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Review Article

Preserved to preservative free prostaglandin analogues in primary open angle glaucoma

Asha S. Morge*, M. D. Kulkarni, S. M. Doifode

Department of Pharmacology, Government Medical College and Hospital, Aurangabad-410001, Maharashtra, India

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***Correspondence to:**
Dr. Asha S. Morge,
Email: ashamorge@gmail.com

ABSTRACT

Glaucoma affecting 60 million people all over the world and it will be 80 million till 2020. There are approximately 11.2 million persons aged 40 years and older with glaucoma in India. Primary open angle glaucoma (POAG) is commonest type, affecting 2/3rd of glaucoma patients. POAG is estimated to affect 6.48 million persons. The estimated number with primary angle-closure glaucoma is 2.54 million.

POAG develops gradually and take long time to get detected and require long term treatment with topical prostaglandin analogues (PGF2) which is the most common as well as most widely used drugs. These PGF2 analogues need to be taken for longer time and more prone to develop adverse drug reactions.

Common ADR seen with PG analogues are irritation on instillation, foreign body sensation, dryness of eyes, pain in eye, increased pigmentation of iris, increased eyelash growth, changes in periorbital sulcus and fat. Some ADRs (Adverse Drug Reaction) are explained by the inherent properties of Prostaglandins and those are not explained are because of preservative used in medication and these ADRs can be minimised by using preservative free drug like Tafluprost which are having same efficacy in decreasing IOP.

Keywords: Primary open angle glaucoma, Prostaglandin analogues, Preservative free prostaglandin analogues

INTRODUCTION

Glaucoma is a group of eye diseases characterized by damage to the optic nerve usually due to excessively high Intraocular Pressure (IOP) which is prime factor in pathophysiology of glaucoma.[1] This increased pressure within the eye, if untreated can lead to optic nerve damage resulting in progressive and permanent vision loss. Increased IOP is because of decrease drainage of aqueous from the eye. Loss of retinal ganglion cell & their axons causes irreversible loss of vision in glaucoma.[2]

Glaucoma affecting 60 million people world wild and it will be 80 million till 2020.[3] There are approximately 11.2 million persons aged 40 years and older are having glaucoma in India. Primary open angle glaucoma (POAG) is estimated to affect 6.48 million persons. The estimated number with primary angle-closure glaucoma is 2.54 million.[4]

TYPES OF GLAUCOMA

There are several types of glaucoma of which primary open angle and angle closure glaucoma are common. POAG is commonest type affecting 2/3 of glaucoma patients[5]. POAG develops gradually and take long time to get detected. Angle closure glaucoma is of acute onset with sudden increase in ocular pressure and further the optic nerve injury. Normal Tension Glaucoma- also called low-tension or normal-pressure glaucoma. In normal-tension glaucoma the optic nerve is damaged even though the eye pressure is not very high.[5] Other variants open angle and angle closure glaucoma are less common & they are

- *Secondary glaucoma*
- *Congenital glaucoma*
- *Pigmentary glaucoma*
- *Pseudoexfoliative glaucoma*
- *Traumatic glaucoma*
- *Neovascular glaucoma*
- *Irido Corneal Endothelial Syndrome (ICE)*

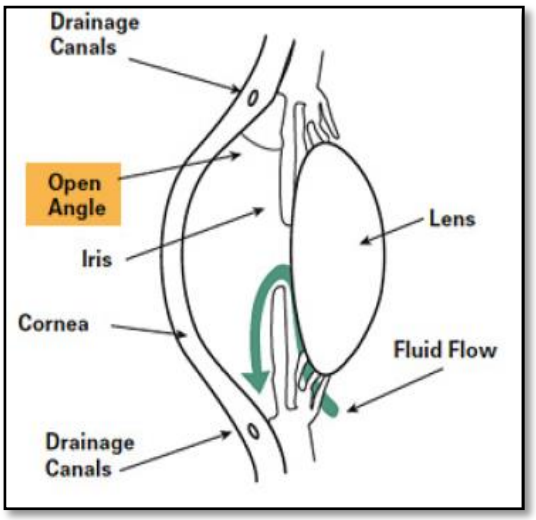


Figure 1: Primary open angle glaucoma.

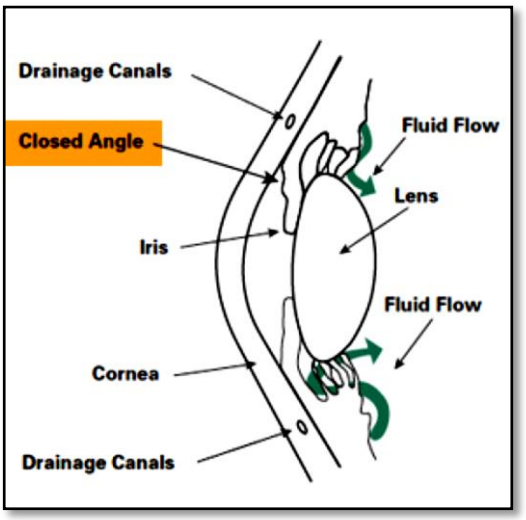


Figure 2: Angle closure glaucoma.

Medications used in the management of POAG include the following:

- Beta-adrenergic blockers (eg, levobunolol 0.25%, 0.5%; timolol maleate/hemihydrate; carteolol ophthalmic solution; betaxolol ophthalmic; metipranolol hydrochloride; levobetaxolol).
- Adrenergic agonists (eg, brimonidine; apraclonidine 0.5%, 1%).
- Less-selective sympathomimetics (eg, dipivefrin, epinephrine, memantine).
- Carbonic anhydrase inhibitors (eg, dorzolamide, brinzolamide, acetazolamide, methazolamide).
- Beta-blocker/carbonic anhydrase inhibitor combination (eg, dorzolamide HCl/ timolol maleate).
- Prostaglandin analogues (eg, latanoprost 0.005%, bimatoprost, travoprost ophthalmic solution, unoprostone, tafluprost)
- Miotic agents (eg, pilocarpine ophthalmic)
- Hyperosmotic agents (eg, isosorbidedinitrate, mannitol, glycerin)
- Beta-blocker/alpha agonist combination (eg, brimonidine/timolol)[6]

PATHOPHYSIOLOGY OF GLAUCOMA

Glaucoma has got multifactorial pathophysiology; elevated IOP and vascular deregulation are the prime contributors. Altered microcirculation in optic nerve and obstructed axoplasmic flow will ultimately end up with cell death due to oxidative stress of nerve injury.[7] Elevated IOP being a major contributor of glaucoma and decreasing IOP will halt the disease process but in near about 30-40% of glaucoma Patients shows normal IOP.[8] Hence elevated IOP is main but not the only factor in development of glaucoma.

1. Increased IOP

IOP is maintained in normal range by dynamic equilibrium between secretion and drainage of aqueous humour within the eye & imbalance in this system will lead to elevated IOP and of course the glaucoma. Alterations in aqueous humour dynamics leads to changes in trabecular meshwork leading to impaired drainage of aqueous humor.[9] In response to raised IOP changes in the cytoskeletal structure and ECM (Extra Cellular Matrix) of trabecular meshwork of drainage pathway of aqueous humor is seen.[10-12]

Remodelling of ECM like collagen 1 and 4, TGF-β_2[13,14,15], increased expression of MMP (Matrix Metalloproteinase) in retinal ganglion cell is detected which causing

↓

Interruption in cell-cell and cell–ECM adhesion.[16]

↓

Increase IOP is associated with increase in proteases, increased expression of MMP 9 in retinal ganglionic cell causing increased degradation of lamininand apoptosis of retinal ganglionic cell.[17,18]

↓

Increased MMP expression as a result of exposure to elevated IOP could be mediated indirectly by the excitatory neurotransmitter glutamate. Up regulation of glutamate receptors in retinal cells was found to be associated with increased MMP-9 expression.[19]

↓

It has also been demonstrated that exposure to elevated IOP leads to activation of retinal astrocytes.[20]

These activated astrocytes release MMPs to bring about changes in the pattern of matrix remodelling. Pressure effects of Increased IOP causing hypoxic injury to Retinal Ganglion Cell (RGC) axons at optic nerve head releases excitatory neurotransmitter glutamate and induces apoptosis of nerve cell and deficiency of BDNF (Brain Derived Natriuretic Factor) can further lead to progression of RGC apoptosis.[21] Up regulation of cytokines like TNF-α in astrocytes due to increased IOP causing direct effect on RGC and indirectly inducing iNOS (inducible Nitrous Oxide Synthase) synthesis. TNF-α (Tumour Necrosis Factor) stimulates optic nerve astrocytes to produce neurotoxic levels of NO (nitrous oxide).[22]

2. Vascular insufficiency

Positive correlation is seen with vascular abnormality and glaucoma also Glaucoma has positive correlation with migraine[23,24] and peripheral vascular abnormality[25,26]. Increased sensitivity to endothelin mediated vasoconstriction is seen glaucoma. Increased level of Endothelin -1 is found in aqueous of glaucomatous eye.[27-30]

3. Endothelin and its receptors

Three receptors are known for Endothelin[31] of which one is predominantly present in human eye and involved in pathogenesis of glaucoma.

Et1: cornea, iris, ciliary body, retina, choroid blood vessels.[32,33] Et-1 is also found in the aqueous humor at concentrations several times higher than in plasma, presumably because it is secreted by the ciliary epithelium and not derived from plasma.[34]

Endothelin binds primarily with 2G-protein coupled receptors, Endothelin A(ETA), located primarily in vascular smooth-muscle cell, and Endothelin B (ETB), located primarily in endothelial cells, neurons, and glia. The actions of the Endothelin are probably not limited to maintaining vascular tone and blood flow, but the action of ET-1 on ETA results in vasoconstriction and on ETB to nitric-oxide-mediated vasoconstriction.[35]

Endothelin mediated vascular insufficiency and optic nerve ischemia is involved in pathogenesis of glaucoma[36]. Patients with compromised Optic Nerve Head (ONH) blood flow are more prone to develop glaucoma and increasing optic nerve head blood flow leads to favourable outcome but strong longitudinal data to confirm this is not available[35]. The effects of Endothelin range from vascular control, modulation of cell signalling, trophic support and cell survival, triggering of astrogliosis and ECM remodelling.[37]

Prostaglandin analogues are promising class of drugs which take cares of both the prime pathologies of glaucoma i.e., rise in IOP and endothelin mediated vasoconstriction.

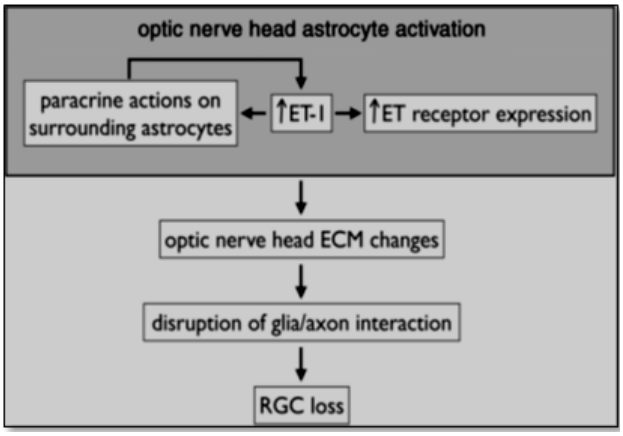


Figure 3: Optic nerve head astrocyte activation.

PROSTAGLANDINS AND THEIR ANALOGUES

Prostaglandins are a group of lipid compounds that are derived enzymatically from fatty acids and have important functions in the animal body. Every prostaglandin contains 20 carbon atoms, including a 5-carbon ring. Prostaglandins are found in most tissues and organs. They are produced by almost all nucleated cells.[38]

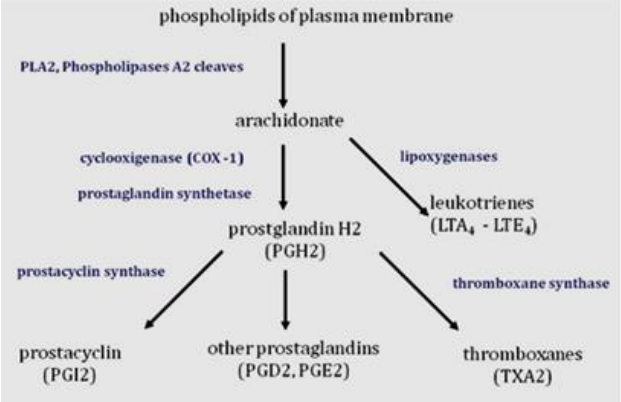


Figure 4: Prostaglandin synthesis.

Synthetic prostaglandin analogues are molecules which are manufactured to bind to a prostaglandin receptor[38]

PG analogues and aqueous humor dynamics

Aqueous humor normally synthesised by epithelia of ciliary process of ciliary body and drained out from eyes through two pathways one is trabecular meshwork and another is Uveoscleralpathway.[39]

Various prostanoid receptors EP, FP, DP present in trabecular meshwork and ciliary muscle.PG analogue increases Uveoscleral outflow by acting through these receptors.[40]

The highest expression of FP receptor protein was found in the corneal epithelium, ciliary epithelium, the circular portion of ciliary muscle, and iris stromal and smooth

muscle cells.[41] EP(1) receptor protein was found in the epithelia of the cornea, conjunctiva, lens, and the ciliary body; trabecular cells; iris vessels; and retinal ganglion cells. EP(2) receptor labeling was most prominent in the corneal epithelium and choriocapillaries. EP(3) and EP(4) receptor labeling was primarily observed in the corneal endothelium andkeratocytes, trabecular cells, ciliary epithelium, and conjunctival and iridal stromal cells.[40]

Mechanism of action of prostaglandin analogues PGF_2 through FC receptors

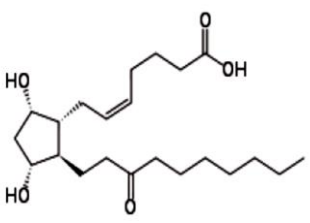
Remodelling of ECM in ciliary muscle & sclera leads to increases drainage of Aqueous.[41,42] PG analogue causes dissolution of collagen 1 & 3 in the connective tissue spaces in ciliary muscle leading increased outflow.[42,43,44] Increased to expression of MMP 1,3,17,14 leading to degradation of extracellular matrix in the ciliary muscle and uveoscleral pathway causing increased drainage.[45,46] PG is thought to increase MMP3, which is involved in decreasing resistance of aqueous outflow. These drugs also increase expression of tissue inhibitors of matrix metalloproteinase which maintain the balance.[47,48]

The IOP-lowering action of PG analogue appears to be associated with induction of cox-2 and subsequent MMP-1 expression in human nonpigmented epithelial cells. MMP-1 released into the aqueous humor would be expected to flow into the ciliary muscle and through the trabecular meshwork and schlemm's canal to potentially increase outflow via multiple routes.[49]

Endothelin-1 is involved in regulating the contractility of the trabecular meshwork. FP receptor agonists can block endothelin-1 induced contractility of the trabecular meshwork. Evidence indicates this inhibition is mediated by the FP and EP receptor. An inhibition of Et-1–induced trabecular meshwork contractility by FP receptor agonists probably increases outflow facility and might decrease IOP.[50]

PGF2 analogues in clinical practice are Latanoprost, Trovoprost, Bimatoprost, Unoprost and Tafluprost. Unoprost is a first PGF2 analogue to be used in glaucoma.[51] Latanoprost, Trovoprost and Bimatoprost are preservative based topical formulation being most commonly used and Tafluprost is preservative free PGF2 analogue.[52]

1. ***Unoprostone****:* Systematic (IUPAC) Name (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]hept-5-enoic acid [53]



Pharmacokinetics

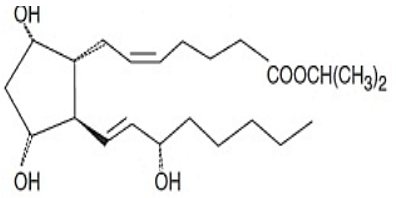
Reduce elevated IOP by increasing the outflow of aqueous humor through the trabecular meshwork.

Absorption: After application to the eye, unoprostone isopropyl is absorbed through the cornea and conjunctival epithelium where it is hydrolysed by esterases to unoprostone free acid.

Distribution and metabolism: The systemic exposure of metabolite unoprostone free acid was minimal following the ocular administration. Unoprostone free acid is further metabolized to several inactive metabolites with lower molecular weight and increased polarity via ε- or β-oxidation. No secondary conjugation is found and no significant effect on hepatic microsomal enzyme activity has been observed.

Excretion: Elimination of unoprostone free acid from human plasma is rapid, with a half-life of 14 minutes,The metabolites are excreted predominately in urine.[54]

2. ***Latanoprost:*** Systematic (IUPAC) Name - Isopropyl(Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)3-hydroxy-5-phenylpentyl]-cyclopentyl] hept-5-enoate 11.[55]



Pharmacokinetics

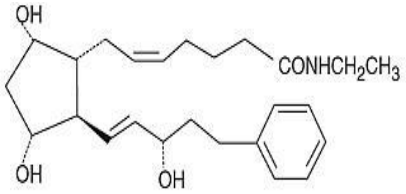
Absorption: Latanoprost is absorbed through the cornea where the isopropyl ester Prodrug is hydrolyzed to the acid form to become biologically active peak concentration is reached in 2 hours. Action starts in 3 to 4 hours and maximum effect is seen at 12 hours. Once daily dosing is sufficient.[56]

Distribution: The volume of distribution in humans is 0.16 ± 0.02 L/kg.[57] Reduction in IOP is 6-8 mm Hg.

Metabolism: Latanoprost, an isopropyl ester Prodrug, is hydrolysed by esterase's in the cornea to the biologically active acid. The active acid of Latanoprost reaching the systemic circulation is primarily metabolized by the liver to the 1,2- dinor and 1,2,3,4- tetranor metabolites via fatty acid β-oxidation.[57]

Excretion: The metabolites are mainly eliminated via the kidneys. Approximately 88% and 98% of the administered dose are recovered in the urine after topical application.[58]

3. ***Travoprost:*** Systematic (IUPAC) Name - propan-2-yl 7-[3,5-dihydroxy-2-[3-hydroxy-4-[3-(trifluoromethyl) phenoxy]-but-1-enyl]-cyclopentyl]hept-5-enoate.[59]



Pharmacokinetics

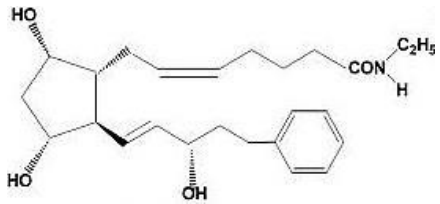
Absorption: Travoprost free acid is a selective FP prostanoid receptor agonist which is believed to reduce intraocular pressure by increasing trabecular meshwork and uveoscleral outflow. Maximal concentrations in the aqueous humour and iris-ciliary body were measured at 1 hour after administration.

Distribution: Maximal plasma concentrations are reached at approximately 30 minutes after ocular administration.[60] Travoprost is estimated to have a plasma half-life of 45 minutes. Reduction in IOP is 7-8 mm Hg.

Metabolism: Travoprost, an isopropyl ester Prodrug, is hydrolysed by esterase's in the cornea to its biologically active free acid. Systemically, travoprost free acid is metabolized to inactive metabolites via β-oxidation of the α (carboxylic acid) chain to give the 1,2- dinor and 1,2,3,4-tetranor analogues, via oxidation of the 15-hydroxylmoiety, as well as via reduction of the 13,14 double bond.[61]

Excretion: Excretion of Travoprost free acid from plasma is rapid through kidney and levels are generally below the limit of quantification within one hour after dosing.[61]

4. ***Bimatoprost:*** Systematic (IUPAC) Name - 7-[3,5-dihydroxy-2- (3-hydroxy-5-phenyl-pent-1-enyl)-cyclopentyl]-N-ethyl-hept-5-enamide.[62]



Pharmacokinetics

Absorption: After one drop of Bimatoprost ophthalmic solution 0.03% blood concentrations peaked within 10 minutes after dosing and was below the lower limit of detection (0.025 ng/mL) in most subjects within 1.5 hours after dosing.

Distribution: Bimatoprost is moderately distributed into body tissues with Volume of distribution of 0.67 L/kg**.** Reduction in IOP is 7-8 mmHg.

Metabolism: Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing. Bimatoprost then undergoes oxidation, N-deethylation and glucuronidation to form a diverse variety of metabolites.

Excretion: 67% of the administered dose was excreted in the urine while 25% of the dose was recovered in the feces.[63]

ADVERSE DRUG REACTIONS OF PROSTAGLANDIN ANALOGUES

These PGF_2 analogues need to be taken for longer time as glaucoma is a chronic condition and so more prone to develop adverse drug reactions. Common ADRs seen with PG analogues are irritation on instillation, foreign body sensation, dryness of eyes, pain in eye, increased pigmentation of iris, increased eyelash growth changes in periorbital sulcus and fat.[64] Increased pigmentation of iris is seen with all the PGF2 analogues as they all increase the melanin synthesis, these changes are seen mainly in mixed coloured iris.[65-67]

Increased growth of eyelashes seen with PGF2 analogues there is increase in length, volume of eyelashes this may be because of reason that prostaglandins stimulates the Anagen phage of hairs.[51]

The other side effects of these drugs are not explained by any properties of prostaglandins action and they are thought to be due to the preservative used in the drugs to keep sterile. Long term use of topical drugs containing BAK (Benzalkonium chloride) as a preservative may induce changes of the ocular surface, tear film instability, epithelial apoptosis conjunctival inflammation, and the loss of goblet cells.[68,69]

PRESERVATIVE USED IN POAG: EFFECTS AND SIDE EFFECTS

Preservatives are contained in most ophthalmic preparations and prolong the shelf life of many by preventing biodegradation and maintaining potency[70], Benzalkoniumchloride (BAK), which has surfactant, bactericidal, and bacteriostatic properties, is the most commonly used preservative in ophthalmic preparations[71]. Other Compound used as preservative in topical medication are PQ (polyquatrnium-1), BAK, Sofzia.[72]

BAK in concentration of 0.01% and 0.020% which is commonly used concentration in medication is cytotoxic to both cornea and conjunctiva. Tear film instability is cause of loss of goblet cells and subconjunctival inflammation. PGAs preserved with BAK had a toxicity close to the toxicity of their respective BAK concentrations alone.[72]

Periorbital changes attributable to topical application of prostaglandin analogues in particular Bimatoprost, reported physical findings include deepening of the orbital sulcus, reversal of dermatochalasis as well as relative Enophthalmos.[73-75]

These effects are attributed to direct effects on Muller's muscle as well as periorbital fat leading to fat atrophy[74,75] & physical findings partially reversed upon cessation of the medication.[70] Loss of periorbital fat could occur by several mechanisms, including the death of mature adipocytes, reduced proliferation of pre-adipocytes, or loss of overall adipose content.[77]

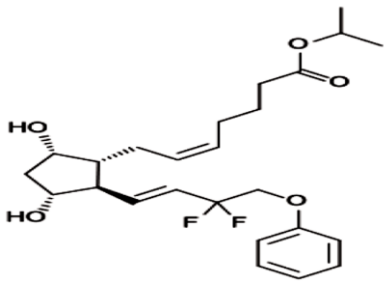
Studies have shown that chronic topical glaucoma therapy can lead to alterations in both tear film and fluorescein staining of the corneal surface, and an increase in inflammatory cytokines among other deleterious effects.[78-81] These ocular surface changes have typically been blamed on the preservative commonly used in multidose bottles of topical medication, BAK. Latanoprost is an effective and well-tolerated IOP-reducing agent that is extensively used for glaucoma treatment. However, contains a high concentration (0.02%) of BAK used as preservative.[82]

Preservative-containing glaucoma drugs have been shown to cause loss of goblet cells increased subepithelial collagen deposition, infiltration of substantia propria by inflammatory cells and to exert a pro-apoptotic effect in the conjunctiva.[83] In patients who need a chronic topical therapy, the preservative-free or the non-BAK preserved drugs should be preferred consenting to maintain a good ocular surface status probably due to the reduced exposure to BAK.[82]

PRESERVATIVE-FREE FORMULATION

Tafluprost is the first topical prostaglandin available in a preservative-free formulation is thought to stimulate the selective prostaglandin F receptor (FP), which results in increased uveoscleral and trabecular outflow of aqueous humor and subsequent decreased intraocular pressure.[84]

Tafluprost: Systematic (IUPAC) name: Isopropyl(5*Z*)-7-{(1*R*,2*R*,3*R*,5*S*)-2-[(1*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl]-3,5-dihydroxycyclopentyl}hept-5-enoate



Pharmacokinetics

Absorption: Bioavailability Prodrug; absorbed through the cornea following ocular instillation and hydrolysed to active form (tafluprost acid). Tafluprost acid: Peak plasma concentrations occur at a median of 10 minutes. Onset Reduction in IOP generally occurs approximately 2–4 hours after ocular instillation and peaks after 12 hours.

Distribution and Metabolism: Hydrolysed by esterase in the cornea to biologically active form (tafluprost acid). Systemically, tafluprost acid is further metabolized via fatty acid oxidation and phase II conjugation reduction in IOP is 5-8 mmHg.

Elimination: Tafluprost acid: Rapidly eliminated from plasma; plasma levels are below the limit of quantitation within 30 minutes following ocular instillation.[85]

CONCLUSION

Prostaglandins are currently the most effective topical medications for decreasing IOP.[86] Prostaglandin analogues generally provided a greater percentage IOP reduction than the beta-blockers. Systematic reviews comparing timolol with travoprost[87] and latanoprost[88] showed prostaglandin analogues to be more effective at decreasing IOP.

The systemic and local side effect of active agents which can be managed by changing the drugs but preservatives, and in particular BAK, are present in almost all of the medications and that it is very difficult to avoid their effects These undesirable effects may reduce the tolerability of drugs, with the risk of a higher rate of discontinuation and poor adherence in patients treated with preserved topical hypotensive therapy.

Use of preservative-free medication should improve the compliance and adherence of the patient, thus the easiest solution to improve ocular tissues should be to switch from preservative-containing to preservative-free drugs when possible. Preservative free tafluprost has IOP reducing effects similar to other available prostaglandin analogues with lesser degree of sign and symptoms of ocular irritation.

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Ethical approval: Not required

REFERENCES

1. Agarwal R, Gupta SK, Agarwal P, Saxena R, Agrawal SS. Current concepts in the pathophysiology of glaucoma. Indian J Ophthalmol 2009;57:257-66.
2. Gupta N, Weinreb RN. New definitions of glaucoma. Curr Opin Ophthalmol 1997;8:38-41.
3. What are the types of glaucoma? Internet www.hopkinsmedicine.org/wilmer/gce/book/chapter types_of _glaucoma). Accessed on l5 June 2013.

4. George R, Ve RS, Vijaya L. Glaucoma in India: estimated burden of disease; J Glaucoma. 2010 Aug;19(6):391-7.
5. Types of Glaucoma. Available at www.glaucoma.org/glaucoma/types-of-glaucoma.php. Accessed on 5 June 2013.
6. Jerald A Bell. Primary open angle glaucoma.(emedicine.medscape.com/article/1206147) 29/07/2013.
7. Kaushik S, Pandav SS, Ram J. Neuroprotection in glaucoma. J Postgrad Med.2003;49:90–5.
8. Hendrickx KH, van den Enden A, Rasker MT, Hoyng PF. Cumulative incidence of patients with disc hemorrhages in glaucoma and the effect of therapy. Ophthalmology.1994;101:1165–72.
9. Clark AF, Miggans ST, Wilson K, Browder S, McCartney MD. Cytoskeletal changes in cultured human glaucoma trabecular meshwork cells. J Glaucoma 1995;4:183-8
10. Lutjen-Drecoll E, Shimizu T, Rohrbach M, Rohen JW. Quantitative analysis of 'plaque material' in the inner- and outer wall of Schlemm's canal in normal- and glaucomatous eyes. Exp Eye Res 1986;42:443-55.
11. Knepper PA, Goossens W, Hvizd M, Palmberg PF. Glycosaminoglycans of the human trabecular meshwork in primary open-angle glaucoma. Invest Ophthalmol Vis Sci 1986;37:1360-7.
12. Lutjen-Drecoll E, Rohen JW. Morphology of aqueous outflow pathways in normal and glaucomatous eyes. In: Ritch R, Shields MB, Krupin T, editors. The glaucomas. St. Louis: Mosby Year; 1996. p. 89-123.
13. Johnson EC, Morrison JC, Farrell S, Deppmeier L, Moore CG, McGinty MR. The effect of chronically elevated intraocular pressure on the rat optic nerve head extracellular matrix. Exp Eye Res 1996;62:663-74.
14. Pena JD, Taylor AW, Ricard CS, Vidal I, Hernandez MR. Transforming growth factor beta isoforms in humen optic nerve heads. Br J Ophthalmol 1999;83:209-18.
15. Cordeiro MF. Beyond mitomycin: TGF-beta and wound healing. Prog Retin Eye Res 2002;21:75-89.
16. Werb Z. ECM and cell surface proteolysis: regulating cellular ecology. Cell 1997;91:439-42.
17. Li G, Moss SE, Alexander RA, Ali RR, Fitzke FW, Cordeiro MF. Retinal ganglion cell apoptosis in glaucoma is related to intraocular pressure and IOP-induced effects on extracellular matrix. Invest Ophthalmol Vis Sci 2005;46:175-82.
18. Grossmann J. Molecular mechanisms of "detachment-induced apoptosis-anoikis". Apoptosis 2002;7:247-60.
19. Yan X, Tezel G, Wax MB, Edward DP. Matrix metalloproteinases and tumor necrosis factor alpha in glaucomatous optic nerve head. Arch Ophthalmol 2000;118:666-73.
20. Agapova OA, Ricard CS, Salvador-Silva M, Hernandez MR. Expression of matrix metalloproteinases and tissue inhibitors of metalloproteinases in human optic nerve head astrocytes. Glia 2001;33:205-16.
21. Nickells W. Retinal ganglion cell death in glaucoma: t0 he how, the witty and the maybe. J Glaucoma 1996;5:345-56.
22. Nakazawa T, Nakazawa C, Matsubara A, Noda K, Hisatomi T, She H, et al . Tumor necrosis factor-mediates oligodendrocyte death and delayed retinal ganglion cell loss in a mouse model of glaucoma. J Neurosci2006;26:12633-41.
23. Wang JJ, Mitchell P, Smith W. Is there an association between migraine headache and open-angle glaucoma? Findings of the Blue Mountains Study. Ophthalmol1997;104:1714-9.
24. Curseifen C, Wisse M, Curseifen S, Junemann A, Martus P, Korth M. Migraine and tension headache in highpressure and normal-pressure glaucoma. Am J Ophthalmol 2000;129:102-4.
25. Gass A, Flammer J, Linder L, Romerio SC, Gasser P, Haefeli WE. Inverse correlation between endothelin-1-induced peripheral microvascular vasoconstriction and blood pressure in glaucoma patients. Graefes Arch Clin Exp Ophthalmol 1997;235:634-8.
26. O'Brien C, Butt Z. Blood flow velocity in the peripheral circulation of glaucoma patients. Ophthalmologica 1999;213:150-3.
27. Cellini M, Possati GL, Profazio V, Sbrocca M, Caramazza N, Caramazza R. Color Doppler imaging and plasma levels of endothelin-1 in low-tension glaucoma. Acta Ophthalmol Scand 1997;224:11-3.
28. Noske W, Hensen J, Wiederholt M. Endothelin-like immunoreactivity in aqueous humor of patients with primary open-angle glaucoma and cataract. Graefes Arch Clin Exp Ophthalmol 1997;235:55.
29. Tezel G, Kass MA, Kolker AE, Becker B, Wax MB. Plasma and aqueous humor endothelin levels in primary open-angle glaucoma. J Glaucoma 1997;6:83-9.
30. Hollo G, Lakatos P, Farkas K. Cold pressor test and plasma endothelin-1 concentration in primary open-angle and capsular glaucoma. J Glaucoma 1998;7:105-10.
31. Kedzierski RM, Yanagisawa M. Endothelin system: the doubleedged sword in health and disease. Annu Rev Pharmacol Toxicol 2001;41:851–76.
32. MacCumber MW, D'Anna SA. Endothelin receptor-binding subtypes in the human retina and choroid. Arch Ophthalmol 1994;112:1231–5.
33. MacCumber MW, Ross CA, Glaser BM, Snyder SH.Endothelin: visualization of mRNAs by in situ hybridization provides evidence for local action. Proc Natl Acad Sci U S A1989;86:7285–9.
34. Lepple-Wienhues A, Becker M, Stahl F, et al. Endothelin-like immune reactivity in the aqueous humour and in conditioned medium from cultured ciliary epithelial cells. Curr Eye Res 1992;11:1041–6.
35. Balwantray C. Chauhan, Endothelin and its potential role in glaucoma; J Ophthalmol 2008;43:356–60.
36. Ernest JT. Pathogenesis of glaucomatous optic nerve disease. Trans Am Ophthalmol Soc 1975;73:366–88.

37. Yorio T, Krishnamoorthy R, Prasanna G. Endothelin: Is it a contributor to glaucoma pathophysiology? J Glaucoma 2002;11:259–70.
38. Prostaglandin - Wikipedia, the free encyclopedia 28/05/2013.
39. Carol b toris,vikas gulati:the biology,pathology and therapeutic uses of prostaglandins in eye ; clin lipidology 2011;6(5):577-591.
40. Schlotzer-Schrehardt U, Zenkelm, Nusing RM; Expression And Localization of EP and FP receptor subtypes in human eye; Invest Opthalmol Vis Sci, May 2002;43(5):1475-87.
41. Ocklind A. Effect of latanoprost on the extracellular matrix of the ciliary muscle. A study on cultured cells and tissue sections. Exp Eye Res.1998;67:179–191.
42. Sagara T, Gaton DD, Lindsey JD, et al. Topical prostaglandin F2alpha treatment reduces collagen types I, III, and IV in the monkey uveoscleral outflow pathway. Arch Ophthalmol. 1999;117:794–801.
43. Lütjen-Drecoll E, Tamm E. Morphological study of the anterior segment of cynomolgus monkey eyes following treatment with prostaglandin F2 alpha. Exp Eye Res. 1988;47:761–769.
44. Tamm E, Rittig M, Lütjen-Drecoll E. [Electron microscopy and immunohistochemical studies of the intraocular pressure lowering effect prostaglandin F2 alpha] Fortschr Ophthalmol. 1990;87:623–629.
45. Nagase H, Woessner JF. Matrix metalloproteinases. J Biol Chem.1999;274:21491–21494.
46. Baker AH, Edwards DR, Murphy G. Metalloproteinase inhibitors:biological actions and therapeutic opportunities. J Cell Sci. 2002;115:3719–3727.
47. Pang IH, Fleenor DL, Hellberg PE, Stropki K, McCartney MD, Clark AF. Aqueous outflow-enhancing effect of tert-butylhydroquinone: involvement of AP-1 activation and MMP-3 expression. Invest Ophthalmol Vis Sci. 2003;44:3502–3510.
48. Parshley DE, Bradley JM, Samples JR, Van Buskirk EM, Acott TS.Early changes in matrix metalloproteinases and inhibitors after in vitro laser treatment to the trabecular meshwork. Curr Eye Res.1995;14:537–544.
49. Hinz B, Rösch S, Ramer R, et al. Latanoprost induces matrix metalloproteinase-1 expression in human nonpigmented ciliary epithelial cells through a cyclooxygenase-2-dependent mechanism. FASEB J. 2005;19:1929–1931.
50. Thieme H, Schimmat C, Münzer G, et al. Endothelin antagonism: effects of FP receptor agonists prostaglandin F2alpha and fluprostenol on trabecular meshwork contractility. Invest Ophthalmol Vis Sci. 2006;47:938–945.
51. Carol b toris,vikas gulati:the biology,pathology and therapeutic uses of prostaglandins in eye:ocular therapeutic uses of PG Agonists & antagonists ; clin lipidology 2011;6(5):577-591.
52. Cory Swymer and Michael W Neville, Tafluprost: The First Preservative-Free Prostaglandin to Treat Open-Angle Glaucoma and Ocular Hypertension; Annals of Pharmacotherapy 2012;46:1506-10.
53. Unoprostone.Internet(http://www.fda.gov/cder/consumerinfo/druginfo/rescula.htm) 28/05/2013.
54. Unoproston.Internet(www.rxlist.com/rescula-drug/clinica pharmacology) 28/05/2013.
55. Chemical structure ofprostaglandin analogue: latanoprost, J Ocul Pharmacol Ther. 2009 December; 25(6): 487–498.
56. Latanoprost, eyedrop solution.medsafe.Internet (www.medsafe.govt.nz/profs/datasheet/a/arrowlatanoprostdrop)06/06/2013.
57. Sjöquist B, Stjernschantz J Ocular and systemic pharmacokinetics of latanoprost in humanswww.ncbi.nlm.nih.gov/pubmed/12204697.
58. Latanoprost ophthalmic solution ;clinical pharmacology.www.rxlist.com/xalatan-drug/clinical-pharmacology 06/06/2013.
59. 59)Chemical structure ofprostaglandin analogue;trovoprost, J Ocul Pharmacol Ther. 2009 December; 25(6): 487–498
60. Travoprost,Ophthalmic-Solution:0.004%(travoprost)solution.Internate (dailymed.nlm.nih.gov) 06/06/2013.
61. Trovoprost ophthalmic solution (0.004%). Internet (dailymed.nlm.nih.gov) 06/06/2013.
62. Wan z Woodward DF, Cornell CL, Fliri HG, Martos JL: Bimatoprost, prostamide activity, and conventional drainage, Invest Ophthalmol Vis Sci. 2007 Sep;48(9):4107-15.
63. DrugBank: Bimatoprost (DB00905). Internet. (www.drugbank.ca/drugs/DB00905; 06/06/2013.
64. Alm A, Grierson I, Shields MB. Side effects associated with prostaglandin analog therapy. Surv Ophthalmol 2008;53 Suppl1:S93–105.
65. Albert S. Khouri, MD; Robert D. Fechtner: Lowering IOP With Medical Therapy in Patients With Glaucoma: First-Line Agents Prostaglandin Analogs. Internet (www.medscape.org/viewarticle/580534_2)25/06/2013.
66. Xalatan. Generic Name: latanoprost ophthalmic. Internet(www.drugs.com › Drugs A to Z › Xa › Xalatan) 25/06/2013.
67. Hysite, Eyedrops, solution-Medsafe. Internet (www.medsafe.govt.nz/profs/datasheet/h/Hysiteeyedrops) 25/06/2013.
68. Kahook MY, Noecker R. Quantitative analysis of conjunctival goblet cells afterchronic application of topical drugs. Adv Ther 2008;25:743-51.
69. Baudouin C. Detrimental effect of preservatives in eyedrops: implications for the treatment of glaucoma. Acta Ophthalmol 2008;86:716-26.
70. Januleviãienò I, Derkaã I, Grybauskiene L, Paulauskaitò R, Gromnickaite R, Kuzmienò L. Effects of preservative-free tafluprost on tear film osmolarity, tolerability, and intraocular pressure in previously treated patientswith open-angle glaucoma. Clin Ophthalmol (Auckland, NZ)2012;6:103.

71. Tressler CS, Beatty R, Lemp MA. Preservative use in topical glaucoma medications. Ocul Surf 2011;9:140-58.
72. David A. Ammar, Robert J. Noecker, Malik Y. Kahook. Effects of Benzalkonium Chloride-Preserved, Polyquad- Preserved, and sofZia-Preserved Topical Glaucoma Medications on Human Ocular Epithelial Cells, Published online: September 30, 2010, Springer Healthcare 2010, 27(11):837-845.
73. Yam JC, Yuen NS, Chan CW. Bilateral deepening of upperlid sulcus from topical bimatoprost therapy. J Ocul Pharmacol Ther 2009;25:471–472.
74. Peplinski LS, Albiani Smith K. Deepening of lid sulcus from topical bimatoprost therapy. Optom Vis Sci 2004;81:574–577.
75. Filippopoulos T, Paula JS, Torun N, Hatton MP, Pasquale LR,Grosskreutz CL. Periorbital changes associated with topical bimatoprost. Ophthal Plast Reconstr Surg 2008;24:302–307.
76. Park J, Cho HK, Moon JI. Changes to upper eyelid orbital fatfrom use of topical bimatoprost, travoprost, and latanoprost. Jpn J Ophthalmol 2011;55:22–27.
77. Leonard K. Seibold, David A. Ammar, and Malik Y. Kahook, Acute Effects of Glaucoma Medications and Benzalkonium Chloride On Pre-adipocyte Proliferation and Adipocyte Cytotoxicity In Vitro, Current Eye Research, 38(1), 70–74, 2013.
78. Horsley MB, Kahook MY. Effects of prostaglandin analog therapy on the ocular surface of glaucoma patients. Clin Ophthalmol. 2009;3:291-295.
79. Noecker RJ, Herrygers LA, Anwaruddin R. Corneal and conjunctival changes caused by commonly used glaucoma medications. Cornea. 2004;23:490-496.
80. Pisella PJ, Debbasch C, Hamard P, et al. Conjunctival proinflammatory and proapoptotic effects of latanoprost and preserved and unpreserved timolol: an ex vivo and in vitro study. Invest Ophthalmol Vis Sci. 2004;45:1360-1368.
81. Kahook MY, Noecker RJ. Comparison of corneal and conjunctival changes after dosing of travoprost preserved with sofZia, latanoprost with 0.02% benzalkonium chloride, and preservative-free artificial tears. Cornea. 2008;27:339-343.
82. Rossi GCM, et al. Efficacy and ocular surface tolerability of preservative-free tafluprost 0.0015%: a 6-month,single-blind, observational study on naı¨ve ocular hypertension or glaucoma patients. Expert Opin. Drug Saf. 2012 ;11(4):519-525.
83. Hannu Uusitalo, Enping Chen, Norbert Pfeiffer,et al, Switching from a preserved to a preservative-free prostaglandin preparation in topical glaucoma medication; Acta Ophthalmol. 2010: 88: 329–336.
84. Cory Swymer and Michael W Neville, Tafluprost: The First Preservative-Free Prostaglandin to Treat Open-Angle Glaucoma and Ocular Hypertension; Annals of Pharmacotherapy 2012;46:1506-10.
85. Laurie Barclay, MD. FDA Approvals: First Preservative-Free Prostaglandin Eye Drops for Glaucoma. Internet. (www.drugs.com ,preservative free prostaglandin analogue:Tafluprost) 25/06/2013.
86. Michael V. Boland, Ann-Margret Ervin, David S. Friedman, Henry D. Jampel, etal. Comparative Effectiveness of Treatments for Open-Angle Glaucoma:A Systematic Review, Annals of Internal Medicine on February 19, 2013;158:271-279.
87. Li N, Chen XM, Zhou Y, Wei ML, Yao X. Travoprost compared with other prostaglandin analogues or timolol in patients with open-angle glaucoma or ocular hypertension: meta-analysis of randomized controlled trials. Clin Experiment Ophthalmol. 2006;34:755-64.
88. Zhang WY, Po AL, Dua HS, Azuara-Blanco A. Meta-analysis of randomised controlled trials comparing latanoprost with timolol in the treatment of patients with open angle glaucoma or ocular hypertension. Br J Ophthalmol. 2001;85:983-90.

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