

All About Prostaglandin Analogues in Eye

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Abstract

Glaucoma is a leading cause of impairment of vision worldwide. Raised intraocular pressure can cause damage to both optic nerve and retinal ganglion cells. Reducing intraocular pressure is the only modifiable risk factor for this disease available presently. It can be achieved either by surgical or medical treatment. Pharmacotherapy is the mainstay of treatment for glaucoma patients. Prostaglandins analogues have replaced beta blockers as the first line anti-glaucoma drug. Their single dose per day, better diurnal control of IOP and long washout period has ensured better compliance and better results in various forms of glaucoma. A lot of clinical research is ongoing in developing new prostaglandin derivatives with safer profiles and more targeted action. This article will be reviewing the various merits and demerits of prostaglandin analogues in practice as well as shed some light on the newer drugs in pipeline.

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Introduction

Glaucoma is a form of optic neuropathy, in which the axons of optic nerve and retinal ganglion cells are damaged. This can result in slowly progressive irreversible loss of vision and specific patterns of visual field defects. It has been estimated that 80 million people will be affected by glaucoma by the year 2020.¹ Glaucoma has also emerged as the leading cause of irreversible blindness worldwide accounting for 14% of worldwide blindness.²

It is mostly asymptomatic and is hence, missed on many occasions and can eventually result in complete loss of vision. It is mainly divided into two subtypes- open and closed angle, which can be further divided into primary and secondary types.³

IOP is considered as the only modifiable risk factor and most of the current treatment modalities are aimed at reducing intraocular pressure. Intraocular pressure, is maintained by a balance between aqueous production and drainage.⁴

The present day treatment methods work either by reducing the aqueous production or by enhancing its drainage from eye and neuro-protection. Drugs used to treat glaucoma include alpha-agonists (brimonidine, apraclonidine), beta-blockers (betaxolol, levobunolol, carteolol, timolol etc.), carbonic anhydrase inhibitors (acetazolamide, brinzolamide, dorzolamide), miotics (pilocarpine), prostaglandin analogues (latanoprost, bimatoprost, travoprost, unoprostone etc.)⁵

Timolol was considered as the gold standard drug of choice for topical glaucoma treatment. PG analogues (PGA's) have emerged as the new first line treatment and are forefront in treating most forms of glaucoma. This is because of the poor safety profile of timolol in systemic conditions like diabetes and hypertension.

PGA's are preferred over other anti-glaucoma drugs due to their nightly single dosage, good maintenance of diurnal variation and fewer local side effects and safe systemic profile.⁵

Prostaglandins

Prostaglandins belong to a class of local hormones that have

multiple receptors having multiple effects. It plays various roles in the body, few of which include relaxation and contraction of smooth muscle, immune system modulation and dilatation and constriction of the blood vessels. The effect of prostaglandins (tromethamine salt of PGF₂) in eye was reported in the year 1985. The first prostaglandin approved by FDA to be used in eye was latanoprost, in the year 1997. Next in line were bimatoprost and travoprost that were FDA approved in 2001. The latest prostaglandin to get FDA approval was tafluprost, in the year 2012.⁶

a. Receptors of PG's:

Prostaglandins have multiple receptors throughout the body. 9 types of receptors have been identified for prostaglandins in human body. These are PGFP receptor, PGE 1-4 receptor, PGD 1-2 receptor 1-2, thromboxane A2 receptor and PGIP receptor. PGFP and PGE are the two main types of receptors present in human eyes and they are mainly located on the Schlemm's canal and on trabecular meshwork.⁶

b. Mechanism of Action in eyes:

It increases the uveo-scleral outflow of aqueous humor and also increases conventional trabecular outflow.

It acts by remodelling the structure of matrix metallo-proteinases. This causes change in shape of the cells and widening of the spaces filled with connective tissue resulting in decreased resistance and increased drainage.

The receptors of prostaglandins are located on TM, ciliary muscle and sclera and hence prostaglandins can affect the aqueous drainage⁷

c. Indications:

- POAG
- OHT
- NTG
- PACG
- Secondary Glaucoma

d. Contraindications:*Absolute-*

- Active uveitis (recent studies have shown that latanoprost is safe in eyes with inactive uveitis)
- Active macular oedema,

Relative contraindications-

- Patients with risk of CME (aphakia or pseudophakia with PC rent)
- Old history of macular oedema
- History of herpetic keratitis
- Pregnant and nursing mothers
- PGA's should not be administered while wearing contact lenses.

e. Side effects:

Ocular: Iris suntan syndrome, burning, stinging, trichomegaly, sensitivity to light, pain, hyperaemia, periocular pigmentation, blurring of vision

Systemic: Headache, flu like symptoms and hypertension

f. Classification:

PGA's: Tafluprost (0.0015%), latanoprost (0.005%) and travoprost (0.004%)

Prostamides: Bimatoprost (0.03 and 0.01%)

Eicosanoids: Unoprostone (0.15%)

Latanoprost:

It acts on FP receptors as a selective agonist and is an ester pro-drug of PGF2a. Conversion of the pro-drug to the free acid form takes place in the corneal epithelium making it more lipid soluble. This increases the corneal permeability of the drug. The drug then binds to the receptors located on the trabecular meshwork and ciliary epithelium causing reduced resistance and increased drainage of aqueous. It is available in strength of 0.005%. IOP reduction achieved by latanoprost is 30-35%, which is superior to timolol. Due to its unique mechanism of action it can have additive IOP lowering effect with all other anti-glaucoma drugs.⁸

Complications like hyperaemia, increased pigmentation of iris and trichomegaly can be seen with long term usage. Systemic side effects are rare. All these side effects are reversible. Hyperaemia caused is reversible and generally reduces after 2 to 4 weeks of using the drug. Cold chain maintenance is required for latanoprost. However, recently latanoprost stable at room temperature has been introduced.⁸

Bimatoprost:

It is a prostamide analogue. The end of carbon chain has an amide ester attached to the carboxyl group, giving it a unique structure. It is available in two strengths, 0.03 and 0.01 %. It increases the uveo-scleral outflow like other PGA's but also acts on the prostamide receptors present in the trabecular meshwork, thus affecting the conventional outflow. This dual action is the reason for IOP control as compared to other prostaglandins as well as timolol and brinzolamide combination. It is the most efficacious drug for monotherapy

in glaucoma. Hyperaemia is more common as compared to the other prostaglandins. To reduce this side effect, newer formulations of bimatoprost with lower concentration of the drug (0.01%) was developed. Compared with the original formulation 0.03%, the new formulation i.e 0.01% has a 4 times greater amount of benzalkonium chloride (BAK) (0.020%).BAK alters the tight junctions found in corneal epithelium. This results in improved penetration of the drug through cornea.⁹

Travoprost:

It belongs to the PGF2a analogue group. Unlike other drugs in its group, it has a hundred percent agonistic action at the receptor site. It is available in strength of 0.004% and has a once daily dosage. IOP control on travoprost monotherapy has been proven better than dorzolamide and timolol combination therapy. It can bring down baseline IOP of 25-28 mm Hg by 8-9 mm Hg. This drug has an excellent stabilization of diurnal variation. It has agonistic action with other anti-glaucoma drugs and combination therapy can reduce further IOP by 5-6 mm Hg.⁹

Tafluprost:

Marketed in strength of 0.0015%, it has partial action on PGF2 receptor. MOA is similar to latanoprost and travoprost. It has a better corneal penetration rate due to its lipophilic nature. For all the prostaglandins the onset of action takes 2-4 hours, peak action is seen after 12 hours and complete washout from the body may takes 6 weeks once you stop the drug. Intraocular pressure is reduced by 25-35% from the baseline.⁹

g. Interswitching among PGA's:

Studies have shown that patients not responding or intolerant to one class of PGA's benefit from switching to another class of PGA's.⁹

h. Combination therapy:

Treatment with multiple drugs is very common in Glaucoma. Due to its action on uveo-scleral pathway, PGA's can have additive effect when combined with other class of anti-glaucoma agents like beta blockers and carbonic anhydrase inhibitors.

Use of fixed dose combinations has shown a rise in last decade. They simplify the dosage, improving compliance. The washout effect of second drug on the first drug seen in combination therapy can also be reduced by using fixed dose combinations. It can also be more cost effective, which is important in long-term usage. Reduced number of drops causes reduced exposure to preservatives like BAK, making it safer than combination therapy.¹⁰

Fixed combination of timolol with all three main prostaglandins is available. They are usually given as once daily dose in the morning as PGA's. Twice daily dosage can cause sub-sensitivity at the FP receptor level or its associated intracellular signalling pathways.¹¹

Studies have shown that fixed combination of timolol and PGA's is less efficacious than the individual drugs when used together. In a systematic review by Webers CA et al, it was seen that the concomitant use of PGA's and timolol

had a larger IOP reduction when compared with the fixed combination.¹²

i. Post treatment care:

Patient should be advised to wash both hands before instillation. Ideally contact lens should be removed before applying these drops. After application, eyelids should be kept closed and digital compression should be applied to the punctum for 1-2 minutes. Excessive drug running down the eyelid must be wiped off to avoid peri-ocular pigmentation. Patient must be educated about all the possible side effects. Follow up should be done after 4-6 weeks of starting the therapy. History must be taken specific to all the side effects and detailed slit lamp examination must be done to identify the signs of side effects.

Refrigeration is required to store unopened bottle of latanoprost. Once opened, the bottle must be used before 6 weeks. Tafluprost is a preservative free form and must be stored in its original pouch in fridge. Must be discarded after 28 days regardless of being opened or unopened.¹¹

j. Future developments:

The only drugs approved by FDA presently act on PGF2 receptors. Current research strategies are focusing on developing compounds that can target PGE2 and PGI2 receptors.

Sulprostone (prostaglandin E2 receptor agonist), butaprost/dinoprost (naturally occurring PGE2 agonist) and iloprost (synthetic PGI2 analogue) are the new promising drugs which can widen the horizon of treatment with PGA's.

Netarsuldil and latanoprost combination: Research on developing this new combination therapy is still in phase III trial. Netarsuldil is a Rho-kinase inhibitor. In trials, this combination appears to be superior to the individual drugs.¹³ Latanoprostene bunod is a nitric oxide donating PGF2 analogue. It has cleared Phase II trials and is awaiting FDA approval.¹⁴

DE-117 is a compound produced by Santen, Japan. It has completed phase II trial. It acts on PGE2 receptor. It also has dual action like bimatoprost. It increases the uveoscleral outflow but also reduces collagen deposition in TM and improves contractility of trabecular cells. This results in improved aqueous drainage.

ONO-9054 is also in phase I trial. It is a PGF and E3 agonist under study.

k. Other uses of topical prostaglandin analogues:

- Helps in improving blood circulation and perfusion of optic nerve head.⁸
- Used in treatment of chemotherapy induce madarosis.⁸

Conclusion

The introduction of prostaglandins for treatment of glaucoma has had an enormous positive effect in treating glaucoma. In majority of glaucoma cases it is the preferred first line

agent used worldwide. It's good IOP control, maximum IOP reduction amongst anti-glaucoma drugs and once daily bedtime dose are the major advantages.

New development of drugs acting against EP receptors has widened the choice of prostaglandins and can help introducing drugs with better IOP reduction and reduced side effects. Tafluprost is a promising new advent in this direction.

Ongoing research is focusing on understanding the molecular basis of actions of prostaglandins on uveo-scleral and trabecular pathways. These developments can help us develop more specific and targeted drugs for treatment of glaucoma.

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