Latanoprost as a new horizon in the medical management of glaucoma

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Latanoprost is a new prostaglandin $F_{2\alpha}$ analogue specifically developed for the treatment of glaucoma. Latanoprost is a selective FP receptor agonist, with a primary mode of action of increased uveoscleral outflow of aqueous humor. A dose of 50 μg/mL (0.005%) once daily has been found optimal in clinical trials. Latanoprost reduces the nocturnal intraocular pressure in addition to the diurnal, and has been shown to be additive to other glaucoma medication. In long-term phase III clinical trials, latanoprost 0.005% once daily has been proven to be at least as effective as timolol 0.5% twice a day. The main side effect of latanoprost is increased iridial pigmentation, which is relatively frequent in patients with mixed color of the iris. This unique side effect is based on the ability of prostaglandins to stimulate melanin formation in melanocytes. The advantages of latanoprost compared with other glaucoma medication comprise different mode of action, good intraocular pressure–reducing effect, once-daily dosing, and absence of systemic side effects. The long-term consequences of increased iridial pigmentation need to be further studied.

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Abbreviations

FNA	fine-needle aspiration
IOP	intraocular pressure

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Several prostaglandins have been shown to reduce the intraocular pressure (IOP) effectively in animals [1,2] as well as in humans [3,4], and these ocular hypotensive autacoids represent a potentially important new class of drugs for the treatment of glaucoma. What makes the prostaglandins interesting, particularly the $F_{2\alpha}$ type, is their unique mode of action and increased uveoscleral outflow of aqueous humor [5–8]. Because the drainage capacity of the uveoscleral route probably is high, provided the fluid can enter the supraciliary-suprachoroidal space, drugs enhancing this outflow mechanism can be expected to have a good IOP-lowering effect. It is also appealing that the obstructed site of the normal drainage pathway, the trabecular meshwork, which is the cause of the elevated IOP in glaucoma, is bypassed in this outflow pathway. Enhanced outflow of aqueous humor through the uveoscleral route offers a new principle for the reduction of IOP in the medical management of glaucoma. The mechanism is reminiscent of a cyclodialysis brought about pharmacologically. The purpose of this article is to review recent preclinical and clinical data obtained with latanoprost.

Chemistry of latanoprost

Latanoprost (code name, PhXA41; 13,14-dihydro–17-phenyl–18,19,20-trinor-$PGF_{2\alpha}$-isopropyl ester) differs from prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), a naturally occurring prostaglandin, in three ways. First, carbons 18–20 in the ω chain have been substituted with a benzene ring. Second, the double bond between carbons 13 and 14 has been saturated. Lastly, the carboxylic acid moiety on carbon 1 in the α chain has been esterified with isopropanol (Fig. 1). The molecular weight of latanoprost is 432.6 and that of the free acid (hydrolysed compound) is 390.5. The octanol-water partition coefficient (logarithmic *P* value) has been determined to be 4.3 at pH 7.4, and the solubility of latanoprost in water is consequently poor. Latanoprost has been tested clinically in concentrations ranging from 12.5 to 350 μg/mL (0.00125–0.035%). A 0.005% concentration has been used in the phase III clinical trials. The eye drop solution is preserved by benzalkonium chloride.

Pharmacology of latanoprost

Latanoprost is a selective FP receptor agonist, with only marginal spill over on most of the other prostanoid receptors [8]. The prostanoid receptor classification has recently been reviewed [9••]. There are at least eight dif-

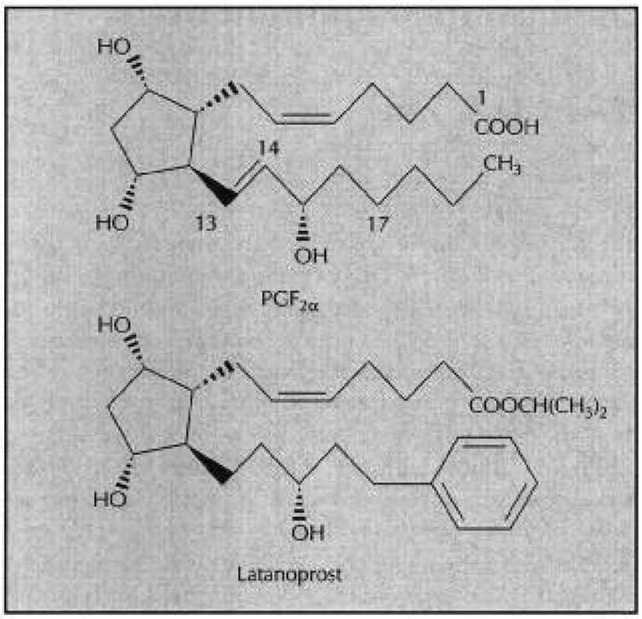

Fig. 1. Chemical structures of $PGF_{2\alpha}$ and latanoprost.

ferent prostanoid receptors: DP, EP_1, EP_2, EP_3, EP_4, FP, IP, and TP. Some of these receptors such as the EP_3 receptor furthermore exist in several splice variants [10–12]. Naturally occurring prostaglandins tend to spill over on many different prostanoid receptors resulting in a mixed pharmacologic response. For instance the ocular irritating effect of $PGF_{2\alpha}$ is probably at least partly due to the fact that this prostaglandin is a relatively effective agonist also on several of the EP receptors. The receptor selectivity of latanoprost explains why this prostaglandin analogue exerts so few and slight side effects at the clinical dose. The receptor profiles of latanoprost, $PGF_{2\alpha}$, and PGE_2 are presented in Table 1.

Mode of action

The main mechanism of action of latanoprost for reducing IOP in primates has been shown to be increased uveoscleral outflow [8]. Treatment of cynomolgus monkeys for 5 days with 3 μg latanoprost daily resulted in an increase of the uveoscleral outflow of approximately 60% [8]. Latanoprost reduces IOP in monkeys but has no or only moderate effect on IOP in cats and rabbits. In a recent study using *in situ* hybridization technique and immunohistochemistry both the FP receptor mRNA and protein were found in the smooth muscle cells of the ciliary muscle in monkeys [13], supporting the hypothesis that the increase in uveoscleral outflow caused by latanoprost is mediated by FP receptors in the ciliary muscle. In a clinical study performed on ocular hypertensive patients and healthy volunteers, latanoprost has also been found to increase uveoscleral outflow [14].

Effects on the microcirculation in the eye

The effects of latanoprost on the ocular microcirculation has been studied extensively in cynomolgus monkeys using radioactive microspheres and radioactive albumin. A topical dose of 6 μg latanoprost or the equivalent amount (10 μg) of PhXA34, an epimeric mixture containing latanoprost as the active epimer, had no effect on the intraocular blood flow or capillary permeability to albumin as tested 1 to 6 hours after administration of the drug. However, some increase was seen in the blood flow of the anterior sclera [8]. In another study, high doses of latanoprost had no effect on the blood-retinal barrier during chronic treatment in aphakic and phakic cynomolgus monkeys as studied with fluorescein angiography [15]. $PGF_{2\alpha}$ and the isopropyl ester of $PGF_{2\alpha}$ cause a marked increase in the blood flow of the anterior segment of the eye in monkeys and rabbits [16,17]. In rabbits the increase in blood flow of the surface structures of the eye induced by $PGF_{2\alpha}$-isopropyl ester seems to be caused at least partly by nitric oxide, but this effect is not mediated by FP receptors [18]. Neither in animals nor in humans has latanoprost been found to have any significant effect on the blood-aqueous barrier [19,20]. Thus, latanoprost has no or only negligible effects on the ocular microcirculation when used at relevant doses.

Effects on iridial pigmentation

Both PGE_2 and $PGF_{2\alpha}$, two naturally occurring prostaglandins, and latanoprost cause increased pigmentation of the iris in cynomolgus monkeys during long-term

Table 1

EC-50 values (in moles/1) of prostaglandin $F_{2\alpha}$, latanoprost (free acid), and prostaglandin E_2 in different prostglandin receptor systems*

Prostaglandin analogue	FP	EP_1	EP_2	EP_3	DP/IP	TP
$PGF_{2\alpha}$	6.7×10^{-9}	3.8×10^{-7}	1.4×10^{-5}	1.1×10^{-7}	3.1×10^{-3}	2.9×10^{-5}
Latanoprost	3.6×10^{-9}	6.9×10^{-6}	3.6×10^{-4}	1.7×10^{-5}	$>1.0 \times 10^{-2}$	1.1×10^{-4}
PGE_2	3.2×10^{-7}	5.0×10^{-9}	1.0×10^{-7}	3.2×10^{-9}	$>5.0 \times 10^{-3}$	$>5.0 \times 10^{-3}$

*The values are based on *in vitro* functional tests (smooth muscle bath and platelet aggregation). The test system does not distinguish between D and I prostanoid receptors.

PGE_2–prostaglandin E_2; $PGF_{2\alpha}$–prostaglandin $F_{2\alpha}$

treatment [21•]. This unique effect seems to be based entirely on melanogenesis in the melanocytes of the iris stroma. Morphometrical analysis of a large number of treated animals indicate that there is no proliferative effect of latanoprost on the melanocytes but rather that the effect is based on de novo synthesis of melanin. The iridial melanocytes in monkeys have been described as postmitotic, but they may retain some melanogenic capacity throughout life [22]. Because the ocular melanocytes are continent [23], *ie*, they do not donate the pigment, pigment dispersion is unlikely to occur. On the other hand, this suggests that the change in pigmentation may be irreversible. Altogether it is likely that this new side effect has only cosmetic consequences. Long-term follow-up of patients affected on continued treatment, however, is needed to determine how progressive the pigmentation is.

Other effects in the eye

Latanoprost causes slight mydriasis in monkeys but has no effect on the pupil in rabbits. In cats and dogs, latanoprost causes marked pupillary constriction because these species have FP-receptors in the iridial sphincter muscle [9••]. Neither latanoprost (free acid) nor $PGF_{2\alpha}$ has any effect on the DC electroretinogram when infused intravitreally in rabbits at relevant concentrations [24].

Systemic effects of latanoprost

Intravenous infusion of latanoprost in cynomolgus monkeys at 10 times the clinical dose had no cardiovascular or pulmonary effects [8]. When latanoprost is used at the clinical dose of one drop in each eye once daily (1.5 μg/eye; total dose approximately 0.04 μg/kg bw) it is unlikely to exert any significant systemic side effects because of the low dose and the rapid metabolism.

Pharmacokinetical properties

Latanoprost is an isopropyl ester prodrug and as such biologically inactive. The ester moiety has to be hydrolyzed for the drug to become active. The prodrug is efficiently and quantitatively hydrolyzed to the free acid both in the cornea and plasma [8]. All drug that enters the aqueous humor has been hydrolyzed to the free acid [25]. However, only a fraction of the drug applied topically is absorbed into the eye (approximately 1%), the rest being absorbed into the systemic circulation either directly through blood vessels in the conjunctiva and the nasal mucosa or through the gastrointestinal tract [26]. After topical application of latanoprost the peak concentration in the monkey eye is reached after about 1 hour. The half-life of latanoprost (free acid) in plasma is about 10 minutes in monkeys [8] and 17 minutes in humans (Unpublished data).

There is practically no metabolism of latanoprost in the eye except for the ester hydrolysis. Latanoprost is a poor substrate for prostaglandin 15-dehydrogenase but undergoes β-oxidation in the liver. The major matabolites in monkeys and humans are 1,2-dinor- and 1,2,3,4-tetranor-13,14-dihydro-17-phenyl-18,19,20- trinor-$PGF_{2\alpha}$. Most of the metabolites are excreted in the urine but some are excreted via the bile [8].

Clinical studies

Dose

Several phase I and phase II dose-finding studies have been performed with latanoprost and PhXA34 [20, 27–31]. A concentration of 50 to 60 μg/mL (0.005%–0.006%) has been found optimal with respect to the IOP reduction. In two studies it has been demonstrated that application of the drug once daily results in maximum effect. Thus Nagasubramanian *et al.* [32] treated 49 patients with ocular hypertension for 2 weeks; 10 with placebo, 19 with 0.006% latanoprost twice daily, and 20 with the same dose applied once daily in the evening.

Both dose-regimens were better than placebo. On the second day of treatment application of latanoprost twice daily was slightly more effective than latanoprost given once daily, but after 2 weeks of treatment the efficacy was reversed for the two groups. Once daily dosage caused a 36% reduction compared with 28% with twice daily. This observation was confirmed in another study in which 50 glaucoma patients with an IOP of at least 22 mm Hg despite twice daily 0.5% timolol treatment were included [33•]. In this parallel-group study 0.006% latanoprost was added to timolol either twice daily or once daily (in the evening) for 3 months. Throughout the study latanoprost once daily reduced IOP more effectively than latanoprost twice daily at all time points. The diurnal IOP reduction on the last examination compared with baseline was significantly greater in the patients who received treatment once daily than the patients who received treatment twice daily. The diurnal IOP was reduced from 24.8 to 15.7 mm Hg in those who received treatment once daily, and from 24.9 to 18.0 mm Hg in those who received treatment twice daily [33•]. The results of these two dose-regimen studies were corroborated by the results of a third study in which hospitalized patients were treated with 0.006% latanoprost once daily [34].

Effect in normal-tension glaucoma

Latanoprost has also been shown to have an effect on IOP in normal-tension glaucoma. In one study, two groups of 10 patients were compared: one treated with placebo and the other with latanoprost at 0.006% twice daily for 2 weeks [35]. The mean diurnal IOP was reduced in both groups; from 16.8 to 14.3 mm Hg (2.6 mm Hg; 15%) with latanoprost and from 18.3 to 17.2 mm Hg (1.0 mm Hg; 5%) with placebo. The difference between the two treatment groups was statistically significant. In another placebo-controlled, crossover dose regimen

study, 0.005% latanoprost was administered once daily to patients with normal tension glaucoma for 3 weeks [36]. From a baseline IOP of 16.9 mm Hg a 0.4 mm Hg (2%) reduction was obtained with placebo and a 3.6 mm Hg (21%) reduction with latanoprost. Thus an adequate IOP reduction has also been achieved in short-term studies in patients with normal-tension glaucoma.

Effect on nocturnal intraocular pressure

In one short-term study the effect of 0.005% latanoprost on nocturnal IOP has been investigated [37]. In patients treated with timolol addition of latanoprost once daily in the morning reduced the mean nocturnal IOP from 23.0 mm Hg to 19.4 mm HG (2.3 mm Hg more than placebo), whereas in patients receiving latanoprost monotherapy the nocturnal IOP was reduced from 22.0 mm Hg to 17.6 mm Hg (3.5 mm Hg more than placebo). Thus, latanoprost also reduces nocturnal IOP.

Combined treatment with other glaucoma drugs

Combined treatment with two drugs is common in glaucoma. In the previously mentioned study by Alm *et al.* [33•] latanoprost reduced IOP by 28% to 35% from a baseline of about 25 mm Hg in patients undergoing timolol treatment. This pressure reduction is of the same order as that expected if only latanoprost was given to patients at that pressure level. From this study it can be concluded that timolol is unlikely to interfere with the action of latanoprost, but the effect of timolol on IOP could not be established as these patients had been receiving timolol for various lengths of time. Such information was obtained in a short-term study where patients were treated with either 0.5% timolol or 0.006% latanoprost, both applied twice daily for 1 week [38]. Latanoprost alone reduced IOP from 28.5 mm Hg by 8.9 mm Hg (31%) and timolol from 24.2 mm Hg by 5.9 mm Hg (24%). The two drugs were then combined for another week of treatment, causing a statistically significant further reduction of about 2.6 mm Hg (14%).

The combination of latanoprost and pilocarpine is particularly interesting because high doses of pilocarpine prevents the pressure reduction of $PGF_{2\alpha}$-isopropyl ester in cynomolgus monkeys [5]. Friström and Nilsson [39], however, found that combining 0.006% latanoprost twice daily with 2% pilocarpine three times a day provided an additive effect. Latanoprost alone reduced IOP from 25.1 mm Hg by 6.0 mm Hg (24%), and pilocarpine from 23.8 mm Hg by 3.5 mm Hg (15%). Both drugs caused a statistically significant further reduction of IOP when added to the other drug. The difference between the clinical study and the study in monkeys is probably due to age or dose or both. The contraction of the ciliary muscle is likely to be weaker in elderly glaucoma patients compared with young animals used in laboratory experiments, and the dose of pilocarpine used in monkeys was twice the maximal dose for complete accommodation to ensure maximal contraction of the ciliary muscle. Two percent pilocarpine is probably a submaximal dose for contraction of the ciliary muscle in the elderly human eye. Further studies are needed to determine the interaction between latanoprost and high doses of pilocarpine (Fig. 2).

Long-term efficacy of latanoprost

Three phase III clinical trials have been performed with latanoprost, one in Scandinavia [40••], one in the United States [41••], and one in the United Kingdom [42••]. In all three studies patients with open-angle glaucoma or ocular hypertension were included. The patients were treated for 6 months with either timolol 0.5% twice daily or latanoprost 0.005% once daily according to randomized, double-masked, parallel group protocols. The Scandinavian study included 267 patients, the United States study 268, and the United Kingdom study 294, altogether 829 patients. Of these, 460 were treated with latanoprost and 369 with timolol. There were minor differences between the three studies. In the US study patients previously treated with timolol were allowed to be included after washout of timolol for 3 weeks. The other two studies excluded patients on β-adrenergic blockers. In the UK and the US studies latanoprost was applied in the evening; in the Scandinavian study a crossover design was implemented with application either in the evening or the morning with a switch after 3 months. In all three studies the efficacy endpoint of the two drugs was based on the difference in mean diurnal IOP after 6 months of treatment. The reduction of mean diurnal IOP after 6 months of treatment is presented in Figure 2.

In the three studies latanoprost reduced the mean diurnal IOP significantly by 27% to 34% from a baseline level of 24.4 to 25.2 mm Hg, and timolol by 20% to 33% from a baseline level of 24.1 to 25.4 mm Hg. The two drugs were equally effective in the UK study. In the Scandinavian and the US studies, however, latanoprost

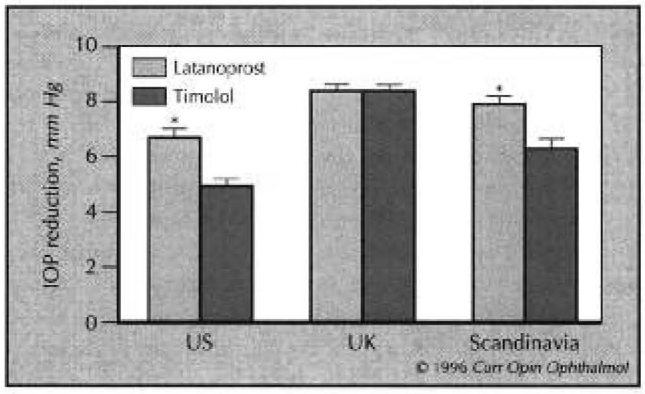

Fig. 2. Reduction of diurnal intraocular pressure (IOP) at 6 months of treatment with latanoprost and timolol in the three phase III clinical trials; values are mean ± SEM. Asterisk denotes $P<0.001$.

was significantly better than timolol. The main difference between the three studies seems to be the efficacy of timolol. In the US study both timolol and latanoprost were less effective than in the two other studies. Some remaining β-adrenergic blockage, despite a 3-week washout of previous timolol treatment, cannot be excluded. In the UK study timolol reduced IOP considerably better than in the US and the Scandinavian studies. Differences in patient demography may also affect the results. In the US study more patients with ocular hypertension (63%) were included than in the other two studies (UK 50%, Scandinavia 46%), and a meta-analysis of the three studies shows that timolol may be less effective in ocular hypertension than in primary open- angle glaucoma. The same meta-analysis demonstrated that timolol seems to be more effective in men than in women, and in the UK study 65% of the study population were men compared with 43% and 44% in the US and Scandinavian studies.

In the three studies an average of 25% of latanoprost-treated patients and 17% of timolol-treated patients were treated in one eye only. Timolol also reduced IOP significantly in the untreated fellow eye between 1.1 and 3.0 mm Hg in the three studies. The effect of latanoprost on the fellow eye was smaller, ranging between 0.4 and 1.2 mm Hg. This difference between timolol and latanoprost probably reflects the fact that timolol, unlike latanoprost, results in effective plasma levels also when applied as eye drops.

The Scandinavian study provided additional information on the importance of the time of application of latanoprost. Evening administration of latanoprost was statistically superior to morning administration. The most likely explanation is the fact that IOP measurements at 8 AM, noon, and 4 PM provide IOP values 24, 4, and 8 hours postdose for morning application and 12, 16, and 20 hours postdose for evening application. A late and prolonged maximum for the effect on IOP favors evening application when IOP is measured during daytime. In patients treated for 1 year with latanoprost, no long-term drift in IOP was detected [43].

Side effects

Conjunctival hyperemia and ocular irritation were pronounced ocular side effects with $PGF_{2\alpha}$-isopropyl ester [44]. In the three phase III clinical studies, latanoprost was also compared with timolol with respect to side effects. There was no difference between the two drugs with respect to ocular irritation or discomfort, but latanoprost caused slightly more conjunctival hyperemia. Nevertheless, the average conjunctival hyperemia caused by latanoprost was modest and in most cases unlikely to be clinically important. Conjunctival hyperemia was reported as an adverse event in 4.6% of patients treated with latanoprost and 1.4% of patients treated with timolol. It was reported more than once in four of 198 patients treated with latanoprost for 1 year indicating that conjunctival hyperemia may be a clinical problem in about 2% of patients on latanoprost.

Punctate keratopathy was observed in 44 patients (9.6%) on latanoprost and 32 (8.7%) on timolol in the three phase III clinical studies combined. Most cases of punctate keratopathy were mild and sporadic, but some were reported as adverse events, 13 (2.8%) on latanoprost and five (1.4%) on timolol. One of 460 patients treated with latanoprost in the three phase III clinical studies was withdrawn from the study because of corneal erosions. Latanoprost, as well as the vehicle used as placebo in these studies, contained twice the concentration of the preservative (benzalkonium chloride) compared with timolol eye drops. This may explain the difference between the two drugs regarding punctate keratopathy particularly because a placebo drop had to be given daily to the latanoprost patients to mask the studies.

Among 460 patients treated for 6 months with latanoprost increased pigmentation of the iris was observed or suspected in 31 patients (6.7%). Most cases have been mild and clinically difficult to detect. The change in iris pigmentation has occurred in eyes with an iris color that is already partly brown (naevi and freckles not included). Thus, a change in iris color of pure blue, gray, green, or brown eyes can be expected to be less frequent than in heterochromatic eyes. All patients who developed increased pigmentation of the iris have been withdrawn from treatment. During follow-up for up to 2 years the change in iris pigmentation has been stable without any sign of reversibility or further increase.

No significant systemic side effect that could be attributed to the use of latanoprost has emerged in any of the three phase III studies. Because of the extremely low concentration of latanoprost in plasma and the rapid metabolism, significant systemic side effects are unlikely to occur with the drug.

In conclusion, latanoprost and other prostaglandins may open up a new horizon in the medical management of glaucoma in that these drugs are highly effective IOP-reducing agents with a unique mode of action and probably good ocular and systemic tolerability. The only disadvantage so far seems to be the increased pigmentation of the iris, which needs to be further studied.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • Of special interest
- •• Of outstanding interest

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