

Fixed combination of topical brimonidine 0.2% and timolol 0.5% for glaucoma and uncontrolled intraocular pressure

Anne J Lee¹
Peter McCluskey^{1,2}

¹Department of Ophthalmology, Liverpool Hospital, Liverpool, NSW, Australia; ²Faculty of Medicine, University of New South Wales, Randwick, NSW, Australia

Abstract: Lowering IOP is the most readily modifiable risk factor to delay the development and progression of glaucoma (POAG). The fixed combination of brimonidine tartrate 0.2% and timolol maleate 0.5% (FCBT) combines a highly selective α_2 -adrenergic agonist (brimonidine) with a non-selective β -blocker (timolol). FCBT reduces aqueous production and enhances uveoscleral outflow. Concomitant brimonidine and timolol have additive effects on reducing intraocular pressure (IOP). Multi-center randomized control trials have documented superiority of FCBT twice daily on IOP control compared with monotherapy with the individual components, and equal efficacy compared with concomitant therapy. IOP reduction with FCBT versus fixed combination dorzolamide 2% and timolol 0.5% (FCDT) was similar in a small study. Other studies ($n > 293$) evaluating concomitant brimonidine and timolol have shown that it is not inferior to FCDT. However, concomitant brimonidine and timolol administered twice daily was significantly less efficacious in IOP reduction than fixed combination latanoprost 0.005% and timolol 0.5% (FCLT). There are no published studies comparing FCBT with FCLT. The side effect profile for FCBT reflects that of its individual components. FCBT was generally well tolerated, with less ocular side effects than brimonidine alone, but more than timolol alone. Documented systemic effects were few, although this could be confounded by selection bias. FCBT is a safe and effective IOP lowering agent for POAG and ocular hypertension.

Keywords: brimonidine, timolol, combigan, glaucoma, combination, ocular hypertension

Several studies have highlighted the impact of glaucoma as a leading cause of blindness (Thylefors and Negrel 1994; Quigley 1996). The estimated number of people with vision loss from glaucoma range from 5.2 (Thylefors and Negrel 1994) to 6.7 million. This is approximately 10% of the total number of affected persons, ranking glaucoma as the second most common cause of world blindness (Quigley 1996). Primary open-angle glaucoma (POAG) is a progressive optic neuropathy with corresponding optic disc cupping and glaucomatous visual field defects. The intraocular pressure (IOP) of the eye often exceeds its tolerance. Data from the Early Manifest Glaucoma trial (Heijl et al 2002) have shown that an additional 1 mmHg of IOP lowering reduces the risk of glaucoma progression by 10%. Participants of the Advanced Glaucoma Intervention Study (AGIS-7 2000) who achieved the target IOP of <18 mmHg at each visit had minimal deterioration of visual field over 96 months. Lowering IOP remains the most readily modifiable risk factor to delay development of glaucoma in subjects with ocular hypertension (OH) and progression of POAG (Kass et al 2002).

Several classes of topical IOP-lowering agents are available. These include β -receptor antagonists (selective or nonselective), prostaglandin $F_{2\alpha}$ -analogs and prostamides, α -adrenergic agonists, carbonic anhydrase inhibitors, and cholinergic agents. Pharmacotherapy usually begins with a single topical agent (monotherapy), traditionally

Correspondence: Peter McCluskey
Department of Ophthalmology, Liverpool
Hospital, Locked Bag 7103, Liverpool BC
NSW 1871, Australia
Email peter.mccluskey2@sswhs.nsw.
gov.au

a β -blocker. Since the introduction of prostaglandin analogues, many ophthalmologists prefer this agent as first-line treatment (Schwartz and Budenz 2004). Subsequent addition of a second agent (combination therapy) or more is often required to achieve target pressures. In the Ocular Hypertension Treatment Study, 40% of treated subjects required >1 medication to achieve the therapeutic goal of 20% IOP reduction from baseline (Kass et al 2002). More than 75% of subjects in the medical treatment arm of the Collaborative Initial Glaucoma Treatment Study (Lichter et al 2001) required ≥ 2 medications after 2 years. One in two patients commenced on initial monotherapy will require additional ocular hypotensives within 2 years to control IOP (Kobelt-Nguyen et al 1998).

Modern adjunctive therapy combines a β -blocker with another class of drug such as a topical carbonic anhydrase inhibitor, prostaglandin analogue, or selective α -agonist (Fechtner and Realini 2004). For example, timolol 0.5% is combined as an invariant with dorzolamide 2% (Cosopt[®], Merck and Co, Inc., Whitehouse Station, NJ, USA), latanoprost 0.005% (Xalacom[®], Pharmacia Inc., Peapack, NJ, USA), brimonidine 0.2% (Combigan[™], Allergan Inc., Irvine, CA, USA), travoprost 0.004% (Duotrav[®], Alcon Inc., Fort Worth, TX, USA), or bimatoprost 0.03% (Ganfort[®], Allergan Inc., Irvine, CA, USA) (Frampton 2006).

Fixed combinations of glaucoma medications offer numerous advantages for patients requiring multi-drug regimens. Most important is enhanced patient compliance. Fixed combinations allow reduction of the number of drops instilled per day and bottles of medication purchased thus overall cost to the individual and the time commitment for drop instillation. There is less confusion with drop regime, particularly for the older patient. There is no washout effect which arises from rapid instillation of multiple medications (Chrai et al 1974). Exposure to preservatives is minimized, thus reducing subclinical ocular surface inflammation and glaucoma filtering surgery failure rates (Broadway et al 1994). However, in some patients, concomitant therapy may be required over fixed dosing for more individually tailored IOP control.

This review focuses on the efficacy and safety profile of fixed combination brimonidine tartrate 0.2% and timolol maleate 0.5% ophthalmic solution for the treatment of glaucoma and ocular hypertension (OH).

Pharmacology – mechanism of action

Fixed combination brimonidine/timolol (FCBT) consists of two active substances: brimonidine tartrate

2.0 mg/mL (1.3 mg brimonidine free base) and timolol maleate 6.8 mg/mL (5.0 mg timolol) (MIMS 2007).

Brimonidine tartrate

Brimonidine tartrate is a potent and highly selective α_2 -adrenergic agonist, compared with apraclonidine or clonidine (Burke and Schwartz 1996; Cantor 2000) thus reducing mydriasis, lid retraction, and vasoconstriction. It is suggested that brimonidine lowers IOP by reducing aqueous humor production (Larsson 2001) and enhancing uveoscleral outflow (Serle et al 1991; Toris et al 1995). In addition, brimonidine has exhibited neuroprotective activity in experimental neuronal injury models, including light-induced photoreceptor damage (Wen et al 1996), optic nerve crush injury (Yoles et al 1999), acute retinal ischemia (Villegas-Perez et al 2000), and ocular hypertensive retinas (WoldeMussie et al 2001). In vivo evidence for neuroprotection is minimal. Reduced retinal nerve fiber layer damage after brimonidine 0.2% compared with timolol 0.5% has been found in OH patients over 1 year (Tsai and Chang 2005). Putative mechanisms of neuroprotection include increase in neurotrophic factors, thus enhancing retinal ganglion cell survival or activation of presynaptic α_2 -receptors with inhibition of neurotransmitter release in particular glutamate. Brimonidine has a rapid onset of action, with peak ocular hypotensive effect at 2 hours post-dosing. The duration of effect is 12 hours or greater.

Timolol maleate

Timolol maleate is a nonselective β -adrenergic antagonist that does not have significant intrinsic sympathomimetic, direct myocardial depressant or local anesthetic (membrane stabilizing) activity. The precise mechanism of action of timolol in IOP lowering is not fully elucidated, but the predominant action relates to suppression of aqueous secretion (Kiland et al 2004). Onset of action is 20 minutes postdosing, with peak effect at 1–2 hours. Significant lowering of IOP has been maintained as long as 24 hours.

The IOP lowering efficacy of brimonidine has been demonstrated in animal models (Burke and Potter 1996), and in human subjects with normal IOP (David et al 1995), ocular hypertension, or glaucoma (Derick et al 1997). Several large clinical trials have also established the efficacy of brimonidine compared with timolol. The Brimonidine Study Group (Schuman 1996; Katz et al 1999) pooled results from Brimonidine Study Groups 1 (Schuman et al 1997) and 2 (Le Blanc et al 1998), 2 large multi-center, randomized, double masked, trials of 12 months' duration. Among 837 patients with glaucoma (61%) or OH (39%),

both brimonidine 0.2% twice daily and timolol 0.5% twice daily significantly reduced mean IOP ($p < 0.001$) from baseline levels at every subsequent follow-up visit, both at peak (2 hours post dose) and trough times (12 hours post dose). Mean changes from baseline IOP ranged from 5.0–6.2 mmHg in the brimonidine group ($p < 0.001$) and 5.8–6.5 mmHg in the timolol group ($p < 0.001$). Overall, brimonidine showed efficacy comparable to that of timolol, and is a safe, effective long-term IOP-lowering agent (Schuman 1996; Melamed et al 2000).

Javitt et al evaluated the efficacy of brimonidine 0.2% twice daily and timolol 0.5% twice daily in 211 POAG and OH subjects (Javitt et al 2000). Subjects were naïve to treatment, thus eliminating possible β -blocker responsiveness and tolerability found in other studies where subjects had responded to β -blockers (Schuman 1996). The overall mean decrease in IOP was 6.5 mmHg with brimonidine and 6.2 mmHg with timolol over 4 months. These rates were comparable with other studies where the inherent selection bias described above could be an issue (Schuman 1996). Approximately 30% of each group did not achieve clinical success.

Van der Valk et al performed a meta-analysis of randomized clinical trials of all commonly used glaucoma agents for POAG or OH subjects (van der Valk et al 2005). In this study, only single agents were evaluated. For brimonidine 0.2% twice daily, the pooled 1-month relative mean IOP-lowering effect from baseline was -25% at peak and -18% at trough levels. For timolol 0.5% twice daily, the values for relative mean IOP-lowering from baseline were -27% (peak) and -26% (trough). Greatest IOP lowering effect at peak was found with bimatoprost at -33% , and at trough was travoprost at -29% . This meta-analysis concluded that bimatoprost, travoprost, latanoprost, and timolol are the most effective IOP-reducing agents in POAG and OH patients (van der Valk et al 2005).

Concomitant brimonidine and timolol therapy

Studies of concomitant brimonidine 0.2% and timolol 0.5% have shown additive IOP-lowering effects. Larsson observed that the reduction in aqueous humor production (58.9%) and IOP (34.7%) was greater after combined brimonidine and timolol, than timolol (reduced aqueous humor production 49.9% and IOP 22.9%) or brimonidine (reduced aqueous humor production 33.1% and IOP 20.3%) monotherapy (Larsson 2001). Yuksel et al also demonstrated additive IOP-lowering effects of adjunctive brimonidine over 2 days (Yuksel et al 1999). POAG or pseudoexfoliative glaucoma subjects

($n = 15$) on timolol twice daily and IOP of ≥ 22 mmHg in at least one eye, were randomized to adjunctive brimonidine 0.2% daily or placebo. A statistically significant decrease in IOP at each time interval (1, 2, 4, 6, and 8 hours post dose at day 1 and 2) was found compared with the placebo/timolol group ($p > 0.05$). Maximum IOP decrease of 7.26 mmHg was documented at 4 hours with concomitant therapy. Overall additional maximum IOP-lowering effect of brimonidine 0.2% daily administered adjunctively with timolol twice daily was 19.23% (Yuksel et al 1999).

Another similar study (Arici et al 2002) evaluated the effect of adjunctive brimonidine in timolol-treated subjects over a longer time period of 3 weeks. IOP reduction of 5.1 mmHg (21.2%), 5.9 mmHg (24.5%), and 5.7 mmHg (23.6%) at weeks 1, 2, and 3 respectively was found. Centofanti et al evaluated unfixed combination of timolol and brimonidine on timolol uncontrolled glaucomatous patients (Centofanti et al 1999). IOP further decreased by 16.1% and 24.7% after 1 and 3 months respectively with adjunctive brimonidine 0.2% twice daily. In a larger study of 552 subjects with POAG or OH and IOP ≥ 20 mmHg in each eye, adjunctive brimonidine also significantly lowered IOP when added to any pre-existing drop regimen (Lee and Gornbein 2001).

Fixed combination brimonidine/timolol trials

There are a small number of studies evaluating fixed combination brimonidine 0.2%/timolol 0.5% (FCBT). The Combigan Study Groups I and II pooled data from two identically designed multicenter, randomized, double masked, parallel-group trials. Both studies evaluated FCBT twice daily versus monotherapy with the individual components; brimonidine 0.2% 3 times daily or timolol 0.5% twice daily. Data at 3 (Craven et al 2005) and 12 (Sherwood et al 2006) months were published. Twelve-month data are discussed here.

Eligible subjects were ≥ 18 years and required bilateral treatment for POAG or OH. Washout period was up to 4 weeks depending on type of IOP-lowering medication at baseline. Baseline IOP after wash-out was 22–34 mmHg in each eye, with no greater than 5 mmHg difference between eyes. Best corrected visual acuity was 20/100 or better in both eyes. Subjects with active ocular disease, functionally significant or progressive visual field loss in the previous year, abnormally low or high blood pressure or pulse rate, or contraindications or sensitivity to any component of the study treatment were excluded.

At the baseline visit, IOP was measured at 0800, 1000, 1500, and 1700 hours. Patients were then randomly assigned

to 1 of 3 treatment groups using a 1:1:1 allocation of FCBT: timolol:brimonidine. Patients self-instilled 1 drop of the appropriate study medication into both eyes 3 times daily, with a vehicle solution in the afternoon if randomized to the brimonidine/timolol or timolol group. Follow-up visits were scheduled at weeks 2 and 6 and at months 3, 6, 9, and 12. IOP was measured at 0800, 1000, 1500, and 1700 at these visits except the 9-month visit when IOP was measured at 0800 and 1000.

Of 1159 patients enrolled in the study, 385 subjects received FCBT, 382 subjects brimonidine, and 392 subjects timolol. A total of 833 patients (71.9%) completed 12 months' treatment. Discontinuation rates were greatest in the brimonidine-treated group (169/1159) compared with the FCBT (99/1159) or timolol (58/1159) treated groups. Demographic characteristics were similar between groups, except more females in the brimonidine-treated group. Mean age was 62.6 years (29–89 years), 75.8% were white.

The mean IOP at the 0800, 1000, and 1500 measurements at baseline were similar between groups. At 1700, mean baseline IOP was lower in the FCBT group than the timolol group ($p = 0.01$) or the brimonidine group ($p = 0.06$). The mean decrease from baseline IOP at the 22 measured time points ranged from 4.4–7.6 mmHg with FCBT, 2.7–5.5 mmHg with brimonidine, and 3.9–6.2 mmHg with timolol. Analyses showed a significantly greater decrease in IOP in the FCBT group compared with timolol group at all measurements, and brimonidine group at all measurements except the 1700 measurements, which was 2 hours after the mid-day brimonidine dose.

Daytime mean IOP was also lower in the FCBT group compared with the timolol group at all measurements ($p \leq 0.002$) and the brimonidine group at 0800, 1000, and 1500 ($p < 0.001$), and 1700 at week 6 ($p = 0.04$). Mean daytime IOP of <18 mmHg was maintained by 39.5% of the FCBT group compared with 14.9% and 21.7% of those treated with brimonidine or timolol respectively. A mean daytime decrease from baseline IOP of greater than 20% at every follow-up visit was significantly greater in the FCBT group (42.1% of patients), than the brimonidine (13.1%) or timolol (27.3%) group.

The distribution of patients across the target pressure ranges of <14.0 , 14.0–17.5, and >17.5 mmHg favored the FCBT group over brimonidine or timolol monotherapy. There was a significantly greater shift towards the lowest pressure range (<14.0 mmHg) in the FCBT group than in either of the monotherapy groups ($p < 0.001$).

In summary, this study (Sherwood et al 2006) demonstrated that the mean decreases from baseline IOP, mean daytime

IOP, and mean daytime IOP <18 mmHg were significantly greater in the FCBT group compared with monotherapy of its constituent parts. Two-fold increased number of FCBT subjects achieved $>20\%$ reduction in IOP compared with timolol monotherapy, and 3-fold compared with brimonidine monotherapy.

Versus concomitant therapy with the individual components

The Brimonidine/Timolol Fixed Combination Study Group (Goni et al 2005) evaluated the efficacy and safety of FCBT twice daily compared with unfixed concomitant use of brimonidine and timolol each given twice daily. Methodology of this randomized multi-center double-masked parallel group study is similar to that of the Combigan Study Group I and II described earlier (Craven et al 2005; Sherwood et al 2006). There are a few differences; this study (Goni et al 2005) also included patients with chronic angle-closure, pseudo-exfoliative or pigmentary glaucoma. IOP elevation was of a similar range (22–34 mmHg) but only required in at least 1 eye and after ≥ 3 weeks of run-in monotherapy of the investigator's choice, continuation of current monotherapy, or cessation of all but one agent if multiple agents used. After baseline IOP measurement at hour 0, subjects were randomized into FCBT or concomitant groups in 1:1 ratio. Run-in monotherapy was discontinued. IOP measurements were taken at hour 0 and 2 at baseline, weeks 2, 6, and 12.

A total of 355 patients (96%) completed the study. Most were white (97.3%) and the majority female (62.8%). Types of run-in monotherapy (β -blockers [65.0%], brimonidine [15.6%], carbonic anhydrase inhibitor [10.5%], prostaglandin analog [7.8%], or other [1.1%] topical medications) were statistically similar between groups.

Both FCBT and concomitant therapy showed statistically significant mean IOP reductions from monotherapy treated baseline at each follow-up time point ($p < 0.001$) (Goni et al 2005). At hour 0 (trough) for each time point (weeks 2, 6, 12), the mean IOP reduction from baseline ranged from 4.4 to 4.9 mmHg in each treatment group. At hour 2 (peak) mean IOP reduction ranged from 4.9 to 5.3 mmHg in the fixed combination group and from 4.7 to 5.3 mmHg in the concomitant group. This was not significantly different between groups.

The mean change from baseline compared with hour 0, week 12 IOP (the primary efficacy endpoint) was -4.9 mmHg for both groups, and the upper limit of the 95% confidence interval (CI) for the difference between groups was 0.79,

thus demonstrating noninferiority of combination treatment compared with concomitant therapy. Mean IOP at follow-up measurements ranged from 17.3 to 20.6 mmHg in the FCBT group and from 17.1 to 20.5 mmHg in the concomitant group, again not significantly different. Among patients run-in on timolol monotherapy, no difference was found between treatment groups. Patients run-in on other medications also showed similar mean changes from baseline IOP between treatment groups.

The percentages of subjects in each treatment group who achieved target pressures of ≤ 18 mmHg were comparable; 33.0% and 37.2% of subjects in FCBT and concomitant group respectively at hour 0, week 12, and 70.2% and 70.5% at hour 2, week 12. An average IOP ≤ 17.5 mmHg over all follow-up measurements was comparable between treatment groups (29.3% FCBT vs 29.5% concomitant group).

This clinical trial has thus demonstrated that FCBT is noninferior to concomitant therapy. The primary efficacy endpoint compared baseline with IOP at week 12, where washout of previous monotherapy would not have confounded results. Measurements for mean change from baseline IOP, mean IOP at follow-up, and percentage of subjects achieving target pressures ≤ 18 mmHg, were also statistically similar between the two groups.

A more recent randomized controlled trial (Konstas et al 2007) has evaluated the 24-hour IOP control of FCBT versus the combination of its individual components, each dosed twice daily, in patients with POAG or OH. After a 6-week wash-out period, 28 patients were randomized to FCBT or to the unfixed combination for 3 months and then crossed over to the opposite treatment for another 3 months. Twenty-four hour IOP measurements (0600, 1000, 1400, 1800, 2200, and 0200 hours) were performed after the wash-out period and each treatment period. The mean 24-hour IOP was 24.6 mmHg for baseline, 19.2 mmHg for the FCBT group, and 19.2 mmHg for the concomitant group. Both FCBT and the unfixed components showed a significant IOP reduction from untreated baseline ($p < 0.0001$). The two treatment groups were statistically equal when compared directly, for each individual time point and for the 24-hour IOP curve ($p > 0.05$).

Versus dorzolamide/timolol

Dorzolamide hydrochloride is a topical carbonic anhydrase inhibitor which was initially developed for use as monotherapy. Carbonic anhydrase found in the ciliary processes of the eye is inhibited, thus decreasing production of

bicarbonate and subsequent sodium fluid transport. IOP is lowered by reducing aqueous secretion. A fixed combination of timolol maleate 0.5% and dorzolamide hydrochloride 2% (FCDT) was introduced in 1998. Clinical studies have demonstrated comparable efficacy of the FCDT product with concomitant administration (Strohmaier et al 1998), and greater than either of its component parts (Boyle et al 1998; Clineschmidt et al 1998).

Centofanti et al (2000) explored the IOP-lowering effect of adding brimonidine 0.2% or dorzolamide 2% on 28 patients (right eye of each subject) with advanced POAG and a visual field mean defect of -10 to -16 dB. Patients were on timolol 0.5% twice daily treatment. Adjunct medication was administered in a masked fashion 2 hours after timolol dose, and IOP measured at 2-hour intervals. Adjunctive treatment was crossed over 3 weeks later, and IOP measured as for visit 1. Mean pretreatment IOP for all the group was 19.36 mmHg. As an adjunct to topical β -blockers, 1 drop of brimonidine 0.2% was more effective ($p < 0.05$) than 1 drop of dorzolamide 2% in lowering IOP at 4 hours (mean IOP decrease 28.4 mmHg vs 17.6 mmHg; $p = 0.04$) and at 8 hours (mean IOP decrease 35.5% vs 21.6%; $p = 0.04$). Safety profiles were not published.

The Alphagan/Trusopt Study Group (Simmons et al 2001) randomly assigned 106 POAG or OH patients using a nonselective or selective topical β -blocker to receive brimonidine 0.2% twice daily or dorzolamide 2% 3 times daily as adjunctive therapy for 3 months. IOP was inadequately controlled on β -blocker monotherapy (IOP 18–34 mmHg in each eye). Cross over of study medication occurred if the target 15% reduction in IOP at peak drug effect was not achieved after 1 month. Most patients were on timolol (61.3%), and most had POAG (61.3%).

Mean baseline IOP (with β -blocker monotherapy) was comparable between treatment groups (21.56 mmHg in the brimonidine vs 20.89 mmHg in the dorzolamide group, $p = 0.284$) (Simmons et al 2001). At 1 month, the mean IOP reduction at peak effect was significantly greater in the brimonidine group (5.95 mmHg, 27.6%) than in the dorzolamide group (4.11 mmHg, 19.7%; $p = 0.007$). This was not statistically different at 3 months (6.39 mmHg with brimonidine and 4.06 mmHg with dorzolamide, $p = 0.059$). However, among patients who had achieved the target IOP reduction at month 1, a greater percentage of brimonidine-treated patients (77.8%, 28/36) met the target IOP at month 3 than did dorzolamide-treated subjects (44.4%, 12/27, $p = 0.007$). Additionally, 2-fold increased rates of IOP reduction of $\geq 25\%$ at month 3 were seen in the brimonidine-treated

group (61.1%) compared with the dorzolamide-treated group (33.3%, $p = 0.029$). These two trials (Centofanti et al 2000; Simmons et al 2001) suggest that brimonidine is more powerful and better sustained in reducing IOP than dorzolamide when added to β -blocker treatment.

Two randomized, observer-masked, multi-center trials have compared the efficacy of FCDT with the concomitant administration of brimonidine 0.2% twice daily and timolol 0.5% twice daily (Sall et al 2003; Solish et al 2004). Sall et al enrolled 293 participants with POAG or OH with IOP ≥ 22 mmHg at hour 2 in at least 1 eye after an open-label 3-week timolol (0.5% twice daily) run-in period (Sall et al 2003). Subjects were randomized to receive FCDT twice daily or the concomitant use of brimonidine twice daily and timolol twice daily for 6 months. At month 3, hour 2, the mean change in IOP in the FCDT group was -5.04 mmHg versus -5.41 mmHg in the brimonidine and timolol group, with a treatment difference of 0.36 mmHg (95% CI of -0.42 to 1.14 mmHg). At all other observed time points treatments were considered comparable as the 95% CI of the treatment difference was within ± 1.5 mmHg. This study was observer-masked to maintain drop stability.

Solish et al aimed to replicate the results of the aforementioned study (Sall et al 2003) using a larger cohort of 492 patients with POAG or OH, and in addition pseudoexfoliative or pigmentary glaucoma (Solish et al 2004). Run-in with timolol 0.5% was conducted in a similar manner to the initial study (Sall et al 2003). Study duration was 3 months. At month 3, hour 2, the mean change from baseline IOP among the FCDT group was -4.30 mmHg versus -5.27 mmHg in the brimonidine and timolol group, with a treatment difference of 0.97 mmHg (95% CI $0.40, 1.53$). The point estimate (0.97 mmHg) was within the ± 1.5 mmHg comparability boundary, although the 95% CI of $0.40, 1.53$ exceeded this boundary. At month 3, hour 0, the mean change in IOP from baseline was -3.31 mmHg compared with 3.52 mmHg for the brimonidine + timolol group. The treatment difference was 0.21 mmHg with 95% CI of -0.39 to 0.82 mmHg (Solish et al 2004). As IOP-lowering effects on all other time points were similar, the authors concluded that the difference found at month 3, hour 2, was not likely to be meaningful clinically and FCDT was comparable to concomitant brimonidine and timolol.

A more recent but smaller prospective, multi-center, randomized, cross-over trial has compared FCBT with FCDT given twice daily in subjects ≥ 18 years with POAG ($n = 16$) or OH ($n = 14$) in at least 1 eye (Arcieri et al 2007). Other inclusion criteria were baseline IOP of 22–34 mmHg (not on

medications) and best corrected visual acuity of 20/200 or better. Of eyes not included in the study, IOP must have been controllable on no medication or on the study medication. After wash-out of previous treatment, subjects were randomized to FCBT or FCDT for the first 4-week treatment period. Subjects then were again washed for 4 weeks and started on the opposite medication for the second 4-week period. IOP was measured at 0800, 1200, and 1600 hours at each baseline and at the end of each treatment period.

The baseline mean diurnal IOP for all 30 subjects (30 eyes) was 22.9 mmHg. No difference was found in the mean diurnal IOP after 4 weeks of therapy (15.0 mmHg for FCBT and 15.4 mmHg for FCDT, $p = 0.510$). No difference was found in the mean diurnal IOP reduction (7.8 mmHg for FCBT and 7.4 mmHg for FCDT, $p = 0.430$). Both fixed combinations significantly reduced IOP compared with baseline ($p < 0.00001$). This study suggests that FCBT and FCDT have similar efficacy in POAG or OH. Patients were not masked to their study therapy, but investigators were masked. Investigators attempted to limit this potential bias through a randomizing crossover design.

Versus latanoprost

Latanoprost is an F2 α -prostaglandin analog and is highly selective for the FP receptor (Stjernschantz and Resul 1992). It reduces IOP levels by increasing uveoscleral outflow with little or no effect on aqueous humour production (Toris et al 1993; Ziai et al 1993). Studies have shown that latanoprost daily is more effective than timolol twice daily in reducing IOP (Alm and Stjernschantz 1995; Camras 1996; Mishima et al 1996). Latanoprost has also been shown to be more effective than brimonidine 0.2% twice daily (Stewart et al 2000a; Stewart et al 2001). In a retrospective review of clinical files, Stewart et al compared the efficacy of latanoprost 0.005%, brimonidine 0.2%, or dorzolamide 2% when added to a topical β -blocker for at least 3 months in patients with POAG or OH (Stewart et al 2000b). Participants on latanoprost ($n = 50$) showed an IOP of 16.7 mmHg and reduction from baseline of -6.3 mmHg. Those on brimonidine ($n = 24$) showed an IOP of 17.4 mmHg and reduction from baseline of -4.2 mmHg, $p < 0.001$ and on dorzolamide ($n = 67$) an IOP of 20.1 mmHg and reduction of -3.1 mmHg, $p < 0.001$. A significant difference was observed between groups in success rates (defined as reduction in IOP ≥ 3 mmHg); latanoprost 70%, brimonidine 58%, dorzolamide 40%, $p = 0.008$ (Stewart et al 2000b).

To date, there are no published studies of FCBT versus fixed combination latanoprost/timolol (FCLT). However,

2 studies have compared FCLT daily versus concomitant brimonidine and timolol twice daily (Stewart et al 2003; Garcia-Sanchez et al 2004). Stewart et al randomized 32 subjects with POAG or OH to FCLT or concomitant brimonidine and timolol twice daily (Stewart et al 2003). IOP in the study eye after 1 month of timolol administered twice daily ranged from 21 to 34 mmHg. Treatment was crossed-over after 6 weeks. IOP was measured every 2 hours between 0800 and 2000 hours at baseline and at the end of each treatment period. Compared with timolol alone (20.9 mmHg) mean diurnal IOP decreased to 17.9 mmHg when patients were treated with fixed combination timolol/latanoprost, and decreased to 19.0 mmHg when patients were treated with brimonidine and timolol ($p = 0.02$). When treatment groups were compared directly, a greater statistical reduction in IOP was found among those using FCLT. The greatest difference in IOP between treatment groups was at 12 hours post dosing. This study suggests that FCLT given in the evening reduces the mean daytime diurnal IOP more than brimonidine and timolol given concomitantly twice daily.

A multi-center European study evaluated IOP in 325 patients with POAG or OH on FCLT given in the morning or concomitant brimonidine/timolol given twice daily (Garcia-Sanchez et al 2004). For inclusion, subjects had IOP ≥ 21 mmHg on monotherapy, or > 16 mmHg on dual therapy. At baseline, mean diurnal IOP was 26.4 mmHg for the FCLT group and 26.5 mmHg for the concomitant brimonidine/timolol group. After 6 months, mean diurnal IOP was significantly lower in the FCLT group (16.9 mmHg) compared with the brimonidine/timolol group (18.2 mmHg), $p < 0.001$. FCLT administered once daily is both more effective and better tolerated than dosing twice daily with unfixed brimonidine/timolol concomitant treatment.

Indeed, in a large post-hoc analysis, addition of brimonidine to a nonselective β -blocker reduced IOP by an additional 15.5% (3.61 mmHg, $p < 0.001$). When brimonidine was added to latanoprost, the mean additional IOP reduction was 2-fold at 32.2% (5.89 mmHg, $p < 0.001$) (Lee and Gornbein 2001). Thus, studies evaluating concomitant latanoprost and brimonidine versus FCBT may also be helpful in determining IOP lowering efficacy. The combination of a prostaglandin analog with an α -agonist will also eliminate the cardiopulmonary adverse effects of timolol.

Pharmacokinetics

Both brimonidine 0.2% and timolol 0.5% are rapidly absorbed into ocular tissues after topical application. After FCBT, the terminal half-life in aqueous (rabbits) for brimonidine

was 1.23 hours, and for timolol 1.12 hours. Peak plasma concentration (C_{max}) and area under the plasma concentration time curve (0–12 hours) (AUC) were not significantly different between FCBT and the respective monotherapies. C_{max} values were 32.7 pg/mL and 0.41 ng/mL, AUC values 128 pg.h/mL and 2.92 ng.h/mL, and time to C_{max} (T_{max}) values 1.28 hours and 2.42 hours for brimonidine and timolol, respectively, after FCBT twice daily administration for 7 days to 16 healthy volunteers. Plasma brimonidine concentration after 2 weeks and 12 months of FCBT twice daily was 61.0 pg/mL and 56.2 pg/mL in one study and 50.6 pg/mL and 51.5 pg/mL for the other study, respectively. Plasma timolol concentration was 0.74 ng/mL and 0.55 ng/mL in one study, and 0.50 ng/mL and 0.54 ng/mL for the other study, respectively. These concentrations were lower than those for respective monotherapies in both studies. Also, concentrations did not increase over time.

When systemically absorbed, brimonidine (29%) and timolol ($< 10\%$) are not extensively bound to human plasma protein. Brimonidine and timolol are partially metabolized by the liver (mediated by aldehyde oxidase and cytochrome P450 for brimonidine), and primarily excreted by the kidneys. After FCBT for 7 days, plasma elimination half-life value was 2.43 hours for brimonidine and 7.32 hours for timolol.

Safety

Tolerability and treatment-related adverse events profile of FCBT were evaluated simultaneously in most of the larger studies mentioned. Use of FCBT was associated with fewer side effects than brimonidine alone ($p = 0.006$), but more than timolol alone ($p < 0.001$) (Sherwood et al 2006). In this study, 28.1% of subjects discontinued treatment; 16.6% had adverse events, 4.6% due to poor efficacy, and 7.0% other reasons. FCBT subjects had a lower incidence of 1+ treatment-related adverse events (53.0% vs 62.8%), discontinuations due to adverse events (14.3% vs 30.6%), and at least a 1-grade increase in severity in biomicroscopic findings (54.8% vs 62.8%) compared with the brimonidine-treated group. Compared with the timolol-treated group, higher rates of 1+ treatment-related adverse events (53.0% vs 40.8%) and discontinuations due to adverse events (14.3% vs 5.1%) were found.

Of individual adverse events, the brimonidine group had higher rates of conjunctival hyperemia (22.8% vs 14.5%), eye pruritus (11.0% vs 5.5%), allergic conjunctivitis (9.4% vs 5.2%), conjunctival folliculosis (9.2% vs 4.9%), oral dryness (9.2% vs 2.1%), and conjunctival allergy/inflammation (39.8% vs 26.0%) compared with the FCBT group (Sherwood

et al 2006). Ocular stinging was more common with FCBT than with brimonidine alone ($p = 0.03$). The timolol group had significantly less conjunctival hyperemia (7.4%), eye pruritus (2.8%), allergic conjunctivitis (0.3%), conjunctival folliculosis (1.8%), oral dryness (0.5%), and conjunctival inflammation (12.0%) than FCBT, and similar rates of ocular stinging (6.6%). Similar adverse events profile has been documented in studies directly comparing brimonidine with timolol (Schuman 1996; Katz et al 1999).

When compared with concomitant brimonidine/timolol, FCBT group had higher incidence of adverse events (30.3% vs 24.6%) or 1+ treatment-related adverse events (20.2% vs 14.2%), although neither was statistically significant (Goni et al 2005). Ocular pain, pruritus, and headache were reported most often. No significant differences between groups were found for discontinuation of treatment from treatment-related adverse events, or biomicroscopic or ophthalmoscopic findings between groups (Goni et al 2005).

Reduced allergy levels with FCBT could be attributed to twice daily dosing as opposed to 3 times daily for brimonidine monotherapy, thus reducing brimonidine exposure. Alvarado postulated that the difference can be explained at a cellular level (Alvarado 2007). Adrenergic agonists reduce cell volume, increase intercellular fluid flow, and potentially allow greater access of proinflammatory mediators to the subconjunctival space. The addition of a β -blocker counteracts the cell volume effects of adrenergic agonists (Alvarado 2007). Interestingly, Osborne et al noted a significant delay in brimonidine-induced allergy among patients previously receiving timolol maleate (Osborne et al 2005). In this study, brimonidine was discontinued due to allergy on 73 per 100,000 patient treatment days, a far higher frequency than for other preparations. Patients with allergy to both brimonidine and another preparation (timolol, dorzolamide, or latanoprost) had a shorter interval between the first and second allergy if brimonidine allergy occurred first.

Reported systemic effects of FCBT in key studies were few and consistent with the individual components (Sherwood et al 2006). Small but statistically significant changes in heart rate (2–3 beats per minute) and blood pressure were found in the FCBT and timolol-treated group. Two patients from the timolol group were hospitalized due to serious treatment-related complications; one patient with respiratory distress, the other with tachycardia, nausea, and sweating (Sherwood et al 2006). No systemic adverse events were noted for brimonidine.

Well-recognized problems of topical timolol identified from other studies include cardiac failure, bradycardia

(Schuman 1996; Katz et al 1999) and heart block, bronchospasm and respiratory arrest. Confusion, headaches, reduced exercise tolerance, nocturnal hypotension, and impotence, have also been reported (Stewart and Garrison 1998). The most frequent systemic side effects reported from brimonidine were fatigue and dry mouth (Derick et al 1997). Some studies have observed statistically significant decreases in mean blood pressure without clinical symptoms with brimonidine 0.2% and 0.5% treatment (Derick et al 1997). Differences to other studies (Craven et al 2005; Goni et al 2005; Sherwood et al 2006) in systemic side effect profile may be explained by selection bias, as patients with a history of adverse events with β -blocker therapy, previous poor response to β -blockers, or systemic contraindications to the medication were excluded. Brimonidine use is not limited by pulmonary and cardiovascular contraindications. Brimonidine does not exhibit tachyphylaxis in clinical trials from 12 months (Nordlund et al 1995; Schuman 1996; Serle 1996) up to 4 years (Adkins 1998; Cantor 2000).

Compared with FCDT, FCBT has significantly less stinging and burning on application ($p = 0.027$) (Arcieri et al 2007). This finding is supported by a single-center, randomized, paired-eye study of 30 subjects without significant ocular surface disease (Chan et al 2007). FCBT was significantly more comfortable than FCDT on instillation ($p < 0.0001$), but not at 5 minutes. This is also in agreement with earlier studies (Sall et al 2003; Solish et al 2004) where FCDT treatment was compared with concomitant brimonidine/timolol. Over a 6-month study period, ocular stinging and burning, and dysgeusia were reported more frequently with FCDT (Sall et al 2003). The study by Arcieri et al may be too short in duration to allow for development of allergic effects and the study not powered sufficiently to detect a difference (Arcieri et al 2007).

Compared with FCLT, concomitant brimonidine/timolol had a similar adverse event profile on one (Stewart et al 2003) but not in another study (Garcia-Sanchez et al 2004). In the latter study, treatment-related adverse events were greater in the FCBT group (18.6% vs 7.3%). Allergy was found in 2.4% of FCLT patients compared with 7.8% of concomitant brimonidine/timolol group. Higher discontinuation rates were found with FCBT (17.3% vs 6.0%), with most subjects discontinuing treatment because of adverse events (10.8% vs 1.8%).

Dosage and administration

FCBT is indicated for the reduction of IOP in patients with POAG or OH who are insufficiently responsive to topical

β -blockers. The recommended dosage is 1 drop into the affected eye twice daily.

Contraindications to FCBT include hypersensitivity to the individual components, monoamine oxidase inhibitor use, bronchospasm, bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or overt cardiac failure or cardiogenic shock (MIMS 2007).

Precautions with FCBT use include cardiac, renal or hepatic failure, depression, cerebral or coronary insufficiency, severe peripheral and central circulatory disorders, Prinzmetal angina, Raynaud's phenomenon, orthostatic hypotension, thromboangiitis obliterans, spontaneous hypoglycemia (diabetes), hyperthyroidism, myasthenia gravis, general anesthesia, history of atopy and anaphylaxis, and use in neonates or pregnancy (MIMS 2007).

Conclusion

Clinical trials and utilization studies have demonstrated that many patients with POAG or OH require multiple medications to achieve adequate control of IOP (Fechtner and Realini 2004). Trials have established IOP additivity of concomitant brimonidine 0.2% 2 or 3 times daily and timolol 0.5% twice daily. FCBT has been shown in large multi-center randomized trials to be more efficacious in lowering IOP than monotherapy with its constituent parts. It is noninferior to unfixed concomitant use of brimonidine and timolol each given twice daily. FCBT or concomitant brimonidine/timolol are as efficacious as FCDT. However, as adjuncts to timolol treatment, brimonidine is more effective in lowering IOP than dorzolamide. Compliance issues with dorzolamide include stinging on application, 3 times daily dosing, and excessive somnolence and fatigue. FCLT provides greater efficacy than concomitant timolol and brimonidine. Unfortunately no published studies have evaluated FCLT compared with FCBT.

Local and systemic adverse events for FCBT were predictable and based on that of the individual components used alone and concomitantly. No unexpected or serious adverse events associated with the fixed combination were reported in the major trials of FCBT. However, this may reflect selection bias, as patients with a history of adverse events with β -blocker therapy, previous poor response to β -blockers, or systemic contra-indications to the medication were excluded. FCBT may be advantageous over FCDT with respect to ocular tolerability and comfort, hence enhanced compliance.

In summary, FCBT is a safe and efficacious treatment for elevated IOP for patients with POAG or OH uncontrolled

on monotherapy. Studies evaluating FCBT compared with FCLT and compared with concomitant brimonidine/latanoprost are required.

Disclosures

Neither author has any conflicts of interest to disclose.

Drug name

Combigan™ (Allergan Inc., Irvine, CA, USA).

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