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Latanoprost

A Review of its Pharmacological Properties, Clinical Efficacy and Tolerability in the Management of Primary Open-Angle Glaucoma and Ocular Hypertension

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Summary

Synopsis

Latanoprost is an ester prodrug analogue of prostaglandin $F_{2\alpha}$ which effectively reduces intraocular pressure (IOP) by increasing uveoscleral outflow rather than altering conventional (trabeculo-canalicular) aqueous outflow. The IOP-lowering effect of latanoprost lasts for 20 to 24 hours after a single dose, which allows a single daily dosage regimen.

Data from 4 randomised double-masked multicentre studies indicate that a once daily dose of topical latanoprost 0.005% is as effective as timolol 0.5% twice daily in the treatment of patients with primary open-angle glaucoma or ocular hypertension. A number of studies also demonstrate that latanoprost enhances IOP-lowering effects when applied in combination with other antiglaucoma agents.

Latanoprost is well tolerated with no, or barely detectable, conjunctival hyperaemia, and, unlike timolol, is not associated with systemic adverse effects. However, 3 to 10% of patients treated with latanoprost 0.005% have shown increased iris pigmentation after 3 to 4.5 months' treatment.

In summary, the available data show that latanoprost is a potent IOP-lowering agent with a number of positive features including a single daily dosage regimen, a novel mechanism of action that enhances the IOP-lowering effect of contemporary agents, and a lack of systemic adverse effects. These properties suitably poise latanoprost for a prominent position in the management of patients with primary open-angle glaucoma and ocular hypertension.

Pharmacodynamic Properties

Latanoprost is an ester prodrug analogue of prostaglandin $F_{2\alpha}$ with high selectivity for the FP subtype of prostanoid receptors. Unlike contemporary antiglaucoma agents, latanoprost reduces intraocular pressure (IOP) by increasing uveoscleral outflow, with little or no alteration of conventional (trabeculo-canalicular) aqueous outflow and no effects on retinal vasculature or permeability of the blood-aqueous barrier.

The reduction in IOP produced by latanoprost is dose-dependent. The IOP-lowering effects after a single dose of latanoprost 0.006% last for up to 20 to 24 hours. Long term (6 months) application of latanoprost is not associated with morphological alterations to the ciliary muscle or trabecular meshwork, according to animal data. Furthermore, other body systems (brain, cardiovascular, respiratory) do not appear to be significantly affected by latanoprost at concentrations up to 10-fold greater than those used clinically for topical application.

Pharmacokinetic Properties

Latanoprost is more lipophilic than its parent prostaglandin and therefore better able to penetrate the cornea. After uptake by the cornea, latanoprost is completely hydrolysed; the drug does not seem to be metabolised by other means in the eye. In monkeys, the highest drug concentrations were observed in the cornea after topical administration; the acid of latanoprost was then released from the cornea into the anterior eye. The drug had an elimination half-life of 3 to 4 hours from the eye tissues.

Drug that is systemically absorbed has a short plasma elimination half-life. The major metabolic pathway is by β-oxidation and the metabolites are excreted primarily via the kidneys. Recovery of radiolabelled drug appears to be complete.

Clinical Evaluation

Dose-ranging studies show that a once daily topical dose of latanoprost (optimal concentration of 0.005 or 0.006%) effectively produces a decrease in IOP in patients

with primary open-angle glaucoma or ocular hypertension. Single daily application of latanoprost is at least as effective as a twice daily dose.

Three of 4 long term (3 or 6 months) randomised, double-masked, multicentre studies indicated that once daily latanoprost 0.005% was more effective than timolol 0.5% twice daily in reducing IOP. A number of clinical studies have also shown that latanoprost applied in combination with other antiglaucoma agents produces enhanced IOP-lowering effects.

Tolerability

Data from phase III clinical studies indicate that topical latanoprost 0.005% once daily application is, overall, as well tolerated as timolol 0.5% twice daily. At clinically effective doses, no or a barely detectable increase in conjunctival hyperaemia was noted in at least 90% of latanoprost or timolol recipients. In contrast to timolol, latanoprost is not associated with systemic adverse effects.

On the other hand, increased iridial pigmentation has been noted in 3 to 10% of patients after 3 to 4.5 months' continuous treatment with latanoprost 0.005%. It occurred only in patients with mixed colour irises (green-brown or blue/grey-brown); freckles or naevi in the iris were not affected.

Dosage and Administration

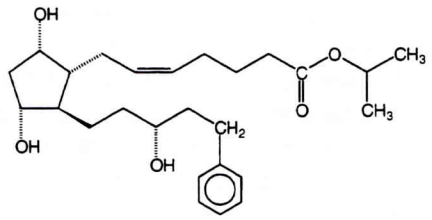
Once-daily topical instillation of latanoprost 0.005% is the recommended dosage regimen for the treatment of patients with primary open-angle glaucoma or ocular hypertension. If used in combination with other topical antiglaucoma agents, the drugs should be instilled at least 5 minutes apart.

Latanoprost (fig. 1) is one of a number of rationally designed ester prodrug analogues of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$)[1-4] that have been investigated as potential treatments for primary open-angle glaucoma (POAG) and ocular hypertension.[5-9] Latanoprost is the *R* component of an approximately equimolar *R/S* epimeric mixture initially identified as PhXA34.[1] The epimeric mixture was originally evaluated for the treatment of POAG and ocular hypertension,[10-12] but later displaced in favour of latanoprost.[1,13]

This review describes the pharmacological properties, clinical efficacy and tolerability of topically applied latanoprost for the treatment of POAG and ocular hypertension.

1. Overview of Glaucoma and Ocular Hypertension

The term glaucoma encompasses a group of diseases that share all or some of the following pathophysiological features: elevated intraocular pressure (IOP), excavation of the optic nerve head, and loss of visual field (see Lesar[14]). Glaucoma is a chronic disorder that, in the majority of patients, results from an imbalance between aqueous humour



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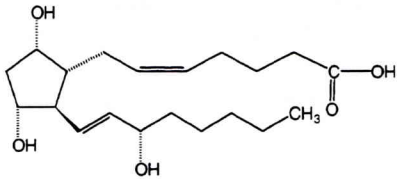

Prostaglandin $F_{2\alpha}$

Fig. 1. Structural formulae of prostaglandin $F_{2\alpha}$ and latanoprost.

Table I. Classification of glaucoma[14]

Primary glaucoma	
Open-angle	
Angle closure	with pupillary block without pupillary block
Secondary glaucoma	
Open-angle	pretrabecular trabecular post-trabecular
Angle closure	with pupillary block without pupillary block
Congenital glaucoma	

production and outflow from the anterior segment of the eye (see Lesar[14]). Broadly, glaucoma can be divided into open-angle, angle closure and primary, secondary and congenital glaucoma (see table I for a detailed classification[14]).

Briefly, POAG, which is diagnosed in ≈90% of patients with primary glaucoma, is bilateral and insidious in onset (visual acuity remains normal until the late stage of the disease).[14,15] It is probably, at least partly, a consequence of inhibited drainage of aqueous humour because of chronic low-grade partial obstruction of either the trabecular meshwork or Schlemm's canal (fig. 2).[14] In patients with POAG the IOP can range from 25 to 45mm Hg, whereas in healthy eyes normal IOP is maintained between 10 and 21mm Hg.[14,16] IOP is usually similar in both eyes but shows considerable circadian variation.[14] Chronic elevation of IOP may cause optic nerve ischaemia and consequent progressive loss of vision.[14]

Patients with ocular hypertension have elevated IOP but normal visual fields and optic discs; this contrasts with patients with normal-tension glaucoma (present in >15% of patients) in whom IOP is normal (<21mm Hg) but there is loss of visual field and the optic disc is cupped.[14,15] Ocular hypertension is often regarded as a pre-glaucoma stage.[17]

Key factors that predispose individuals to developing glaucoma (for review see Quigley[18]) include high IOP, family history of glaucoma, age >40 years, systemic vascular disease, high degree of myopia, diabetes, long term topical or systemic corticosteroid use and ethnicity (particularly Americans of African heritage, Russians, Scandinavians and the Irish).[14,19]

2. Pharmacodynamic Properties

2.1 Mechanism of Action

Latanoprost is a highly selective agonist of the FP subtype of prostanoid receptors;[20] its affinity for this receptor is considerably higher than that for other prostanoid receptors.[21] Latanoprost, like its congeners,[22-24] lowers IOP by increasing uveoscleral outflow, with little or no effect on the conventional aqueous outflow facility.[25] In the normal eye (fig. 2), outflow of aqueous humour occurs by filtration through the trabecular meshwork to Schlemm's canal (i.e. conventional or trabeculocanalicular route) and via uveoscleral outflow through the ciliary muscle, suprachoroidal space and the sclera.[26,27] The difference in the outflow rates between the 2 routes is marked: uveoscleral outflow occurs at 0.2 to 0.5 µl/min, compared with 1.5 to 1.8 µl/min via the conventional route.[14]

The process by which latanoprost produces an IOP-lowering effect (i.e. increasing uveoscleral outflow) is novel compared with that of existing nonprostaglandin agents used to treat glaucoma, which act by increasing aqueous humour outflow via the trabecular meshwork or by inhibiting aqueous humour production.[28] The basis for the precise mechanism of action by which prostaglandins decrease IOP remains unclear at present (see review by Camras[29]) and the precise prostanoid receptor(s) involved has not been fully elucidated. Nevertheless, the FP subtype of prostanoid receptors appears to be important as evident from the IOP-lowering effect of latanoprost (section 4).

2.2 Ocular Effects

Most ocular effects of latanoprost in humans parallel those seen with its congeners.[25] As previously stated, latanoprost produces an increase in uveoscleral outflow; an increase from 0.39 (at baseline) to 0.87 µl/min ($p < 0.05$) occurred after 8

days of twice daily application with latanoprost 0.006% in volunteers.[25] Latanoprost 0.006% twice daily for 5 days increased tonographic outflow facility (by 24 to 30%) in 1 study (n = 20 patients/20 volunteers)[30] but not in another study of 22 volunteers administered the same dosage regimen.[25] Latanoprost did not affect fluorophotometric outflow facility,[25] which was represented by the ratio of pharmacologically induced changes in aqueous flow : changes in IOP. At doses that effectively reduced IOP, latanoprost also did not affect retinal vasculature[31] or permeability of the blood-aqueous barrier – as indicated by minimal effects on the rate of entry and polarisation of fluorescein or aqueous flare intensity.[30]

Latanoprost, like $PGF_{2\alpha}$-1-isopropyl ester[5,8] and PhXA34,[12] lowered IOP without altering aqueous flow in volunteers and patients.[25,30] Placebo-controlled (contralateral eye) studies in humans with normotension or ocular hypertension have shown significant decreases in IOP (by 22 to 25%) after 5 to 8 days of treatment with latanoprost 0.006% twice daily.[25,30] Maximal decreases in IOP occurred within the first 2 days of initiating latanoprost treatment (as is also the case with pilocarpine[32]) in patients with POAG or ocular hypertension.[32-38] The IOP-lowering effect was independent of the time of application of the agent.[39,40] Reductions in IOP with latanoprost can last for 20 to 24 hours after a single dose;[34,36,41] the reason for this sustained effect is not adequately understood, although it can be explained, in part, by the high lipophilicity of the prodrug and consequent corneal trapping of the de-esterified drug (see section 3.1).

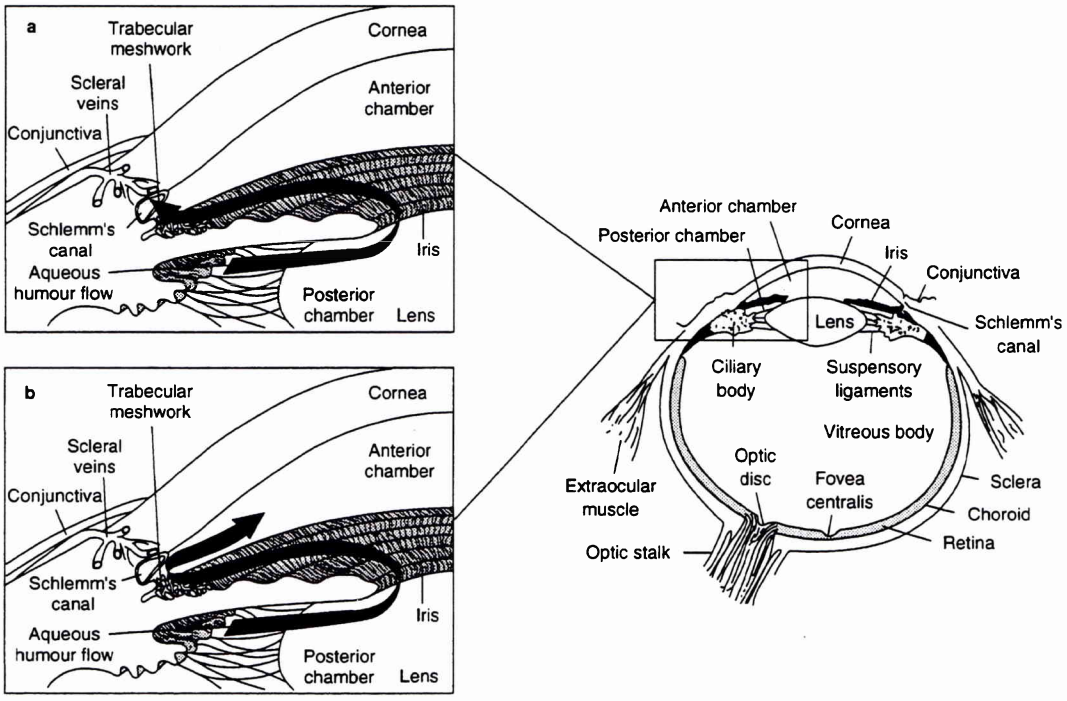

Fig. 2. Anatomical features of the human eye under normal conditions **(a)** and in primary open-angle glaucoma **(b)**. In the normal eye, aqueous humour (secreted into the posterior chamber) enters the anterior chamber through the pupil. In the anterior chamber, it passes through the trabecular meshwork into Schlemm's canal and from there into the venous system. In primary open-angle glaucoma, the eye appears anatomically normal but the flow of aqueous humour is obstructed at the trabecular meshwork or Schlemm's canal, resulting in elevated intraocular pressure.

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