New drugs in glaucoma therapy

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The balance between surgery and medical therapy in glaucoma management has changed significantly in recent years. This can be traced primarily to the availability of several new therapeutic agents. This article takes a more detailed look at the prostaglandin analogues latanoprost and travoprost and the prostamide bimatoprost.

Chronic simple (open-angle) glaucoma is a disease associated with progressive loss of visual field which can eventually lead to blindness. It has been estimated that about 3% of a typical UK metropolitan population over the age of 65 years suffer from the condition, with a further 7% suspected of having it (Reidy et al, 1998).

Treatment of glaucoma is currently targeted at reducing intraocular pressure (IOP). Until recently, the medical management of glaucoma has been dominated by drugs which act via the autonomic nervous system. Ophthalmic beta-blockers – such as timolol – were the drugs of first choice, with drugs such as pilocarpine and dipivefrine added if adequate control could not be maintained on beta-blocker monotherapy. Failure of maximal medical therapy usually leads to the need for glaucoma-filtering surgery (trabeculectomy), although in some cases, patients may undergo laser trabeculoplasty. In some centres, early surgery may be preferred since it has been shown to provide better preservation of visual function and the lowest mean IOPs (Migdal et al, 1994).

However, a UK survey has demonstrated that the rates of trabeculectomy have dropped dramatically since 1995, against a background of an overall increase in ocular surgery (Whittaker et al, 2001). The investigators attribute this change, in part, to the introduction of new medical therapies during this time period. These have included alpha-agonists, topical carbonic anhydrase inhibitors and, most significantly, the prostaglandin analogues. Latanoprost has been available for several years and recently travoprost (a prostaglandin analogue) and bimatoprost (a prostamide) have been introduced.

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MODE OF ACTION

Prostaglandins have been shown to reduce IOP in a variety of animal models and in humans (Bito, 2001). The application of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) as the tromethamine salt in normotensive human subjects caused a significant reduction in IOP but was accompanied by ocular irritation and conjunctival hyperaemia (Lee et al, 1988). Esterification of the carboxyl group in $PGF_{2\alpha}$ improves corneal penetration, and substitution of a phenyl group into the resulting isopropyl ester provides analogues that are both effective and more comfortable to use (Bito et al, 1993; Resul et al, 1993). The first molecule of this type to become widely available for clinical use was latanoprost (Bito et al, 1993; Stjernschantz, 2001). This has been followed by travoprost (Hellberg et al, 2001). A third, unoprostone, is available in some countries but appears to be less effective (Aung et al, 2001; Stjernschantz, 2001; Sponsel et al, 2002). Another hypotensive lipid that can be used to lower IOP is the synthetic prostamide bimatoprost (Woodward et al, 2001).

Aqueous humour is produced by the ciliary epithelial cells and, in the normal eye, the outflow of aqueous humour must balance production if a stable IOP is to be maintained. Aqueous humour exits the eye through the trabecular meshwork (trabecular route, also known as the pressure-sensitive route) and also via extracellular spaces within the ciliary muscle and then through the suprachoroidal space (uveoscleral or pressure-insensitive route). Trabecular outflow is the main route of aqueous drainage from the eye, with uveoscleral outflow contributing only about 10% of total drainage in the normal human eye.

Prostaglandin analogues reduce IOP by increasing uveoscleral outflow of aqueous humour and have only a minimal effect on trabecular outflow (Crawford and Kaufman, 1987; Bito, 2001; Stjernschantz, 2001). The prostamide bimatoprost enhances trabecular outflow and also increases outflow through the uveoscleral pathway (Brubaker, 2001).

The prostaglandin analogues work by binding to specific ciliary muscle prostanoid receptors (FP receptors). Activation of these receptors results in a complex series of responses including cAMP formation and induction of c-Fos and c-Jun expression (Schachtschabel et al, 2000). This, in turn, activates biosynthesis of matrix metalloproteinases, a family of neutral proteinases that can cleave extracellular matrix molecules. These metalloproteinases are thought to alter collagens in the ciliary muscle to increase spaces among ciliary fibres and reduce resistance to uveoscleral outflow (Schachtschabel et al, 2000; Stjernschantz, 2001).

Studies in vitro have indicated that travoprost has higher potency and affinity of binding at the FP receptor than latanoprost, and that unoprostone is less selective for the FP receptor than travoprost and latanoprost (Hellberg et al, 2001; Kondor, 2001; Sharif et al, 2002). It is unclear at which receptor bimatoprost acts, although it was reported to show no significant pharmacological activity at FP receptors (Woodward et al, 2001).

COMPARISON WITH BETA-BLOCKERS

The results of clinical studies comparing latanoprost with timolol have generally demonstrated that latanoprost 0.005% given once daily produces better reductions in IOP than timolol 0.5% given twice daily. Camras and the United States Latanoprost Study Group (1996) examined 268 patients who received either latanoprost 0.005% once daily or timolol 0.5% twice daily for 6 months and found that latanoprost 0.005% produced a mean IOP reduction of 6.7 mmHg from baseline diurnal IOP values compared with 4.9 mmHg with timolol 0.5% ($P<0.001$). Alm et al (1995) also showed that latanoprost 0.005% given in the evening was better than timolol 0.5% twice daily at reducing IOP. Watson et al (1996) showed that latanoprost 0.005% given once daily in the evening reduced IOP at least as well as timolol 0.5% given twice daily.

A pooled data analysis of the 6-month data from these three randomized, double-masked comparative studies ($n=829$) found that latanoprost reduced diurnal IOP to a significantly greater extent than timolol (7.7 mmHg compared with 6.5 mmHg; $P<0.001$). Furthermore, a greater proportion of patients receiving timolol experienced tachyphylaxis than those receiving latanoprost (30% of timolol patients who originally experienced an IOP reduction of 4.0–5.9 mmHg failed to reach an IOP reduction of 4.0 mmHg at 6 months compared with 14% for latanoprost) (Hedman and Alm, 2000). This analysis suggests that latanoprost has significantly greater effects on IOP than timolol after 6 months of therapy.

Although this pooled data analysis did not examine the incidence and degree of conjunctival hyperaemia, data from the three original studies demonstrate that latanoprost treatment was associated with a higher incidence and degree of hyperaemia than timolol, but with both agents, the extent of hyperaemia was mild (Alm et al, 1995; Camras et al, 1996; Watson et al, 1996). In the study by Alm et al, latanoprost produced hyperaemia in 31.4% of cases compared with 15.9% of cases in the timolol group. The most significant ocular side effect occurring with latanoprost was increased pigmentation of the iris, particularly in patients with mixed iris colour. This side effect appears to be based on the ability of prostaglandins to stimulate melanin formation in melanocytes rather than any proliferative effect on the iridal melanocytes themselves (Bito, 2001; Stjernschantz, 2001).

Comparative studies with timolol have shown that travoprost, as with latanoprost, can produce significantly greater falls in IOP. In a 9-month study ($n=573$), in which travoprost 0.004% once daily was compared with timolol 0.5% twice daily, mean IOP was consistently lower with travoprost therapy than timolol therapy (Goldberg et al, 2001). The difference in mean IOP, pooled across all visits, was significantly in favour of travoprost at 9.00 am (0.7 mmHg; $P=0.0246$), 11.00 am (0.9 mmHg; $P=0.0039$) and 4.00 pm (1.2 mmHg; $P=0.0004$). The mean IOP after treatment with travoprost 0.004% was always lower than after treatment with timolol, statistically significantly lower at 11 of 15 visits. The statistically significant differences in mean IOP ranged from 0.7–1.4 mmHg. The mean decreases from baseline IOP were significantly greater ($P<0.0001$) with travoprost (range 8.0–8.9 mmHg) than with timolol (6.3–7.9 mmHg). In the same study, more patients developed hyperaemia in the travoprost group (32.5%) than in the timolol group (7%). Eyelash changes were also more common with travoprost (76.2% *vs* 3.2%). Iris pigmentation changes occurred in 3.6% of the travoprost group but none of the timolol group.

The efficacy and safety of the prostamide bimatoprost has been compared with timolol in three studies (Brandt et al, 2001; Laibovitz et al, 2001; Sherwood et al, 2001). Both the 6-month study of Sherwood et al (2001), which recruited 1198 patients with elevated IOP, and the 3-month study of Brandt et al (2001), which recruited 596 patients, demonstrated that therapy

with bimatoprost 0.03% once daily was associated with a significantly greater reduction in IOP compared with timolol 0.5% twice daily (8.1 mmHg for bimatoprost *vs* 5.6 mmHg for timolol at 6 months, $P<0.001$ and 9.2 mmHg for bimatoprost *vs* 6.7 mmHg for timolol at 3 months, $P<0.001$). In addition, more patients reached lower target pressures with bimatoprost. Bimatoprost therapy was associated with higher rates of conjunctival hyperaemia (31.2% *vs* 7.9%, $P<0.001$) (although this was mild in most cases), eyelash growth (35.7% *vs* 3.7%, $P<0.001$) and increased iris pigmentation (1.1% *vs* 0%) than timolol (Sherwood et al, 2001).

COMBINATIONS OF A PROSTAGLANDIN ANALOGUE AND BETA-BLOCKER

A recent double-masked study has examined the efficacy and safety of a single preparation containing both latanoprost 0.005% and timolol 0.5% (Higginbotham et al, 2002). A total of 418 subjects were randomized to treatment with timolol twice daily, latanoprost once daily or latanoprost and timolol once daily combined as a single preparation, following a 2–4-week run-in period with twice-daily timolol. At 6 months, the combination agent produced a greater IOP reduction than either agent alone, producing a 1 mmHg greater reduction in IOP than latanoprost ($P<0.005$) and a 2.9 mmHg greater reduction in IOP than timolol ($P<0.001$). There was no statistically significant difference between the combination agent and latanoprost in the number of patients achieving a target IOP of <18 mmHg or <21 mmHg.

RELATIVE CLINICAL PERFORMANCE OF PROSTAGLANDINS AND PROSTAMIDES

The activity of travoprost and latanoprost has been compared in a large-scale, randomized, multicentre, double-blind study involving 801 patients with open-angle glaucoma or ocular hypertension (Netland et al, 2001). Travoprost 0.004% was compared with latanoprost 0.005% (both given once daily) and timolol 0.5% (given twice daily). Treatment lasted for 12 months. Both travoprost and latanoprost produced significantly lower mean IOPs than timolol at all time points. Travoprost 0.004% produced lower mean IOPs than latanoprost at 13 of 18 assessment times, significantly lower at two of the time points at week two. The difference in IOP for all visits (pooled) between travoprost 0.004% and latanoprost was statistically significant at the 4.00 pm time point (0.8 mmHg lower than latanoprost). This was the furthest time point from dosing, when any effect reaches a trough.

The frequency of iris pigmentation changes was similar for latanoprost and travoprost (5% for latanoprost and 3.1% for travoprost). More patients experienced a clinically significant change from baseline in ocular hyperaemia on travoprost 0.004% than latanoprost (49.5% compared with 27.6%). However, the average ocular hyperaemia score was less than 1 on a scale of 0–3 for all treatment groups, indicating that it rarely exceeded levels judged as 'trace to mild' and did not interfere with treatment. Eyelash changes occurred in 57.1% of the travoprost group and 25.8% of the latanoprost group, but patient complaints related to this were minimal.

The percentage of patients considered as responders to treatment was assessed using criteria of an IOP reduction from diurnal baseline of ≥30% or a final IOP of ≤17 mmHg. In total 54.7% of travoprost-treated patients, 49.6% of latanoprost-treated patients and 39% of timolol-treated patients were classified as responders. The differences in response rates between the travoprost, latanoprost and timolol groups were statistically significant ($P\leq0.043$ and $P\leq0.001$ respectively). Non-responders to treatment were considered to be those patients with a decrease in IOP of ≤3 mmHg, 20 hours post-dose. When data were pooled across visits and times, the non-responder rates were 8.6% for travoprost, 13.5% for latanoprost and 22.5% for timolol.

The efficacy of bimatoprost in comparison with latanoprost has been investigated in two short-term studies (DuBiner et al, 2001; Gandolfi et al, 2001) and one 6-month trial (Noecker et al, 2003). In the larger of the two short-term studies, which recruited 232 patients, therapy with bimatoprost 0.03% once daily was associated with a consistently lower mean IOP than latanoprost 0.005% once daily, although the between-group difference was not always statistically significant. More patients achieved a lower target IOP with bimatoprost ($P<0.006$) (Gandolfi et al, 2001). In the longer-term study, involving 269 patients, mean change from baseline IOP was significantly greater with bimatoprost than latanoprost at all assessment points (P values ranging from <0.001 to <0.049). The percentage of patients achieving target pressures ranging from ≤13 mmHg to ≤20 mmHg was always greater with bimatoprost treatment and statistical significance was reached at many points. The responder rate, defined as patients who achieved a reduction in IOP of at least 20% at 6 months, ranged from 69 to 82% in the bimatoprost group and 50 to 62% in the latanoprost group. Bimatoprost therapy was associated with a significantly greater rate of

hyperaemia than latanoprost (55.4% *vs* 42.5%), and eyelash growth was also more common with bimatoprost. There was only one reported case of increased iris pigmentation in the bimatoprost group (Noecker et al, 2003).

There have been no published direct comparisons of bimatoprost with travoprost.

These results indicate that these newer agents are among the most effective molecules currently available for reduction and diurnal control of IOP. Once-daily dosing and the relative absence of significant systemic side effects, in comparison with topical beta-blockers (Atkins et al, 1985; Diggory et al, 1994), will help in the rapid acceptance of these agents by ophthalmologists.

STABILITY

Another challenge facing the formulators of prostaglandin analogues in eye drop form is their stability. Latanoprost ophthalmic solution has been shown to be susceptible to degradation at high temperatures (≥50 °C) and in the presence of ultraviolet light, even for short periods of time (Morgan et al, 2001). Therefore, it is generally recommended that latanoprost ophthalmic solution is refrigerated before opening and protected from light. In contrast, travoprost has been found to be physically and chemically stable over a broad range of temperatures and upon exposure to light, so refrigerated storage is not required (Kondor, 2001). Bimatoprost does not require refrigeration. This difference is unlikely to be clinically significant if correct storage precautions are followed.

CONCLUSIONS

Newer topical agents such as the prostaglandin analogues and the prostamide bimatoprost are gradually replacing beta-blockers as the first-line medical treatment for glaucoma. They provide the benefits of improved diurnal control of IOP, coupled with once-daily dosing and a good systemic side-effect profile. Unusual ocular side effects, such as iris colour changes, do not seem to be of significant clinical concern.

The availability of these new agents has increased the number of glaucoma patients who can initially be controlled on acceptable medical therapy and this is one factor that is having an impact on the demand for glaucoma surgery. Latanoprost is the most commonly used prostaglandin analogue currently in use but research is continuing to find even more potent ocular hypotensive therapies. Newer prostaglandin analogues, such as travoprost, can be differentiated from the earlier agent latanoprost in terms of their potency and selectivity at the FP receptor and their stability profile. The prostamide bimatoprost also appears to have promising effects on IOP profile and further studies will undoubtedly focus on comparisons between these newer agents. HM

Conflict of interest: Mr Cunliffe is currently conducting research for Allergan, Pharmacia and Alcon Laboratories.

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KEY POINTS

- Treatment of primary open angle glaucoma is targeted at reducing the intraocular pressure (IOP).
- The rates of glaucoma surgery (trabeculectomy) have fallen dramatically in the UK in recent years against a background of a general increase in ophthalmic surgery.
- This decrease can be explained, at least in part, by the introduction of a new set of topical agents.
- The first prostaglandin released, latanoprost 0.005%, appears to be associated with a greater degree of IOP control than the reference ophthalmic beta-blocker therapy, timolol 0.5%.
- Two new agents have recently been released, the prostaglandin analogue travoprost 0.004% and the prostamide bimatoprost 0.03%, and early results suggest they may have potential benefits over latanoprost 0.005%.

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