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Tafluprost for the Reduction of Interocular Pressure in Open Angle Glaucoma and Ocular Hypertension

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Abstract: Tafluprost is an FP receptor antagonist that has been shown in clinical studies in Europe and Japan to be extremely useful in treating elevated intraocular pressure and glaucoma. The drug is well tolerated and appears to be at least equal in effectiveness and perhaps superior to other prostanoids for routine use comparison to be superior to other treatments for the elevated IOP as the side effects and other related symptomology appear to be less, while maintaining a level of pressure control for prolonged periods.

Keywords: Tafluprost, glaucoma, IOP, drug

Ophthalmology and Eye Diseases 2011:3 13–19

doi: [10.4137/OED.S4253](https://doi.org/10.4137/OED.S4253)

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Introduction

Glaucoma is a progressive atrophy of the optic nerve of the eye which will often cause blindness in affected individuals if left untreated. There are two manifestations of glaucoma, primary open angle and closed angle. Primary open angle glaucoma (POG) is the most common form of glaucoma. It is a progressive disease with few overt symptoms, but is often accompanied by increased intraocular pressure (IOP). With this manifestation of the disease the peripheral field defects are caused by retinal ganglion loss and excavation of the optic nerve head. The trabecular meshwork is partially closed, blocking naturally efficient fluid removal from the eye. Fluid removal slows below an optimal physiological level. Closed angle glaucoma occurs when the iris of the eye expands forward to at least partially block the drainage angle formed by the cornea and the iris. As a result, the ability of intraocular fluid to reach the trabecular network is curtailed, so IOP will increase. The aim of all glaucoma treatment is to maintain visual function and thus quality of life.

In 2000 an estimated 67 million people world wide suffered from primary glaucoma.¹ A more recent study indicates that the incidence has stabilized but is expected to increase to 80 million people by 2020.² Since many individuals remain undiagnosed, it is difficult to demonstrate a precise number. Anecdotally some practitioners place the number of individuals' world wide with glaucoma or elevated IOP as double the reported value.

Treatments for glaucoma involve a reduction in IOP. These options include laser therapy, surgery and the use of topical medications. Laser therapies include trabeculoplasty. Surgical options include drainage tube implantation and ciliary body cyclodestruction. The laser and surgical options reduce IOP by increasing outflow of aqueous humor through the trabecular meshwork. However, these are not cures. Such surgical treatments are often accompanied by continual drug treatment.

Medications lower IOP by either reducing the production of aqueous humor or by increasing the outflow of aqueous humor in the eye. There are various classes of medications used in glaucoma treatment including Adrenoceptor agonists, Carbonic anhydrase inhibitors, Beta-adrenoceptor antagonists,

acetylcholine receptor agonists and prostaglandin analogues (PGA). PGA treatment is becoming increasingly important and popular with ophthalmic care givers and patients as there have been fewer acute toxic side effects reported as compared to older more established drugs. There has also been reported increase in patient comfort with the use of prostaglandins, especially since they are usually proscribed as once daily treatment.^{3,4} One of the newest of these PGAs is tafluprost. Tafluprost is an FP-receptor agonist which has been shown to be extremely effective in lowering IOP.³⁻⁷

Chemistry of Tafluprost

Tafluprost (trade name Tafflotan) has a molecular weight of 452.53. The systematic IUPAC name is isopropyl (5Z)-7-((1R,2R,3R,5S)-2-[(1E)-3,3-difluoro-4-phenoxybut-1-en-1-yl]-3,5-dihydroxycyclopentyl) hept-5-enoate. Tafflotan contains 15 µg/mL Tafluprost and may be formulated preservative free.

Chemically tafluprost consists of a difluorinated prostanoid FP-receptor agonist.⁸ Two fluorine atoms replace the 15-position hydroxyl group. Thus, ketonization by the 15-hydroxyl-dehydrogenase is prevented. The ester is a lipophilic pro-drug of the carboxylic acid of tafluprost, which is the pharmacologically active form of the drug.

Recent studies with 15-monofluorinated- and 15, 15-difluorinated prostanoids showed that replacement of the hydroxyl group on that position with the halogen atom(s) can increase the desired FP-receptor-related activities while decreasing the side effects.⁹

Tafluprost varies from similar compounds (latanoprost, travoprost, bimatoprost) (other prostanoids) as it possesses two fluorine atoms at the carbon 15 position, instead of a hydroxyl group.^{10,11} Tafluprost is an isopropyl ester (AFP-168) and is hydrolyzed to the active form by corneal esterases to the free acid of tafluprost (AFP-172).¹⁰⁻¹² Tafluprost free acid (AFP-172) is a FP receptor agonist, with a K_i of 0.4 nM.^{10,12} Its affinity for the human prostanoid FP receptors is greater than that of carboxylic acid of latanoprost or unoprostone.^{11,12} Tafluprost increases in vivo uveoscleral outflow measured by flurofotometry.¹¹ The plasma concentration is low after repeated topical dosing. Tafluprost acid (active) could be detected in plasma for up to



1 hour after topical administration, with a peak after 10 minutes.^{13,14}

Tafluprost is available in two formulations. It is formulated as a preservative-free drug in Europe Taflotan[®] (Santen Oy, Finland), both in 0.0015% (15 µg/ml) concentration.¹⁵ In Japan it is formulated with BAK- Tapros[®] (Santen Pharmaceutical Co. Ltd. Osaka, Japan).

Mechanism of Action of Tafluprost

Tafluprost has demonstrated affinity for the prostanoid FP receptor that seems to be greater than for other prostaglandins available. Further, tafluprost has almost no affinity to bind to other receptors. It is believed that prostanoid FP-receptor agonists such as tafluprost reduce IOP by increasing the uveoscleral outflow of aqueous humor. There is some evidence that tafluprost may lower IOP by interaction with the EP3 receptor. This receptor is stimulated by prostaglandin produced by cyclo-oxygenase, through the prostanoid FP (prostaglandin F) receptor, thus lowering IOP by interaction with the EP3 receptor. Further, Dong and co-workers have shown evidence that tafluprost relaxes ciliary artery in smooth muscle.¹⁶ These authors suggest that the relaxation phenomenon may occur due to inhibition of Ca²⁺ from extra-cellular spaces.

Esterification of the carboxyl group on the α -side chain of these prostaglandins seems to enhance penetration into the cornea.^{17,18} The presence of esterase activity in the cornea and sclera capable of hydrolyzing these derivatives to the corresponding acids for uptake during absorption into aqueous humor is also well established.²⁰ This pro-drug ester allows for greater delivery of carboxylic acid (active) to the aqueous humor.^{9,11,12}

Pre-Clinical Studies

Rat models have shown extensive metabolism of Tafluprost largely in the ocular space.²¹ The maximum amount of tafluprost was detected in rat tissues within 15 minutes of dosing and declined thereafter indicating that the drug is rapidly metabolized. The active component (tafluprost acid) was the lone component detected by high performance liquid chromatography in the cornea and ciliary body for at least 8 hours following dosing.²¹ These authors showed an ocular

absorption of about 75% suggesting high availability of Tafluprost with about 10% on the cornea and thus the greatest concentrated activity associated there. Neuro-protective and regenerative effects have also been seen in rats.²² This same group showed that apoptosis suppression was concentration dependent and that tafluprost administration following optic nerve crush provided for the increased survival of retinal ganglion cells.

The interactions of rabbit ciliary arteries with tafluprost have been studied by Dong and co-workers.¹⁶ This group showed that tafluprost caused a concentration dependent relaxation of ciliary artery segments. These authors speculate that this effect may be caused by inhibition of capacitative Ca(2+) from the extra-cellular space.

Application of tafluprost (0.0015%) was shown to decrease IOP in a variety of mouse species.²⁰ Measurements taken 3 hours post eye drop inoculation showed that pretreatment of diclofenac Na (prior to tafluprost administration) would curtail the lowering of IOP in some strains of mice but not in others. These authors suggest (using genetically manipulated mice) that tafluprost may act on the EP3 receptor that is normally stimulated by endogenous prostaglandin.

Tafluprost appears to decrease the IOP in vivo mainly by increasing the uveoscleral outflow.¹¹ In both ocular normotensive and laser-induced ocular hypertensive monkeys, a single instillation of 0.0025% tafluprost solution lowered IOP significantly more than 0.005% latanoprost. Tafluprost (0.001%–0.005%) was applied once daily for 5 days to the eyes of normotensive monkeys and had the advantage of a reduced IOP at the trough time of 24 h after dosing, whereas 0.005% latanoprost did not. Tafluprost also had less stimulating effects on melanogenesis in vitro, whereas tafluprost acid possessed a greater affinity for the prostanoid FP-receptor than the acid form of latanoprost.¹¹ Recent results of a clinical study involving healthy volunteers also showed increased tolerability (as compared to latanoprost) of 0.0025 and 0.005% tafluprost ophthalmic solutions and greater IOP reduction by 0.005% tafluprost than 0.005% latanoprost.²³ In this study, the two drugs were given one drop daily for seven days with IOP was monitored daily.



Clinical Work with Tafluprost

There have been several clinical studies of various design conducted during the last several years which demonstrated the efficacy of tafluprost. In a crossover study published in 2008 the investigators compared preservative free tafluprost with benzalkonium chloride preserved tafluprost.²⁴ This group found that both formulations of tafluprost were equivalent in lowering IOP. Hommer et al conducted an open label study in Germany with 544 patients published in 2010.²⁵ This study was conducted with a preservative free formulation of tafluprost (0.0015%). The results of the study which was conducted over a twelve week period indicate an overall decrease to <18 mmHg in about 80% of the eyes evaluated. Additionally, the authors report that many of the patients in this study were on multi-dose, multi-drug regimens.

The safety and tolerability of tafluprost in healthy volunteers was assessed in a phase I clinical study.²⁶ The study design included tafluprost (or placebo) was given in concentrations from 0.0025% to 0.005 for 7 days. A decline in IOP from recorded baseline values was 4.3 mmHg for 0.0025% tafluprost, 6.8 mmHg for 0.005% tafluprost, and 3.1 mmHg for placebo. The decline of IOP values versus baseline was significant for all treatment groups. The study also included 0.005% latanoprost. When latanoprost was compared with 0.005% tafluprost, there was also a significant difference favoring tafluprost.

Sutton and co-workers conducted a phase I, placebo controlled study giving increasing doses of tafluprost: 0.0001%, 0.0005%, 0.0025% and 0.005%.²⁶ For all concentrations of tafluprost given a decrease in IOP was observed when compared to controls, which was statistically significant for all concentrations except 0.0005% (lowest). The IOP lowering effect was maximal after 12 hours post-administration.

In Japan, the therapeutic concentration of tafluprost was set at 0.0015% as a result of phase II dose-response study.^{25,26} This study showed that 0.0015% tafluprost decreased IOP from baseline by 9.7 ± 3.3 mmHg. The study also contained a and 0.005% latanoprost treatment arm. Results showed a 8.8 ± 4.3 mmHg decrease in IOP from baseline.²⁷

Usitolo and co-workers obtained results that were in line with the van der Valkmet analysis study in Europe.^{28,29} Kuywayama compared and contrasted efficacy of tafluprost with that of placebo

in 94 patients with open angle glaucoma and ocular hypertension. After 4 weeks of administration they observed percentage reductions of $27.6\% \pm 9.6\%$ in the tafluprost group as compared to placebo.³⁰ Clinical data from another Japanese phase III study with 351 patients having open angle glaucoma or ocular hypertension showed that the reduction of the IOP was stable throughout one year. IOP varied only from 4.9 to 5.7 mmHg.¹⁵ In another European study, with open angle glaucoma and ocular hypertension in 533 volunteers comparing 0.0015% tafluprost and 0.005% latanoprost it was found a potent and significant lowering effect throughout study- average declines from diurnal time points were 27%–31% for tafluprost and 29%–35% for latanoprost.²⁸ These results are in line with those of other studies as shown in van der Valk metaanalysis.²⁹

Hamacher et al conducted a randomized multi-center study was to evaluate pharmacodynamics and safety of preserved and non-preservative 0.0015% tafluprost in patients with open angle glaucoma and ocular hypertension. The results of this study showed similar IOP reductions about 5 mmHg for both with preservative-free and preserved formulations of tafluprost.²⁴ Non-preserved tafluprost formulations also lowered IOP in 544 volunteers which had poor control with other drug therapy. Following 12 weeks on study, 79.5% of eyes treated with preservative-free formulation of tafluprost achieved an IOP ≤ 18 mmHg after changing therapy to tafluprost.³¹

Safety and Tolerability

A phase I study was conducted with tafluprost and latanoprost. Similar observations were comparing safety and tolerability between the two drugs.²⁶ In this study the most frequent observed adverse effect was mild, concentration-dependent hyperemia.²⁶ In 12.5% of volunteers receiving 0.0001% tafluprost chemosis was observed. The investigators report adverse effect rates that were comparable among 0.0001% and 0.0025% tafluprost and 0.005% latanoprost groups but ocular hyperemia was significantly lower in eyes receiving latanoprost.²⁶ The authors did not find either cellular infiltration or flare in the anterior chamber. No adverse effects of the cornea or deeper vitreal layers in any eyes were reported during the study. Treatment was not stopped in any of these studies for any patient.^{23,26}



Uusilato et al reported no serious side effects of volunteers when given preservative and preservative-free formulations of tafluprost. Further there were no systemic findings. The most prevalent ocular adverse events were mild or moderate in severity. The most prevalent reported were ocular hyperaemia and redness.²⁸ In the two year study with 533 volunteers, lantanoprost and tafluprost were well tolerated. The reported adverse events were mild to moderate. Non-ocular adverse events were reported with low incidence in both treatment groups. No clinically significant changes in blood pressure or heart rate were reported during the two year study. Corrected visual acuity (BCVA) remained stable. Ocular adverse effects were reported by 48.1% of patients in tafluprost group and by 44.3% patients in latanoprost one. Most frequently reported were conjunctivalhyperaemia and ocular redness. Corneal thinning during the study was observed in both groups of patients.

In 2007 Sutton et al observed in phase I clinical study that systemic safety was similar with tafluprost, latanoprost and placebo administered to eyes.²³ Investigators did not observed clinically significant changes in laboratory parameters and vital signs or ECG in any of 49 participating persons throughout the course of the study. Visual acuity and fundoscopic pictures of tested eyes were stable, too. Aqueous flare measured by a laser flare cell meter decreased over time. Ocular adverse effects were only mild or moderate in severity. The most common was ocular hyperemia. It was more frequent after administration of tafluprost in concentration either 0.0025% or 0.005%, than after administration 0,005% latanoprost.²³ The incidence of photophobia was greater in tafluprost receiving group than in latanoprost one. It should be noted that doses used in this study excided doses in currently available preparations (0.0015%). Phase III study described by Uusilatto analyzed safety of treatment with 0.0015% tafluprost versus 0.005% latanoprost lasting for 24-months on representative group of 533 patients.²⁸ Both drugs were well tolerated. Reported adverse events were only mild to moderate. The authors found, that during the complete 24-month study period, at least one adverse event was reported by 176 of 264 (66.7%) patients receiving tafluprost, and by 162 of 264 (61.4%) patients receiving latanoprost.

Non-ocular adverse events reported 133 (50.4%) patients treated with tafluprost, and 114 (43.2%) with latanoprost but respectively only 11 in tafluprost group and 9 in latanoprost group were considered to be related to treatment.²⁸ Most frequently reported were conjunctivalhyperaemia and ocular redness. The stimulating growth of eyelashes effect was absent or mild in >90% of patients after 24th month in both tafluprost and latanoprost receiving groups. A light overall tendency for corneal thinning during the study was observed in both groups of patients, but changes were comparable between them.²⁸

Compliance

Little work to date has addressed the issue of patients' satisfaction and compliance. The Comparison of Ophthalmic Medications or Tolerability (COMTol) questionnaire was used in the Ussilato study.^{14,32} COMTol was used to assess the drop discomfort in patients that were treated with both preserved latanoprost and then switched to non-preservative tafluprost.^{14,32} In this study 30% of the volunteers reported no negative effect on the quality of life, 59% experienced "a little or some", 10% "quite a bit much" and 1% "extremely negative".¹⁴ After switching (during week 12) therapy to non-preserved tafluprost no negative quality of life issues were reported 52% of volunteers, 46% reported "a little or some", 2% "quite a bit" and 0% "very much". The percentage of totally satisfied with therapy with latanoprost patients at the baseline of the study was 16%, very satisfied- 36%. At 12 week of treatment with preservative-free tafluprost totally satisfied were 32% of patients as compared to 16% using latanoprost at time zero. This disparity continued throughout the course of the study.¹⁴ In another study, volunteers with poor tolerance of their medications noticed improvement of subjective symptoms and clinical signs after changing their therapy to 0.0015% non-preserved tafluprost.³¹

Conclusions

The introduction of Tafluprost into the marketplace indicates an expansion of prostaglandin therapy for the treatment of various forms of glaucoma and elevated interocular pressure. This new drug being used in Europe and Asia is successfully treating patients with decreased levels of discomfort. It remains to



be seen whether patient compliance in the success of the drug will be a major factor as there is little data anecdotal or study driven to draw any firm conclusions. The available data indicate that patients will be happy with Tafluprost as a prostaglandin therapy. In general tafluprost seems to have fewer toxic reactions associated with it than the other major classes of glaucoma drugs.^{4,14} Although at least one group disputes this.³³ Future research will confirm or deny the hypothesis.

In summary, with the information currently available, tafluprost appears to have the potential to be a major contributor for the treatment of the various forms of glaucoma and elevated interocular pressure. It has comparable efficacy with currently available prostaglandin therapy and few side effects.

Disclosure

This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author and peer reviewers of this paper report no conflicts of interest. The author confirms that they have permission to reproduce any copyrighted material.

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