The role of prostanoids in the modern management of glaucoma

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Educational Aims

- To identify the role of prostainoids in glaucoma
- To highlight the mode of action and advantages of the latest drug therapy
- To better appreciate clinical applications and awareness of side effects
- To better understand combination therapy and its advantages

Keywords
Intraocular pressure (IOP), glaucoma, prostanoids, prostaglandin analogues, prostamide

The history of glaucoma pharmacology begins in 1862 with the isolation of physostigmine from the calabar bean.[1] The discovery of epinephrine's intraocular pressure lowering capacity came just after WWI. During the 20th century, drug discovery and development accelerated, with the introduction of carbonic anhydrase inhibitors, beta-blockers (1970s), alpha-agonists and lately prostanoids(1990s).[2] Prostanoids have been divided into PG analogues and prostamides because of differences in molecular structures. The drugs share a novel mechanism of action that produces a potent ocular hypotensive effect and a novel local adverse effect of increased iridial pigmentation. Anti-glaucoma medication targets different key pathophysiological aspects of the disease and overlap in the mechanisms of action of these drugs proved to be important. The development of a completely new class of drugs added to the suppressive armamentarium against this blinding condition. More drug variety skewed glaucoma care away from the theatre, effectively changing the timing of glaucoma surgery.

Pharmacology of prostaglandin analogues
These drugs are lipid structural derivatives and are synthetic prostaglandin F2a analogues.[3] They are actually prodrugs and these arachidonic acid derivatives are hydrolyzed by corneal esterases to a biologically active free acid. Bimatoprost is a subclass and is actually a prostamide rather than a prostaglandin analogue. Prostamides do not appear to bind to prostaglandin FP receptor as PG analogues.

Mechanism of Action
Prostaglandin analogues increase uveoscleral outflow rather than altering conventional trabeculo-canalicular aqueous outflow.[4]
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 four randomized 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.[5]
Uveoscleral outflow is enhanced because of:

- Ciliary body muscle relaxation
- Dilation of spaces between ciliary muscle bundles
- Altered metabolism of the extracellular matrix surrounding the ciliary muscle cells (modulation of tissue matrix metalloproteinases)
- Altered cellular morphology.[6]

Uveoscleral outflow does not end in the episcleral venous circulation so it is possible to get an intraocular pressure around episcleral venous pressure (~10mmHg).[7] This is very important especially in normal tension glaucoma where optic nerve damage occurs in the presence of lower intraocular pressures.

Bimatoprost is an active drug in contrast to latanoprost and travoprost which, as described above, require activation by corneal enzymes. Bimatoprost increase aqueous outflow by increasing both trabecular outflow facility and uveoscleral outflow.

Latanoprost 0.005% once daily was compared to timolol 0.5% twice daily in three large studies. The former reduced the IOP by around 30% and was found to be predominantly more effective than the beta-blocker. Peak effect of PG analogues occurs 12 hours post-instillation. There was no loss of effect after a year. Travoprost is very similar to latanoprost, though the

Table 1. Commercially available prostanoids in drop form

commonly used	*concentration of drug per drop*
Latanoprost	0.005%
Travoprost	0.004%
Bimatoprost	0.03%
Less commonly used	
Unoprostone	0.15%
Tafluprost	0.0015%

former binds to the FP receptor with a higher affinity. They have the same mechanism of action and are prescribed once daily, preferably in the evening.[8]

Bimatoprost was also compared to timolol and was found to be much more superior in efficacy. An interesting trial comparing the three drugs for 12 weeks found no statistical significance in the difference of IOP lowering, however in the long term (6months), bimatoprost was found to be more effective. Some glaucoma specialists postulate a switch from one prostanoid to another. This was hinted at in a study that showed that patients who were not responsive to latanoprost have a likelihood of 13/15 of obtaining at least 20% reduction in IOP if switched to bimatoprost.[9] In certain situations one might also combine a prostaglandin analogue with the prostamide bimatoprost, especially in the presence of multiple intolerance to other anti-glaucoma medications.

There is evidence that latanoprost lowers IOP in angle-closure glaucoma and its efficacy is not related to angle width.[10]

Role of Combination therapy

Combining an aqueous suppressant with a prostaglandin analogue enhances IOP-lowering effect as both aqueous inflow and outflow are targeted. For example, combining latanoprost 0.005% once daily with timolol 0.5% twice daily achieves 13-30% increase in IOP-lowering effect.[11]

Prostaglandin analogues side effects

Table 2 shows an exhaustive list of known side-effects of prostaglandin analogues.

More specific side-effects

Iris pigmentation[12] - Eyes with a concentric heterochromia (more pigment around the pupil than in the periphery) before treatment are more at risk of iris pigmentation. Eyes that already have more iris melanocytes are more prone to pigmentation. Hence green-brown eyes are more at risk than blue or blue-grey irises. PG analogues do not cause iris melanocyte proliferation but merely stimulate these cells to produce more melanin hence making this iris look darker.[13] Iris pigmentation is irreversible and seems to be least associated with bimatoprost. Iris naevi are not affected by PG analogues.

Hyperaemia[14] This is conjunctival injection which is not related to an allergic follicular conjunctival response or actual tissue inflammation. The bimatoprost–related hyperameia was mild to moderate and only 4% of patients using this drug stopped treatment because of this. This hyperaemia is sometimes compounded with a burning sensation and occurs primarily at the initial stages of treatment and eventually improves. Clinical examination did not show an increased anterior chamber flare.

Meibomian gland disease is slightly more prevalent with prostaglandin analogues because they may stimulate meibomian gland secretion which may predispose to the formation of chalazia and seborrhoeic blepharitis.[15]

Eyelash growth - Some consider this as a beneficial side-effect. Some recent topical preparations exist which contain a prostaglandin analogue to minimize radiation-induced eyelash loss in an oncological setup.[16]

Prostaglandin analogues increase the risk of macular oedema because there is evidence that they alter blood-ocular barrier especially in pseudophakic and aphakic patients.[17]

Periorbital fat atrophy.[18] This visually noticeable side effect has features demonstrable on MRI scanning. The periorbital fat atrophy is most apparent with uniocular use and both doctors and patients need to be aware of this side effect before commencing treatment. The effects, however, appear to be reversible with treatment cessation.

Systemic safety of prostaglandin analogues

Latanoprost has a plasma half-life of 17 minutes and is administered in very low doses so only minimal side effects are anticipated. No effect was found on cardiovascular integrity, metabolic function and the haematologic profile of the human body.

Tafluprost

Tafluprost is a recent addition to the prostaglandin analogue spectrum of drugs and is already commercially available. Early studies comparing tafluprost with the earlier travoprost 0.004% found that travoprost 0.004% monotherapy produced lower diurnal IOP than tafluprost 0.0015% in patients with primary open-angle glaucoma or ocular hypertension, but exhibited a similar safety profile.[19]

Table 2. Prostaglandin analogues side effects

Side Effect	Incidence/comment
Non-specific	
Conjunctival hyperaemia	36%, more prominent with bimatoprost
Burning and stinging	25%
Blurred vision	17%
Pruritus	15%
Foreign body sensation	33%
Tearing	6%
Ocular pain	13%

When to use what type of Prostanoid

It is important to be aware that not all these types of prostanoids were available to prescribe all at once and historically molecular modifications were implied so as to make the newer drug more efficient with less potential side-effects. As pointed above, all the prostanoids have similar therapeutic effects but overall they changed the approach of treating glaucoma, as it was found out that they are very effective as first-line drugs.[20]

Conclusion

The introduction of a new class of IOP-lowering drug with a completely different mode of action to the already existing ones slows down the pathophysiological process of this optic neuropathy. High intraocular pressure is one of the most prominent risk factors for the development of glaucoma. Anomalous ocular blood flow orchestrated by endothelin also contributes to this disease progression. Current studies are on the go to identify new molecular structures that have anti-endothelin effects in the context of disease progression in glaucoma in patients with a normal intraocular pressure.

Key points

- The drugs share a novel mechanism of action that produces a potent ocular hypotensive effect.
- Prostaglandin analogues increase uveoscleral outflow rather than altering conventional trabeculo-canalicular aqueous outflow.

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