Medical treatment of glaucoma

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Recent developments in the medical management of glaucoma are reviewed for the period of October 1989 through September 1990. Topics discussed include: the protection afforded by β-adrenergic antagonists against the progression of glaucomatous damage; new studies demonstrating the efficacy of topically active carbonic anhydrase inhibitors; the efficacy and mechanisms of action of new formulations of topically administered prostaglandins; the vascular actions and consequent potential concerns as well as benefits of β-adrenergic antagonists, of calcium channel blockers, and of α_2-adrenergic agonists; and possible new horizons in the medical therapy of glaucoma arising from the study of angiotensin converting enzyme inhibitors and atrial natriuretic peptides.

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β-Adrenergic antagonists

A major management dilemma exists over the question of when, and indeed whether, to begin therapy in patients exhibiting moderate elevation of intraocular pressure (IOP) but who have neither optic nervehead nor visual field abnormalities. Moreover, does pharmacologic reduction of IOP retard the progression of such damage? In an earlier randomized study of the effect of long-term IOP reduction by timolol compared with no treatment in 143 patients with ocular hypertension (OHT) but without visual field loss, it was noted that the number of patients who developed visual field defects or optic disk changes was virtually identical in the treated and the untreated groups [1]. However, two important recent publications have sought to provide evidence that the use of β-adrenergic blocking drugs to reduce IOP in such patients may indeed retard the advent of glaucomatous damage. This issue has taken on new significance because substantial loss of retinal ganglion cell axons may precede measurable disk or field pathology [2]. It appears that, at least for selected patients, acting *in advance* of demonstrable disk or field defects may be beneficial.

Kass *et al.* [3••] carried out a randomized, double-masked, prospective long-term clinical trial to determine whether topical timolol therapy is effective in delaying the onset of disk or visual field abnormalities in patients with OHT. Sixty-two patients with bilateral IOPs between 24 and 35 mm Hg were treated in one eye, chosen at random, with timolol 0.25% and with placebo in the other eye. If an eye showed IOP greater than 20 mm Hg after treatment, the bottle was changed; in the case of the timolol-treated eye, the concentration was increased to 0.5%. Because of selection criteria, enrolled patients had a higher than normal vertical cup:disk ratio (average, 0.48), unusually low outflow facility (0.12 μL/min/mm Hg), and a very high incidence of family history of glaucoma (52%), of diabetes (21%), and of exfoliation syndrome (6.4%). Cases were followed until visual field loss could be repeatedly detected in either eye. The development of optic nervehead changes, as judged from stereo photographs, was noted, but participation in the trial was not altered by this development. IOP was not used as an endpoint in the study. Cases not showing either of these changes were followed for a minimum of 5 years, and some for as long as 8 years. Forty-three of the original 62 patients completed the minimum 5 years of follow-up or developed visual field loss. As expected, timolol therapy significantly lowered IOP in the timolol-treated eye relative to the placebo-treated eye. Reproducible visual field loss occurred in 4 timolol-treated eyes and in 10 placebo-treated eyes, a significant difference. Cupping of the disk occurred in 4 timolol-treated eyes, and 8 placebo-treated eyes, a difference not statistically significant. Optic disk pallor was quantitatively assessed from photographs using a computerized image analysis system; all cases followed for 4 years or more had disk images compared against baseline photographs. The increase in pallor in timolol-treated eyes was 0.86% and in the placebo-treated eyes was 1.80%, a significant difference. The study thus shows a protective ef-

Abbreviations

ACE—angiotensin converting enzyme; **CAI**—carbonic anhydrase inhibitor; **IOP**—intraocular pressure; **OHT**—ocular hypertension; **$PGF_{2\alpha}$**—prostaglandin $F_{2\alpha}$; **$PGF_{2\alpha}$-IE**—prostaglandin $F_{2\alpha}$-1-isopropylester; **POAG**—primary open-angle glaucoma.

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fect of timolol therapy in patients with high IOPs and, as a group, a greater than usual number of risk factors for development of glaucoma. The authors refrain from providing a risk factor analysis, however, owing to the small sample size and low rate of progression to glaucoma.

In a second study on this important topic, Epstein *et al.* [4••] conducted a prospective randomized trial in which 107 patients with IOP between 22 and 28 mm Hg, but neither disk abnormalities nor Goldmann visual field defects, were either treated with timolol 0.5% twice daily or merely followed without any treatment. The cases were followed for an average of 4.5 years, and were considered to have "failed" the chosen course of management if they exhibited either IOP greater than 32 mm Hg on two occasions, disk changes (judged in a masked fashion from stereo photos), or visual field progression. Timolol treatment significantly reduced IOP. During the cumulative follow-up period, 17 of 54 patients (31%) who were untreated "failed" (*ie*, developed glaucoma), whereas 9 of 53 patients (14%) being treated with timolol "failed." However, of the 9 treated "failures," 6 had actually discontinued treatment before failure. The difference between the survival curves of the two groups was significant, indicating a protective effect of timolol. However, when failures were defined only by disk and field criteria, the difference between the survival curves was not significant unless patients who stopped timolol were considered to be immediately lost to follow-up.

Other interesting observations were that average baseline IOP did not statistically predict failure in either group. However, baseline IOP asymmetry between eyes of at least 3 mm Hg, baseline facility of outflow of 0.12 μL/min/mm Hg or less, and baseline cup:disk ratio of 0.5 or greater all were strong risk factors for failure. The authors conclude that for patients with moderate elevation of IOP but no signs of damage, timolol therapy is beneficial.

The aforementioned studies have examined the use of only timolol and their results are not fully consistent. Clearly, more prospective trials will be necessary to determine whether each of the classes of ocular hypotensive agents deters glaucomatous damage and when in the course of disease to commence such therapy.

Betaxolol, a cardioselective β-adrenergic blocking agent, previously available only as the 0.5% solution, offers the advantage of producing fewer systemic side effects compared with the nonselective β-blockers, but unfortunately appears to be less efficacious in reducing IOP than the latter drugs. A new suspension of betaxolol, in which the drug is delivered in a vehicle of 5 μ polymer resin beads, is available in a 0.25% concentration. It has now been reported that the two formulations of betaxolol are equally efficacious, and that the 0.25% suspension is better tolerated as an ocular medication.

Weinreb *et al.* [5•] published a multicenter, double-masked, prospective, randomized comparison of the effects on IOP of 0.5% betaxolol solution and 0.25% betaxolol suspension. There was no placebo control. Subjects included 352 patients with primary open-angle glaucoma (POAG) or OHT. All subjects were either unmedicated or were receiving a single ocular hypotensive medication prior to enrollment, and, if medicated, all underwent satisfactory washout before beginning the study. All patients had a baseline morning IOP, after washout, of at least 24 mm Hg in at least one eye. The patients took one of the two formulations twice daily for 3 months, and IOP was recorded at 2 weeks, and at 1, 2, and 3 months. There was no significant difference between the two groups at any of the times IOP was measured. Baseline IOP at 8 AM was 26.0 mm Hg for both groups. After 3 months, an identical reduction of IOP of 14% was found in both groups of patients with measurements taken at 8 AM. At 4 PM the 0.25% betaxolol suspension group showed a 19.7% reduction of IOP, compared with a 17.6% reduction in the 0.5% betaxolol solution group. Regarding side effects, 13% of the patients in the 0.25% betaxolol suspension group reported burning or stinging, while 37% in the 0.5% betaxolol solution group reported these symptoms. This difference was significant. No other ocular side effect occurred with a significantly different incidence in the two groups.

A comparison of the 0.25% suspension and 0.5% solution of betaxolol with respect to exercise-induced pulse changes, pulmonary function, and other systemic side effects would be of interest as the suspension might have enhanced ocular bioavailability, accounting for an equivalent effect on IOP and a reduction of systemic side effects. Nevertheless, fewer complaints of burning or stinging should improve compliance and would seem an important consideration.

Topically active carbonic anhydrase inhibitors

Systemically administered carbonic anhydrase inhibitors (CAIs) are frequently limited in their utility by adverse side effects such as malaise, paresthesias, and gastrointestinal disturbances. In addition, there are risks of associated nephrolithiasis, blood dyscrasia, hepatic encephalopathy, and teratogenicity. Therefore, the recent development and forthcoming introduction of effective, topically given CAIs are events of therapeutic significance in the treatment of glaucoma. Three topical formulations are currently being tested in clinical studies: MK-927, MK-417, and L-671,152, also known as MK-507. All are thieno-(2,3-b)-thiopyran-2-sulfonamide derivatives. MK-417 is the S-enantiomer of the racemic mixture MK-927. MK-507, an analogue of MK-927, is a more potent inhibitor of human erythrocyte carbonic anhydrase II, and is now regarded as the likeliest of these to be released for approved use in humans. Here we discuss only publications in refereed journals, but the interested reader should know that published abstracts reflect current activity in this

rapidly developing field more closely than do journal articles. Table 1 summarizes the results of recent unpublished studies of topical CAIs; useful recent reviews with discussion of abstracts include those by Higginbotham [6] and by Serle and Podos [7].

Pfeiffer *et al.* [8•] reported a single-dose trial of MK-927 in 24 patients with bilateral OHT or POAG. The study was a double-masked, placebo-controlled, randomized, prospective trial in which one eye was treated with 2% MK-927, the other with placebo. All patients underwent satisfactory washout periods of previous ocular medications. The single dosage, given at 10 AM, caused a significant reduction in IOP as early as 1 hour after administration; IOP remained depressed for 8 hours, the duration of the study. Comparing a prestudy diurnal curve and the day-of-treatment diurnal curve, there was a significant difference in the mean IOP of eyes treated with MK-927 at all times. Taking diurnal fluctuation into account, the peak reduction of IOP produced by MK-927 was 7.5 mm Hg (27%), down from a pretreatment baseline of 27.5 mm Hg. The peak lowering occurred 4.5 hours after administration. Placebo caused a peak reduction of 1.4 mm Hg 1 hour after administration. Eight hours after topical application of MK-927, the reduction of IOP was 3.7 mm Hg (14%). Side effects were minimal and were not notably different between the two eyes.

Higginbotham *et al.* [9••] also examined single-dose response to MK-927, but compared placebo with three concentrations of drug: 0.5%, 1.0%, and 2.0%. The study was double-masked, randomized, prospective, and placebo controlled, and utilized a four-period crossover design in which, on 4 different treatment days, one eye of 24 patients with POAG or OHT was treated with a single drop of one of the three drug concentrations or with placebo. The other eye was treated with placebo. Suitable washout of previous ocular medications and experimental drops was undertaken between each phase of the study. IOP was measured at various times for one full day after administration. Taking diurnal fluctuation into account, compared with placebo the 0.5% concentration was statistically ineffective in reducing IOP. The 1.0% drops, however, significantly reduced IOP for up to 6 hours after administration, and the 2.0% drops did so for up to 8 hours. None of the three concentrations produced a statistically significant reduction of IOP as compared with placebo at 12 or 24 hours. IOP reduction following administration of 2% MK-927 was significantly greater than that following treatment with 0.5% MK-927 at all hours up to 8 hours after dosing. Differences between other pairwise comparisons of doses were significant only at occasional times, and nonsystematically. Diurnal fluctuation and placebo effect were considerable compared with the drug effect. For example, at 6 hours after administration, at which time the 2.0% concentration exerted diurnally corrected maximum effect, IOP fell 14% after placebo was given, 14% after the 0.5%

Drug	Study	Subjects	Results
MK-927 vs timolol	Serle *et al.**	OHT	bid, 6 wk; both effective, MK-927 less so; no long-term side effects
MK-417	Airaksinen *et al.*†	POAG, OHT	tid, 2 wk; reduces intraocular pressure
MK-417	Greve *et al.*†	POAG, OHT	bid, 2 wk; additive to timolol
MK-417	Nakajima *et al.*‡	POAG, OHT	bid vs tid, 1 wk; tid more effective
MK-417	Lippa *et al.*§	POAG, OHT	tid vs timolol bid, 4 d; timolol slightly more effective
MK-507	Hofman *et al.*‡	Normal human	3 drops; reduces intraocular pressure
MK-507	Lippa *et al.*‡	POAG, OHT	3 drops, 36 h; reduces intraocular pressure
MK-507	Wang *et al.*¶	Normal monkey	1 drop; intraocular pressure reduced, facility unaffected, aqueous flow reduced
MK-507	Sugrue *et al.***	Glaucoma monkey	1 drop; 2% equals efficacy of timolol 0.5%; 4% extends duration
MK-507 vs MK-417	Bourgeois *et al.*††	POAG, OHT	bid 6 d; equally effective
MK-507 vs MK-417	Weinreb *et al.**	POAG, OHT	Also bid vs tid; MK-507 tid slightly more effective

*Serle *et al.*, and Weinreb *et al.*, Papers presented at the American Academy of Ophthalmology Annual Meeting, Atlanta 1990; †Airaksinen *et al.*, and Greve *et al.*, Papers presented at the meeting of the Glaucoma Society of the International Congress of Ophthalmology, Bali, 1990; ‡Nakajima *et al.*, Hofman *et al.*, and Lippa *et al.*, Papers presented at the Glaucoma Symposium, International Congress of Ophthalmology, Singapore, 1990. §Lippa *et al.*, *Invest Ophthalmol Vis Sci* 1990, 31(suppl):232; ¶Wang *et al.*, *Invest Ophthalmol Vis Sci* 1990, 31(suppl):149; **Sugrue *et al.*, *Invest Ophthalmol Vis Sci* 1990, 31(suppl):232. ††Bourgeois *et al.*, *Invest Ophthalmol Vis Sci* 1990, 31(suppl):233.
OHT—ocular hypertension; POAG—primary open-angle glaucoma.

Table 1. Recent unpublished studies of topical carbonic anhydrase inhibitors. Summary of results of clinically important recent studies available to date in abstract form only. (*Modified from* Serle and Podos [7]; with permission.)

dose, 21% after the 1.0% dose, and 25% after the 2.0% dose. Reported side effects were minimal, and were not significantly different between placebo- and drug-treated groups.

Diestelhorst *et al.* [10•] compared the efficacy of the racemic mixture MK-927 with MK-417, the S-enantiomer of MK-927. Both drugs were tested at 1.0% concentrations, and were compared with placebo in a double-masked, prospective, randomized trial with crossover design. Twenty-seven patients with either OHT or POAG in both eyes were studied. Washout of all ocular medications was undertaken. Morning IOP was 23 mm Hg or greater in all enrolled subjects. A single drop of drug or placebo was given; IOP was monitored up to 8 hours after administration. MK-417 caused a fall of IOP from a pretreatment mean of about 27 mm Hg to about 21 mm Hg (20%) 2 hours after treatment, and to 20 mm Hg (24%) at 6 hours after treatment. The effect of MK-417 was slightly (about 1 mm Hg) greater than that of MK-927 at all times tested.

Wang *et al.* [11••] tested L-671,152, now also known as MK-507, in monkey eyes having experimental argon laser–induced glaucoma. IOP was measured diurnally for 1 day prior to treatment, then for 2 days with vehicle only given twice a day, and then either for 1 day with one drop of 0.5% MK-507, for 1 day with one drop of 1.0% MK-507, or for 5 days with twice-daily 2% MK-507. Single-dose 0.5% MK-507 significantly reduced IOP for up to 5 hours, with peak effect from 2 to 4 hours after administration, lowering IOP 17% from a mean baseline of 30 mm Hg. Single-dose 1.0% MK-507 also significantly reduced IOP, with peak effect at 3 hours after dosing, IOP being lowered 33% from a mean of 33 mm Hg. Twice-daily 2% MK-507 for 5 days significantly reduced IOP for up to 8 hours after the first dose was given, continued to do so for at least 16 hours after the second dose, and had maximum effect between 2 and 5 hours after each dose. On day 5, for example, IOP was lowered from 30 to 20 mm Hg (a decrease of 33%). There was a trend toward greater reduction in IOP from day 1 to day 5 at each point on the diurnal curve. Thus, all three concentrations were effective; 1.0% and 2.0% concentrations were not significantly different. The duration of effect of MK-507 appeared to be greater than that of MK-927 reported in similar previous studies.

Sugrue *et al.* [12••] conducted a comparison of MK-927 and MK-507 (L-671,152) in glaucomatous monkey eyes. Baseline IOP was recorded 3 days prior to single-drop treatment with either 2% MK-927 or 2% MK-507 or vehicle. IOP was recorded hourly for 6 hours. After treatment with MK-507, IOP was maximally reduced after 5 hours from a mean IOP of 37 to 23 mm Hg (a decrease of 37%). The maximal effect after MK-927 dosing occurred at 4 hours, with IOP changing 27% from a baseline of 37 mm Hg. The mean decline in IOP after 6 hours was 13.5 mm Hg for MK-507 and 6.4 mm Hg for MK-927. IOP reduction was significantly greater from 2 hours up to 6 hours after treatment with MK-507 as compared with treatment with MK-927.

These results are significant and extremely promising. The greater duration of action, and the efficacy at lower concentration, of MK-507 seem to make this compound the currently favored candidate for human clinical use. The first trials of MK-507 in humans have been presented and published in abstract (Table 1).

Prostaglandins

The major ocular hypotensive mechanism of action of prostaglandins is thought to be increased uveoscleral outflow, a conclusion based on studies of the monkey eye. Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and one of its congeners have been shown to reduce IOP in normal humans and in glaucoma patients. Theoretically, the prostanoids may be especially useful in conditions in which the major route remaining for aqueous humor egress is uveoscleral outflow, such as glaucoma secondary to peripheral anterior synechiae, in which the conventional outflow channels are blocked. In earlier studies of $PGF_{2\alpha}$ tromethamine salt, the ocular hypotensive effect is reported to require dosages as great as 62.5 μg [13] causing significant side effects such as headache, burning, and hyperemia. Prostaglandin $F_{2\alpha}$-1-isopropylester ($PGF_{2\alpha}$-IE), however, is a lipophilic prodrug that penetrates the cornea well and is effective at far lower concentrations while causing fewer local side effects.

The efficacy of $PGF_{2\alpha}$-IE was demonstrated in patients with OHT and POAG. Camras *et al.* [14••] performed a randomized, double-masked, placebo-controlled, prospective study in which the ocular hypotensive effects of either 0.25 or 0.5 μg of $PGF_{2\alpha}$-IE was compared with vehicle alone in the contralateral, control eyes (Fig. 1). Drops were given twice daily to one eye of each of the subjects, who were taking no concurrent medications. After 8 days of treatment there was a significant dose-dependent reduction in IOP. Beginning 4 hours after the 1st dose (for 0.5 μg), and lasting at least 12 hours after the 14th dose (for both concentrations), IOP for both concentrations was 4 to 6 mm Hg lower than baseline or contralateral control values. Mean tonographic outflow facility was significantly increased only after treatment with 0.5 μg. However, outflow facility increased by too small of an amount to account for the reduction in IOP, implying (coupled with earlier evidence that $PGF_{2\alpha}$ has no effect on aqueous flow) that the main effect was on uveoscleral outflow. Some patients reported mild foreign body sensation or mild transient headache. Photographic grading of hyperemia showed a mild dose-dependent effect that resolved less than 12 hours after treatment. There was no effect on visual acuity, accommodative amplitude, pupil size, anterior chamber inflammation, or blood pressure.

Villumsen *et al.* [15•] also reported that $PGF_{2\alpha}$-IE reduces IOP in glaucoma patients, many of whom had

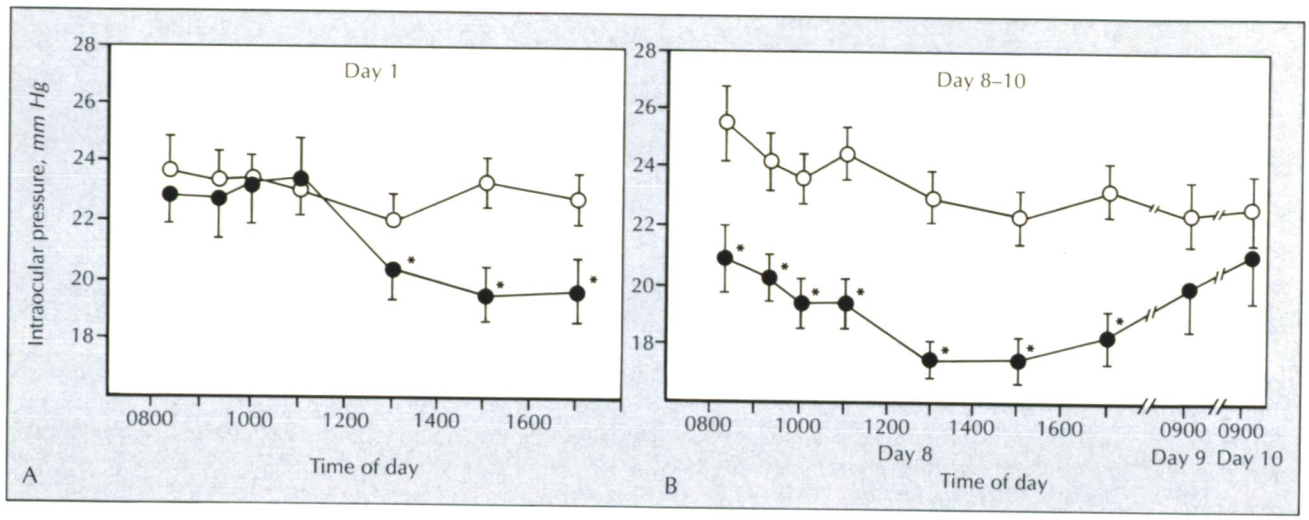

Fig. 1. A, Effects on IOP of a single 0.50-μg dose of $PGF_{2\alpha}$-IE (*closed circles*) to one eye and its vehicle (*open circles*) to the contralateral control eye of 13 OHT or glaucoma patients. **B,** Effects on IOP just before and after the last (15th consecutive) 0.50 μg dose of $PGF_{2\alpha}$-IE (*closed circles*) and its vehicle (*open circles*) given twice daily for 8 days to 13 OHT or glaucoma patients. Measurements at 8:30 AM on day 8, on day 9, and on day 10 were made 11.5, 24, and 48 hours, respectively, after the previous dose. *Circles* represent means, and the *bars* represent ± 1 SEM. *Asterisks* indicate measurements in which the treated eye and the control eye were significantly different ($p < 0.05$) from one another using a two-tailed, paired *t*-test. (*From* Camras *et al.* [14••]; with permission.)

pseudoexfoliation syndrome. They conducted an unmasked, open-label prospective study in which 30 patients with previously untreated open-angle glaucoma had one eye treated twice, 12 hours apart, on one day, with 0.5 μg of $PGF_{2\alpha}$-IE. Ten of the patients who were found to be good responders to treatment were selected for further testing, in the same fashion, for 6 additional days. The reduction of IOP was calculated as the difference in change from baseline diurnal IOP levels between the treated and the untreated eye. A highly significant drug-related reduction in IOP, from a daily mean of approximately 31 mm Hg, was noted beginning 4 hours after therapy. The mean reduction was 2.7 mm Hg (9%) 4 hours after the first dose was given, and increased steadily to 5.8 mm Hg (19%) by 12 hours after the second dose. In the subgroup that was treated for 1 week, the reduction of IOP was more marked after the 7th day of treatment (7.6 mm Hg 12 hours after the 14th and final dose) than after the first day (4.3 mm Hg 12 hours after the second dose). Slight to moderate conjunctival hyperemia was observed in most patients 30 minutes after administration; this mostly disappeared 3 to 4 hours later. Cells or flare were not observed. Slight to moderate foreign body sensation was experienced for up to 1 hour by about half the patients. No systemic symptoms were reported.

As prostaglandins appear to lower IOP by increasing uveoscleral outflow [21•,22•,23••], pilocarpine, which is known to decrease uveoscleral flow, may not have an additive effect on IOP reduction. In fact, the ocular hypotensive effect of $PGF_{2\alpha}$ has been shown to be antagonized by pilocarpine in monkeys [16]. However, β-adrenergic blockers, which lower IOP by reducing aqueous production, a physiologically independent action, are a promising class of compounds for combined therapy with prostaglandins.

Villumsen and Alm [17••] studied the additivity of 0.5 μg $PGF_{2\alpha}$-IE to timolol 0.5% in eyes of glaucoma patients with uncontrolled IOP. They conducted a randomized, masked, placebo-controlled, prospective study in 30 patients with POAG. Patients having an IOP in one eye of at least 22 mm Hg despite treatment with timolol 0.5% given twice a day received either 0.5 μg $PGF_{2\alpha}$-IE or placebo in addition to the timolol. Both agents were administered twice daily for 1 week. Concealment of group assignment from the experimenter was impossible, because some patients developed conjunctival hyperemia associated with use of $PGF_{2\alpha}$-IE, but bias was reduced by having the tonometer scale concealed from the examiner and read by a naive assistant. IOP was lower following treatment with $PGF_{2\alpha}$-IE after one day. After 1 week, IOP was reduced 4.5 mm Hg from the timolol baseline (17.4%) in eyes treated with timolol plus prostaglandin, while IOP was unaltered in the group receiving timolol plus placebo. All eyes treated with $PGF_{2\alpha}$-IE, but none in the placebo group, experienced conjunctival or episcleral hyperemia. Thirteen of 15 patients in the $PGF_{2\alpha}$-IE group reported foreign body sensation, compared with none in the placebo group. No other differences in side effects or symptoms were observed. Neither adverse reaction was severe enough to cause any patient to discontinue the study. The effect of $PGF_{2\alpha}$-IE appeared completely additive to that of timolol, since in a previous study by the same authors [15•], 0.5 μg $PGF_{2\alpha}$-IE applied twice daily for 1 week reduced IOP by 19%. Further studies must concentrate on the reduction of side effects by alteration of the prostanoid congener or its formulation, which alteration could also result in increased efficacy.

The fate of prostaglandins after topical administration in humans is still unclear. The rabbit eye lacks the ability to metabolize $PGF_{2\alpha}$. However, important differences in the response to prostanoids between rabbit and human make studies of rabbit metabolism of $PGF_{2\alpha}$ suggestive at best [18]. Cheng-Bennett *et al.* [19•] have now shown that iris-ciliary body homogenate of the human eye similarly fails to degrade this compound utilizing *in vitro* incubation and assaying radiolabeled $PGF_{2\alpha}$ with high-performance liquid chromatography. They also report that rabbit lung homogenate does cause time-dependent reduction in concentration of $PGF_{2\alpha}$. The significance of these results is that ocular selectivity of the action of $PGF_{2\alpha}$ may be enhanced because it remains unaltered in the eye and is degraded when it reaches the lungs and perhaps other tissues. This study also supports the idea that $PGF_{2\alpha}$ lowers IOP by acting directly on ocular tissue and not through a metabolic by-product.

The ocular site of action of $PGF_{2\alpha}$-like compounds remains unknown. Woodward *et al.* [20•] have suggested that the ocular hypotensive effect of $PGF_{2\alpha}$ is not related to the FP–receptor in rabbits or cats, the currently recognized receptor for this prostaglandin. The cat iris sphincter is a classic model for the study of the FP–receptor. In this study, the rank-order of potency of $PGF_{2\alpha}$ analogues for decreasing IOP in rabbits and cats correlates negatively with the rank order of potency for cat iris sphincter contraction. For example, they report that the potent and selective FP–receptor agonist fluprostenol was highly effective in causing sphincter contraction, but inactive in altering IOP. The authors conclude that a different receptor or mechanism of action must exist. A problem with the study is that the effect of different compounds on reduction of IOP and on the iris sphincter is confounded with possible differences in *in vivo* bioavailability at different sites.

As mentioned, increased uveoscleral outflow is the apparent mechanism of ocular hypotensive action of prostaglandins, and evidence for this hypothesis continues to accumulate. Gabelt and Kaufman [21•] studied cynomolgus monkey eyes treated with $PGF_{2\alpha}$-IE. They measured trabecular facility by monitoring flow into the general circulation of intraocular perfusate containing radioactive label. Because fluid leaving the anterior chamber via the trabecular pathway enters the general circulation almost immediately, whereas fluid leaving via the uveoscleral pathway requires several hours to penetrate periocular tissues and reach the general circulation, the facility calculated from isotope accumulation over an initial short period essentially reflects trabecular outflow only.

They simultaneously measured gross or total facility of outflow by measuring overall flow into the intact eye from an external reservoir at two different IOPs (15 and 24 mm Hg). Total outflow facility following 5 days of twice-daily $PGF_{2\alpha}$-IE was 40% to 60% greater in treated than in control eyes, whereas conventional (trabecular) outflow facility was unaffected by treatment. The results are somewhat mitigated by high variability of the measurements, and the interpretation of the study is limited by the possibility of changes of pseudofacility (the IOP–dependence of aqueous formation) or of ocular volume in addition to increased uveoscleral outflow. Nevertheless, considered with previous studies on outflow and aqueous production, it appears that the action of prostaglandins is primarily on uveoscleral outflow rather than on the conventional outflow pathway in monkeys.

A similar study was reported by Nilsson *et al.* [22•], who measured the effects of a single dose of $PGF_{2\alpha}$-IE on the IOP, aqueous humor flow, conventional outflow, and uveoscleral outflow of normal cynomolgus monkeys. The eyes of 27 monkeys were triple cannulated; one cannula was used for IOP transduction and the other two for pumped extrusion of aqueous, mixture with radioactively labeled albumin, and reperfusion of the mixture into the eye. Detection of radioactivity in the mixture was used to calculate the dilution of radioactivity and therefore the rate of aqueous formation. Radioactivity was simultaneously measured in blood samples. Because (as mentioned) initial plasma radioactivity can be assumed to have left the eye via the conventional outflow pathway, this measure was used to calculate conventional outflow rate. The difference between aqueous formation and conventional outflow was then considered to represent uveoscleral outflow. These parameters were monitored for 4 hours after administration. They found that 1 µg of $PGF_{2\alpha}$-IE did not alter blood pressure but did reduce IOP by a maximum of 2.9 mm Hg as compared with the vehicle-treated control eye 3 hours after treatment. Mean aqueous humor flow was slightly higher in the experimental eye than the control eye. Mean conventional or trabecular outflow was actually *lower* in the treated eye (0.36 µL/min) than in the control eye (0.55 µL/min). Uveoscleral outflow was increased in the treated eye by over 50% (mean, 0.98 µL/min versus 0.61 µL/min). The effects of $PGF_{2\alpha}$-IE on IOP and uveoscleral outflow were abolished by topical application of pilocarpine, although conventional outflow was enhanced by treatment with this cholinergic agonist.

Gabelt and Kaufman [23••] reported direct measurements of uveoscleral outflow, total outflow, and total facility in normal cynomolgus monkeys, and confirmed that $PGF_{2\alpha}$-IE causes a large redirection of outflow from the conventional to the uveoscleral route. They treated one eye of each of 11 cynomolgus monkeys with 2 µg of $PGF_{2\alpha}$-IE twice daily for a total of nine doses. After IOP measurements, deep anesthesia was induced and each eye was triple cannulated. IOP was continuously monitored, and total facility was measured using the two-level constant-pressure perfusion technique previously described. The entire anterior chamber contents were then replaced with mock aqueous containing radioactively labeled albumin, and this infusate was then slowly instilled over the next hour. After copious rinsing of the anterior cham-

ber with unlabeled infusate, the animal was sacrificed, and ocular and periocular tissues were dissected and counted for radioactivity. Uveoscleral outflow was determined by calculating the volume per unit time of anterior chamber fluid necessary to have deposited the observed amount of radioactive material. Blood samples were also collected to assess systemic radioactivity and thereby to calculate conventional outflow, as described. Total outflow was found to be about 20% lower in treated than in untreated eyes, a nonsignificant difference. Uveoscleral outflow was 2 to 3.5 times higher in treated than in untreated eyes, and conventional outflow was reduced by 75% in the treated eyes compared with untreated eyes, both highly significant results.

Vascular actions of selected drugs

β-Adrenergic antagonists

Systemically administered β-blockers are used for their vascular actions; ocular vascular actions of topical β-blockers must be better understood, both to avoid unwanted effects and to uncover potential beneficial applications.

Grunwald [24•] used Doppler velocimetry and monochromatic fundus photography to measure vessel diameter, maximum erythrocyte velocity, and volumetric blood flow rate in one of the major retinal veins of OHT patients both before and after administration of one drop of timolol 0.5% or placebo. Neither arterial diameters nor arterial blood flow were measured. The study employed a masked, randomized design, and measured posttreatment effects 2 hours after administration, when timolol effect reaches its peak. Compared with baseline, following treatment with timolol the average erythrocyte velocity increased 12% and volumetric blood flow increased 8.4%, both significant changes. Vessel diameter was unaffected. Placebo-treated eyes showed insignificant change from baseline, and the effect of timolol versus placebo was significantly greater only for erythrocyte velocity. Comparison with fellow placebo-treated eyes might have underestimated the effect due to the small but significant contralateral crossover effect of timolol. Perfusion pressure of the eye, defined as two thirds of mean brachial artery blood pressure minus IOP, was found to be increased by topical timolol. This was due entirely to the IOP reduction following timolol administration.

Hoste *et al.* [25•] examined the contractile response *in vitro* of bovine retinal arteries to topical propranolol and timolol. Both caused relaxation of potassium-induced arterial contraction, propranolol more so than timolol. The effect of timolol was weak and was significant only at the highest doses. As retinal arteries are thought not to contain β-adrenergic receptors but do possess functional α_1-adrenergic receptors, the possibility that the effect was mediated by an indirect action of β-blocker on the α agonist system was ruled out by measurements with propranolol after pretreatment with 6-hydroxydopamine, which functionally destroys adrenergic nerve endings. Results were unchanged. Also, the action of propranolol was similar in several respects, although weaker in magnitude, to the profound relaxing effect of the calcium channel blocker, verapamil. This suggests that β-blockers may exert a calcium antagonistic effect on retinal arteries. Extrapolating these results to intact human retina, it may be that topical β-blockers can cause retinal arterial dilation in patients.

Van Buskirk *et al.* [26•] used microvascular corrosion casting of rabbit ciliary vessels after single-dose or long-term treatment with timolol 0.5%, betaxolol 0.5%, or phenylephrine 2.5%, all delivered topically 1 hour before casting, to arrive at a different view of the action of β-blockers on ocular vasculature. After a single dose, the precapillary arteriolar sphincters adjacent to the major arterial circle of the iris showed marked constriction following treatment with each of the three drugs, with constriction of 32% after phenylephrine treatment, 23% after timolol, and 30% after betaxolol. Downstream diameters of radial arterioles were unaffected by any of the drugs. After 50 days of treatment, the eyes treated with timolol showed arteriolar sphincter constriction of 21%, unchanged from the single-dose value. The long-term phenylephrine-treated eyes showed 20% constriction, a reduction in response that was nevertheless significantly greater than the control level of 10%. Betaxolol caused only a 16% constriction, not significantly different from control. α-Adrenergic stimulation thus causes focal vasoconstriction, as does β_2 blockade, acting indirectly. Betaxolol, a relatively selective β_1-adrenergic antagonist, seems to have a lesser long-term action in this regard. The effect of the reduction in ciliary blood flow after vasoconstriction on aqueous production is unclear.

Calcium channel blockers

Since Phelps and Corbett [27] reported that about one half of their low-tension glaucoma patients suffered from migraine, the idea that vasospastic disease of the optic nervehead contributes to glaucoma has been prevalent. Gasser *et al.* [28•] selected 16 patients who had optic nerve excavation and glaucomatous visual fields despite having normal IOPs, who also exhibited nailbed capillary vasospasm in a digital cooling test. A group of 10 control patients was identical except they did not display nailbed vasospasm. Automated visual field tests were then performed while one of the subject's hands was continuously immersed in cold water. Subsequently, visual field testing was repeated 1 hour following ingestion of 10 to 20 mg of the calcium channel blocker nifedipine. Twelve of 16 patients in the vasospastic group showed deterioration of mean sensitivity of the visual field after cold water immersion, while only 4 of 10 in the nonvasospastic group showed deterioration. Statistical analysis was not provided. After nifedipine treatment, 15 of the 16 vasospastic pa-

tients showed improvement of mean sensitivity, a significant effect, while amongst the control group, 4 of 10 showed improvement. The authors conclude that visual field defects show different behavior after cold water provocation and after calcium channel blocker therapy in patients with as compared to those without digital vasospasm. They speculate that ocular vasospasm may have a role in the genesis of glaucoma.

The role of vascular pathology in visual field loss among low-tension glaucoma patients, and the vascular responsiveness of these patients to nifedipine, was also investigated by Kitazawa *et al.* [29••]. They undertook a retrospective, nonrandomized, nonmasked factor analysis of two unmatched groups of patients, all of whom had glaucomatous visual field loss and IOPs less than 21 mm Hg on diurnal measurement. Twenty-five consecutive patients were treated with nifedipine 10 mg orally three times daily for 6 months, during which time patients received no antiglaucoma medications. Patients were then assigned to one of two groups based on whether the global index of mean sensitivity (a measure of generalized depression) on monthly Octopus G1 visual fields performed throughout the treatment period showed improvement (6 patients) or not (19 patients). The reactivity of peripheral vasculature before and during nifedipine treatment was then assessed by measuring temperature recovery time of a finger following 10 seconds of immersion in ice water. Prior to nifedipine administration, the two groups had equivalent temperature recovery times. The group that showed visual field improvement also showed statistically significant shortening of temperature recovery time during nifedipine treatment, whereas the group that had no visual field improvement had unchanged temperature recovery time during nifedipine treatment. The authors speculate that patients who show visual field improvement may retain vasodilatory reactivity of peripheral vessels to nifedipine, possibly including increased optic nerve blood flow.

Interpretation of this intriguing study is complicated by methodologic difficulties. The conclusion that a beneficial effect of nifedipine occurs in some cases of low-tension glaucoma requires comparison with a control group treated with placebo in a prospective design. In addition, other factors that were found to vary between the two groups, such as age and baseline corrected loss variance, may account for observed differences in visual field change.

α-Adrenergic agonists

The availability of apraclonidine, an α_2-receptor agonist approved for topical use to suppress acute elevations of IOP after various laser treatments, is a welcome addition to the medical armamentarium. Current knowledge of the mechanism of action, clinical response, and ocular and systemic side effects has been recently reviewed by Zimmerman and Price [30••]. An important concern about the use of apraclonidine has been raised by Serdahl *et al.* [31•], who found that instillation of apraclonidine significantly decreased conjunctival oxygen tension along with IOP. The study was a randomized, prospective study of 10 normal volunteers who received topical anesthetic in both eyes and apraclonidine 1% in one eye. Measurements made 1, 3, and 5 hours after treatment were performed by an observer unaware of which eye had been treated. All subjects showed conjunctival blanching as well as significant measured conjunctival hypoxia in the apraclonidine-treated eye. At 1 hour there was an average decrease in oxygen tension of 76% from baseline, and at 3 hours average tension was reduced by 56%, both significant changes. By 5 hours, tension was reduced by 10%, not statistically distinct from baseline. These results may be compared with those of an earlier study showing that phenylephrine 2.5% reduced conjunctival oxygen tension by 46% at 16 minutes, with tensions returning to baseline after only 80 minutes [32]. The present study raises questions concerning a possible contribution of apraclonidine to ischemia, and possible effects on oxygen tensions in diabetic patients and patients recovering from recent surgery. These concerns should be borne in mind by ophthalmologists prescribing apraclonidine on a chronic basis, a currently unapproved application.

New horizons

Angiotensin converting enzyme (ACE) is found in human aqueous humor, choroid, and ciliary body, and a topically delivered ACE inhibitor, SCH 33861, has been shown to decrease IOP in rabbits [33] and to slightly increase IOP in humans with OHT [34].

Vogh and Godman [35•] confirmed this effect in the rabbit eye, showing that the ACE inhibitor captopril given topically in a 2% preparation caused a 39% reduction of IOP from a baseline of 28 mm Hg 3 hours after treatment, without an effect on blood pressure. By comparison, in the same study intravenous injection of 50 mg/kg of methazolamide, the potent carbonic anhydrase inhibitor, caused a 45% reduction of IOP at 3 hours. The effect of these drugs on aqueous flow was assessed by measuring the dilution of sulfacetamide that had been injected into the anterior chamber. Topical captopril 2% caused a 36% decrease in flow rate, comparable to the 38% decrease in flow rate following intravenous injection of methazolamide. When topical captopril and intravenous methazolamide were given together, IOP was unfortunately not measured in a way that permits comparison with the previously mentioned values. Aqueous flow was reduced by 41%, demonstrating almost complete lack of additivity of effect and suggesting a commonality of pathway of action. However, the authors also showed that captopril does not inhibit carbonic anhydrase, indicating that the site of action of captopril is elsewhere then at this enzyme.

Al-Sereiti and Turner [36•] failed to demonstrate an ocular hypotensive effect using an orally administrated

ACE inhibitor. They studied nine healthy young volunteers using a crossover placebo-controlled design and found no ocular hypotensive effect of 50 mg of oral captopril up to 4 hours after administration, although they found oral timolol, 20 mg, to have a highly significant effect. It may be that captopril given orally fails to reach the site of action in the eye at that dosage.

Atrial natriuretic peptides are synthesized by cardiac atrial cells and other tissues, and are known to have a broad range of direct and indirect fluid and electrolyte homeostatic actions. They bind to receptors in the eye but are not synthesized there. They have previously been shown to reduce IOP in rabbits [37].

Korenfeld and Becker [38•] confirmed that intravitreal injection of atrial natriuretic peptide in rabbits causes a decrease in IOP. Ten µg of APIII (a member of the class of atrial natriuretic peptides) given intravitreally to 25 rabbits lowered IOP significantly at 1 hour and had a maximal effect of about 5.5 mm Hg at 4 hours. Topical and subconjunctival dosings did not alter IOP. Aqueous flow, as assessed by both fluorophotometry and aqueous humor ascorbate concentration, was judged to be reduced by 20% to 40% 4 hours after intravitreal injection, suggesting that the mechanism of action includes decrease in aqueous production.

Intravitreal injection of atrial natriuretic peptide increases the aqueous humor concentration of cyclic guanosine monophosphate in rabbit. Becker [39•] has reported that topical application of 4% 8-bromo-cyclic guanosine monophosphate produces a significant decrease of IOP in rabbits between 30 minutes and 4 hours after a single drop is given (maximum effect of about 24% at 3 hours), without irritation or inflammation, without a change in outflow facility, and with an additive effect to that of intravenous acetazolamide.

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