REVIEW ARTICLE

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Prostaglandin Analogues in the Treatment of Glaucoma

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Abstract

Prostaglandin (PG) analogues are a new class of ocular hypotensive drugs that have been developed for the treatment of open angle glaucoma. Two of these drugs, latanoprost and unoprostone, are presently commercially available.

Latanoprost was introduced in 1996 in the US and Europe. Presently it enjoys the most widespread use and is the most well documented drug of this group. It reduces the intraocular pressure (IOP) by a mechanism of action different from other drugs; namely by increasing the uveoscleral outflow. The aqueous inflow

is not affected. The optimal dose regimen is one drop of 50 ∝g/ml once daily, which reduces the IOP by approximately 30% in patients with glaucoma. A more pronounced ocular hypotensive effect is demonstrated when latanoprost is combined with other glaucoma therapies, including β-blockers, adrenergic and cholinergic agonists or carbonic anhydrase inhibitors. Latanoprost is well tolerated. The drug reaches a plasma concentration below that needed for stimulation of the FP-receptor, which may explain its favourable systemic tolerability profile. The major ocular adverse effect is increased iris pigmentation, which is due to increased synthesis of melanin in the melanocytes of the iris stroma. It is most frequently seen in green-brown eyes and it is probably permanent. A low frequency of cystoid macular oedema has also been reported, predominantly in predisposed eyes.

Unoprostone was launched in Japan in 1994, but there is little experience with this drug outside the Japanese market and the documentation is more limited. Its main mechanism of action is on outflow, but this is not yet fully elucidated. The recommended dosage regimen is 1 drop of 1.2 mg/ml twice daily. No comparative studies in humans between the 2 drugs have yet been published.

A new class of ocular hypotensive agents, prostaglandin (PG) analogues, has been developed for the treatment of glaucoma. Two preparations for topical use are presently commercially available. In 1994, isopropyl unoprostone was launched on the Japanese market. Two years later latanoprost was introduced in the US and in many European countries. The purpose of this article is to give the rationale for the use of PG analogues in the management of glaucoma and to report the present clinical experience with these drugs.

1. Glaucoma and Glaucoma Treatment

Glaucoma is a major cause of blindness all over the world. It is reported to be the second most common cause in the US and the most frequent in the Black population.[1,2] Glaucoma can be divided into several clinical entities of which primary open angle glaucoma (POAG) is the most common.[3] In the Scandinavian countries the pseudoexfoliation glaucoma is often added to this group.

Glaucoma may be defined as a progressive optic neuropathy with characteristic changes of the optic nerve head and the visual field. Elevated intraocular pressure (IOP) is an important risk factor that aggravates the course of the disease. Other mechanisms such as neurotoxicity or impaired blood circulation may contribute to the damage, but the only risk factor amenable to therapeutic intervention today is the IOP.

IOP is maintained by the balance between inflow and outflow of aqueous humour in the eye (fig. 1). Aqueous humour is produced by the non-pigmented ciliary epithelium in the ciliary body and it escapes from the eye at the irido-corneal angle. A major drainage route is via the trabecular or conventional route, i.e. through the trabecular meshwork, into Schlemm's canal, collector channels, aqueous veins and, finally, the general venous circulation. Another route is the uveoscleral or unconventional route,[4] i.e. across the iris root and the ciliary muscle, through the connective tissue between the muscle bundles, into the suprachoroidal space and out through the sclera.

The elevated IOP is the result of an impaired outflow of aqueous humour but treatment, both surgical and medical, can be aimed at inflow as well as outflow. Surgical treatments affecting inflow include all cyclodestructive procedures. Filtering procedures as well as laser trabeculoplasty aim at increasing outflow. β-blockers, α-agonists and carbonic anhydrase inhibitors suppress aqueous humour production. Cholinergic and adrenergic agonists increase trabecular outflow. PGs are the first drugs where the main effect on IOP is caused by increased uveoscleral outflow.[5-11]

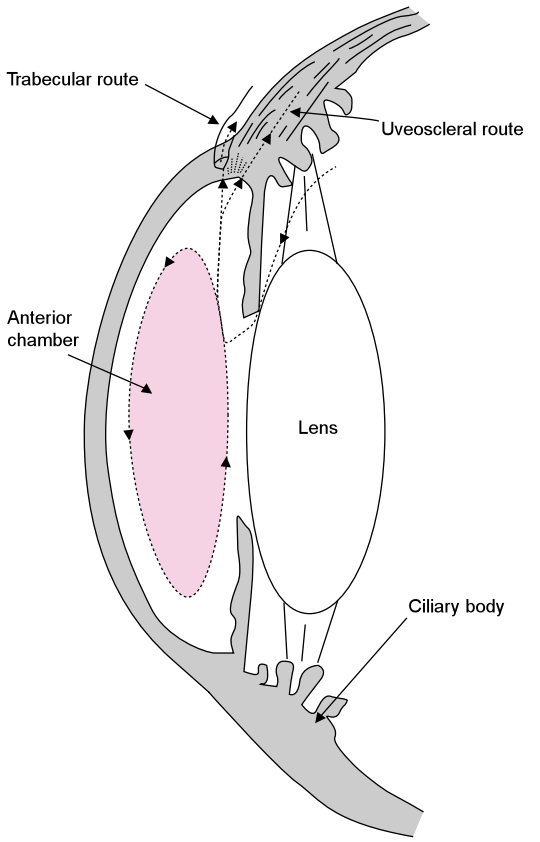

Fig. 1. Anterior segment of the eye with aqueous humour circulation indicated.

2. Brief Prostaglandin (PG) Pharmacology

Eicosanoids can be defined as the further metabolic products of arachidonic acid, a polyunsaturated fatty acid (straight chain C-20 carboxylic acid). PGs constitute a group of naturally occurring hydroxylated fatty acids, found in small concentrations in mammalian tissues. They are characterised by high pharmacological potency and a diverse spectrum of biological activities. The biological properties of the various PGs are mainly dependent on the oxidation state of the cyclopentane ring. They are biosynthesised from free arachidonic acid, which is released from membrane phospholipids after activation of phospholipase A_2 or C by a variety of physiological stimuli. They do not appear to be stored free in tissues, but they are biosynthesised and released on demand. PGs together with thromboxanes and leukotrienes constitute the principal eicosanoids. Thromboxane (TXA_2) is another metabolite of arachidonic acid, which is classified as a PG. However, strictly speaking it is not a PG since the prostanoic acid cyclopentane ring is missing. Naturally occurring PGs, $PGF_{2\alpha}$, PGE_2, PGD_2 and prostacyclin (PGI_2) together with TXA_2 are designated as prostanoids.

The last letter of the abbreviations of the naturally occurring PGs (e.g. F) refers to the ring structure, while the figure in the subscripts refers to the number of double bonds. The Greek letter subscript refers to the orientation of the hydroxyl groups, above or below the plane of the ring. Thus, $PGF_{2\alpha}$ derives from arachidonic acid, has 2 double bonds, 1 in each side chain and has its hydroxyl groups below the plane.

PGs are not metabolised locally but released into the circulation. In the eye, inactivation of PGs is a result of removal of PGs from the eye by outward-directed active transport systems in the blood-ocular barriers.[12] PGs reaching the circulation are rapidly inactivated, mainly during their passage through the lung,[13] and the plasma half-life ($t_{1/2}$) of most PGs is <1 minute.[14] However, the $t_{1/2}$ of latanoprost is 10 minutes in monkeys[11] and 17 minutes in humans (B. Sjöquist, personal communication, 1997). Latanoprost is mainly inactivated in the liver, and while most of the metabolites are excreted in the urine, a minor part is eliminated in the faeces.[11]

2.1 PG Receptors

The diversity of the effects of PGs is explained by the existence of a number of different prostanoid receptors. The receptors are named DP-, EP- (4 subtypes), FP-, IP- and TP-receptors for the natural PG (PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2 or TXA_2) for which they have the greatest affinity.[15] All natural PGs have affinity for more than 1 receptor resulting in a mixed pharmacological response. Thus, selective agonists or antagonists can be expected

to have more specific effects than naturally occurring PGs.

The FP receptor has a widespread distribution within the tissues of the eye including the ciliary muscle and the ciliary processes.[16]

2.2 Brief History of PGs

In 1930, 2 American gynaecologists, Kurzrok and Lieb,[17] observed that the human uterus muscle contracted when it was exposed to seminal fluid. Goldblatt[18,19] in England and von Euler[20] in Sweden independently verified that seminal fluid contracted smooth muscle. Von Euler[20] identified 2 substances which he called PGs as he assumed they derived from the prostate. One was soluble in ether and the other in phosphate (that is 'fosfat' in Swedish). Consequently, they were named prostaglandins E and F. The name prostaglandin has been retained although it was discovered that the 2 PGs did not originate from the prostate gland, but from the seminal vesicles and that PGs were also generated from a variety of other tissues.

Ambache[21,22] made the first observation of PG effects in the eye. He isolated a substance in iris extracts capable of contracting the cat iris. It was named irin. It was later shown that irin was a mixture of PGs, mainly $PGF_{2\alpha}$ and PGE_2.[23-25]

2.3 Early Animal Experiments

In an early attempt to administer PGs topically, PGE_1 was applied to rabbit eyes in doses from 0.5 to 50 ∝g and caused a dose-dependent increase in IOP, hyperaemia and breakdown of the blood-aqueous barrier (BAB).[26] Later, it was reported that a topically applied low dose of another PG, $PGF_{2\alpha}$ 0.5∝g, gave a reduction in IOP in the rabbit eye lasting for several hours.[27] Subsequent studies have confirmed that $PGF_{2\alpha}$[28] as well as PGE_2, PGD_2,[29] PGE_3 and PGD_3[30] reduce IOP in the rabbit eye. Persistent IOP reduction was shown also for $PGF_{2\alpha}$ and PGE_2 in normo- or hypertensive eyes of several species including cats, dogs and monkeys.[6,28,31-36]

2.4 Early Human Studies

The first report on the ocular effects of topically applied $PGF_{2\alpha}$ (fig. 2) in volunteers was published in 1985.[37] 200 ∝g of the tromethamine salt (dinoprost) reduced IOP significantly for 4 to 24 hours in normotensive eyes, but caused marked hyperaemia, ocular pain and headache.

With the purpose of reducing the adverse effects and to increase the bioavailability, $PGF_{2\alpha}$ was made more lipid-soluble by esterification of the carboxyl group.[38] $PGF_{2\alpha}$-isopropyl ester ($PGF_{2\alpha}$-IE) penetrates the corneal epithelium more readily and can be used in much lower doses than the tromethamine salt. It is hydrolysed to $PGF_{2\alpha}$ during its passage through the cornea by the enzymes, butyryl-cholinesterase and carboxylesterase.[39,40]

In the first study performed on healthy volunteers 1 to 10 ∝g of $PGF_{2\alpha}$-IE was found to reduce

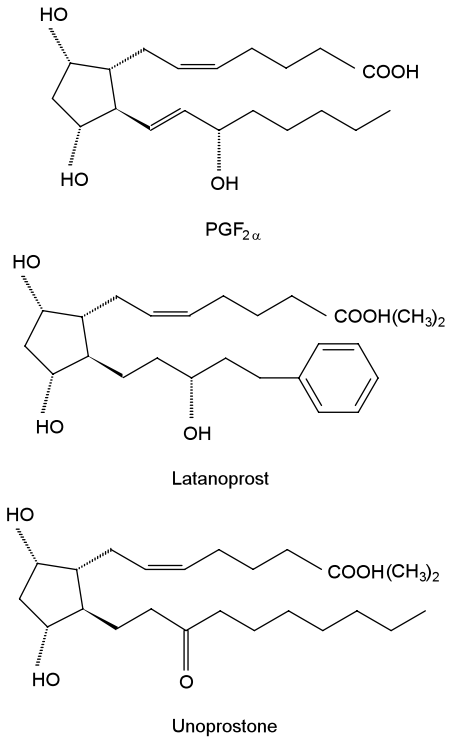

Fig. 2. Structural formulas of prostaglandin (PG) $F_{2\alpha}$, latanoprost and unoprostone.

IOP in a dose-dependent manner, but the adverse effects were still a problem with the higher doses.[41] A diester was also tried, but it did not improve the therapeutic index.[42]

3. Latanoprost

In the attempts to find a more selective FP-receptor agonist, a part of the omega chain was substituted with a phenyl-ring. The result was PHXA34, the mixture of the 15-R and 15-S epimers of latanoprost (13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE; PHXA41) [fig. 2]. Latanoprost is the pure 15-R epimer, which is about 10 times more biologically active than the 15-S epimer.[43] Therefore, twice the dose of PHXA34 is required to reach an effect similar to that of latanoprost.

Latanoprost is a biologically inactive prodrug. It is hydrolysed to its active form in cornea or in plasma. About 1% of topically applied latanoprost enters the monkey eye.[11] In human aqueous humour a peak concentration is reached approximately 2½ hours after application.[44]

Latanoprost is a more selective FP-receptor agonist than $PGF_{2\alpha}$[11] and this has resulted in an improved therapeutic profile with much less hyperaemia and negligible irritation compared with $PGF_{2\alpha}$ and a retained IOP lowering effect.[45-47]

The drug concentration in a vial of latanoprost (50 μg/ml) is about 10^{-4} mol/L, whereas in aqueous humour and in plasma the peak concentrations reach about 10^{-7} mol/L and 10^{-10} mol/L, respectively.[44] The EC_{50} for the affinity of latanoprost to the FP-receptor is $3.6 \cdot 10^{-9}$ mol/L.[11]

3.1 Dose

The optimal latanoprost concentration for reducing IOP in volunteers has been found to be about 50 μg/ml, i.e. 0.005%.[48-50] The maximum IOP reduction is seen 6 to 12 hours after the administration of a single drop.[49,51]

Once daily administration is superior to twice daily with regard to the ocular hypotensive effect during the day (i.e. the IOP remains higher with twice daily administration compared with once daily).[52-55] The mechanism behind this is not completely understood. A likely explanation may be a true reduction of the efficacy of latanoprost by development of subsensitivity.[55]

3.2 Mechanism of Action

Latanoprost reduces IOP in monkeys by increasing uveoscleral outflow.[11] An increase of 60% in uveoscleral outflow was found after the application of latanoprost 3 μg daily for 5 days, whereas trabecular outflow was unchanged.[11] This confirms the previous results from studies of $PGF_{2\alpha}$[5,6] and $PGF_{2\alpha}$-IE[7-9] in monkeys. There is also indirect evidence to support the same mode of action of latanoprost in humans.[10] The exact mechanism behind the increase in uveoscleral outflow is not known, but latanoprost is able to induce transient changes in the extracellular matrix of the ciliary muscle.[56-59] Such an effect could explain the fact that IOP is not restored to pretreatment levels until 2 to 3 weeks after withdrawal of treatment.[54]

Neither $PGF_{2\alpha}$, $PGF_{2\alpha}$-IE or latanoprost reduce aqueous inflow in monkeys[6,7] or in humans.[10,51,60,61]

3.3 Therapeutic Use

3.3.1 Intraocular Pressure (IOP)

Short term use of latanoprost 1 to 4 μg once or twice daily reduced the IOP by 19 to 38% in initial clinical trials in healthy volunteers[49] and in patients with ocular hypertension and glaucoma.[50,62] In subsequent long term studies (6 months or more) in patients where latanoprost was administered once daily the diurnal IOP was reduced 27 to 34% without evidence of loss of effect.[45-47,63,64] Similar results were obtained in a 3-month study.[65] Latanoprost also reduces IOP during the night.[66]

3.3.2 Ocular Blood Flow

Ocular blood flow in the anterior uvea of cynomolgus monkeys, measured with labelled microspheres, increases after topical application of $PGF_{2\alpha}$.[67] However, topical administration of latanoprost 6 μg in each eye, i.e. about 4 times the clinical dose, showed an increase in the blood flow

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