Initial Clinical Studies with Prostaglandins and Their Analogues

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Abstract. Several prostaglandins (PGs), their prodrugs, and their analogues have been shown to reduce intraocular pressure (IOP) in normotensive volunteers and in patients with elevated IOP. Initial clinical trials demonstrated efficacy with most of these agents, but a PGE_2 analogue, PGD_2, and BW245C (an analogue selective for the DP-receptor) cause an initial rise in IOP with a minimal subsequent reduction. Although $PGF_{2\alpha}$ tromethamine salt, $PGF_{2\alpha}$-isopropyl ester ($PGF_{2\alpha}$-IE), and 15-propionate-$PGF_{2\alpha}$-IE are all very effective in reducing IOP, they produce unacceptable side effects, including conjunctival hyperemia and ocular irritation. Isopropyl unoprostone, a 22-carbon chain $PGF_{2\alpha}$ metabolite, produces a 10–25% reduction in IOP lasting approximately 2–5 hours, is well tolerated, and is commercially available for use in Japan. 17-phenyl substituted $PGF_{2\alpha}$-1E analogues, such as PhXA34 or latanoprost, effectively reduce IOP by 30–40% for at least 24 hours, and are very well tolerated with minimal conjunctival hyperemia and without irritation. Latanoprost is the more potent 15R-epimer of PhXA34, and has become a useful agent in glaucoma therapy. (**Surv Ophthalmol 41 [Suppl 2]:** S61–S68, 1997)

Key words. clinical trials • isopropyl unoprostone • latanoprost • prostaglandins

On the basis of the initial studies in rabbits and monkeys demonstrating an impressive prostaglandin (PG)-induced reduction of intraocular pressure (IOP),[10a,11,14] clinical studies were carried out with a variety of PGs and their analogues. One of these analogues, latanoprost (PhXA41; Xalatan™), has undergone testing in randomized, international, multicenter trials, and recently has become available for commercial use. A second analogue, isopropyl unoprostone (UF-021; Rescula®), has completed testing in multicenter trials in Japan, where it is approved for commercial use. This article summarizes the results of the initial clinical trials that have been reported with PGs and their analogues. Details of these trials are shown in Table 1. Summaries of the large, multicenter trials with latanoprost or isopropyl unoprostone are included in this supplement.[2,52]

$PGF_{2\alpha}$ Tromethamine Salt ($PGF_{2\alpha}$-TS)

In the first clinical study evaluating the effects of PGs, a single dose of 200 μg (0.5%) of $PGF_{2\alpha}$-TS (Fig. 1) was topically applied to one eye in each of 18 normotensive volunteers in a randomized fashion.[20] $PGF_{2\alpha}$-TS significantly reduced IOP for 24 hours with a mean reduction of as much as 3–4 mm Hg occurring at 7 hours. Neither aqueous flare, abnormal leakage of the iris after fluorescein angiography, an anterior chamber cellular response, nor miosis was observed. However, $PGF_{2\alpha}$-TS produced marked conjunctival hyperemia, "smarting," foreign body sensation, and headaches in one-third of patients. Although most of these side effects dissipated over the first 23 hours after application of the PG, they were severe enough for the author to conclude that the use of $PGF_{2\alpha}$-TS in clinical therapy would be limited by its external irritative effects.[20]

A double-masked, randomized, parallel group study comparing three concentrations of $PGF_{2\alpha}$-TS was performed in 45 normotensive volunteers.[27] A single dose of 62.5 μg (0.125%), 125 μg (0.25%), or 250 μg (0.5%) of $PGF_{2\alpha}$-TS was applied to one eye in each of the 15 subjects. $PGF_{2\alpha}$-TS caused a mean reduction of IOP of as much as 2–3 mm Hg in each of the three groups of subjects. A peak reduction occurred at 2–9 hours. The duration of the hypotensive effect was 12, 21, and >24 hours for the 62.5, 125, and 250 μg doses, respectively. Confirming results of the previous study,[20] $PGF_{2\alpha}$-TS caused dose-dependent conjunctival hyperemia, irritation, foreign body sensation, and headaches (50% of patients

TABLE 1

Efficacy and Side Effects of Prostaglandins or their Prodrugs/Analogues in Initial Randomized, Double-masked, Vehicle-controlled Clinical Trials

PG or PG Analogue	NT or OHT	n	Concentration	SD or Freq × Duration	Ctrl IOP (mm Hg)	Initial ↑IOP	Lowest IOP (mm Hg)	Max ↓IOP
$PGF_{2\alpha}$-TS	NT	18	0.5%	SD	14	–	10	30%
	NT	15	0.125–0.5%	SD	16	–	12.5	20%
PGE_2 Analogue (RS 18492)	NT	20	0.02%	SD	15	+	13	10%
PGD_2	NT	5–8	0.01–0.1%	SD	14	+	12	15%
BW245C	NT	7	0.005%	SD	11	+	10	10%
$PGF_{2\alpha}$-IE	NT	6	0.0004%–0.04%	SD or BID×16d	15	–	9.5	35%
	OHT	30	0.002%	BID×1d	30	–	24	20%
	OHT	10	0.002%	BID×7d	25	–	17	30%
	OHT	11–13	0.001%–0.002%	BID×8d	24.5	–	18	25%
15-Propionate-$PGF_{2\alpha}$-IE	NT	12	0.005%–0.025%	SD	14	–	12	15%
S-1033	NT	6	0.1%–0.4%	SD or BID×8d	12.5	–	10	20%
Unoprostone	NT	7–10	0.12%	SD or BID×4wks	12	–	10	15%
	NT	8–11	0.03%–0.12%	SD	15	–	11.5	25%
	NT	7–8	0.06%–0.12%	BID×2wks	14.5	–	10.5	25%
	OHT	29–34	0.03%–0.12%	BID×4wks	22.5	–	19.5	15%
PhXA34	NT	16–18	0.003%–0.03%	SD or QD×7d	12.5	–	8	35%
	NT	8–10	0.003%–0-.03%	SD or BID×5d	12	–	8.5	30%
	OHT	8	0.001%–0.03%	SD	23	–	14.5	35%
	OHT	9–10	0.003%–0.01%	BID×1wk	25	–	15	40%
Latanoprost	NT	6–16	0.003%–0.01%	SD or BID×5d	15	–	10	35%
	OHT	15	0.003%–0.01%	BID×4wks	22.5	–	14	35%
	OHT	6–9	0.006%	QD×5d	23	–	17	25%
	OHT	11–12	0.002%–0.01%	SD	23	–	17	25%
	OHT	20	0.006%	QD×2wks or BID×2wks	23	–	15	35%

Abbreviations: PG = prostaglandin; NT = normotensive volunteers; OHT = ocular hypertensive and/or glaucoma patients; n = number of subjects evaluated for each dose; SD = single dose; Freq = frequency; Ctrl = control of contralateral vehicle-treated, parallel group of vehicle-treated, or baseline measurements; IOP = intraocular pressure; ↑ = increase; Max = maximum; ↓ = decrease; CH = conjunctival hyperemia; $PGF_{2\alpha}$-TS = prostaglandin $F_{2\alpha}$ tromethamine salt; HAs = headaches; FBS = foreign body sensation; $PGF_{2\alpha}$-IE = prostaglandin $F_{2\alpha}$-isopropyl ester; Rx = treatment.

treated with the 125 or 250 μg doses), and occasional erythema of the skin of the lower lid. Pupillary diameter was not altered. Neither aqueous flare nor an anterior cellular response was observed in any eyes.[27]

PGE_2 Analogue

After demonstrating an ocular hypotensive effect in rabbits,[48] a single application of PGE_2 analogue, RS 18492 (Fig. 1) 0.02%, was administered to one eye in each of 20 normotensive volunteers in a randomized, double-masked fashion.[19] This PG analogue caused an initial mean rise in IOP of as much as 3–4 mm Hg, peaking at 1–2 hours. As an extreme, two individual patients showed rises of 13–20 mm Hg. Following this initial hypertensive response, mean IOP was reduced by no more than 1–2 mm Hg at six hours. Similar to the effects seen with the $PGF_{2\alpha}$-TS, this PGE_2 analogue caused conjunctival hyperemia, aching, tenderness, and photophobia,

TABLE 1
(Continued)

Time (hrs) Max ↓IOP	Duration (hrs)	Max CH*	Maximum Irritation*	Other Side Effects/Comments	References
7–10	24	3+	3+	HAs, FBS	Giuffre[20]
2–9	24	3+	3+	HAs, FBS, lid erythema	Lee et al[27]
6	24	3+	3+	HAs, FBS, tenderness, photophobia	Flach & Eliason[19]
2–4	4	3+	2+	Itching, FBS, burning	Nakajima et al[31]
3	4	3+	2+	Itching, FBS, burning	Nakajima et al[31]
4–12	12–24	2+	1–2+	Dose-dependent CH & irritation; FBS, photophobia & pain with higher doses only	Villumsen & Alm[42]
12	12	1–2+	1+	CH usually resolved after 3–4 hrs; mild FBS × 1 hr; not progressive with multiple dosing	Villumsen et al[45]
12	12	1–2+	1+		
4–6	12	1–2+	1+	Max CH occurred 30 min after each dose; mild dose-dependent irritation, FBS, discomfort	Camras et al[17]
4–12	12	1–2+	1+	Mild dose-dependent FBS	Villumsen & Alm[43]
2–8	8	1+	1+	Slight & transient smarting sensation; 0.4% produced apparent contralateral ↓IOP	Ando et al[6]
3–6	10	0	0	1 mmHg ↓IOP occurred after 2 wks of Rx, but no signif. ↓IOP was present after 4 wks of Rx	Sakurai et al[35]
2	2–5	0	0		Takase et al[41]
?	?	0	0		Takase et al[40]
?	?	0	0		Azuma et al[7]
10	48–144 (2–6d)	2–3+	1+	↓CH over the 1 wk of Rx; ↓discomfort to 0 after a few doses	Alm & Villumsen[4]
12	48	1+	0	↓CH over the 5d of Rx	Hotehama & Mishima[24]
12	24	1–2+	1+		Villumsen & Alm[44]
12	48	1–2+	0	↓CH when tonometry was suspended	Camras et al[16]
5–8	48	1+	0	No signif CH with repeated doses of 0.006%	Hotehama & Mishima[24]
?	12	1+	1+	↓CH over the 4 wks of Rx; mild irritation was signif on day 2 only	Alm et al[5]
15–24	24	1+	0	Mild CH reported on single occasion in 2 patients	Racz et al[32]
8	24	0.5–1+	0		Hotchama et al[25]
8–20	20	1+	0	Max CH on day 2	Nagasubramanian et al[30]

*Graded in relative units of 0–3+ with 0 = absent, 0.5 = barely detectable, 1 = mild, 2 = moderate, 3 = severe.

beginning within the first hour and lasting up to six hours after administration.

PGD_2 and its Selective Analogue

Studies have demonstrated that PGD_2 and BW245C, an agonist selective for the DP-receptor, are not only effective ocular hypotensive agents, but the best tolerated PGs in terms of the blood-aqueous barrier and ocular surface pathology in rabbits.[22,50,51] Therefore, a dose response study was carried out in 5–9 normotensive volunteers.[31] Like the PGE_2 analogue, PGD_2 caused a dose-dependent initial rise in IOP of 1–4 mm Hg for the 5 μg (0.01%), 10 μg (0.02%), and 50 μg (0.1%) doses, peaking at 30 minutes.[31] A subsequent mean reduction in IOP of no more than 1.5–2 mm Hg peaked at 1.5–2 hours after a single application. BW245C 2.5 μg (0.005%) induced an initial rise in IOP of 3–4 mm Hg at 30 minutes, followed by a reduction of 1–1.5 mm Hg at three hours (Table 1). PGD_2 and BW245C caused

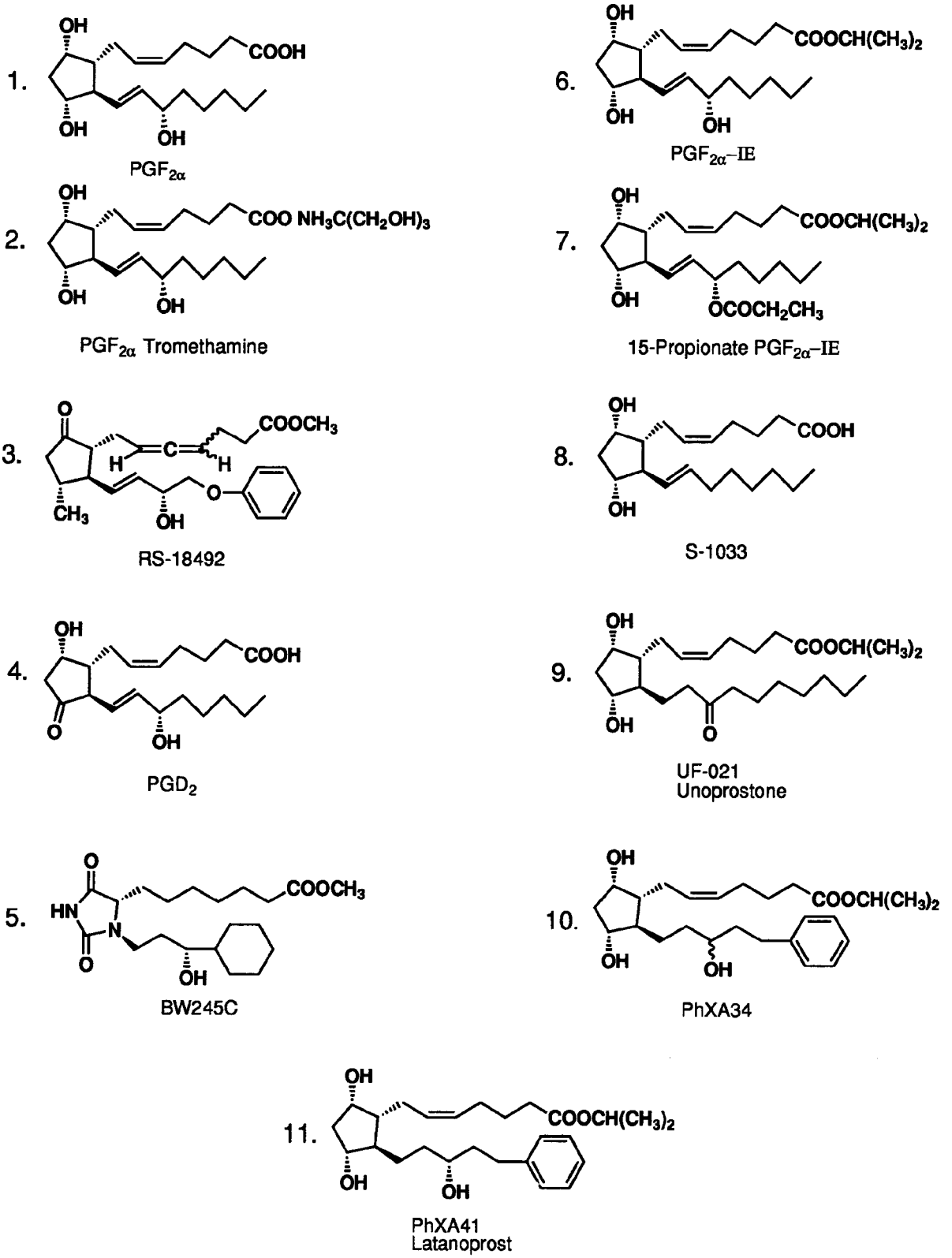

Fig. 1. Chemical structure of prostaglandins and their prodrugs/analogues used in clinical trials.

conjunctival hyperemia, foreign body sensation, itching, and burning during the first two hours after application. Neither aqueous flare nor an anterior chamber cellular response was observed. Similar to the PGE_2 analogue and $PGF_{2\alpha}$ tromethamine salt, PGD_2 and BW-245C had a poor therapeutic index and side-effect profile. These findings with BW-245C in clinical trials were consistent with a study which demonstrated poor tolerance in monkeys.[46]

$PGF_{2\alpha}$-1-Isopropyl Ester ($PGF_{2\alpha}$-IE)

The first important improvement in therapeutic index for PGs occurred with the development of the isopropyl ester of $PGF_{2\alpha}$ (Fig. 1). The enhanced lipophilicity resulting from esterification of the carboxylic acid group improved corneal penetration to increase potency.[9] Maintaining efficacy similar to that of $PGF_{2\alpha}$ at considerably lower concentrations in rabbits, cats,[8,10] and monkeys,[12,47] $PGF_{2\alpha}$-IE produced less external ocular side effects. Analogous to the relationship between dipivefrin and epinephrine, $PGF_{2\alpha}$-IE is a prodrug of $PGF_{2\alpha}$ and is converted to the free acid by esterases in the cornea.[9]

In a dose-response study in six normotensive volunteers, single applications of $PGF_{2\alpha}$-IE produced a dose-dependent reduction of IOP at 8–12 hours by 1.9, 1.9, 3.3, and 5.7 mm Hg at doses of 0.1 μg (0.0004%), 0.5 μg (0.002%), 2.5 μg (0.01%), and 10 μg (0.04%), respectively.[42] Only the highest doses showed a tendency toward an initial rise in IOP at 30 minutes. The reduction of IOP was maintained for 12–24 hours with the higher two doses. Twice-daily application of 0.5 μg (0.002%) in 10 normotensive volunteers produced a 1.5–2.5 mm Hg reduction of IOP for the 16 days of treatment. Compared to $PGF_{2\alpha}$, $PGF_{2\alpha}$-IE reduced IOP with a lower incidence and intensity of conjunctival hyperemia, pain, foreign body sensation, and photophobia.[42]

Based on these initial favorable results in normotensive volunteers, $PGF_{2\alpha}$-IE was tested in patients with ocular hypertension or glaucoma.[17,45] Doses of 0.25 μg (0.001%) or 0.5 μg (0.002%) reduced IOP by as much as 6 mm Hg (25%). A 4–6 mm Hg IOP reduction was maintained on the eighth day of twice-daily treatment.[17,45] Although conjunctival hyperemia and irritation were noted by many patients, these side effects were reduced compared to those observed with $PGF_{2\alpha}$.

This esterified prodrug of $PGF_{2\alpha}$ provided evidence that with appropriate modification of PGs or their analogues, external ocular side effects could be reduced without sacrificing ocular hypotensive efficacy. Nevertheless, local side effects, although reduced, persisted at levels sufficient to lead to problems with medical compliance, and would prevent $PGF_{2\alpha}$-IE from becoming a useful primary therapy for glaucoma.

15-Propionate-$PGF_{2\alpha}$-IE

In an effort to reduce the irritation and conjunctival hyperemia produced by $PGF_{2\alpha}$-IE, an esterification at the 15-carbon position, in addition to esterification at the carboxylic acid moiety (Fig. 1) was tried.[43] In a double-masked, dose-response, comparative study with $PGF_{2\alpha}$-IE, 15-propionate-$PGF_{2\alpha}$-IE effectively reduced IOP in 12 normotensive volunteers, but failed to offer any advantages compared to $PGF_{2\alpha}$-IE in terms of therapeutic index.[43]

15-Deoxy-$PGF_{2\alpha}$ (S-1033)

S-1033 is $PGF_{2\alpha}$ without the hydroxyl group at the 15th carbon position (Fig. 1). It was found to reduce IOP in rabbits, cats, dogs, and monkeys with minimal side effects.[21] In the only clinical trial using this agent, a dose-dependent reduction of IOP of as much as 2–3 mm Hg peaked at 2–8 hours after a single application of 0.3% solution in six normotensive volunteers.[6] The highest dose of 0.4% resulted in both an ipsilateral and contralateral reduction of IOP of 4–5 mm Hg at eight hours. This contralateral effect was difficult to explain. S-1033 0.3% produced mild conjunctival hyperemia in three of the six subjects, and a slight "smarting" sensation in all six patients lasting for a few minutes after a single application. Twice-daily application of S-1033 0.3% in the six normotensive volunteers reduced IOP by 2–3 mm Hg for the eight days of treatment.

Isopropyl Unoprostone, a Modified $PGF_{2\alpha}$ Metabolite

Isopropyl unoprostone (UF-021; Rescula®; 20-ethyl-13,14-dihydro-15-keto-$PGF_{2\alpha}$-isopropyl ester) is the isopropyl ester prodrug form of the 20-ethyl derivative of the common pulmonary metabolite of $PGF_{2\alpha}$ (Fig. 1). In a dose-response study involving 8–11 normotensive volunteers, isopropyl unoprostone 0.03%, 0.06%, 0.09%, and 0.12% caused a dose-dependent reduction of IOP with a peak of 1–4 mm Hg at 1–2 hours after a single dose.[41] Compared to all previously discussed PG analogues, isopropyl unoprostone seems to be best tolerated in terms of external ocular surface side effects.[41] In another dose-response study involving normal volunteers treated twice daily for two weeks, isopropyl unoprostone 0.06% or 0.12% produced a similar dose-dependent reduction of IOP without ocular or systemic side effects.[40] In 10 normotensive volunteers, isopropyl unoprostone 0.12% caused a peak reduction of IOP of 1–2 mm Hg at six hours.[35] Twice-daily treatment in seven normotensive volun-

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