Prostaglandins in Glaucoma

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Prostaglandins comprise the latest class of drugs added to the list of glaucoma medications. They are ubiquitous local hormones that produce ocular inflammation and hypertension in high levels but in smaller amounts reduce 10P1-4. Ambache’5-6 made the first observation of prostaglandin effects in the eye by isolating a substance which was a mixture of PGE2 and F2α7-9 in iris extracts that could produce miosis in cats. Four agents are included in the category of prostaglandins also called hypotensive lipids. These are

- Latanoprost (approved by USFDA in 1996)
- Travoprost (approved in 2001)
- Unoprostone (approved in 2000)
- Bimatoprost (approved in 2001)

Pharmacology

Prostaglandins are eicosanoids which are metabolic products of arachidonic acid, a 20C structure10 (refer Fig 3).

For the prostaglandins, the last letter refers to specific chemical modifications of the ring structure. The subscripted number refers to the number of double bonds in the molecule. The Greek letter subscript refers to the orientation of the hydroxyl group in relation to the ring structure e.g. PGF2α.

Prostaglandins are fatty acids which structurally carry a negatively charged – COOH group while prostanides are fatty acid amides that do not carry the negative charge. Both classes are derived from membrane lipids and are formed by different biosynthetic pathways (Fig 1).

Prostanoid Receptors

Endogenous Prostaglandins have 4 subtypes of receptors 11 and prostaglandins have affinity for more than one receptor.

4 subtypes
- EP receptor → PGD2
- FP receptor → PGE2
IP receptor $\rightarrow$ PGF$_2\alpha$

TP receptor $\rightarrow$ PGI$_2$/TxA$_2$

PGE$_2$ and F$_2\alpha$ binding sites are seen in the ciliary muscle and iris sphincter muscle. FP and EP$_2$ receptors are seen in human trabecular meshwork, EP$_4$, IP and TP receptors to a lesser amount in the trabecular meshwork and EP$_1$, EP$_2$ and FP receptors are seen in human scleral fibroblasts.

**Structure**

Chemical modifications made to the lipid molecule -

1. To improve the molecule solubility, C$_1$ carboxyl group modified with -
   - an ethyl amide - Bimatoprost
   - an isopropyl ester - Latanoprost, Travoprost, Unoprostone

2. Phenyl ring addition to the omega chain improves FP receptor selectivity and IOP reduction (i.e Latanoprost, Travoprost and Bimatoprost)

3. Saturation of C$_{13-14}$ doublebond on omega chain reduces hyperemia

**Mechanism of Action**

Prostaglandins have an unusual effect on aqueous humor dynamics – it increases the non-conventional outflow through ciliary body face and iris root to suprachoroidal space.

Topical PG ester is absorbed into cornea (ref Fig:4)

1. It is converted to free PG. Free PG passes into aqueous
2. It is carried into ciliary muscle and binds to the FP receptor on the ciliary muscle cell surface
3. Binding initiates a single cascade inducing transcription of MMP genes
4. Gene products are translated to proMMP’s
5. Pro MMP’s are secreted into the extracellular space around ciliary muscle fibers
6. Proteolytic truncation induces activation of the MMP’s
7. This initiates collagen degradation in ECM
8. Decreases hydraulic resistance and facilitates uveoscleral outflow

To summarize, possible mechanisms by which prostaglandins improve uveoscleral outflow are by a reduction of ECM collagen I, III, IV, V, VI laminins, fibronectins in the interstitial spaces of the ciliary muscle and induction of ciliary muscle to produce MMP 1, 2, 3 and 9.

**Storage**

- Unopened bottles of Latanoprost should be refrigerated. Once opened they can be stored at room temperature (25°C or 77°F) for six weeks. Other Prostaglandin analogues can be stored at room temperature (15°C to 25°C/59°F to 77°F for Bimatoprost, 2°C to 25°C/36°F to 77°F for Travoprost and Unoprostone).

**Drug efficacy and interactions (Table 1)**

Latanoprost (0.005%) applied once daily produces a mean IOP reduction of 27% compared to 20% with...
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| 1     | Latanoprost (PGF₂α analogue) | 0.005% (50 µg/ml) 1 drop contains 1.5 µg the drug | Increases uveoscleral outflow | OD | 24-40 hrs | • Prodrug  
• Peak concn. In aqueous 2 hrs after administration  
• Liver metabolism  
• Urine elimination | Proved side effects  
• Iris color darkening (11-23%)  
• Eyelash changes  
• Mild conjunctival hyperemia (5-15%)  
Unproven casual relationship  
• Cystoid macular oedema  
• Iritis  
• Herpes simplex keratitis  
Minimal systemic side effects  
• No effect on resting HR, BP, urine or blood parameters  
• Relatively safe in asthma and coronary artery disease  
• Headache, joint pain, muscle pain, upper respiratory tract syndrome  
• Conjunctival hyperemia (15%-45%)  
• Increased pigmentation and growth of eyelashes  
• Increased iris pigmentation and periorbital tissue pigmentation (only 1.5%/year)  
• Others – ocular pruritus, burning, foreign body sensation, SPK’s, blurring vision, lid retraction  
• Systemic effects – very less, rarely raised LFT  
• Cautious use in: aphakes, pseudo phakes with PC rent, uveitis, macular edema  
• Not studied in CCF, Heart block, respiratory failure  
• Conjunctival hyperemia (35-50%)  
• Similar to latanoprost  
• Hyperemia conjunctiva (10-25%)  
• Mild ocular surface irritation  
• Increased iris pigmentation reports  
• Others similar to latanoprost |
| 2     | Bimatoprost (a synthetic structural analogue of PGF₂α) | 0.03% (0.3 mg per ml) | 50% increase in uveoscleral outflow  
35% increase in trabecular outflow  
Minimal FP receptor agonist activity  
Alternate signal pathway based on intact molecule responsible for its effects | OD | 24-40 hrs | • not a PRODRUG so less corneal hydrolysis  
• scleral and corneal drug penetration  
• blood concn peak in 10 mts, 10P decreases in 4 hrs and max effect in 8-12 hrs  
• Renal elimination | Convulsions  
• Conjunctival hyperemia (15%-45%)  
• Increased pigmentation and growth of eyelashes  
• Increased iris pigmentation and periorbital tissue pigmentation (only 1.5%/year)  
• Others – ocular pruritus, burning, foreign body sensation, SPK’s, blurring vision, lid retraction  
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• Similar to latanoprost  
• Hyperemia conjunctiva (10-25%)  
• Mild ocular surface irritation  
• Increased iris pigmentation reports  
• Others similar to latanoprost |
| 3     | Travoprost (PGF₂α analogue) | 0.004% | Preferential affinity for FP receptor | OD | 24-40 hrs | • PRODRUG produces a lower mean 10P in black patient compared to latanoprost  
• A 22 carbon structure  
• Prodrug | Conjunctival hyperemia (35-50%)  
• Similar to latanoprost  
• Hyperemia conjunctiva (10-25%)  
• Mild ocular surface irritation  
• Increased iris pigmentation reports  
• Others similar to latanoprost |
| 4     | Isopropyl unoprostone (a docosanoid) | 0.15% | Increased uveoscleral outflow  
Poor binding with FP receptor | Twice daily | 12 hrs |  |  |
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- Timolol 0.5% twice daily and 21% with Brimonidine Tartarate 0.2% twice daily. Latanoprost when combined with Timolol twice daily produces an additional IOP reduction of 13% - 37%. When oral Acetazolamide 250mg twice daily or Dipivefrine 0.1% is combined with Latanoprost an additional 15% IOP reduction has been observed respectively. In clinical trials it was apparent that Pilocarpine did not impair the IOP lowering effect of Latanoprost.

Bimatoprost (0.03%) applied once daily produces IOP reduction of 33-36%. It successfully lowers IOP in patients unresponsive to Latanoprost. Mean IOP reductions were 8mm Hg (32.4%) and 5.5mm Hg (22.7%) with Bimatoprost 0.03% and Timolol 0.5% twice daily respectively. Comparing Bimatoprost efficacy with Travoprost 0.004%, studies have shown 7.4 -8.8mm Hg (34-36%), 4.6 -7.2mm Hg (19-29%), a three month prospective study by Parrish and colleagues showed almost similar IOP lowering efficacy between Latanoprost, Bimatoprost and Travoprost but the Bimatoprost/Latanoprost study group compared the percentages of treated patients achieving IOP reduction after six months of treatment which showed that significantly fewer patients receiving Latanoprost achieved a 15% or 20% decrease in IOP at each time point. On patients uncontrolled on topical Beta blockers alone, Bimatoprost lowered IOP more than combination with Dorzolamide. Bimatoprost and the combination of Latanoprost plus Timolol were equally effective in lowering IOP in glaucomatous patients. There is no additive role in adding other prostaglandin analogues to patients who are on Latanoprost or Bimatoprost.

Uses
- Prostaglandins are potent ocular hypotensives as first line therapy for ocular hypertension and POAG. In addition, Latanoprost has been found to be useful in Juvenile OAG, Primary Angle closure glaucoma following YAG PI if IOP elevation persists. Prostaglandins are however a relative contraindication in inflammatory glaucomas and Posner Schlossman syndrome due to their association with CME and uveitis. The role of prostaglandin analogues in glaucoma associated with penetrating keratoplasty is uncertain. In chemical burns, they have to be cautiously used.

Summary
Prostaglandin analogues are highly efficient ocular hypotensives, well tolerated and systemically safe and have a promising future as first line drugs, adjunctive drugs and as substitutes in the medical management of glaucoma.

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