Prostaglandin analogues for glaucoma

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Structural formulas of prostaglandin analogues for IOP lowering

- Travoprost
- Latanoprost
- Bimatoprost
- Tafluprost

Prodrug - isopropylesther (AFP-168) facilitates penetration
Hydrolized to carboxylic active form (AFP-172)

Takagi, Nakajima et al. 2004
Pg analogues

Metabolites of arachidonic acid

Inflammatory mediators like tromboxans and leukotriens

Lower IOP ↓ 25-33 % increasing uveoscleral outflow Effect starts in 2-4 h, peak 8-12 h, max effect 3-5 weeks

Very few systemic side effects

LOCAL SIDE EFFECTS

iris and skin hyperpigmentation, hypertrichosis,
not clear reaction to inflammatory process, allergy, cystoid macular edema
Pg ANALOGUES
Systemic effects

• Circa 80% of a topical ocular drop enters the nasolacrimal ducts immediately after instillation and is available for absorption into systemic circulation.

• SYSTEMIC peak concentration of latanoprost acid 5 minutes after topical application and reached a level of 53 pg/ml with an elimination half-life of 17 minutes.

Numerous synthetic FP-class prostaglandin (PG) analogs stimulated the contraction of isolated non-pregnant female rat uterus in a concentration-dependent manner.


Bimatoprost potently contracted the rabbit isolated uterus. In contrast, bimatoprost exhibited weak excitatory activity in human myometrium from pregnant and nonpregnant donors.


Eleven cases of latanoprost exposure in pregnancy were referred to Teratology Information Service. One case was lost to follow-up, and one case was complicated by miscarriage. Nine cases had a complete follow-up without congenital anomalies.

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It is not known whether the drugs or their metabolites are excreted in human milk.
Dechallenge and rechallenge data seems strong and reproducible, making the association likely.

Up to 5% of patients treated with latanoprost can develop anterior uveitis after several months.

163 eyes of 94 patients receiving latanoprost, eight eyes (4.9%) of six patients (6.4%) developed anterior uveitis. None of these patients had a history of iritis or any medical condition associated with uveitis. Anterior uveitis resolved in all patients with discontinuation.

Probable breakdown of the blood–aqueous barrier, downstream stimulation of proinflammatory eicosanoids, and increased production of IL-1 and IL-6 in tears and the anterior chamber.

Controversy exists concerning their use in uveitic patients due to the theoretically higher risk of anterior uveitis. There is little evidence that PGA disrupt the blood-aqueous barrier and only anecdotal evidence suggesting an increased risk of these rare findings.


Pg ANALOGUES and Uveitis

Four patients with complicated open-angle glaucoma who had anterior uveitis associated with the use of latanoprost. Only in the eye receiving latanoprost. 4/5 eyes had prior inflammation and/or prior incisional surgery. All rechallenged positive.


Acute uveitis in a patient using bimatoprost, after long and well-tolerated treatment with a prostaglandin analog, suggests a distinct potential pro-inflammatory action of prostanamides.


Two cases of cytomegalovirus (CMV) anterior uveitis following topical prostaglandin analogue administration for glaucoma.

163 eyes of 84 consecutive patients with uveitis and raised IOP treated with a PG analogue at two tertiary referral uveitis clinics were identified over a 3-month period.

**No significant difference** in the frequency of anterior uveitis in those eyes treated with PG analogues and those treated with non-PG agents ($p=0.87$).


58 patients with anterior or intermediate uveitis and elevated IOP or glaucoma were randomly assigned to receive treatment either with latanoprost (30) or with dorzolamide/timolol (28).

There was **no statistical difference** between the two groups in respect of inflammatory relapses ($p = 0.21$).

Pg ANALOGUES and uveitis

Causality has not been clearly demonstrated for anterior uveitis

Caution is recommended when administering latanoprost to patients at risk for this condition. I

Some individuals may have prostaglandin receptors that are hypersensitive, with increased release of arachidonic acid and enhanced production of proinflammatory eicosanoids.

Pg ANALOGUES and Cystoid Macular Edema

Inflammatory mediators (including endogenous PGAs) break down the blood-aqueous and blood-retinal barriers, which leads to increased vascular permeability. Eosinophilic transudate accumulates in the outer plexiform and inner nuclear layers of the retina to create cystic spaces that coalesce to form larger pockets of fluid.

Pg ANALOGUES and CME

Retrospective review
136 eyes of 94 glaucoma patients on latanoprost clinical CME in two eyes (1.2%), one had a ruptured posterior capsule during cataract surgery and AC IOL, the other was pseudophakic with an intact posterior capsule, with a history of anterior uveitis 1 month prior to starting latanoprost.

**Pg ANALOGUES** and blood-aqueous barrier alterations

Latanoprost therapy enhances disruption of the blood-aqueous barrier and increases the incidence of angiographic CME formation in early postoperative pseudophakias.


Latanoprost, travoprost, and bimatoprost had no statistically significant effect on the blood-aqueous barrier of phakic patients with POAG or OHT.

Published reports of the occurrence of cystoid macular edema (CME) in eyes being treated with latanoprost have led to concern regarding a possible causal relation between the two.

Sixty-eight eyes of 38 patients with glaucoma and no risk factors for CME were studied. Latanoprost ophthalmic solution did not influence retinal thickness in the fovea at any investigated time points compared with the time before instillation.

It is unlikely that topical latanoprost induces retinal disorders, such as cystoid macular edema, in glaucomatous eyes with a normally functioning blood-ocular barrier.

All cases described to date had other risk factors for the development of CME.

There is no evidence for CME developing in a phakic eye without risk factors for CME.

It would appear, therefore, that the risk of CME is extremely low to non-existent in low-risk eyes (no intraocular surgery or uveitis) and that even in high-risk eyes the incidence is relatively low.
A PGA may not be the first drug of choice in patients that are at high risk for CME (aphakia, pseudophakia with a ruptured posterior capsule during surgery, history of uveitis, or retinal inflammatory or vascular disease), the incidence of CME associated with PGA therapy is low even in these patients and it is not felt to constitute an absolute contraindication to PGA therapy.

Bimatoprost, latanoprost, tafluprost, travoprost and unoprostone should be used with caution in these patients although concurrent administration of nonsteroidal ant-inflammatory agents, such as diclofenac, might decrease the side effects.

Recurrence HSV keratitis, case reports

Three cases of HSV K after initiation of latanoprost therapy. In one cleared with discontinuation of latanoprost but recurred when rechallenged. Another patient with bilateral recurrence, could not be eradicated with antiviral therapy until latanoprost was discontinued.


Two patients treated with latanoprost for primary open angle glaucoma developed herpes keratitis.

A total of 93,869 eligible glaucoma patients, 21 different ocular hypotensive agents, and 192,840 agent-utilizing patient combinations were identified. In all, 411 patients had an OHSV event.

Ocular herpes simplex virus is extremely rare in patients treated with ocular hypotensive therapies, and its prevalence is similar to that found in the general population. The current analysis revealed no association between the use of particular topical ocular hypotensive therapies and OHSV.

LONG-TERM SIDE EFFECTS

Prostaglandin Periorbital Effects

PGA - ASSOCIATED PERIOBITOPATHY

Berke SJ, Pasquale L 2012
PATIENTS FIRST

MILD PTOSIS

PGA - ASSOCIATED PERIOBITOPATHY

DEEP SUPERIOR SULCUS

DARKER IRIS

DARKER LONGER LASHES
Upper eyelid sulcus deepening frequently occurred with bimatoprost usage, and this effect should be sufficiently elucidated before starting bimatoprost treatment.

**Pg ANALOGUES** and trabeculectomy

- Long-term glaucoma medication has been suspected to be a risk factor for bleb failure following trabeculectomy.


- It has been proposed that in patients exposed to excessive preoperative topical medication, postoperative fibroblast proliferation occurs secondary to a cascade of cellular events induced by subclinical inflammation.

levels of MMP-3 and TIMP-2 increase after treatment with latanoprost. Tenon fibroblasts may be the target cells for attempts to influence the tissue levels of MMPs and TIMPs in the context of conjunctival wound healing after glaucoma surgery.


Latanoprost induced collagen gel contraction mediated by human Tenon fibroblasts. This action of latanoprost appeared to depend on the formation of stress fibers and the activation of mitogen-activated protein kinases, focal adhesion kinase, Rho-associated kinase, phospholipase C, and myosin light chain kinase in human Tenon fibroblasts. Latanoprost may therefore influence subconjunctival wound healing by affecting the contractility of Tenon fibroblasts.

Pg ANALOGUES and trabeculectomy

The preservative, especially benzalkonium chloride, has consistently demonstrated its toxic effects in laboratory, experimental, and clinical studies, could induce or enhance inflammatory changes.


Subclinical inflammatory changes preoperatively may lead to a higher rate of trabeculectomy failure.

Increased preoperative exposure to ophthalmic solutions preserved with BAK is a risk factor for earlier surgical failure, independent of the number of medications used.

However, latanoprost-treated conjunctival specimens showed a decreased stromal collagen density and a less pronounced inflammatory infiltration. The upregulation of MMP-1 and MMP-3 in latanoprost-treated eyes might explain the reduced extracellular matrix accumulation in the conjunctival stroma. Therefore, latanoprost therapy might have a more favourable effect on the outcome of glaucoma filtering surgery.


Ilatanoprost and unoprostone, may inhibit postoperative wound healing after glaucoma surgery.

8 YO BOY

Dx: congenital glaucoma

Initial IOP 25

On topical meds for 2 years

Treated IOP IOP 20 – 22

Second opinion for surgery

“very sad case, severe daily life difficulties, family devastatingly worried”
PATIENTS FIRST

PROFOUND DIFFICULTIES AT SCHOOL, SUPPORT TEACHERS NEEDED, UNDER PSYCHO HELP

NORMAL VA / ONH / FIELD

WOULD FALL ASLEEP AT SCHOOL AND IN THE AFTERNOONS
BETABLOCKER BID PROSTAGLANDIN HS
BRIMONIDINE TID
CCT 720

TREATMENT UNNECESSARY, CONTRAINDIATED, CAUSING HANDICAP
THE PRESCRIPTION OF TOPICAL TREATMENT: A COOKBOOK FORMULA

DATA: POPULATION >40 in MIL
PREVALENCE OF POAG
DIAGNOSED CASES/MISSED CASES
NUMBER OF UNITS-BOTTLES/MONTH

28 MIL >40 YO - 2% OAG is 560k
50% DIAGNOSED is 280k
UNITS/YEAR are 17 MIL

THEORETICAL BOTTLES PER TRUE GLAUCOMA Pt PER MONTH = 5
BAC MG/ML as PRESERVATIVE

- Latanoprost: 0.20 mg/ml
- Travoprost: 0.15 mg/ml
- Bimatoprost: 0.05 mg/ml
- Tafluprost: 0.0 mg/ml

Legend:
- **Latanoprost**
- **Travoprost**
- **Bimatoprost**
- **Tafluprost**
Preservative-free tafluprost/timolol fixed dose combination: A 6-month double-masked, randomised, multicenter P-III study comparing efficacy and safety to its individual preservative-free components in patients with glaucoma or ocular hypertension

Norbert Pfeiffer, Carlo E. Traverso, Yury Astakhov, Ernest Boiko and Auli Ropo

**Purposes:** Efficacy, tolerability and safety of the preservative-free (PF) fixed dose combination (FDC) of tafluprost 0.0015% and timolol 0.5% (once daily) were compared to those of the individual components (PF tafluprost 0.0015% once daily and PF timolol 0.5% twice daily) in patients inadequately controlled with prior timolol or prostaglandin monotherapy.

**Methods:** A total of 189 prior timolol users were randomised within the timolol stratum (TS) to receive FDC (n=95) or timolol (TIM; n=94). In the stratum of prior prostaglandin users (PS) a total of 375 patients were randomised to receive FDC (n=188) or tafluprost (TAF; n=187). Study visits included baseline-visit, 2 and 6 weeks, 3 and 6 months. IOP was measured at 8 a.m., 10 a.m., 4 p.m. and 8 p.m. Primary efficacy variable was the change in average IOP from baseline at month 3.

**Results:** In the TS a significant reduction from baseline IOP was seen with FDC and TIM throughout the study. Average diurnal IOP change from baseline at month 3 was -8.55 mmHg (32%) for FDC and -7.35 mmHg (28%) for TIM. The estimated overall treatment difference (FDC–TIM) was -0.885 mmHg (95% CI: -1.745 to -0.024; p=0.044) demonstrating superiority of FDC over TIM. In the PS a significant reduction in IOP was seen with both FDC and TAF throughout the study. Average diurnal IOP change from baseline at month 3 was -8.61 mmHg (33%) for FDC and -7.23 mmHg (28%) for TAF. The estimated overall treatment difference (FDC–TAF) was -1.516 mmHg (95% CI: -2.044 to -0.988; p<0.001) demonstrating superiority of FDC over TAF. In the TS related ocular adverse events (AEs) were more frequent for patients treated with FDC compared to TIM (16.8 vs 6.4%) whereas related non-ocular AE’s were more frequent with TIM compared to FDC (2.1% vs 0.0%). In the PS related AE’s were similarly distributed between FDC and TAF.

**Conclusions:** The preservative-free FC of tafluprost and timolol provided a significant IOP reduction in both strata. The IOP reduction was superior to both, tafluprost and timolol given as monotherapies. The study treatments were safe and well tolerated.

*Poster at WGA 2013*
PARADIGM SHIFT IN TREATMENT PATTERNS
ANALOGUES
ONCE DAILY
ONCE DAILY
MANY RESPONDERS
WORK IN ANGLE CLOSURE AND IN SECONDARY FORMS
PRESERVATIVE FREE AVAILABLE
GENERIC LATANOPROST AVAILABLE
NEUROPROTECTION SUSPECTED
IN EUROPE Rx NUMBERS ARE SURPASSING BETABLOCKERS