

Prostaglandin Analogs

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ABSTRACT

The prostaglandin analogs have emerged as effective, well-tolerated agents for the reduction of intraocular pressure (IOP) in patients with primary open-angle glaucoma and ocular hypertension. Based on the available clinical data, bimatoprost, latanoprost and travoprost appear to be more effective than the erstwhile gold standard, timolol, while the effectiveness of unoprostone is similar or slightly less. Prostaglandin analogs may be used in conjunction with other antiglaucoma medications, although further studies must establish the optimal combination. Whether clinical experience will yield outcomes in favor of one of the prostaglandin analogs remains to be determined. This review attempts to concisely cover all the clinical aspects of currently available prostaglandin analogs for ocular use.

Keywords: Antiglaucoma drugs, Prostanoids, Prostaglandins, Uveoscleral outflow.

INTRODUCTION

Prostaglandins, also known as autacoids, are a class of local hormones exerting multiple effects through several types of receptors. They have several favorable characteristics that render them as one of the most potent weapons in combating glaucomas.

BACKGROUND

In 1978, timolol maleate was introduced as the first topical anti-glaucoma medication. Thereafter, in 1980s and early 90s, several selective and nonselective beta-blockers were introduced into the market. Timolol became the gold standard against which all other drugs were compared for their intraocular pressure (IOP) lowering ability. The nonselective alpha adrenergic agonist apraclonidine and the selective brimonidine were introduced in 1988 and 1996 respectively. Dorzolamide as the first topical carbonic anhydrase inhibitor became available for use in 1995.¹

The effects of prostaglandins on eye were first reported in 1985 as tromethamine salt of PGF₂ alpha which produced sustained IOP lowering for more than 24 hours. It was, however, associated with severe conjunctival hyperemia and discomfort.^{2,3} Less polar substitutes like 17-phenyl PG F₂ alpha had increased corneal penetration and significant IOP lowering with minimal discomfort and hyperemia.^{4,5} The more potent R-epimer of the above received US FDA approval in 1996 as latanoprost.

Currently available Prostaglandin Analogs

FP receptor analogs,⁶ amides:

1. Latanoprost
2. Travoprost
3. Bimatoprost

4. Unoprostone

5. Tafluprost.

DP receptor agonist:

1. AL-6598

EP2 receptor agonist:

1. Butaprost
2. 8-iso PGE₂
3. 17-phenyl trinor 8-iso PGE₂.

EP4 receptor agonist:

1. 3,7-dithia PGE₁

Mechanism of Action

Prostaglandin analogs act primarily by increasing the uveoscleral outflow and also produce a variable increase in the trabecular outflow.

The various mechanisms proposed by which prostaglandins increase the uveoscleral outflow include the following:

1. Remodeling of the extracellular matrix of the ciliary muscle and the sclera causing changes in the permeability of these tissues and widening of the connective tissue spaces among ciliary muscle bundles. This is caused by dissolution of collagen 1 and 3 by alterations induced in the concentrations of matrix metalloproteinases and tissue inhibitor of matrix metalloproteinase.^{23,24}
2. Ciliary muscle relaxation which also widens the connective tissue spaces. This is responsible for the initial fall in IOP with topical prostaglandins.²⁵
3. Changes in the shape of the ciliary muscle fibers caused by relocalization of actin and vinculin in the muscle cells.²⁶

Prostaglandin analogs also produce a variable increase in the trabecular outflow by directly stimulating matrix metalloproteinase and neutral protease induced extracellular matrix degradation.

Individual Agents

Latanoprost and travoprost are ester prodrugs of 17-phenyl PGF2 alpha. These are converted by corneal hydrolases to their respective free acids in the corneal epithelium. The esterification makes them more lipid soluble and less polar thereby increasing their corneal permeability. The respective free acids then bind to specific PGF2 receptors in the trabecular meshwork and the ciliary body in turn increasing the aqueous outflow through these routes. Latanoprost requires maintenance of cold chain prior to uncapping of the bottle and, thereafter, has a limited shelf life of 44 days at room temperature. Travoprost has no such considerations. Travoprost is also available as a benzalkonium chloride preservative free travoprost 0.004% ophthalmic solution probably having a better side effect profile (Travoprost Z).⁷

Bimatoprost on the other hand is an amide prodrug of 17-phenyl PGF2 alpha and hence characterized as a prostamide.⁸ It is converted to its free acid, Bimatoprost acid which is a potent stimulator of PGF2 receptor.⁹ It is also postulated that bimatoprost may act through a novel prostamide receptor.¹⁰ Bimatoprost acid is three to 10 times as potent as latanoprost acid.¹¹ In spite of this, the therapeutically used concentration of Bimatoprost is six times that of latanoprost. This is because of the slow conversion of bimatoprost to bimatoprost acid.¹²

The recommended dosing regimen for latanoprost, travoprost and bimatoprost is once daily topical application preferably in the evening to reduce the early morning diurnal spike.³³ Studies have shown that all the available classes of prostaglandins have excellent 24-hour IOP control despite once a day dose making it extremely patient convenient. Infact, multiple dosing has been shown to reduce the IOP lowering effect.

outflow.¹⁹ It is available in concentrations of 0.12% and 0.15% for a twice daily (BD) dosing.

Tafluprost is a new difluoro prostaglandin analog undergoing clinical trials in Japan. Animal studies have shown it to act by increasing the uveoscleral outflow. In addition, it may also act by stimulating PGF receptor mediated endogenous prostaglandin production in turn acting via prostanoid EP3 receptor.^{20,21} It is approved in some countries (Denmark since April 2008 and Germany since May 2008) as a preservative free 0.0015% solution for once daily dosing.

In general, the reduction of IOP starts approximately 2 to 4 hours after the first administration of the prostaglandin analog with the peak effect reached in about 8 to 12 hours. Maximum IOP lowering effect is achieved 3 to 5 weeks from commencement of treatment.

Butaprost and other EP agonists are being investigated for their therapeutic potential in animal studies.²²

Indications

1. Primary open angle glaucoma—latanoprost, travoprost and bimatoprost have all received the EMEA and FDA approval as first line agents for treatment of open angle glaucoma or ocular hypertension
2. Normal tension glaucoma²⁷
3. Chronic angle closure glaucoma²⁸
4. Pigment dispersion syndrome²⁹
5. Exfoliation syndrome.³⁰

There are limited reports of clinical experience of these drugs in other types of glaucomas.

Pharmacokinetics, % of IOP reduction from baseline and compared to timolol of the three commonly used prostaglandin analogs

	One drop content (mcg)	Plasma t1/2 (min)	Concentration (%)	Dosing frequency	% IOP difference from baseline (peak)	% IOP difference from baseline (trough)	Avg IOP reduction > timolol as shown by RCTs (mm Hg)
Latanoprost ¹³	1.5	17	0.005	OD	-33%	-28%	1.2 ¹⁴
Travoprost ¹⁵	1.2	45	0.004	OD	-31%	-29%	1 ¹⁶
Bimatoprost ¹⁷	9	45	0.03	OD	-31%	-28%	1.7-2.0 ¹⁸

Unoprostone is a docosanoid. It is a pulmonary metabolite of PGF2 alpha. It is much less potent compared to the previous three prostaglandin analogs with an IOP lowering effect of up to 18% from baseline. It has minimal effect on uveoscleral outflow in humans and mainly acts by increasing the trabecular

Contraindications and Cautious Use

1. Patients allergic/sensitive to prostaglandins³¹
2. Pregnant or nursing mothers³¹
3. Children—responses may be inadequate in some³²

Pressure lowering effect of commercially available prostaglandin analogs (European glaucoma society's terminology and guidelines for glaucoma)

Prostaglandin analog	Pressure lowering effect (mm Hg)
Latanoprost	6-8 (baseline 24-25)
Travoprost	7-8 (baseline 25-27)
Bimatoprost	7-8 (baseline 26)
Unoprostone	3-4 (baseline 24-25)
Tafluprost	5-8 (baseline 24-25)

4. Uveitic glaucomas
5. Patients with iritis
6. Patients with active or healed herpes simplex keratitis
7. Immediate postoperative period following any intraocular surgery
8. Patients with risk factors for cystoids macular edema, like aphakia, pseudophakia with torn posterior capsule, history of uveitis, retinal inflammation or vascular diseases
9. Patients should not administer these drugs while wearing contact lenses, but contact lenses can be reinserted 15 minutes following administration of the drugs.

Side Effects

The well-documented and more common local side effects with prostaglandin therapy include:³⁵

1. Conjunctival hyperemia, burning and stinging
2. Elongation and darkening of eye lashes
3. Induced iris darkening
4. Periocular skin pigmentation.

The former two are less frequently seen with latanoprost compared with bimatoprost and travoprost.³⁶ The mechanism for the latter two is increase in the melanin content of melanocytes due to increase in the size or the number of melanin granules in the cytoplasm of the melanocytes.³⁷ Induced iris darkening is more commonly seen in hazel irises that have mixed coloring and is usually irreversible.³⁸ On the other hand, periocular skin pigmentation involving mostly the eyelid skin is usually reversible.³⁹ The above side effects are an important consideration prior to starting a patient on prostaglandin analogs for unilateral glaucomas.

The less common but more sight threatening complications include:

5. Iris cysts
6. Anterior uveitis
7. Cystoid macular edema
8. Reactivation of herpes simplex keratitis.

Due to their low therapeutic concentration and rapid systemic inactivation, topical prostaglandins have an excellent systemic safety profile. Dyspnea, asthma and exacerbation of asthma are the systemic complications that have been identified during the postmarketing use of topical prostaglandin analogs in clinical practice. As they are voluntarily reported from a population of unknown size, estimates of their frequency cannot be made.

Pregnancy and Nursing Mothers

There are no adequate and well-controlled studies on topical prostaglandin use in pregnant women. At present, they may be used during pregnancy only if potential benefit justifies the potential risk to fetus. Whether the drugs or their metabolites are excreted in breast milk is also not known.

Class Interswitch among Prostaglandins

Studies comparing the interclass switching among prostaglandins have shown good IOP control, feasibility and tolerability on class switch from latanoprost to bimatoprost and latanoprost to travoprost. Clinical experience with this class of drugs shows that often patients unresponsive or intolerant to one class of prostaglandins benefit from switching over to another class of prostaglandin analogs. The wash-out time for most of the prostaglandin analogs varies from 4 to 6 weeks.

Drug Interaction and Drug Additivity

Topical preparations containing thiomersal as preservative form a precipitate with latanoprost, and hence must be instilled with a gap of at least 5 minutes between the two.

Clinical studies have demonstrated additive effects of prostaglandins with all other antiglaucoma medications, including beta blockers,⁴⁰ alpha adrenergic agonists,⁴¹ carbonic anhydrase inhibitors⁴² and cholinergic agonists.⁴³

As the nonselective beta blockers and prostaglandin analogs may both be effective with OD dosing, fixed drug combination of timolol 0.5% with each of the three frontline prostaglandin analogs are commercially available. These have been shown to have significantly more IOP lowering effect than either drug used alone.⁴⁴ Also, the IOP reduction achieved is not significantly less than concomitant treatment with prostaglandin analog OD and timolol BD.⁴⁵

Prostaglandin Analogs Head to Head

A meta-analysis would be a reliable means of comparing the IOP lowering ability of the various ocular hypotensive medications.⁴⁶ The results of the meta-analyses assessing the efficacy of the three frontline prostaglandin analogs are as follows:

S. no.	Condition	No. of trials	Sponsor	Result
1 ⁴⁷	POAG/OH	9	Alcon	Trav = Bimat > Lat
2 ⁴⁸	POAG/OH	12	Independent	Trav = Bimat = Lat
3 ⁴⁹	POAG	42	Allergan	Bimat > Lat = Trav
4 ⁵⁰	POAG/OH	27	Independent	Trav = Bimat = Lat
5 ⁵¹	POAG/OH	15	Pfizer	Lat = Trav = Bimat
6 ⁵²	POAG/OH	8	Independent	Bimat > Lat = Trav
7 ⁵³	PACG	9	Independent	Lat = Trav = Bimat

Lat: Latanoprost; Trav: Travoprost; Bimat: Bimatoprost; POAG: Primary open-angle glaucoma; OH: Ocular hypertension; PACG: Primary angle closure glaucoma

It is notable that three independently performed meta-analyses found the three prostaglandin analogs to have equivalent IOP lowering ability.

Adherence, Persistence and Tolerability among Prostaglandin Analogs

‘Adherence’ in simple terms refers to the extent to which the patient behavior conforms to the health care provider’s

As regards tolerability, a recent meta-analysis comparing the three prostaglandin analogs reported a significantly lower conjunctival hyperemia with latanoprost and travoprost compared to bimatoprost.⁵² Moreover, in a recent study comparing the preservative-free travoprost with the BAK-preserved prostaglandins found significantly better ocular surface disorder profile, decreased hyperemia and equal or better IOP control with the preservative-free travoprost.⁵⁶

Cost considerations of some of the commercially available prostaglandin/combination brands

Prostaglandin brand	Packaging volume per bottle (ml)	Cost per bottle (₹)	Manufacturing pharmaceutical company
Latanoprost 0.005% brands			
Ioprost	2.5	199	FDC
Latochek	2.5	220	Indoco
Ioptame	2.5	264	Cadila
Latodrops	3.0	275	Intas
Latoprost	2.5	310	Sun
9 PM	2.5	343	Cipla
Xalatan	2.5	1142	Pharmacia and Upjohn
Travoprost 0.004% brands			
Travo	2.5	260	Micro
Travatan	2.5	652	Alcon
Bimatoprost 0.03% brands			
Careprost	3.0	210	Sun
Intaprost	3.0	350	Intas
Lumigan	3.0	433	Allergan
Latanoprost 0.005% + timolol 0.5% FDC brands			
Latochek-T	2.5	250	Indoco
Latocom	2.5	307	Sun
Latim	2.5	362	Cipla
Xalacom	2.5	1320	Pfizer
Travoprost 0.004% + timolol 0.5% FDC brand			
Travocom	2.5	695	Alcon
Bimatoprost 0.03% + timolol 0.5% FDC brands			
Careprost plus	3.0	230	Sun
Ganfort	3.0	445	Allergan

prescription. Having recently replaced the term ‘compliance’ to highlight the patient’s responsibility and involvement in their care, it plays an important role in chronic diseases, such as glaucoma. ‘Persistence’ on the other hand, refers to continued following of treatment orders over a period of time, such as refilling of prescriptions.

Studies have shown that both adherence and persistence to topical ocular hypotensive therapy are poor.⁵⁴ Among the available agents, prostaglandins have been reported to have higher rates of persistence than other classes. Among the three major prostaglandin analogs, latanoprost users were reported to have greater odds of achieving medication possession and had more days covered in the first therapy year compared to travoprost and bimatoprost.⁵⁵

CONCLUSION

As a class, prostaglandin analogs have several unique properties. These agents act by increasing the uveoscleral outflow which is different from that of other antiglaucoma drugs, which either decrease aqueous production or increase the trabecular outflow. This novel mechanism of action empowers them to potentially lower the IOP below the episcleral venous pressure—a potential advantage in normal tension glaucoma. Also, this makes these drugs additive with all other classes when used in combination. These analogs effectively lower the IOP during night as well as day—an advantage over the beta blockers. Their once a day dosing improves patient compliance. Finally, due to their low therapeutic concentrations and rapid systemic inactivation, they have few systemic side effects.

However, as relatively recent additions to the antiglaucoma armory, only time and continued experience with these agents will reveal their long-term side effects and absolute safety.

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