

Comparing Prostaglandins

How they work singularly and in combination therapies.

BY GEORGE SHAFRANOV, MD

When the first prostaglandin was discovered in 1936, it was thought to be a single substance, but subsequent investigations described a variety of these naturally occurring and synthesized compounds.¹⁻⁴ Prostaglandins belong to a chemical group called *prostanoids*, part of an even larger group called *eicosanoids* that is derived from 20-carbon arachidonic acid. Prostaglandins are classified by variations of their ring structure as well as the number and location of side-chain double bonds. In the early 1980s, researchers demonstrated that the topical application of prostaglandin analog $F_{2\alpha}$ ($PGF_{2\alpha}$) reduced IOP in monkeys.⁵ The development of commercially available prostaglandin analogs (hypotensive lipids) for the lowering of IOP ensued. This article describes how prostaglandins work alone and in conjunction with other drugs.

MECHANISMS OF ACTION

Overview

Prostaglandins are thought to stimulate the synthesis of matrix metalloproteinases⁶ that subsequently dissolve the extracellular matrix of the ciliary muscle, thus reducing IOP by enhancing uveoscleral outflow.⁷ For unknown reasons, prostaglandin analogs have relatively poor corneal penetration,⁸ and their efficacy was reportedly reduced in patients with thick corneas.⁹

The response to prostaglandins varies among species as well.¹⁰ $PGF_{2\alpha}$ causes various ocular responses in laboratory animals, including the breakdown of the blood-aqueous barrier and subsequent IOP elevation in rabbits¹¹ and miosis in cats.¹² Diurnal IOP curves differ among various prostaglandins, but all achieve a flatter curve and better 24-hour IOP control than other groups of IOP-lowering medications.

Latanoprost

Latanoprost, which in 1996 became the first commercially available prostaglandin to treat glaucoma, is derived from $PGF_{2\alpha}$. The drug is highly selective for the FP type of

prostanoid receptors. Latanoprost is absorbed through the cornea, where esterases hydrolyze this prodrug and change it into a biologically active acid form. Latanoprost 0.005% lowers IOP by between 6 and 8 mm Hg.^{13,14} Although the agent reaches peak concentration in the aqueous humor approximately 2 hours after instillation, the maximal reduction of IOP occurs between 8 and 12 hours after dosing. The sustained effect lasts for at least 24 hours, thereby allowing once-a-day administration. In fact, latanoprost, as well as other hypotensive lipids, is more effective when used once daily than with more frequent dosing.^{15,16} If latanoprost is discontinued, IOP reportedly reaches pretreatment level after 14 days.¹⁷

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The agent reduces IOP to a similar degree as bimatoprost and travoprost, but latanoprost produces less irritation to the ocular surface (causing hyperemia in 5% to 15% of patients). Because the drug is generally well tolerated, patients seem to be more persistent with latanoprost treatment than with other groups of ocular hypotensive medications¹⁸ and other prostaglandins.¹⁹ Although latanoprost has a strong additive IOP-lowering effect in patients already on maximal medical therapy,²⁰ it is more commonly used alone, as the first-line treatment for open-angle glaucoma and ocular hypertension. The reported side effects of latanoprost include cystoid macular edema,²¹ benign changes in the iris' color,²² and the growth of lashes and hair around the eyelids.²³

Travoprost

In 2001, the FDA approved travoprost, a highly selective FP prostanoid receptor agonist and a powerful IOP-lowering compound, for the treatment of glaucoma. Initial studies suggested that travoprost was more effective in blacks than whites.²⁴ Similar claims were also made for latanoprost²⁵ and bimatoprost, however.²⁶ None has been validated thus far.

Travoprost begins reducing IOP 2 hours after instillation, and its effect peaks after 12 hours. One study suggested that the drug's IOP-lowering effect lasts for up to 84 hours after a single administration.²⁷ Other prostaglandins' effect on IOP may be similarly long lasting. As of this article's publication, no reports regarding that subject had been published. The side effects of travoprost include conjunctival hyperemia, eyelash growth, and changes in the iris' color.²⁸

Bimatoprost

The FDA approved bimatoprost, a once-daily hypotensive lipid, in 2001. Often classified as a prostamide because of the presence of the amide group on the first carbon of the molecule, bimatoprost has a target receptor that appears to be unrelated to typical prostaglandin receptors. Studies have suggested that the agent is not a prodrug, because it remains largely unchanged in the eye after instillation.²⁹ Researchers once attributed bimatoprost's ocular hypotensive effect to its prostamide-mimetic properties.²⁹ The drug's IOP-lowering effect is more significant than that of timolol³⁰ but similar to that of latanoprost and travoprost.³¹ Bimatoprost has also been reported to lower IOP by an additional 1 to 2 mm Hg at some points during the day when compared with latanoprost.^{32,33} This difference may not always be clinically significant due to some statistical shortcomings of the studies.³⁴

Bimatoprost irritates the eye significantly more than other prostaglandins.³¹ Although the majority of patients tolerate conjunctival hyperemia, a small number may discontinue their use of bimatoprost as a result of this side effect. Additional reported side effects are similar to those of other prostaglandins, such as the excessive growth of eyelashes and hair³⁵ and uveitis.³⁶

Unoprostone

Since 1994, unoprostone (0.12%) has been used for glaucoma treatment in Japan. The agent was introduced to the US market in 2000 in a slightly stronger concentration (0.15%). The drug is derived from a 22-carbon lipid acid and, therefore, is not an eicosanoid but a docosanoid. Unimpressed by its lack of IOP-lowering effect, physicians in the US³⁷ and Japan³⁸ abandoned unoprostone in favor of other prostaglandins.

ADVERSE EVENTS

Although uncommon, systemic side effects from prostaglandin analogs exist. They include flu-like symptoms, chest pain, and back/muscle pain. Local side effects are corneal changes, conjunctival hyperemia, iris pigmentation, periorbital pigmentation, cystoid macular edema, an excessive growth of the eyelashes and hair, photophobia, and uveitis.

ADJUNCTIVE THERAPY

Prostaglandins appear to be additive to all commercially available classes of IOP-lowering medications. Latanoprost and the beta-blocker timolol were shown to be additive to each other, decreasing IOP by another 13% to 25%.^{39,40} When both components were used in a fixed combination, the additivity of timolol and latanoprost was minimal.⁴¹ Adding brimonidine to latanoprost may lower IOP an additional 1.5 to 3.0 mm Hg, and adding dorzolamide to latanoprost produces similar or slightly stronger results.⁴²⁻⁴⁴ Bimatoprost and brimonidine also have significant additivity.⁴⁵ Initially, researchers considered it inappropriate to use miotics with prostaglandins, because pilocarpine, for example, causes the ciliary muscle to contract and decreases uveoscleral outflow. The clinical use of latanoprost and pilocarpine together, however, has shown a modest additive IOP-lowering effect.⁴⁶

Clinicians rarely use two topical medications from the same class to lower IOP. This practice generally pertains to prostaglandins as well due to the agents' similar mechanisms and concerns over a possibly increased risk of inflammation. Despite research demonstrating prostaglandins' additivity in monkeys,⁴⁷ the combination of bimatoprost and latanoprost actually appeared to increase IOP in patients with glaucoma.⁴⁸ Therefore, the use of two or more prostaglandins in patients with glaucoma remains controversial and is not recommended.

FIXED COMBINATIONS

Because both topical beta-blockers and prostaglandins may be used once daily, it seems logical to combine these agents in one bottle. Fixed combinations of timolol and latanoprost, travoprost, or bimatoprost are all currently under investigation. None of the ongoing clinical trials has uniformly demonstrated the greater efficacy of a combination agent.

When treatment with one prostaglandin fails to achieve the targeted IOP, switching to another prostaglandin may benefit some patients.^{49,50} Clinicians should make this decision on an individual basis, however, because most published studies on switching prostaglandins have inadequacies in their design,⁵¹ and therefore the results are difficult to interpret.

CONCLUSION

Despite structural differences in the prostaglandins and occasional dissimilarities in published studies, all of the currently available hypotensive lipids lower IOP comparably. Clinical decisions about which hypotensive agent to use should depend on the individual patient. For example, in eyes with uveitic glaucoma,⁵² or pediatric glaucoma,⁵³ an agent of another class would be sufficient or preferable. For the majority of patients, however, any of the three most common prostaglandins is an excellent choice for treating an elevated IOP. □

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