Effects on IOP restoration and blood-aqueous barrier after long term treatment with latanoprost in open angle glaucoma and ocular hypertension

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Abstract
Aims—To evaluate whether long term treatment with the prostaglandin analogue latanoprost has a deleterious effect on the blood-aqueous barrier (BAB) and to determine the duration of the effect on intraocular pressure (IOP) after withdrawal of treatment.

Methods—Patients with ocular hypertension or glaucoma were topically treated with latanoprost 50 µg/ml once daily for 6–12 months. In 26 patients IOP was followed for 14 days after withdrawal of treatment. Aqueous flare was measured with a laser flare meter during 6–12 months’ treatment in 16 patients.

Results—On the last day of treatment IOP was 6.9 mm Hg (95% CI 5.3–8.5) lower than before treatment. It increased slowly during the follow up period but was still 1.3 mm Hg (95% CI 0.2–2.5) lower than pretreatment IOP 14 days after cessation of treatment. No change in aqueous flare was seen throughout the study.

Conclusion—Latanoprost has no clinically significant effect on the permeability of the BAB and IOP will return to pretreatment levels within a few weeks, indicating that latanoprost is safe for long term treatment.

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Latanoprost (13,14-dihydro-17-phenyl-18,19,20-trinor-PGF\textsubscript{2\alpha}-isopropyl ester), is a prostaglandin F\textsubscript{2\alpha} (PGF\textsubscript{2\alpha}) analogue currently undergoing evaluation in long term clinical trials. The substance effectively reduces IOP in human.

Its main mechanism of action seems to be an increase in uveoscleral outflow of aqueous humour but the exact mechanism is not known. Morphological changes have been found in the ciliary muscle in monkeys after topical application of PGF\textsubscript{2\alpha}. These include widening of intramuscular spaces and loss of collagen type I and III fibrils in the connective tissue between the muscle bundles.

The investigators suggest that structural changes of the ciliary muscle can contribute to the pressure reducing effects of prostaglandins. They found that significant morphological changes are probably limited to the ciliary muscle and they found no evidence of an effect on the blood-aqueous barrier (BAB). Such an effect has been observed in rabbits while the BAB in monkeys seems to be much more resistant. No signs of BAB breakdown have been noted in human eyes during short term studies.

The possibility of morphological changes occurring in the human ciliary muscle is particularly important since the drug is intended for long term treatment. Irreversible changes in the ciliary muscle could result in a persisting ocular hypotensive effect. For this reason we observed the time for restoration of IOP to pretreatment levels after withdrawal of latanoprost. IOP was followed for 14 days after discontinuation of treatment in a group of 26 patients treated with latanoprost for 6–12 months within the framework of a phase III clinical trial (6 month report). Additionally, we addressed the question of whether long term treatment with latanoprost has a deleterious effect on the BAB. Thus, 16 patients treated in one of the centres were followed with a laser flare meter.

Material and methods

STUDY OF IOP RESTORATION

Patient selection

After completion of a Scandinavian 6 month, multicentre, double masked clinical trial on latanoprost versus timolol or its open labelled extension, patients from two centres (Umeå and Uppsala) were invited to participate in a follow up study. To be eligible for the present study at least one eye had to be topically treated with latanoprost 50 µg/ml once daily for a minimum of 6 months. Fifteen of the 26 patients accepting the study procedure had been receiving latanoprost for 1 year.

Examination schedule and procedures

All patients were examined on the last day of latanoprost treatment (day 0) and 1, 3, 7, and 14 days later. The time for the last eye drop was noted and the patient was allowed to choose visiting hours, either 8 am or noon. The same time schedule had to be maintained throughout the study. Pretreatment values were obtained from the corresponding time points at the baseline day of the long term study—that is, before any treatment had been initiated.

Within each centre the same calibrated Goldmann applanation tonometer was utilised for the IOP determinations and all tonometry on a given patient was made by the same person. The median of three readings in each eye were treated the mean IOP of the two eyes was used in the analyses. p Values less than 0.05 with Student’s paired t test were considered statistically significant.
Results
Statistically significant.

All two patients were excluded from the analysis because they had had less than 6 months’ follow up. This was because of the study design and length of follow up. In two patients the baseline measurement was made after 2 weeks’ treatment. At each time point 10 determinations were performed and the mean was used for calculations. If both eyes were treated the mean was used. p Values less than 0.05 with Student’s t test were considered statistically significant.

Discussion
The IOP reduction after 6–12 months of treatment declined slowly but some reduction remained for 14 days after discontinuation of treatment. A correspondingly slow restoration of the IOP is seen after withdrawal of timolol. This is thought to be due to the binding of timolol to melanin, giving a slow release effect. Latanoprost, on the other hand, is not bound to melanin and it cannot be found in aqueous humour 24 hours after topical administration (unpublished observations). Latanoprost is the biologically active epimer of PhXA34. In previous studies where PhXA34 was applied for 1–2 weeks a significant retained effect on IOP was observed 210 to 613 days later. The results of the present study show that the IOP reduction is transient even after treatment for up to 12 months. Thus, the effect on IOP of possible morphological changes in the ciliary muscle involved in the IOP reduction is reversible and will be restored to pretreatment levels within a few weeks after discontinuation of treatment. As latanoprost seems to be as effective as PGF2α in terms of reducing IOP it may be reasonable to assume that the two drugs cause similar changes in the ciliary muscle morphology. In monkeys treatment with large doses of PGF2α or its isopropyl ester for 4–8 days induces loss of extracellular material between, but not within, the ciliary muscle bundles. Collagen type I and III fibrils are lost and ciliary muscle fibres are thin or relaxed. Whether similar changes occur in human eyes is not known. As latanoprost is a much more specific prostaglandin F receptor (FP receptor) agonist than PGF2α it is also possible that the effect on the ciliary muscle morphology differs. If the morphological changes are similar the slow restoration of IOP after long term treatment suggests a correspondingly slow

Figure 1 Mean difference (pretreatment IOP − IOP during follow up) versus time after cessation of latanoprost treatment. Error bars denote 95% confidence interval. (n = 26.)

Figure 2 Mean flare intensity versus time. Filled circles represent treated eyes, open circles untreated eyes. Error bars denote half the 95% confidence interval. (n = 10–16.)
rebuilding of extracellular material, but morphological examinations of relevant tissue specimens are needed to clarify this issue.

Several short term studies with different techniques—for example, iris fluorescein angiography,\textsuperscript{10} fluorophotometry,\textsuperscript{11, 14, 21} and laser flare meter measurements\textsuperscript{15} have failed to detect any significant effect of the BAB caused by topical treatment with PGF\textsubscript{2\alpha} and latanoprost. These results have been confirmed in the present investigation, where 16 patients treated with latanoprost once daily were followed with laser flare measurements for 6–12 months. There was no statistically significant difference between the means of the treated and the non-treated eyes at any time or between pre- and post-treatment measurements in treated eyes, nor did any treated eye show a larger change in flare values than could be seen in non-treated eyes. It may thus be concluded that latanoprost has no effect on the permeability of the BAB to proteins.

In conclusion, long term treatment with latanoprost has no clinically important effects on the permeability of the BAB and IOP will return to pretreatment levels within a few weeks after discontinuation of treatment. The results indicate that latanoprost is safe for long term treatment with respect to the BAB and that the effect on IOP of possible morphological changes in the ciliary muscle are reversible.

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