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A Preliminary Risk-Benefit Assessment of Latanoprost and Unoprostone in Open-Angle Glaucoma and Ocular Hypertension

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Contents

Abstract

Latanoprost and unoprostone (isopropyl unoprostone) represent the first commercially available prostaglandin analogues to be used for the treatment of glaucoma. Both compounds reduce intraocular pressure by enhancing uveoscleral outflow.

Latanoprost, when used once daily in the evening, produces a greater reduction in pressure than timolol. Latanoprost produces mild conjunctival hyperaemia compared with timolol in some patients. Darkening of the irides has been reported, especially in green-brown, yellow-brown and blue/grey-brown irides. Hypertrichosis and hyperpigmentation of the eyelashes have also been demonstrated. Although latanoprost has not been proven to cause uveitis or cystoid macular oedema, case reports of an association exist. Latanoprost does not produce systemic adverse effects nor does it alter routine blood analyses.

Unoprostone, when given twice daily, produces less of a reduction in intraocular pressure than timolol or latanoprost. Three times daily use may be required to approach the effectiveness of timolol. Unoprostone may have a similar adverse effect profile to latanoprost, but may to cause more corneal epithelial problems. Unoprostone is also not known to cause systemic adverse effects.

Both agents are welcome additions to the treatment of glaucoma. However, additional studies and more experience are needed with each agents.

The development of latanoprost has pioneered a new class of glaucoma medications, the prostaglandin analogues. Latanoprost and unoprostone (isopropyl unoprostone) are both chemically and functionally different from any previous glaucoma medication. In this review, the key features of the commercially available prostaglandin analogues, latanoprost and unoprostone will be discussed. Specific attention will be made to the efficacy and adverse effects of these unique agents. Although the ultimate role of either agent is not known, the goal of this review is to enable a better understanding of both agents and their ability to reduce intraocular pressure in open-angle glaucoma and ocular hypertension. When possible, independent analysis of published data was performed using Statistica for Windows 95 (Statsoft, Tulsa, Oklahoma, USA).

1. Introduction to Latanoprost

Latanoprost, chemical name, 13,14-dihydro-15R-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-1-isopropyl ester,[1] is a prodrug of a synthesised chemical analogue of $PGF_{2\alpha}$. Its mechanism of action is via increased uveoscleral outflow,[2,3] that is, the 'unconventional' outflow other than through the trabecular meshwork of the anterior chamber angle.

2. Efficacy of Latanoprost

2.1 Concentration

A prospective, randomised, double-masked and placebo-controlled trial of twice daily latanoprost did not reveal any difference in effectiveness between 0.003%, 0.006% or 0.012% concentrations over a 30-day period.[4] Another report did not reveal a difference in response between latanoprost 0.005% given as a single drop versus 3 drops in the evening, but the statistical power of the study was not stated.[5] Independent direct comparisons of once daily 0.005% versus twice daily 0.0015% concentrations also found the once daily application of the higher concentration (0.005%) to have a statistically significant greater effect on lowering intraocular pressure.[6,7] A single dose of 0.0025, 0.005 or 0.010% provided a dose-dependent intraocular pressure lowering from baseline over a 24-hour period.[8] The higher doses (0.005 and 0.010%) produced statistically significant reductions from 4 to 24 hours.

2.2 Administration: Once Versus Twice Daily

A summary of the placebo-controlled literature reporting intraocular pressure lowering by latanoprost is presented in table I. Studies without placebo-controls are summarised in table II. A single dose has been shown to be effective in lowering

intraocular pressure,[8,12,13] but the drug activity is reported to peak on day 2 of usage[9,10] and persist for up to 2 weeks after discontinuation from long term use.[23] A 2-week, placebo-controlled study found greater effectiveness of the 0.006% concentration given once versus twice daily.[9] Another direct comparison found greater intraocular pressure reduction with once nightly administration in 18 healthy volunteers.[5] A 3-month, multicentre additivity study with timolol found a statistically lower intraocular pressure in the once nightly group (37%, n = 23) versus the twice daily group (28%, n = 25).[24] A study specifically designed to address this issue used a randomised, double-masked design with 40 healthy volunteers.[13] Intraocular pressure was measured on 4 different days (3 times per day) during the 17-day period. On day 2, there was a 3.3 and 3.4mm Hg drop in intraocular pressure for once and twice daily usage, respectively (not significantly different), but by day 15 this had changed to 3.3mm Hg for once daily, and 2.7mm Hg for twice daily ($p < 0.001$). This difference was significant for every time-point throughout the day (08.00, 12.00, 16.00h).

The majority of direct comparison studies support the conclusion that once daily use of latanoprost is more efficacious than twice daily use.[5,9,13,24] Once daily administration has also been shown to produce good control of intraocular pressure without appreciable fluctuation in 24-hour studies.[10,11]

2.3 Administration: Morning Versus Night

Does the time of day affect the activity of latanoprost? A direct comparison of morning versus evening administration, which included a crossover and comparison with timolol, but did not include a placebo control, found evening dose administration more effective, 36% (n = 96) reduction versus 31% (n = 89).[15] Both before and after the crossover, the group taking latanoprost in the evening had a significantly lower intraocular pres-

Table I. Summary of placebo-controlled studies of latanoprost

Study	Patient types	n	Concentration (%)	Administration	Duration	Baseline IOP[a] (mm Hg)	Δ IOP[a] (mm Hg)	Δ IOP[a] (%)
Hotehama et al.[8]	OHT/OAG	35[b]	0.0025	Single morning	24h	23.1	–3.4	–15
			0.005	dose			–4.9	–21
			0.010				–5.9	–26
Nagasubramanian et al.[9]	OHT	20	0.006	qpm	14 days	24.8	–7.2	–29
		20	0.006	bid		25.0	–5.3	–21
		10	placebo	bid		25.3	–1.7	–7.0
Alm et al.[4]	OHT	15	0.003	bid	28 days	23.0	–6.1	–26
		15	0.006	bid		23.6	–6.2	–26
		15	0.012	bid		23.0	–6.0	–26
		15	placebo	bid		23.4	+0.4	+2.0
Rácz et al.[10]	OAG	15	0.006	qpm	6 days	24.4	–4.7	–19
Toris et al.[3]	Normal	6	0.006	bid	7 days	21.6	–3.7	–17
	OHT	16						
Ziai et al.[2]	Normal	20	0.006	bid	5 days	12.6	–2.1	–17
	OHT	20				20.2	–4.8	–24
Rácz et al.[11]	OHT/OAG	10	0.005	qam	9 days	22.5	–3.5	–16
Hotehama & Mishima[12]	Normal	6	0.005	bid	6 days	15.0	–4.6	–31
Lindén & Alm[5]	Normal	18	0.005	qpm	14 days	14.7	–3.2	–22
				qpm × 3			–3.9	–26
				bid			–2.0	–14

a Intraocular pressure change (Δ IOP) has been adjusted for changes in the placebo-control eye or group when possible.

b Total number of patients in study.

bid = twice daily; **IOP** = intraocular pressure; **OAG** = open angle glaucoma; **OHT** = ocular hypertension; **qam** = every morning; **qpm** = every evening.

Table II. Summary of latanoprost studies without placebo control

Study	Patient types	n	Concentration (%)	Administration	Duration	Baseline IOP (mm Hg)	Δ IOP (mm Hg)	Δ IOP (%)
Lindén & Alm[13]	Normal	40[a]	0.005	qpm	15 days	13.6	–3.4	–25
				bid	15 days	13.5	–2.7	–20
Rulo et al.[14]	OHT/OAG	9	0.006	bid	7 days	28.5	–8.9	–31
Diestelhorst et al.[6]	OAG	20[b]	0.005	qpm	21 days	29.2	–9.6	–33
			0.0015	bid		27.2	–6.6	–24
Lusky et al.[7]	OHT/OAG	50[b]	0.005	qpm	3 wk	24.7	–7.5	–30
			0.0015	bid			–6.1	–25
Alm et al.[15]	OHT/OAG	89	0.005	qam	3 mo	24.8	–7.7	–31
	OHT/OAG	94	0.005	qpm	3 mo	25.5	–9.1	–36
Camras et al.[16]	OHT/OAG	118	0.005	qpm	6 mo	24.8	–6.7	–27
Watson et al.[17]	OHT/OAG	149	0.005	qpm	6 mo	25.2	–8.5	–34
Mishima et al.[18]	OHT	56	0.005	qam	12 wk	23.1	–6.3	–27
	OAG	31						
Nicolela et al.[19]	OHT	6	0.005	qam	7 days	26.7	–6.8	–26
	OAG	9						
Camras et al.[20]	OHT/OAG	119	0.005	qd	6 mo	24.1	–6 to –8	–25 to –30
Bucci et al.[21]	OAG	50	0.005	qd	6 mo	22.0	–5.5	–25
Mastropasqua et al.[22]	OAG	18	0.005	qpm	12 mo	NA	–5.9	NA

a Total number of patients in study.

b Crossover study.

bid = twice daily; **Δ IOP** = intraocular pressure change; **NA** = data not available in text; **OAG** = open angle glaucoma; **OHT** = ocular hypertension; **qam** = every morning; **qpm** = every evening; **qd** = every day.

sure than the timolol control group, whereas there was no difference between latanoprost in the morning and timolol twice daily. It has been suggested[15] that the apparent difference in efficacy of the morning and evening times is the result of peak and trough sampling times, but an around-the-clock study[11] found minimal circadian fluctuation of effectiveness.

Although the direct comparison[15] indicates that once nightly application of latanoprost provides the greatest intraocular pressure lowering effect, an open label study did not reveal a difference between morning or evening usage (n = 98).[20]

2.4 Failure to Control Intraocular Pressure

While most studies have noted intraocular pressure failures, none have been designed to determine the rate of failure to control intraocular pressure. It is possible to obtain a rough estimate of the failure rate by using the reported failure times and or study termination time as an endpoint for life table analysis. In such an analysis, the patients are censored by the duration of treatment, which varied among the studies. This analysis reveals a failure rate of about 1% by 1 year.[2-4,9-11,14-19] This is not a true meta-analysis but only an estimation. It is notable that most failures occurred between 1 and 3 months of usage.

3. Adverse Effects of Latanoprost

3.1 Conjunctival Hyperaemia

Early prostaglandin work with $PGF_{2\alpha}$-isopropyl ester and similar compounds demonstrated that conjunctival hyperaemia was a notable occurrence.[25,26] Therefore, this potential adverse effect of latanoprost was carefully evaluated in subsequent studies. In direct comparisons with timolol, the latanoprost group had a nearly identical adverse effect profile despite having 2- to 4-fold as much benzalkonium chloride exposure in its vehicle.[6,24,15-18] The large, independent 6-month multicentre trials reported very mild increases in hyperaemia,[15-17] but only 1 reported a

statistically significant increase.[17] All of the cases reported were mild.

An unmasked comparison did reveal a very small but statistically significant increase in hyperaemia in the group changing from timolol to latanoprost.[20] The degree of hyperaemia reported was also mild and not clinically important.

The majority of evidence leads to the conclusion that there is a very mild increase in conjunctival hyperaemia from exposure to latanoprost compared with timolol, as well as a mild increase in hyperaemia from baseline. The degree to which the vehicle contributes to this adverse effect is not known.

3.2 Iris Pigmentation

Darkening of the irides occurs with prolonged use of latanoprost. This colour change has been reported to occur as early as 2 months after beginning treatment,[20] and predominantly in irides of mixed colour (green-brown, blue-grey, yellow-brown).[15-17,20,27,28] In one study, 10 of 27 (37%) green-brown irides showed possible colour change, as did 2 of 7 yellow-brown (29%) and 4 of 35 (11%) blue/grey-brown irides.[27] No study has found a serious consequence of this colour change, nor any evidence that iris nevi are affected. Histological examinations of iris specimens from human eyes treated with latanoprost have failed to detect a difference from controls by light[29-31] and electron[30,31] microscopy.

3.3 Hypertrichosis and Hyperpigmentation of the Eyelashes

There has been a case report[32] and a case series report[33] noting an increase in both number of lashes and pigmentation of the lashes in patients treated unilaterally with latanoprost. This had been noted in only 1 of the longer comparison studies of latanoprost versus timolol[15] and was not reported in the others.[16,17] Perhaps this failure to observe this effect in clinical trials was due to the small number of unilaterally treated patients, or the failure to closely observe the eyelashes. Further investigation is needed.

3.4 Cystoid Macular Oedema and Uveitis

There are several anecdotal reports of cystoid macular oedema or iritis temporally associated with latanoprost use,[34-39] most involving eyes that have undergone incisional surgery and/or have other risk factors for inflammation.

A retrospective, uncontrolled case series found prevalences of cystoid macular oedema and anterior uveitis of 2 and 6%, respectively, in 94 patients during an 11-month period.[39] This degree of cystoid macular oedema and uveitis was not seen in the primary long term studies[15-17,20,27] or in 63 patients receiving latanoprost followed for 2 years.[28] Compassionate use of latanoprost in 160 patients did not reveal any cases of cystoid macular oedema or uveitis.[40]

After extended use for 6 to 12 months, no change in aqueous flare, as determined by a sensitive laser flare-cell metre, was found upon discontinuation of latanoprost use.[23] The authors concluded that this result demonstrated a lack of alteration of the blood-aqueous barrier, confirming the short term studies that also employed sensitive techniques.[2,6,12,41]

A study specifically designed to address postoperative inflammation and angiographic cystoid macular oedema found statistically more flare by laser flare cell metre and more perifoveal leakage by fluorescein angiography at several time-points post cataract surgery in the groups using fluorometholone with or without latanoprost.[42] However, there was no difference found in the group using placebo and diclofenac compared with the group using latanoprost and diclofenac. Diclofenac completely blocked any latanoprost-induced effect on aqueous flare or perifoveal leakage detected by these very sensitive techniques.

It is reasonable to conclude that latanoprost is an unlikely direct cause of uveitis or cystoid macular oedema. It has been suggested that latanoprost may incite iritis or cystoid macular oedema in eyes with multiple risk factors by indirect means.[42] This causal relationship has not yet been proven. Future work may clarify the protective role of cor-

ticosteroid and nonsteroidal agents in high risk situations.

3.5 Other Ocular Adverse Effects

A low frequency of adverse effects such as tearing, itching, burning, punctate epitheliopathy and headache have been reported in multiple studies. It is not clear whether these adverse effects are due to latanoprost, the vehicle (benzalkonium chloride) or chance. Large masked studies comparing timolol and latanoprost found an equal occurrence of these adverse effects in each group.[15-18]

3.6 Systemic Effects of Latanoprost

No systemic adverse effects have been attributed to latanoprost. Heart rate, systemic blood pressure and standard laboratory chemistries are unaltered by latanoprost.[15-18]

4. Introduction to Unoprostone

Unoprostone is a prostaglandin-related compound of chemical structure isopropyl 20-ethyl-9α,11α-dihydroxy-15-keto-cis-Δ^5-prostanoate.[43] Like latanoprost, its mechanism of action is believed to be by enhancing uveoscleral outflow.[43] Much of the unoprostone literature is not available in English. Summaries from the English abstracts of articles written in Japanese have been used when no alternatives were available and have been identified as such in the reference list. Table III presents a summary of unoprostone studies.

Table III. Summary of studies of unoprostone

Study	Patient types	n	Concentration (%)	Administration	Duration	Baseline IOP[a] (mm Hg)	Δ IOP[a] (mm Hg)	Δ IOP[a] (%)
Azuma et al.[44]	OHT/OAG	70	0.12	bid	12 wk	23.5	–5.2	–22
Azuma et al.[45]	OHT/OAG	57	0.06	bid	52 wk	NA	–3.4	NA
		57	0.12				–4.5	
Takase et al.[46]	OHT/OAG	34[b]	0.006	bid	3 wk	NA	0	NA
			0.06				0	
			0.12				–1.7 to –2.0	
Azuma et al.[47]	OHT/OAG	33	0.03	bid	4 wk	NA	NA	–14
		29	0.06					–16
		34	0.12					–23
		33	Placebo					–11
Stewart et al.[48]	OHT/OAG	24[c]	0.12	qd	1 drop	23.4	–2.9	–12
		11	Placebo	qd	1 drop	24.4	–2.2	–9.0
			0.12	bid	2 wk	–[d]	–4.1	–18
			0.12	tid	2 wk	–[d]	–3.9	–17
Sakurai et al.[43]	Normal	7	0.12	qd	29 days	9.9	0	0
Tetsuka et al.[49]	Normal	8	NA	NA	NA	NA	NA	NA
Takase et al.[50]	Normal	15[b]	0.06	bid	2 wk	NA	–1.1 to –2.4	NA
			0.12				–2.6 to –3.4	
Takase et al.[51]	Normal	8[e]	0.03	NA	NA	NA	NA	NA
			0.06					
			0.09					
		11[e]	0.06					
			0.12					

a Change in intraocular pressure (Δ IOP) has not been adjusted for placebo control.

b Total number of patients in study.

c 24 active therapy and 11 placebo recipients were enrolled in the study.

d A placebo group was used instead of paired-eye control. Washout was not performed between 1 drop, bid and tid administration. The entry baseline was used throughout the entire study.

e Total number of patients in each arm of the study.

bid = twice daily; **IOP** = intraocular pressure; **NA** = data in Japanese; **OAG** = open angle glaucoma; **OHT** = ocular hypertension; **qd** = every day; **tid** = 3 times daily.

5. Efficacy of Unoprostone

5.1 Concentration

A dose-response study comparing 0.03, 0.06 and 0.12% twice daily application for 4 weeks versus placebo reported a net 12% decrease in intraocular pressure for the 0.12% group after subtracting for placebo.[47] The lower concentrations did not produce a significantly lower intraocular pressure compared with baseline or placebo. Although a concentration higher than 0.12% was not included, the authors suggest that the 0.12% twice daily application is the 'optimum dose'. A phase I and II pilot study used 0.03, 0.06, 0.09 and 0.12% once daily applications and also reported a dose-dependent intraocular pressure reduction.[51]

5.2 Administration

In 7 healthy volunteers, a decrease in intraocular pressure was seen as early as 3 hours after initial application and maintained for 10 hours with a peak reduction of 1.6mm Hg at 6 hours.[43] The majority of studies have employed a twice daily schedule.

A diurnal intraocular pressure evaluation of single dose versus placebo, and twice or 3 times daily unoprostone 0.12% versus timolol maleate 0.5% was reported in a pilot study with 35 patients (24 unoprostone, 11 timolol).[48] Single dose unoprostone had no effect at the 24-hour trough, 2.9 ± 3.2mm Hg ($n = 24$) change from baseline for unoprostone versus 2.2 ± 2.9mm Hg ($n = 11$) for placebo (not significant). There was no significant difference in intraocular pressure between these groups at any time-point in the diurnal curve. Twice daily unoprostone produced a mean decrease in intraocular pressure at the 12-hour trough of 4.1 ± 4.1mm Hg versus 6.3 ± 2.4mm Hg for twice daily timolol ($p > 0.05$). Unoprostone administered 3 times daily lowered intraocular pressure at a 12-hour trough by 3.9 ± 3.1mm Hg versus 4.4 ± 2.1mm Hg for twice daily timolol ($p > 0.05$ for all time-points). Diurnal intraocular pressure graphs demonstrate that the mean of the 3 times daily unoprostone group was equivalent to timolol, while the twice daily unoprostone group was less effective at every time-point. This was reported as not significant, but the low power of the study, 40% to discriminate a 2mm Hg difference, gave a 60% chance of reaching this conclusion. It is unfortunate that the authors chose to use group comparisons from baseline instead of pre-drug/post-drug difference between control group and crossover. Had the appropriate analysis been employed, it is likely that the twice daily effect of unoprostone (–4.1mm Hg) would have been significantly different from timolol (–6.3mm Hg). A larger, placebo-controlled, cross-over design study would be desirable to determine the duration of action of unoprostone and whether 3 times daily application is required.

5.3 Failure to Control Intraocular Pressure

A 12-week masked comparative study of unoprostone and timolol reported 7 out of 79 (9%) patients withdrew from treatment for unoprostone versus 2 out of 79 (3%) for timolol.[44] Unfortunately, the reasons for withdrawal from the study were not explicitly stated, but the 2 drugs had equal effects on intraocular pressure when measured 4 hours after the last dose of each drug. The 12-hour trough intraocular pressure was not assessed.

A 1-year study reported that 12 out of 57 (21%) patients experienced treatment failure because of insufficient intraocular pressure control with 0.06% unoprostone and 2 out of 57 (4%) with 0.12% (data taken from an English review[52] of the original study[45]). The authors did not perform a comparison, but assuming that the other patients who withdrew from therapy did not have poor intraocular pressure control as a best-case assumption, a χ^2 analysis demonstrates this to be a significant difference in treatment failure between the 2 concentrations ($\chi^2 = 8.1$, $p < 0.01$). Additional long term studies are needed before a reasonable estimate of the rate of treatment failure can be calculated. These studies should specifically address the 12-hour trough point for twice daily studies and the 8-hour trough for 3 times daily studies.

6. Adverse Effects of Unoprostone

6.1 Conjunctival Hyperaemia

A 4-week study reported no conjunctival irritation in 7 healthy volunteers.[43] A larger study found 3 out of 75 (4%) cases of conjunctival hyperaemia in the unoprostone group, versus 3 out of 79 (4%) cases in the timolol group (not significant).[44] The 1-year study found hyperaemia in 7 out of 57 (12%) cases using the 0.12% concentration.[52] However, additional studies with vehicle controls are needed to assess vehicle and drug adverse effects.

6.2 Iris Pigmentation

Unoprostone was not found to change iris colour in the major studies,[44,45,47] which were performed in eyes with dark brown irides of Japanese patients, and without photographic assessment. A recent case report has documented an increase in pigmentation of a confluent brown iris.[53] This type of iris colour is rarely changed by latanoprost.[15-18,20,27,28,54]

6.3 Hypertrichosis and Hyperpigmentation of the Eyelashes

Unoprostone has been reported to change eyelashes in a similar manner as latanoprost.[55]

6.4 Other Ocular Adverse Effects

Corneal epithelial keratopathy has been reported in 13 out of 71 eyes (18%)[56] and in 19 patients (13%)[57] within 2 weeks of usage. Other effects such as itching, blepharitis, dry mouth and headache have been reported in small numbers. It is not possible to distinguish these latter effects from vehicle treatment or from random occurrences.

6.5 Systemic Effects of Unoprostone

No systemic effects can be directly attributed to unoprostone at this time. Transient headache and nausea have been reported, but not of great enough severity to necessitate discontinuation of treatment.

7. Efficacy of Latanoprost Versus Unoprostone

At this time there is only one direct comparison of the 2 agents. Serle et al.[58] compared twice daily 0.005% latanoprost with twice daily 0.12% unoprostone for 5 days in 8 normotensive and 8 glaucomatous cynomologus monkey eyes. They found intraocular pressure was significantly reduced up to 18 hours after the 3:30pm dose of latanoprost, but not for unoprostone. The magnitude of reduction was greater for latanoprost (–5.4mm Hg) than for unoprostone (–3.8mm Hg). From study day 2 until study end (day 5), latanoprost reduced intraocular pressure significantly more than unoprostone. They conclude that 'latanoprost appears to be more efficacious and potent than unoprostone in reducing intraocular pressure in glaucomatous monkey eyes'.

8. Conclusions

Latanoprost and unoprostone represent the first commercial ventures into prostaglandin receptor modulation of intraocular pressure. Both have been shown to reduce intraocular pressure in eyes with glaucoma and ocular hypertension. Both have produced mild local adverse effects without systemic complications. Latanoprost 0.005% used once nightly is more effective than timolol 0.5% twice daily. Additional studies of unoprostone are needed to determine its effectiveness but, when given twice daily, it appears to be less effective than latanoprost given once daily or timolol given twice daily. Although the rate of failure to control intraocular pressure appears higher in the unoprostone studies, comparative studies are needed before this can be confirmed. Both agents have been shown to affect the pigmentation of ocular structures. No harm has been documented from this pigment change, but continued monitoring is warranted. The issue of latanoprost and cystoid macular oedema or uveitis requires additional study and may represent an indirect effect.

Both agents are welcome in the struggle against glaucoma. Direct comparative trials between latanoprost and unoprostone are needed to determine their relative efficacy and safety. The increasing use of both agents will likely reveal additional risks and benefits of each.

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