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REVIEW

An evidence-based review of unoprostone isopropyl ophthalmic solution 0.15% for glaucoma: place in therapy

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Abstract: Glaucoma is a progressive, neurodegenerative optic nerve disease that can cause significant visual morbidity and affects over 60 million people worldwide. The only known modifiable risk factor for glaucoma at this time is elevated intraocular pressure (IOP), which may be treated with medications, laser therapy, and/or incisional surgery. Topical ocular medications are commonly used as first-line therapy for glaucoma, although side effects may limit their use. Unoprostone is a novel 22-carbon ocular hypotensive agent that may be advantageous in treating some patients with open angle glaucoma or ocular hypertension. Unlike the 20-carbon prostanoids, such as latanoprost, that lower IOP primarily through an increase in uveoscleral outflow, unoprostone may lower IOP through increased aqueous outflow via the conventional trabecular meshwork pathway. Although not as efficacious as other prostanoids, unoprostone is effective for IOP reduction both as monotherapy and adjunctive therapy with timolol. Unoprostone has decreased affinity for the prostaglandin F2α receptor, which may explain its well tolerated ocular and systemic side effect profile compared with other prostanoids.

Keywords: unoprostone, Rescula®, prostaglandin, glaucoma, medication

Introduction

Glaucoma is defined as a group of diseases with a characteristic optic neuropathy and associated visual function changes. The visual loss that occurs from glaucoma is irreversible. It represents a significant public health problem, given that over 60 million people have glaucoma worldwide and this number is increasing.[1] It is the second most common cause of blindness in the world following cataract, and the main cause of irreversible blindness.[1,2] Risk factors for glaucoma include elevated intraocular pressure (IOP), family history, age, race, a thin central cornea, and low ocular perfusion pressure.[3,4] Elevated IOP is currently the only known modifiable risk factor for glaucoma. Lowering IOP has been shown to slow visual field deterioration and is protective against both the development and progression of glaucoma.[5–7] Current glaucoma treatment is focused on lowering IOP with medications, laser therapy, and/or incisional surgery.

Medical therapy is commonly employed as first-line treatment for glaucoma. Current options for topical therapy include alpha agonists, beta antagonists, carbonic anhydrase inhibitors, miotics, and prostaglandin analogs. Most topical ocular hypotensive agents used today are well tolerated, although side effects can limit their effectiveness due to poor patient compliance. Having a large selection of ocular hypotensive agents allows clinicians to better tailor medication regimens for glaucoma patients to balance clinical efficacy and side effects. With increasing medical treatment options, more invasive glaucoma therapy, such as laser or surgery, may be delayed or avoided altogether.

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Unoprostone is an IOP-lowering docosanoid and part of a family of lipid IOP-lowering agents, or prostanoids. Under the trade name Rescula®, unoprostone isopropyl ophthalmic solution 0.12% was developed by R-Tech Ueno, Ltd (Tokyo, Japan) and has been marketed there since 1994.[8] It first received approval as a second-line agent for the treatment of glaucoma and ocular hypertension by the US Food and Drug Administration (FDA) in 2000 as a prostaglandin analog and was marketed by Ciba Vision, a unit of Novartis (Basel, Switzerland), as a 0.15% solution.[8] In 2009, Sucampo Pharmaceuticals, Inc. (Bethesda, MD, USA) acquired the commercialization rights for unoprostone in the USA and Canada.[8] In 2011, these rights were expanded to include all territories worldwide, excluding parts of Asia.[8] Last year, the FDA revised its formal label for unoprostone to include a first-line indication for the treatment of glaucoma and ocular hypertension.[9] Also, the FDA removed its description of the drug as a prostaglandin analog. Unlike the prostaglandin analogs, which are 20-carbon derivatives of the eicosanoid prostaglandin F2α, unoprostone is a 22-carbon derivative of docosahexaenoic acid with little to no affinity for the prostaglandin receptor (see Figure 1).[8,10] Additionally, recent studies show it may work, at least in part, by activating potassium (BK) and chloride (CIC-2 type) channels, leading to relaxation of the trabecular meshwork and increased outflow of aqueous humor though the conventional pathway.[9]

Description

Unoprostone isopropyl is a synthetic docosanoid molecule and a derivative of docosahexaenoic acid, which is a naturally occurring omega-3 polyunsaturated fatty acid endogenous to the central nervous system and retina.[8,11] Its chemical name is isopropyl (+)-(Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]-5-heptenoate, and its chemical formula is $C_{25}H_{44}O_5$.[9] Docosahexaenoic acid is essential for the development and proper functioning of photoreceptor cells, and has been shown to prevent photoreceptor apoptosis associated with oxidative stress in cell cultures.[11–13] Unoprostone 0.15% (Rescula) is formulated as a sterile, isotonic, buffered aqueous solution of unoprostone isopropyl with a pH of 5.0–6.5 and preserved with 0.015% of benzalkonium chloride.[9]

Pharmacokinetics

Unoprostone isopropyl is readily hydrolyzed by esterases to its active form, unoprostone free acid (M1), (3-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]propionic acid), as shown in Figure 1.[8] Unlike the prostaglandin analog latanoprost, which is metabolized only by corneal esterases, unoprostone undergoes additional metabolism once inside the eye by iris and ciliary body esterases.[14] This effect may explain the shortened clinical efficacy of unoprostone when compared with latanoprost. In a study of 18 healthy volunteers given unoprostone isopropyl 0.15% ophthalmic solution twice daily in both eyes for 14 days, the mean peak unoprostone free acid plasma concentration was <1.5 ng/mL and dropped below the lower limit of quantitation (<0.250 ng/mL) 1 hour following instillation, indicating low systemic absorption and rapid plasma excretion.[9] Excretion is rapid through the kidneys, with a half-life of 14 minutes. Unoprostone will begin to reduce IOP 30 minutes after ocular instillation.[15] A clinically sustained effect, however, requires at least 2 weeks of twice-daily therapy.[8]

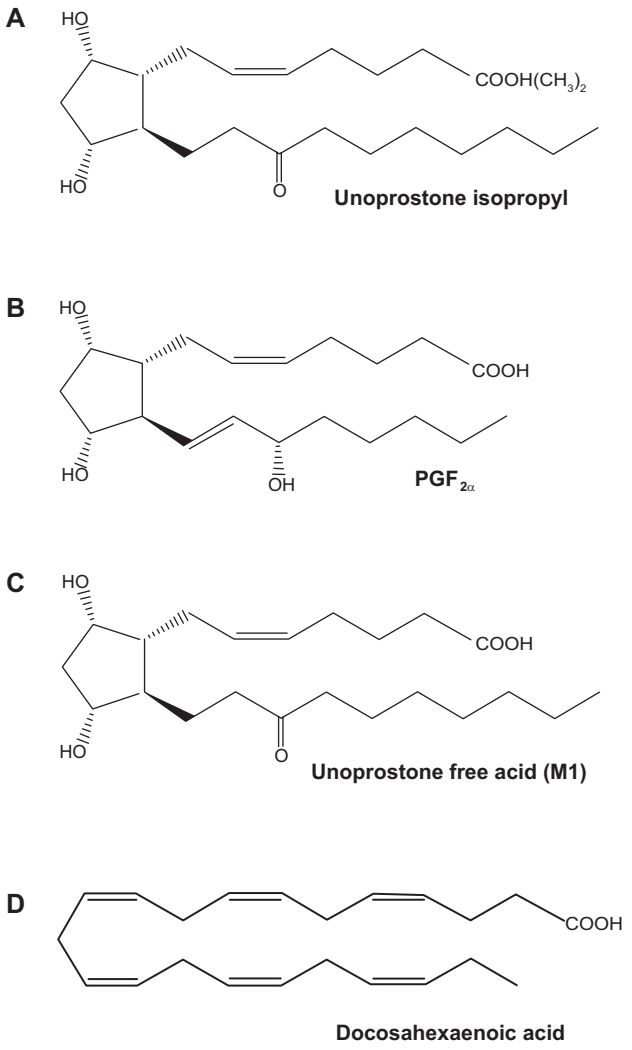

Figure 1 Molecular structure of unoprostone isopropyl and related molecules.
Notes: Unoprostone isopropyl (**A**) is a 22-carbon derivative of docosahexanoic acid (**D**), a naturally occurring fatty acid found in the central nervous system and retina. Following ocular instillation, unoprostone is hydrolyzed by corneal esterases to its active form, unoprostone free acid (**C**). The 20-carbon prostanoids, such as latanoprost, are derived from the eicosanoid, prostaglandin $F_{2\alpha}$ (**B**).

Mechanism

The mechanism of action for the IOP-lowering effect of unoprostone is controversial. Early studies showed that unoprostone increases aqueous humor outflow through the uveoscleral pathway similar to the 20-carbon prostaglandin analogs, such as latanoprost.[8] More recent evidence, however, shows that it may work, at least in part, through stimulation of Ca^{2+}-activated BK and CIC-2 type channels, leading to increased trabecular meshwork outflow. It is these later studies which have prompted the FDA to remove the prostaglandin designation from its formal label.[9]

The prostaglandin analogs, including prostaglandin F2α, latanoprost, and travoprost, mediate their ocular hypotensive effect by stimulating the prostaglandin F2α (FP) receptor.[16–18] These medications have been confirmed in the literature as FP receptor agonists, and induce ciliary muscle relaxation leading to early IOP reduction via increased uveoscleral outflow.[16–20] The early ocular hypotensive effect of prostaglandin F2α is blocked with concurrent use of pilocarpine, which contracts the longitudinal muscle of the ciliary body. This contraction counteracts prostaglandin-mediated ciliary muscle relaxation, thus blocking the early hypotensive effect.[16,21]

With long-term prostaglandin use, the ciliary muscle undergoes remodeling of the cytoskeletal proteins actin and vinculin via mediation of collagen turnover, further contributing to increased uveoscleral outflow and sustained IOP reduction.[16] Other studies have suggested that some aqueous humor outflow may also occur at least in part through the trabecular meshwork pathway as well.[22] The remodeling and turnover of the extracellular matrix in the ciliary muscle is believed to be related to the balance between matrix metalloproteinase (MMP) and tissue inhibitors of metalloproteinase (TIMP). Prostaglandin F2α showed increased c-Fos expression in human ciliary muscle cells, which induces expression of MMPs.[16,23–25] Bimatoprost, latanoprost, and unoprostone all increase MMP activity in human ciliary body smooth muscle cells except for MMP-2.[26] Unoprostone was found to decrease MMP-2 activity and increase TIMP activity. This difference in MMP/TIMP balance between the prostaglandin analogs may explain the lower clinical efficacy of unoprostone.

In contrast with latanoprost, unoprostone has only weak activity on the FP receptor, and its ocular hypotensive effect is believed to involve more than FP receptor activation alone. As opposed to increasing uveoscleral outflow, unoprostone has been shown to increase outflow facility through the trabecular meshwork.[27]

Unoprostone acts on BK channels that, upon activation, lead to cell hyperpolarization.[28,29] Endothelin-1 (ET-1) is known to induce trabecular meshwork contractility mediated via glutamate-associated increases in intracellular Ca^{2+}.[28,30] Through BK channel activation, unoprostone is believed to block this increase in intracellular Ca^{2+} in trabecular meshwork cells and contribute to increased trabecular meshwork outflow and IOP reduction. This mechanism is supported by studies of iberiotoxin, a specific inhibitor of BK channel activation. Iberiotoxin was found to inhibit the hyperpolarization effect of unoprostone.[13,28,30] Another study found that unoprostone also acts on L-type Ca^{2+} channel currents in the trabecular meshwork and that it reduced trabecular meshwork contractility independent of ET-1.[31]

The effect of unoprostone on ET-1 is also believed to mediate a possible neuroprotective benefit.[8] ET-1 is believed to play a role in cell apoptosis and ocular blood flow. The glutamate-associated hypercalcemia that accompanies injury-induced retinal and ganglion cell apoptosis may be mediated by ET-1.[13,28,29] ET-1 is known to cause vasoconstriction of vascular smooth muscle, and unoprostone may allow for increased ocular blood flow by blocking this vasoconstriction.[32–36] This effect was studied in healthy subjects and patients with normal tension glaucoma using a scanning laser Doppler flowmeter, and measures of ocular microcirculation were found to be improved with unoprostone treatment.[37] A study done in healthy individuals given intravenous ET-1 found that topical unoprostone significantly decreased the reduction in choroidal blood flow induced by ET-1.[35]

Several animal studies have found protective effects of unoprostone on nerve injury, specifically on retinal ganglion cell death,[38–40] although one study did find that suppression of ET-1 occurred with travoprost and not unoprostone.[41] These findings suggest possible neuroprotective properties associated with unoprostone. A recent study by Tawada et al evaluated the effect of twice-daily topical unoprostone on central retinal sensitivity in 30 patients with retinitis pigmentosa.[42] After 6 months of therapy, retinal sensitivity improved significantly by fundus microperimetry and visual field mean deviation. Further research is needed to investigate the potential role of unoprostone as a neuroprotective agent in retinal disease.

Efficacy

Unoprostone as monotherapy

Early Japanese studies of unoprostone found modest IOP reduction with fewer ocular side effects compared with prostaglandins E2 and F2α.[42–46] Unoprostone typically lowers IOP by 10%–25% from baseline, with a duration of effect of 2–5 hours compared with a 25%–30% reduction in IOP with latanoprost which may last up to 24 hours and beyond.[47] Table 1

Table 1 Randomized controlled trials of unoprostone as monotherapy

Reference	Year	Patients (n)	Duration	Comparisons	IOP reduction efficacy (mmHg, %)	Side effect profile	Notes
Azuma et al[48]	1993	36	4 weeks	Unoprostone 0.12% BID Timolol 0.5% BID	Timolol = Unoprostone	Decreased blood pressure with timolol; otherwise similar side effect profile	
Stewart et al[49]	1998	36 (POAG, OHT)	2+2 weeks	Unoprostone 0.12% BID Unoprostone 0.12% TID Timolol 0.5% BID	–4.1 (18%) –3.8 (16%) –6.9 (28%) NS	Similar between both groups	Unoprostone BID compared with timolol BID for 2 weeks, then unoprostone TID compared with timolol BID for 2 weeks Supported in part by Ciba Vision
Nordmann et al[50]	1999	40 (POAG, OHT)	2+6 weeks	Unoprostone 0.12% BID Timolol 0.5% BID	Timolol = Unoprostone	Increased stinging with unoprostone	2 weeks of timolol then switch to timolol or unoprostone for 6 weeks
Shimazaki et al[51]	2000	40 (POAG, NTG, OHT)	24 weeks	Unoprostone 0.12% BID Timolol 0.5% BID	Timolol > Unoprostone (P=0.014)	Timolol caused ocular surface dysfunction	
Kobayashi et al[52]	2001	18 (OHT)	8 weeks	Unoprostone 0.12% BID Latanoprost 0.005% QD	–3.0 (13%) –6.3 (28%)*	Increased stinging with unoprostone	Monocular comparison
Saito et al[53]	2001	52 (POAG)	6+6 weeks	Unoprostone 0.12% BID Latanoprost 0.005% QD	–3.3 (15%) –6.0 (26%)* No benefit with combined therapy	No serious adverse event	6 weeks of monotherapy followed by 6 weeks of dual therapy
Susanna et al[54]	2001	108 (POAG, OHT)	8 weeks	Unoprostone 0.12% BID Latanoprost 0.005% QD	–3.3 (14%) –6.7 (28%)*	Similar between both groups	Supported by Pharmacia Corporation
Aung et al[55]	2001	56 (POAG, OHT)	4+4 weeks	Unoprostone 0.12% BID Latanoprost 0.005% qPM + placebo qAM	–4.2 (18%) –6.4 (27%)*	Similar between both groups; more irritation with unoprostone; more redness with latanoprost	4 weeks of monotherapy, 3 week washout, 4 week crossover therapy
Tsukamoto et al[56]	2002	48 (POAG, OHT)	8 weeks	Unoprostone 0.12% BID Latanoprost 0.005% QD	–3.3 (14%) –6.7 (28%)*	No significant difference	
Jampel et al[57]	2002	165 (POAG, OHT)	8 weeks	Unoprostone 0.15% BID Latanoprost 0.005% QD	–3.9 (15%) –7.2 (28%)*	No serious adverse event; increased stinging with unoprostone	Supported by Pharmacia Corporation
Aung et al[58]	2002	28 (POAG, OHT)	4+4 weeks	Unoprostone BID Latanoprost QD	–4.9 (20%) –6.1 (25%)*	Similar between both groups	4 week monotherapy followed by 4 week dual therapy

Sponsel et al[59]	2002	25 (POAG, OHT)	4 weeks	Unoprostone 0.15% BID Latanoprost 0.005% QD	–1.6, –2.4[+] (8%–13%) –2.6, –3.1 (14%–22%)*	No adverse event reported	Latanoprost showed increased pulsatile ocular blood flow Supported in part by Pharmacia Corporation
Nordmann et al[60]	2002	556 (POAG, OHT)	6 months	Unoprostone 0.15% BID Timolol 0.5% BID Betaxolol 0.5% BID	–4.3 (18%) –5.8 (25%)* –4.9 (21%) NS between unoprostone and betaxolol	Similar between groups except for increased burning, stinging, itching, and hyperemia with unoprostone	Sponsored by Novartis
Stewart et al[61]	2004	33 (POAG, OHT)	6+6 weeks	Unoprostone 0.15% BID Brimonidine 0.2% BID	–3.0 (14%) –3.1 (14%) Brimonidine: greater peak IOP reduction Unoprostone: complete diurnal IOP reduction	Increased stinging with unoprostone	6 weeks of monotherapy + 6 weeks of switch therapy Sponsored by Novartis
Arcieri et al[62]	2005	80 (POAG, pseudophakia, aphakia)	6 months	Unoprostone 0.12% Latanoprost 0.005% Bimatoprost 0.03% Travoprost 0.004% Lubricant drop with BAK (placebo)	–3.1 (14%)* –5.4 (26%)** –5.8 (28%)** –5.9 (29%)** –0.4 (3%)	Increased flare, angiographic CME with the prostaglandins compared with unoprostone Increased hyperemia with bimatoprost Hyperemia with unoprostone similar to placebo	

Notes: *Statistically significant. **Statistically significant difference with unoprostone. [+]IOP reduction (morning, afternoon).

Abbreviations: POAG, primary open angle glaucoma; OHT, ocular hypertension; NTG, normal tension glaucoma; NS, no significant difference; QD, once a day; BID, twice a day; TID, three times a day; qAM, every morning; qPM, every evening; BAK, benzalkonium chloride; IOP, intraocular pressure; CME, cystoid macular edema.

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