S T R A C T

Objective of this study was to evaluate the intraocular pressure-reducing effect of latanoprost as monotherapy after replacing current dual therapy in glaucoma patients. The 6-months study comprised 189 patients with primary open angle glaucoma who were treated at least 6 months with two different kind of topical medications (-blockers, pilocarpine, dorzolamide and brimonidine). Due to local side effects, multiple dosing regime and inadequately controlled intraocular pressure (IOP), they where switched to latanoprost 0.005% monotherapy. After switched to latanoprost, mean (IOP) was measured at baseline, after l5 days, 2 and 6 months of treatment. After six-months 178 patients had completed the study. These analyses enrolled all patients (n=189), thus, the Intention-To-Treat (ITT) results were shown instead of the results of the reduced population. IOP was clinically importantly reduced from baseline level. Five patients had uncontrolled IOP. The difference between IOP before (21.9 2.4) and after 15 days (17.4 1.7), 2 months (16.7 1.8) and 6 months (16.6 1.4) was statistically significant (p< 0.001). 90% patients has reached target IOP ≤18 mm. A conjunctival hyperaemia in 18 (9%), stinging and itching in 7 (4%) patients was reported. Increased iris pigmentation was seen in 3 (2%) patients. The results of this study indicate that dual therapy in open-angle glaucoma can effectively be replaced by latanoprost monotherapy in many patients.

Introduction

Latanoprost is a prostaglandin F_2 analog and a selective F-prostaglandin receptor agonist that effectively reduce intraocular pressure (IOP) in patients with

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glaucoma[1–3]. Latanoprost markedly increased uveoscleral outflow[4,5]. It has been found that latanoprost does not alter the aqeous humour production to a clinically significant extent[5]. In many patients topical adrenergic antagonists alone do not sufficiently lower IOP and additional medications have to be prescribed. Administration of several medications may be inconvenient for the patients[6]. Switching to another drug is an alternative in patients in who two different kind of topical medications no longer control the IOP sufficiently. A long-term maintance with monotherapy in the management of glaucoma would therefore be advantageous for the patients.

The purpose of this study was to evaluate the pressure-reducing effect of latanoprost as monotherapy, after replacing current dual therapy (-blockers, pilocarpine, dorsolamide and brimonidine) in glaucoma patients whose IOP was inadequately controlled, over time from baseline to six months.

Material and Methods

This multicentre study included 189 glaucoma patients from 6 centers in a 6-month open-label comparison of latanoprost monotherapy to the current dual therapy: 132 were on timolol and pilocarpin, 43 timolol and dorsolamde and 14 brimonidine and timolol combination. After obtaining approval from the appropriate regulatory authorities and ethics commitees, oral consent was obtained from all patients before entering the study. The study protocol followed the guidelines of the Declaration of Helsinki.

All participants, aged 51–74 (mean 61.1 13.2 years), enrolled in study were diagnosed as suffering of primary open-angle glaucoma, based on having inadequately controlled IOP on current local therapy, open angle on gonioscopy, no evidence of underlying ocular or systemic cause of high IOP, glaucomatous visual field defect and papillary excavation (C/D vertical > 0.3). The patients were included in the study by the judgement of the investigator based of the disease status of each individual patient. In addition the patients should be on therapy with topical -adrenergic antagonists in combination with pilocarpine, brimonidine or dorzolamide. Exclusion criteria included any treatment with more than two glaucoma medications and any previous treatment with latanoprost, current use of contact lenses, previous filtering surgery, argon laser trabeculoplasty, pregnant women and any ocular inflammation within three months were reasons for excluded from study. The patients were examined at a prestudy visit within 4 weeks of trial

TABLE 1
SCHEDULE OF EXAMINATION

Examinations	Four weeks before baseline	Time after commencement of the therapy (months)			
		Baseline	0.5	2	6
Gonioscopy	X				
Visual field	X	X			
Ophthalmoscopy	X	X	X	X	X
Visual acuity	X	X	X	X	X
Adverse events	X	X	X	X	X
Slit-lamp examination	X	X	X	X	X
Intraocular pressure	X	X	X	X	X

treatment initiation. Table 1 presents the schedule of examinations.

Intraocular pressure was measured by Goldmann applanation tonometer. In each eye three measurements were performed and the mean of the three measurements was used in the statistical analyses. IOP were recorded at baseline and 15 days, 2 months and 6 months after the initiation of latanoprost. Examinations were done at 9 a.m., 1 p.m. and 5 p.m.

Statistical analysis was done. Analysis of variance model was used the IOP reduction as response, and center as factor.

The minimal true mean IOP reduction that the trial was designed to determine was 4 mmHg with power 90%, 5% significance level and it was estimated of the standard deviation (SD) 1.5 mmHg of the IOP reduction.

Results

Of the 189 patients enrolled in the study, 178 had completed the study. Six patients were lost to follow up. Five patients had uncontrolled IOP and they underwent on trabeculectomy. In this study the results were presented as the Intention-To-Treat (ITT) results based on 189 patients. The missing IOP values were replaced with the last measurement IOP value for each patient.

Table 2 shows that there was no clinically important differences in IOP values between centers.

TABLE 2
INTRAOCULAR PRESSURE ON EACH MEASUREMENT AT ALL ENROLLED PATIENTS (N=189) IN 6 CENTERS

	Center 1	Center 2	Center 3	Center 4	Center 5	Center 6
Baseline IOP*	22.2	20.1	21.3	22.2	21.9	23.4
Baseline SD	2.4	2.9	2.2	1.2	2.3	2.2
Baseline SEM	0.4	0.6	0.4	0.3	0.4	0.4
Baseline –95%	21.3	18.7	20.4	21.6	20.9	22.6
Baseline +95%	23.0	21.5	22.2	22.7	22.7	24.3
15 days IOP*	17.7	16.3	17.5	17.2	17.3	17.0
15 days SD	1.9	1.5	1.7	1.8	1.5	1.5
15 days SEM	0.3	0.3	0.3	0.3	0.3	0.3
15 days –95%	17.0	15.7	16.9	17.1	16.7	16.5
15 days +95%	18.4	17.1	18.2	18.3	17.8	17.6
2 months IOP*	17.6	15.9	16.6	16.7	16.7	16.4
2 months SD	2.0	2.4	1.5	1.6	1.6	1.4
2 months SEM	0.3	0.5	0.3	0.3	0.3	0.2
2 months –95%	16.9	14.8	16.0	16.2	16.0	15.9
2 months +95%	18.3	17.0	17.2	17.2	17.4	17.0
6 months IOP*	16.5	16.3	16.3	16.7	16.6	16.8
6 months SD	1.5	2.0	1.0	1.4	1.2	1.5
6 months SEM	0.2	0.4	0.2	0.2	0.2	0.3
6 months –95%	16.0	15.4	16.0	16.2	16.2	16.2
6 months +95%	17.0	17.3	16.8	17.1	17.1	17.4

* The mean IOP values in mmHg of three measurements from 9 a.m. to 5 p.m

TABLE 3
INTRAOCULAR PRESSURE ON EACH MEASUREMENT AT ALL ENROLLED PATIENTS (N=189)

Latanoprost treatment duration	IOP* (mmHg)	SD	SEM	–95%	+95%
Baseline	21.9	2.4	0.18	21.6	22.3
After 15 days	17.4	1.7	0.13	17.1	17.6
After 2 months	16.7	1.8	0.13	16.5	17.0
After 6 months	16.6	1.4	0.25	15.9	16.9

* The mean IOP values of three measurements from 9 a.m. to 5 p.m.; F=2.7, df=20, p<0.001.

TABLE 4
PRESSURE-REDUCING EFFECT OF LATANOPROST AFTER SIX MONTHS

The number of patients	The initial value IOP (mm Hg)	Pressure reducing effect	SEM	Different studies
149	25.2	8.5	0.3	Watson et al. (1995)
89	24.8	8.6	0.4	Alm et al. (1995)
244	25.1	6.2	0.2	Camras et al. (1998)
829	24.8	7.7	0.1	Hedman et al. (2000)
129	21.9	5.3	0.1	Mandić et al. (2001)

The mean IOP at each measurement is presented on Table 3. The results from Table 2 and Table 3 are presented with the standard deviation (SD), with the standard error of the mean (SEM) and 95% confidence interval (CI) at each treatment duration. At baseline the mean IOP was 21. 9 2.4 mm Hg. At the end of the study after 6 months of treatment, the mean IOP was 16.6 1.4 mmHg.

The pressure-reducing effect of latanoprost as monotherapy and comparison with the results of other studies is presented on Table 4. The results are presented with mean IOP values and SEM.

TABLE 5
PERCENTAGE AND NUMBER OF PATIENTS WITH REPORTED OCULAR ADVERSE EVENTS (N=189)

Conjunctival hyperemia	18 (9%)
Itching	7 (4%)
Increase iris pigmentation	3 (2%)

90% patients reached target IOP 18 mmHg (besed on the ITT population).

Adverse ocular events was reported by 15% patients on Table 5.

No systemic adverse event was reported.

Discussion

Combination of two topical medications is common in the treatment of glaucoma. A topical medications that reduces inflow such as -adrenergic antagonist or carbonic anhydrase inhibitors preferably is combined with medication that increase outflow such as pilocarpine and latanoprost. A multidosing regime may be inconvient for the patients and can result in poor compliance[6]. It is a great importance to consider the option of switching a patient from dual therapy to monotherapy when the IOP is inadequately controlled. In our study patients with glau-

coma inadequately controlled on current dual therapy with topical adrenergic antagonists in combination with pilocarpine, or dorsolamide or brimonidine were switched to treatment with latanoprost once daily.

The IOP measured at baseline, after 15 days, 2 months and 6 months, was considered a relevant point of clinical efficacy for one tratment arm-latanoprost, in patients who were switched from several combinations of previous tratment. At six months 178 patients had completed the study. The difference between IOP before and after l5 days, 2 months and 6 months was significant and 90% patients has reached target IOP 18 mmHg. This results show that latanoprost applied topically once daily is at least effective in reducing the IOP as the other combinations of topical medications. Similar results were founded in other studies[1–4,7,8].

No serious side effects were observed. Mild conjunctival hyperemia was observed in 16 patients, stinging and itching in 7 patients. Slit lamp examinations revealed increased iris pigmentation in 3 patients.

Glaucoma is a chronic disease and the effect of the drugs over time is of clinical interest. With prolonged treatment many drugs including -blockers lose some of their initial effect[9,10]. Only five patients had uncontrolled IOP and they underwent trabeculectomy.

The results of this multicenter study showed that latanoprost 0.005% applied topically once daily is effective in reducing the IOP, and dual therapy in open-angle glaucoma can effectively be replaced by latanoprost monotherapy in many patients.

REFERENCES

1. ALM, A., J. STJERNSCHANTZ, Ophthalmology, 102 (1995) 1743. — 2. WATSON, P., J. STJERNSCHANTZ, Ophthalmology, 103 (1996) 126. — 3. CAMRAS, C. B., Ophthalmology, 103 (1996) 1387. — 4. TORIS, C. B., C. B. CAMRAS, M. E. YABLONSKI, Ophthalmology, 100 (1993) 1297. — 5. GAGELT, B. T., P. L. KAUFMAN, Exp. Eye Res., 49 (1989) 389. — 6. WAINREB, R. N., J. Glaucoma, 1 (1992) 134. — 7. MISHIMA, H. K., K. MASUDA, Y. AZUMA, M. ARAIE, Arch. Ophthalmol., 114 (1996) 929. — 8. HEDMAN, K., A. ALM, Eur. J. Ophtalmol., 10 (2000) 94. — 9. BOGER, W. P., C. A. PULIAFITO, R. F. STEINERT, D. P. LANGSTON, Ophthalmology, 85 (1978) 259. — 10. GANDOLFI, S. A., Invest. Ophthalmol. Vis. Sci., 31 (1990) 354.

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EVALUACIJA INTRAOKULARNE HIPOTENZIVNE UČINKOVITOSTI LATANOPROSTA KAO MONOTERAPIJE KOD GLAUKOMA OTVORENOG KUTA

S A Ž E T A K

Cilj rada bio je odrediti učinak latanoprosta, kao monoterapije kojim je zamijenjena dvojna terapija, na sniženje intraokularnog tlaka kod glaukomskih bolesnika. Longitudinalna 6-mjesečna studija uključila je 189 bolesnika sa glaukomom otvorenog kuta. Svi bolesnici koristili su terapiju dvama lijekovima (-blokeri, pilokarpin, dorzolamid i brimonidin) najmanje 6 mjeseci. Zbog lokalnih neželjenih popratnih promjena, potrebe za prečestim doziranjima, te neodgovarajućoj kontroli intraokularnog tlaka prebačeni su na liječenje jednim lijekom – latanoprostom 0.005%. Po zamjeni terapije mjeren je intraokularni tlak na dan zamjene, nakon 15 dana, te nakon 2 i 6 mjeseci. Nakon 6 mjeseci 178 bolesnika uspješno je završilo studiju. Međutim, prema terapijskoj namjeri (eng. Intention-To-Treat), ovim su analizama prikazani rezultati svih 189 bolesnika koji su uključeni u ispitivanje, a ne njihov reducirani broj. Došlo je do klinički značajnog smanjenja intraokularnog tlaka. Pet bolesnika imalo je nekontrolirano visok intraokularni tlak. Razlika tlaka prije (21.9 2.4), nakon 15 dana (17.4 1.7), nakon 2 mjeseca (16.7+1.8) i nakon 6 mjeseci (16.6 1.4) statistički je značajna ($p<0.001$). 90% bolesnika doseglo je takozvani ciljani intraokularni tlak (manji ili jednak 18 mmHg). Zabilježena je konjunktivalna hiperemija kod 18 (9%), te subjektivni simptomi peckanja i bockanja kod 7 (4%) bolesnika. Pojačana pigmentacija šarenice zabilježena je kod 3 (2%) bolesnika. Rezultati ove studije ukazuju da dvojna terapija može biti uspješno zamijenjena terapijom latanoprostom kao monoterapijom kod mnogih bolesnika sa glaukomom otvorenog kuta.