Differential pharmacology and clinical utility of preservative-free tafluprost in the treatment of ocular hypertension and glaucoma

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Abstract: Glaucoma is a chronic disease requiring lifelong treatment. Discomfort due to medications may affect patients’ quality of life and may cause poor compliance, which leads to poor intraocular pressure control. To minimize the side effects of long-term treatment, preparations with lower benzalkonium chloride concentrations, preservative-free preparations and alternative preservatives have been developed and reported to have a lower rate of side effects. Tafluprost, launched on the ophthalmic market in 2008, is a new 16-phenoxy analogue of prostaglandin F2α, clinically used as an ocular hypotensive agent for the treatment of glaucoma and ocular hypertension. The safety and intraocular pressure-lowering efficacy of tafluprost has been demonstrated in various preclinical and clinical studies.

Keywords: tafluprost, AFP 168, glaucoma, intraocular pressure, preservative

Glaucoma is a group of diseases with a characteristic pattern of progressive optic neuropathy and a decrease in retinal sensitivity that cause visual loss. It is one of the most common causes of blindness worldwide. Due to aging of the population, the number of patients with glaucoma is expected to rise. It is a major public health problem and has economic consequences. Once the disease is diagnosed, treatment is required to stop progressive optic nerve damage. If glaucoma is not diagnosed and treated properly, it can lead to total and irreversible blindness.

The role of intraocular pressure (IOP) in glaucoma was suggested nearly 150 years ago and ocular hypotensive agents were used in treatment even before the exact mechanism by which they lowered IOP was understood. A large body of evidence has established the importance of IOP.1 Lowering IOP as much as possible improves the likelihood of delaying or halting the progression of optic nerve damage and visual field loss.2

Medical management is the first therapeutic approach to the treatment of glaucoma. Today, there is a large armamentarium of ocular hypotensive medications and physicians must consider various factors in determining the appropriate medication for patients. Efficacy, safety and tolerability, the mechanism of action for lowering IOP, compliance, and cost are important factors in drug treatment. The most commonly used criteria for evaluating efficacy is IOP decrease in the treated subjects. Control of IOP over a 24-hour period is also important; IOP must stay fairly constant. The side effects of medications must be evaluated for each patient prior to treatment. In terms of compliance, patients comply more easily with treatment regimens if they instill eye drops less frequently.3
Prostaglandin derivatives and prostamides, which are a relatively new class of ocular hypotensive agents, are very effective in lowering IOP. They are biologically active derivatives of arachidonic acid. Arachidonic acid is later converted to prostaglandins, which are normally present in ocular tissues and mediate or modulate a broad spectrum of biological processes. Prostaglandin analogues are a very effective and useful class of drugs in the treatment of glaucoma. They reduce IOP by increasing uveoscleral outflow and to some degree, conventional outflow. Latanoprost, bimatoprost, and travoprost are used once daily and unoprostone is used twice daily. Because very low concentrations are used in glaucoma treatment and the plasma half-life is short, systemic side effects are rare. Conjunctival hyperemia, stinging, burning, eyelash changes, increased iris pigmentation, cystoid macular edema in aphakic and pseudophakic eyes, reactivation of herpes keratitis, and anterior uveitis are local side effects.4

Latanoprost is an analogue of prostaglandin F$_{2\alpha}$. It reduces IOP very effectively with minimal systemic side effects. Although the underlying mechanism remains unclear, latanoprost lowers IOP by increasing uveoscleral outflow. It was hypothesized that prostaglandins may stimulate collagenase and other metalloproteinases to degrade the extracellular matrix between ciliary muscle bundles.5 Studies have reported a 20%-40% decrease in IOP after latanoprost treatment. Ocular hypertension and primary open-angle glaucoma (POAG) patients had a high chance of experiencing a sufficient IOP reduction with latanoprost treatment; therefore, to minimize the side effects of long-term treatment, preparations with lower benzalkonium chloride (BAC) concentrations, preservative-free preparations, and alternative preservatives have been developed and have been shown to have a lower rate of side effects.12

There is a growing body of evidence demonstrating that some local adverse effects may be the result of preservatives rather than active compounds. BAC is a cationic detergent and the most commonly used preservative in topical ophthalmic preparations. It ranges in concentration from 0.02%-0.004% and is used in approximately three quarters of all eye drops. BAC interacts with membrane proteins and may change the ionic resistance of the cornea by intercalating into the cellular membrane.13 It can accumulate in ocular tissues for long periods and may induce cell toxicity in a dose-dependent manner. The detergent effect of BAC may cause loss of tear film stability, toxicity of the corneal and conjunctival epithelium, and immunological reactions.13,14 Corneal cell dysfunction and lysis were caused by BAC.16 Other ophthalmic preservatives are thiomersal, concentrations of BAC and by apoptosis at low concentrations of BAC.16 Other ophthalmic preservatives are thiomersal, benzododecinium bromide, cetrimide, EDTA, phenylmercuric nitrate, chlorobutanol, PHBG, sodium perborate, sorbic acid, chlorhexidine digluconate, and parahydroxybenzoate.14,17
Purite, PQ-1, and SofZia are other ophthalmic preservatives designed to eliminate the toxic adverse effects of preservatives.

An ex vivo and in vitro study has demonstrated that preserved formulations of latanaprost and timolol induced higher proinflammatory, proapoptotic, and toxic effects on conjunctival cells than a nonpreserved timolol preparation. Other adverse effects of BAC include significant instability of precorneal tear film, toxicity to the trabecular meshwork, and an increased rate of failed glaucoma surgery. Reduction in corneal cell proliferation and viability causing epithelial barrier problems, a significant degree of squamous metaplasia, inflammation, and subconjunctival fibrosis have been observed with preservatives even though some of these effects are still being debated. There is general acceptance that a change from preserved to nonpreserved preparations was associated with a significant decrease of the signs and symptoms of ocular irritation. Even though BAC was shown to increase the corneal permeability of pharmacological agents, controversial data exists that BAC and BAC-free formulations have similar efficacy. BAC was demonstrated to act as an absorption enhancer to improve drug penetration through cellular membranes in the cornea. The absorption of acyclovir increased tenfold with 0.01% BAC. However, in a study comparing nonpreserved and preserved 0.1% T-Gel eye gel, the preservative did not have an effect on the IOP-lowering efficacy. BAC-free travoprost 0.004%, formulated with the SofZia system, (Travatan Z®; Alcon, Hünenberg, Switzerland) was compared to BAC-preserved marketed formulation travoprost 0.004% (Travatan, Alcon) and was found equivalent in terms of safety and efficacy. Single-dose unit preservative-free glaucoma medications such as timolol gel 0.1% and a timolol and dorzolamide combination have been introduced by free glaucoma medications such as timolol gel 0.1% and a timolol and dorzolamide combination have been introduced to the market. Even though single-dose unit eye drops remained free of bacterial contamination for up to 1 day after opening, their cost and difficulty of use for older patients are major disadvantages. Corneal penetration of preserved and nonpreserved formulations of topical tafluprost applications in rabbit eyes were compared. The penetration of topically applied nonpreserved tafluprost 0.0015% eye drops into the aqueous humor of rabbits was similar to the penetration of tafluprost 0.0015% eye drops preserved with 0.01% BAC. BAC did not have an effect on the corneal penetration of tafluprost into the aqueous humor.

Prostaglandin 

The ocular hypotensive efficacy of tafluprost has been demonstrated in various preclinical animal studies. Single-dose applications of tafluprost have demonstrated IOP-lowering efficacy in both ocular normotensive and laser-induced ocular hypertensive monkeys. A statistically significant IOP reduction was achieved after a single dose...
of 0.0005% and 0.0025% tafluprost when compared to a vehicle. An IOP-lowering efficacy of 0.0025% tafluprost was greater than 0.005% latanoprost and 0.0005% tafluprost was almost equal to 0.005% latanoprost. Kurashima et al switched monkeys which had a low susceptibility and an inadequate IOP reduction by latanoprost treatment to tafluprost treatment. It was demonstrated that the IOP reduction induced by tafluprost 0.0015% (2.4 mmHg) was significantly greater than latanoprost 0.005% (0.4 mmHg) in all monkeys tested. This effect disappeared after switching back to latanoprost. Latanoprost low responders exist among monkeys and these results suggested that tafluprost may be effective for latanoprost nonresponder patients. The IOP-lowering and these results suggested that tafluprost may be effective for latanoprost nonresponder patients. The IOP-lowering effect and mechanism of action was studied in prostanoceptor-deficient mice. It was concluded that tafluprost lowers IOP through the prostanoceptor FP receptor. Part of the ocular hypotensive effect of tafluprost was attributed to FP receptor-mediated prostaglandin production acting through the prostanoceptor EP3 receptor.

The pharmacodynamics, safety, and tolerability of tafluprost were evaluated in various clinical studies. The efficacy, safety, and tolerability of tafluprost 0.0015% were compared to the efficacy, safety, and tolerability of latanoprost 0.005% in patients with POAG, exfoliation glaucoma, or ocular hypertension in a randomized, double-masked, active-controlled, parallel-group, multinational, and multicenter phase II study. Maximum IOP reduction was achieved by day 7 and was sustained in both groups. Tafluprost and latanoprost had comparable effects on the extent, duration, and stability of IOP reduction, and were well tolerated in patients. The long-term efficacy and safety of tafluprost 0.0015% were compared to long-term efficacy and safety of latanoprost 0.005% in eyes drops in patients with POAG or ocular hypertension in a double-masked, active-controlled, parallel-group, multinational, multicenter, phase III study conducted at 49 centers in eight countries. Both treatments had a substantial IOP-lowering effect that persisted throughout the study (−7.1 mmHg for tafluprost and −7.7 mmHg for latanoprost at 24 months). Although the IOP-lowering effect was slightly greater with latanoprost, the difference was clinically small and the non-inferiority of tafluprost to latanoprost over all diurnal IOP measurements was shown. Both drugs were well tolerated and adverse events were mild to moderate. The most frequently reported adverse effect was conjunctival hyperemia. The stimulating effect on eyelash growth was absent or mild in 90% of patients in both groups after 24 months. More cases of iris pigmentation were reported in the latanoprost group (28%) than in that treated with tafluprost (26.1%), but the differences were not significant. The pharmacokinetics and efficacy of preserved and preservative-free tafluprost 0.0015% were evaluated in a randomized, investigator-masked, multicenter, crossover phase III study. The drugs were administered for 4 weeks in 43 patients with POAG or ocular hypertension. After 4 weeks, no significant difference in pharmacokinetic parameters between the formulations after single or repeated dosing was observed. Ocular hyperemia occurred with the same frequency in both groups, but was predominantly of moderate severity in eyes treated with preserved tafluprost, compared to only mild severity with the preservative-free formulation. In another study, the diurnal IOP-lowering efficacy and safety of travoprost 0.004% and tafluprost 0.0015% was compared. The drugs were administered to patients with POAG or ocular hypertension in a randomized, double-masked, active-controlled, crossover design trial for six weeks and then the alternative treatment was administered for a subsequent six weeks. The 12-hour mean diurnal IOP was significantly lower with travoprost than with tafluprost (16.9 mmHg versus 17.5 mmHg). Neither treatment produced a significant increase from baseline in light sensitivity, blurred-dim vision, stinging/burning, foreign body sensation, or pain. Hyperemia was increased with both therapies. Investigator-observed hyperemia was also significantly increased from baseline for both travoprost and tafluprost. The increase with travoprost treatment was significantly smaller than with tafluprost. Abnormal vascular regulation has been suggested to be involved in the development of POAG. Studies have shown decreased optic nerve head (ONH) and retinal blood flow in patients with POAG. The short-term effect of topical tafluprost on feline retinal circulation was investigated using a laser Doppler velocimetry system. Tafluprost 0.0015% significantly increased retinal blood flow and blood velocity for 120 minutes after instillation, while there was no significant change in vessel diameter. Akaishi compared the effects of repeated administrations of three prostaglandin E2 analogs (tafluprost, latanoprost, and travoprost) on ONH blood flow in normal rabbits using laser speckle flowgraphy. They found that ONH blood flow increased after 28 days of treatment with any of the three agents. The effect of tafluprost was significantly greater than that seen with travoprost and tended to be greater than that seen with latanoprost. Another study investigated the effects of topically administered tafluprost 0.0015%, 15-hydroxyl tafluprost (15-OH tafluprost) 0.0015%, latanoprost 0.005%, or travoprost 0.004% on
ONH blood flow and on endothelin-1-induced contractions in isolated rabbit ciliary artery segments. All therapies relaxed the endothelin-1-induced ciliary artery contractions. Improvement of the ocular circulation seemed superior with tafluprost compared with the other prostaglandin F\textsubscript{2\alpha} analogs."45

Ocular surface and impression cytology samples have been compared between tafluprost and other prostaglandin analog therapies. Uusitalo et al investigated whether patients who exhibit limited tolerability to latanoprost benefited from switching to preservative-free prostaglandin tafluprost. Throughout the treatment period of 3 months, the drugs were equally effective. There was a dramatic decrease in the number of patients exhibiting subjective symptoms during preservative-free tafluprost treatment (around 50% compared to latanoprost at baseline), and a decrease in most of the signs of ocular side effects.

The decrease in the number of patients with abnormal levels of HLA-DR-positive conjunctival epithelial cells and with abnormal levels of MUC5AC-expressing goblet cells after preservative-free tafluprost treatment when compared to preserved latanoprost at baseline indicates less harmful effects on the conjunctiva during treatment with a preservative-free prostaglandin solution. Preservative-free tafluprost caused less conjunctival hyperemia than the latanoprost. Hyperemia with the use of the commercially available latanoprost formulation may partly be caused by the very high concentration of BAC. Preservative-free tafluprost was better tolerated than the commercially available formulation of latanoprost in patients who exhibited ocular surface side effects during latanoprost treatment at the baseline visit."46

In another study, conjunctival and corneal reactions of commercially available latanoprost and preservative-free tafluprost were compared in rabbit eyes. The rabbits received phosphate buffered saline, preservative-free tafluprost 0.0015%, latanoprost 0.005%, or BAC 0.02%. All solutions were applied at 5-minute intervals for a total of 15 times. There were higher expressions of CD45+ and TNFR1+ in latanoprost- or BAC-instilled groups compared with preservative-free tafluprost and saline groups. Latanoprost induced fewer positive cells for inflammatory marker expressions in specimens compared with BAC alone, both of which were higher than with preservative-free tafluprost or saline. Immunohistology showed the same tendency of toxic ranking."47

In conclusion, preservative-free tafluprost is a promising new prostaglandin agent in the treatment of glaucoma.

**Disclosure**
The author reports no conflicts of interest in this work.

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