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Efficacy and side effects of latanoprost monotherapy compared to adding dorzolamide to timolol in patients with glaucoma and ocular hypertension - A three-month randomised study

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PURPOSE. *To compare the efficacy and safety of latanoprost monotherapy or dorzolamide and timolol in glaucoma patients inadequately controlled on adrenergic beta-receptor antagonist therapy.*

METHODS. *A total of 164 patients with primary open-angle glaucoma, capsular glaucoma or ocular hypertension were included in a three-month, open-label, randomised multicentre study. Patients with open-angle glaucoma were required to have IOP at least 22 mmHg and patients with ocular hypertension were required to have IOP at least 27 mmHg, on treatment with one or two ocular hypotensive drugs of which at least one had to be a beta-blocker. All patients were treated with timolol, 5 mg/ml twice daily, for a 2-4 week run-in period. They were then randomised to latanoprost, 50 µg/ml once daily, or timolol 5 mg/ml plus dorzolamide, 20 mg/ml twice daily. The difference in mean diurnal IOP change from baseline to month 3 was compared in the two groups.*

RESULTS. *When patients were switched to latanoprost, mean diurnal IOP was reduced by 5.2 mmHg (23%) compared to 4.0 mmHg (17%) in the group in which dorzolamide was added to timolol. The difference of 1.2 mmHg was statistically significant (p= 0.005). The majority of adverse events during both treatments were judged as mild.*

CONCLUSIONS. *The results suggest that a switch to latanoprost monotherapy is an alternative to combined treatment with timolol and dorzolamide in patients inadequately controlled on a topical adrenergic beta-receptor antagonist alone. (Eur J Ophthalmol 2000; 10: 198-204)*

KEY WORDS. *Glaucoma, Ocular hypertension, Latanoprost, Timolol, Dorzolamide, Additivity*

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INTRODUCTION

The recent introduction of several new drugs for the treatment of open angle glaucoma provides a wider choice for the management of intraocular pressure (IOP). With time an initially successful treatment often becomes insufficient and the regimen needs to be changed. Most of the present glaucoma drugs can be combined and their effect on IOP is additive. Thus, adding another drug is an obvious choice when IOP is no longer adequately controlled. As a rule combined therapy calls for a more complex schedule involving an increased number of instillations of eye drops. A previous study has shown that many patients who are no longer controlled on timolol do as well on monotherapy with latanoprost as with addition of an-

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other drug to timolol (1). Thus the present study was designed to compare the efficacy and side effects of latanoprost monotherapy versus dorzolamide added to timolol in patients no longer controlled by an adrenergic beta-receptor antagonist.

PATIENTS AND METHODS

This three-month multicentre study involved eight eye centres throughout Spain. Approvals were obtained from the appropriate regulatory authorities and ethics committees for each centre, and the study was performed according to the Declaration of Helsinki. All patients signed informed consent before enrolment.

To be included in the study the patients had to be 18 years or older and have a diagnosis of unilateral or bilateral primary open-angle glaucoma, capsular glaucoma or ocular hypertension (OH), currently treated with one or two ocular hypotensive drugs of which at least one had to be an adrenergic beta-receptor antagonist. For an eye to be eligible the IOP had to be at least 22 mmHg in patients with glaucoma at the pre-study examination or at least 27 mmHg in patients with OH. When both eyes were included in the study, the mean IOP of the two eyes was used in the analysis.

Exclusion criteria included any treatment with more than two glaucoma drugs simultaneously during the last six months. Patients who had received any previous treatment with dorzolamide or latanoprost were excluded. Concurrent use of contact lenses was not allowed. A history of angle closure, filtering surgery at any time, any other ocular surgery or laser trabeculoplasty within the last three months, any ocular inflammation or infection within the last three months, or any condition preventing reliable applanation tonometry were also reasons for exclusion. Patients who were pregnant or nursing or considering pregnancy were also excluded. Any patients who had participated in a clinical trial within the last month or were unable to adhere to the study schedule were not accepted.

This was a three-month, randomised, open-label study comparing latanoprost monotherapy with the combination of timolol and dorzolamide. All patients were initially allocated to treatment with timolol, 5 mg/ml twice daily, during a 2-4 week run-in period. They were then randomised to two parallel study groups: one group continued on timolol and dorzolamide, 20 mg/ml twice daily, was added to the treatment, the other group switched from timolol to latanoprost 50 µg/ml once daily in the evening. Morning eye drops were applied at approximately 7:30 am and evening drops at approximately 10:00 pm. The first eye drops of the study therapy were applied in the evening at the baseline visit. The last drops of timolol and dorzolamide were administered in the morning on the day of the three-month visit, and the last drop of latanoprost was administered in the evening before the day of the three-month visit.

The schedule of examinations is presented in Table I. A pre-study visit was scheduled 2-4 weeks before the baseline examination to determine eligibility. At this visit the eye examination included a slit-lamp examination, IOP measurement and ophthalmoscopy. Con-

TABLE I – SCHEDULE OF EXAMINATIONS AND PROCEDURES

Examination	2-4 weeks before baseline	Baseline	2 weeks	3 months	Follow-up 2-4 weeks after study end
Medical and ocular history	X				
Adverse events		X	X	X	X
Visual acuity		X	X	X	
Refraction		X	X	X	
Slit-lamp examination	X	X	X	X	
Intraocular pressure	X	X	X	X	
Ophthalmoscopy	X			X	

comitant medications were recorded. Patients eligible to participate were given timolol eye drops, 5 mg/ml, to be used twice daily during the run-in period.

At baseline and at the three-month visit IOP was measured with a calibrated Goldmann tonometer at 9:30 am, 12:30 noon and 3:30 pm. At the two-week visit IOP was measured before 12:00 noon. Three measurements were taken for each eye, and the mean of the three was used in the statistical analysis.

Any abnormal ocular finding or any adverse event was graded (mild, moderate, severe) and recorded. Two to four weeks after the end of the study, a visit was scheduled to follow-up patients with adverse events at completion of the trial or to detect late adverse events. Adverse events were also recorded during the run-in period. An adverse event was defined as any undesirable event occurring in a subject regardless of whether it was considered related to the study drugs or not. A serious adverse event was defined as an event that was potentially fatal, life-threatening, sight-threatening, permanently disabling, requiring hospitalization, or requiring intervention to prevent permanent impairment or damage.

Statistical analysis

The diurnal IOP was defined as the mean of the three IOP recordings (morning, noon and afternoon). An analysis of covariance (ANCOVA) was done with diurnal IOP change from baseline to month 3 for the study eye(s) as response, treatment group and centre as study effects and baseline diurnal IOP as a covariate. A 90% confidence interval was constructed for the difference in mean diurnal IOP reduction between the treatment groups [latanoprost minus (timolol + dorzolamide)].

RESULTS

Of the 164 patients included in the study, 81 were randomised to latanoprost and 83 to the combination of timolol and dorzolamide (Tab. II). The analysis of efficacy included 156 patients, 77 on latanoprost and 79 on timolol plus dorzolamide. Three patients were withdrawn from each group. The reasons for withdrawal are presented in Table III. Two more patients, one in each treatment group, were excluded from the analysis because of incorrect administration of the study drugs.

TABLE II - PATIENTS' MAIN CHARACTERISTICS

	Latanoprost (n = 81)	**Timolol + dorzolamide (n = 83)**
Age (years)		
Mean ± SD (Range)	64 ± 13 (24-95)	68 ± 9 (46-92)
Sex (f/m)	36/45	51/32
Diagnosis		
Primary open-angle glaucoma	64	65
Capsular glaucoma	16	17
Ocular hypertension	1	1
Medication prior to timolol run-in		
Timolol	45	46
Carteolol	9	15
Levobunolol	14	8
Betaxolol	10	11
Timolol + dipivefrin	1	0
Carteolol + dipivefrin	1	1
Levobunolol + dipivefrin	1	1
Carteolol + pilocarpine	0	1

n = number of patients

TABLE III - REASONS FOR WITHDRAWAL FROM THE STUDY

Reason	**Latanoprost (n = 3)**	**Timolol + dorzolamide (n = 3)**
Lost to follow-up	1	0
Intolerance to dorzolamide	0	1
IOP not controlled	2	1
Conjunctivitis	0	1

n=number of patients

The diurnal IOP at baseline was 23.0 ± 3.1 mmHg (mean ± SD) for patients randomised to latanoprost and 23.7 ± 5.8 mmHg for patients randomised to timolol + dorzolamide. At the end of the study, after three months of treatment, IOP was 17.7 ± 2.7 and 19.2 ±

TABLE IV - INTRAOCULAR PRESSURE IN mmHg (mean ± SD) IN EACH GROUP AT ALL TIME POINTS

Time	Latanoprost (n = 77)	Timolol + dorzolamide (n = 79)
Baseline		
9:30 am	23.0 ± 2.7	24.0 ± 5.9
12:30 noon	23.2 ± 3.8	23.7 ± 6.0
3:30 pm	22.9 ± 3.7	23.4 ± 6.3
Week 2		
12:00 noon	17.9 ± 4.7	19.1 ± 4.9
Month 3		
9:30 am	17.6 ± 3.0	18.9 ± 4.4
12:30 noon	17.8 ± 2.8	19.6 ± 5.0
3:30 pm	17.6 ± 2.9	19.3 ± 4.5

n = number of patients

TABLE V - PERCENTAGES OF PATIENTS WHO REACHED A SPECIFIC DIURNAL IOP REDUCTION AT THREE MONTHS

Diurnal IOP reduction	Latanoprost (n=77)	Timolol + dorzolamide (n=79)
≥ 40%	8	3
≥ 35%	16	9
≥ 30%	25	16
≥ 25%	39	29
≥ 20%	57	44
≥ 15%	81	62
≥ 10%	88	67

n = number of patients

TABLE VI - SYSTEMIC AND OCULAR ADVERSE EVENTS REPORTED DURING THE TIMOLOL RUN-IN PERIOD

Adverse event	Number of events (n = 20)
Systemic	
Aggravated hypertension	2
Headache	1
Influenza-like symptoms	6
Dyspepsia	1
Neck pain	1
Insomnia	1
Mucosis	1
Giddiness	1
Ocular	
Eye irritation	4
Conjunctivitis	2
Chalazion	1
Hyperemia	1
Eye pain	1
Total number of adverse events	23

n = number of patients

4.5 mmHg, respectively. IOP was reduced from baseline by 5.2 ± 0.3 mmHg (mean ± SEM, ANCOVA; 23%) for the patients treated with latanoprost and by 4.0 ± 0.3 mmHg for the patients treated with timolol + dorzolamide. The mean difference in diurnal IOP reduction between treatment groups was 1.2 mmHg, which was statistically significant (p = 0.005; 90% confidence interval (CI) –1.9 to –0.5 mmHg). The IOP at each measurement at baseline and after two weeks and three months of treatment is presented in Table IV. Compared with baseline, the diurnal IOP reduction at three months was significant in both groups (p<0.001).

The percentages of patients in each treatment group who achieved a specified IOP reduction from 10 to 40% are presented in Table V. Patients who received latanoprost were more likely to reach any of these levels and the difference between the two groups was striking at IOP reductions of 30% or more. In 19% of the patients in the latanoprost group the IOP reduction was less than 15%, compared with 38% of the patients in the timolol + dorzolamide group.

Ocular and systemic adverse events reported during the timolol run-in period and study treatment are presented in Tables VI-VIII. The majority were judged as mild. During the run-in period on timolol, 23 adverse events, 14 systemic and 9 ocular, were recorded, none of them serious. During the study, 41 ocular adverse events were reported for patients treated with latanoprost and 39 for patients given timolol and dorzolamide. There was no marked difference between the two groups in the number of ocular events. However, systemic adverse events were reported in 14 patients (19 events) treated with latanoprost, and 21 (30 events) for patients treated with timolol and dorzolamide. One serious adverse event (unstable angina) was reported in a patient treated with timolol plus dorzolamide.

TABLE VII - OCULAR ADVERSE EVENTS REPORTED DURING STUDY TREATMENT

Ocular adverse event	Latanoprost (n = 28)	Timolol + dorzolamide (n = 27)
Eye irritation	11	17
Conjunctivitis	6	6
Hyperemia	3	4
Blepharitis	4	6
Blurred vision	4	1
Decreased vision	1	1
Iris pigment deposit	2	0
Conjunctival hemorrhage	2	0
Increased iris pigmentation	1	0
Other*	7	4
Total number of adverse events	41	39

n = number of patients
*Latanoprost: conjunctival disorder, epiphora, dry eye, uveitis, vitreous disorder, chalazion, endothelial pigment deposit. Timolol + dorzolamide: corneal disorder, eye pain, keratitis, pigment deposit on lens

TABLE VIII - SYSTEMIC ADVERSE EVENTS REPORTED DURING STUDY TREATMENT

Systemic adverse event	Latanoprost (n = 14)	Timolol + dorzolamide (n = 21)
Influenza-like symptoms	5	7
Headache	4	3
Anxiety/depression	0	3
Pain	2	3
Respiratory inflammation	2	1
Dry mouth/bad taste	0	3
Heart disorder/angina pectoris	1	2*
Inflammation	2	3
Other**	3	5
Total number of adverse events	19	30

n = number of patients
* One event reported as serious
** Latanoprost: alopecia, diabetes mellitus, insomnia. Timolol + dorzolamide: allergy, anemia, fracture, sore throat, urinary tract infection

DISCUSSION

Treatment of open-angle glaucoma is aimed at reducing the IOP on the assumption that this will aid in preserving visual function. Limited information is available on the relationship between the efficacy of the IOP reduction and progression of the disease. Determining the clinical value of drugs used in glaucoma requires long-term studies with careful follow-up of visual function. However, comparing various treatment alternatives in terms of their effect on IOP and side effects is a reasonable first step towards obtaining information on the usefulness of these approaches.

In most patients medical treatment is the first choice. In many patients, however, stable IOP cannot be achieved with a single drug during long-term treatment either because of lack of efficacy or disease progression, and a change of treatment is warranted. In the present study many cases had been treated with timolol for several years. There is no information on the drug's initial effect in these patients, but one can assume that the initial response to timolol was adequate since treatment was continued. Whether the high IOP necessary for inclusion in the present study was due to a progressive increase in outflow resistance or to loss of efficiency of timolol is not clear. Gandolfi and Vecchi reported that almost half of the patients on timolol showed an upward drift of the IOP during 3-4 years' treatment (2). It is therefore possible that including patients who are no longer controlled on timolol tends to select cases with a diminished response to the drug. However, the study design was chosen to simulate the clinical situation and limited resources tend to favour a simple solution, i.e. to add a second drug. Ideally the current effect of timolol on IOP should be determined by a washout period.

Combinations of two or more drugs are used to lower IOP, but complex treatment can affect the quality of life of glaucoma patients (3, 4). Perfetti et al (4) reported that an increased number of medications had a negative impact on quality of life. One of the treatment alternatives used in the present study, timolol plus dorzolamide, is now available as a fixed combination but requires twice-daily application for optimal effect. A simple treatment schedule is also desirable for good compliance (5). Thus, the aim should be the simplest treatment schedule that will achieve the most effective IOP reduction believed to prevent progression or at least sufficiently slow down the progression of the disease and prevent a visual handicap (6).

Predicting the IOP that will achieve this goal is not yet possible, but the ophthalmologist tries to estimate the "target pressure" for each patient, based on several aspects of the disease including the degree of damage and at what pressure level the damage occurred (7). During follow-up, signs of progression will signal the need to re-assess the target pressure. Whether target pressures are reached with various glaucoma therapies can, for example, be examined by comparing the probability of achieving a specific IOP level or reduction with different treatments. The superiority of latanoprost in the present study is reflected in the higher percentage of patients who reached specific IOP reductions after three months on the drug.

Treatment regimens can be simplified by switching to another drug rather than combining therapies. Switching to latanoprost from timolol instead of adding another drug to timolol should achieve a similar effect on IOP (1, 8). The present study confirms this, since switching to latanoprost was as effective as adding dorzolamide to timolol treatment in patients no longer sufficiently controlled on timolol. The IOP was significantly reduced by both treatments. Switching to latanoprost was, in fact, significantly more effective ($p = 0.005$) than adding dorzolamide to timolol. Latanoprost lowered the mean diurnal IOP from 23.0 to 17.7 mmHg, a reduction of 23%. The corresponding figure for dorzolamide plus timolol was a reduction of 17%, from 23.7 to 19.2 mmHg. The mean difference in diurnal IOP reduction with the two treatments was 1.2 mmHg. It is not clear whether this will have a clinically significant effect on the progression of the optic nerve damage but, as pointed out above, it will increase the odds of reaching the desired target IOP.

In our study dorzolamide was administered twice daily as part of a combination therapy. It has now been reported that latanoprost monotherapy is more effective than dorzolamide monotherapy three times daily (9).

Ocular adverse events did not differ significantly between the two treatment groups. The majority of the adverse events were judged as mild. Flare was noted at one examination in one patient treated with latanoprost and reported as an uveitis. The patient had no symptoms and the flare resolved without treatment while the patient remained on latanoprost. More systemic events were reported in the timolol+dorzolamide group than the latanoprost group. One serious adverse event was reported, a case of unstable angina in a patient treated with timolol+dorzolamide. In general, both treatments were well tolerated during the three-month trial. Adverse events occurring after treatment longer than three months cannot be evaluated from this study.

This study confirms previous reports (1, 7) that switching to latanoprost monotherapy is an effective alternative to adding drugs in patients no longer controlled on topical beta-blockers.

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