Twenty-four hour efficacy of glaucoma medications

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Abstract

Current medical therapy of glaucoma aims to attain a meaningful and consistent reduction of intraocular pressure (IOP) to a predetermined level of target IOP, which will commensurate with either stability, or delayed progression of visual loss. Glaucoma is a 24-h disease and the damaging effect of elevated IOP is continuous. Therefore, it is reasonable that we should endeavor to identify the true efficacy of currently available and future antiglaucoma medications throughout the 24-h period. This review chapter deals first with the concept and value of diurnal and 24-h pressure monitoring. It then evaluates existing evidence on the 24-h efficacy of medical therapy options. Unfortunately, significant gaps exist in our present understanding of the short-term and particularly the long-term 24-h efficacy of most antiglaucoma medications. More long-term controlled evidence is needed in the future to improve our understanding of the 24-h efficacy of current medical glaucoma therapy, the ideal 24-h target pressure and the precise impact of IOP characteristics upon the different stages of the various forms of glaucoma.

Keywords

Intraocular pressure, 24-h Intraocular pressure, 24-h Efficacy, Diurnal IOP, Circadian IOP characteristics, Glaucoma medical therapy

1 INTRODUCTION

Several randomized-controlled trials have established that a significant reduction in intraocular pressure (IOP) results in a decrease, or even arrest in the rate of progression of visual impairment in most glaucoma patients (Palmberg, 2002). Thus, the current aim of glaucoma management is the preservation of a patient's visual function and quality of life by means of targeted and individualized IOP reduction (European Glaucoma Society, 2014). Typically, a clinician decides upon a predetermined target-pressure for each patient based on several parameters such as age, visual field damage, baseline IOP, rate of progression, and overall risk profile (European Glaucoma Society, 2014). Therefore, an individualized target IOP represents the best estimate of the IOP level that will ensure stability of a patient's vision within his/her predicted lifetime. The hypothesis is made however that IOP control implies a single, or occasionally, a few day-time IOP measurements overtime. Although the follow up of glaucoma patients with single IOP measurements is quick and expedient, such measurements often do not accurately reflect IOP control during the 24-h period (Konstas et al., 1997b; Wilensky, 1991, 2004). Since glaucoma is a 24-h disease and the harmful effect of elevated IOP is continuous, it is logical that we should also aim to control the IOP well throughout the 24-h period (Wax et al., 2002).

It is important to recognize the limitations of contemporary glaucoma practice. Current everyday glaucoma evaluation involves single-sitting IOP readings at each visit owing to time/cost considerations. Yet, one IOP measurement gives data for only 1 min of the day and will not replicate the dynamic IOP equilibrium during the other 1.439 min of that day, or the IOP levels between clinical visits. Even with 2 or 3 day-time IOP measurements, substantial IOP pathology may be missed and we will therefore not succeed in verifying glaucoma control in certain patients. Unsurprisingly, in progressive glaucoma patients, published evidence consistently indicates that a random single IOP measurement in the clinic is a poor surrogate for IOP levels throughout the day and across visits (Konstas et al., 2010b; Sultan et al., 2009). Consequently, the quality of untreated IOP data, which we rely upon to diagnose and treat glaucoma and to come to a decision between available therapeutic options (medical therapy, laser, surgery) is often inadequate and can be misleading (Fogagnolo et al., 2009, 2013; Hughes et al., 2003; Moodie et al., 2010; Wax et al., 2002; Wilensky, 1991). Thus, by employing single, infrequent IOP measurements to monitor the success of medical therapy not only is it difficult to reliably assess true efficacy of the selected medication regimen, but there is also insufficient knowledge of the "real" IOP control in many patients.

The missing evidence can better be gathered by performing a pressure curve. The need for a diurnal, or when feasible, a 24-h curve arises predominantly in cases when glaucoma patients deteriorate despite "apparently good IOP control" in the clinic. Additional indications arise in patients with advanced glaucoma who are on maximum medical therapy and in treated young glaucoma patients due to their higher risk of eventual visual loss. By monitoring diurnal or 24-h IOP, the quality of IOP control

can be ascertained and future management becomes more proactive (i.e., before further visual field damage occurs). When the option is available, complete 24-h monitoring will prove valuable in delineating the underlying IOP pathology in those glaucomas which exhibit worse, or more unpredictable 24-h IOP characteristics (e.g., exfoliative glaucoma (XFG), closed-angle glaucoma, normal tension glaucoma, etc.).

At present, clinical efforts focus upon determining acceptable alternatives to night-time IOP measurements. After all, if a complete 24-h curve can be avoided IOP monitoring in glaucoma will become far more practical. Initial promising results have been reported with supine representative morning IOP readings, a combination of day-time readings at specific time points and the use of the water-drinking test as a predictive tool (Fogagnolo et al., 2009, 2013). It is worth noting here that the first study that compared the value of daytime versus 24-h IOP monitoring in progressive glaucoma patients (Moodie et al., 2010) documented the mean day-time IOP to be significantly greater than the mean night-time IOP ($p = 0.03$). Further, in this study, there was no significant difference in the frequency changes in management that occurred as a result of daytime compared with 24-h monitoring results ($p = 0.65$). This implies that even in the absence of a complete 24-h evaluation a diurnal pressure curve can in many cases provide essential management information.

Interestingly, the two published studies that have explored the precise impact of 24-h IOP monitoring in glaucoma practice (Barkana et al., 2006; Hughes et al., 2003) have determined that 24-h monitoring led to a change in management in between 36% and 79% of their glaucoma patients. In the first study (Hughes et al., 2003), peak 24-h IOP was found to be 4.9 mm Hg higher compared with the higher IOP value recorded in the office with single IOP readings. In a similar fashion, the second study, (Barkana et al., 2006) reported peak and fluctuating IOP to be significantly greater in 24-h curves as compared with single visit-to-visit office IOP measurements. Current glaucoma management entails the reduction of IOP to a predetermined level of target IOP, which is commensurate with either stability, or delayed progression of visual loss. Following diagnosis, the vast majority of glaucoma patients are treated with medical therapy (European Glaucoma Society, 2014). According to established guidelines and conventional clinical practice, the individualized predetermined target IOP is obtained with a monotherapy agent first and when this proves inadequate combined medical therapy is employed (European Glaucoma Society, 2014). In the present glaucoma therapy paradigm, the hypothesis is made that target IOP can be evaluated via a single IOP measurement performed infrequently overtime. This approach may be flawed and costly in terms of eventual visual outcome. In contrast to setting a target IOP with single IOP measurements, a diurnal or 24-h target IOP profile, first without and then following treatment, will optimize target IOP selection and monitoring in glaucoma management. By documenting more precisely the true IOP pathology, we can set a target range of diurnal, or in ideal circumstances 24-h IOP that will ensure IOP stability for the individual glaucoma patient. This approach will also help us to more wisely determine the future probability of visual deterioration and to attain a better prognosis.

For each glaucoma patient diurnal, or 24-h IOP data will enhance our understanding of the role of elevated IOP in glaucoma initiation and progression. Although in this context, it would appear ideal to obtain information on the 24-h control of all glaucoma patients this is not a realistic strategy for most patients in most health systems. In contrast, reliable guidance on the 24-h efficacy of all available treatment options can be obtained by carrying out well-designed, randomized-controlled trials which when published can impact everyday practice. With regard to medical therapy, a complete 24-h assessment will allow better separation between two monotherapy treatment options and guide our day-to-day clinical management. Then, controlled 24-h IOP studies can supply convincing evidence for the superiority of a fixed combination, or a specific combined therapy regimen thus optimizing stepwise therapy. This is supported by previously published evidence comparing various medical therapy regimens where the true efficacy profile would not have been detected if it had not been for a complete 24-h IOP study. As evidenced by such studies, 24-h efficacy can differ meaningfully from day-time efficacy (Konstas et al., 2012b, 2013c; Liu et al., 2010). In the future, this research can also remove ambiguity as to the true efficacy of laser therapy and the overall success of a number of novel surgical options versus the gold standard surgical selection of trabeculectomy with mitomycin C (Agarwal et al., 2002; Greenidge et al., 1983; Konstas et al., 2006c; Kóthy et al., 2010; Mansouri et al., 2008; Matsuoka et al., 2013). Therefore, cumulative 24-h efficacy evidence will facilitate a better understanding of the best future treatment algorithm in glaucoma.

As previously discussed, ideally, therapeutic options should be selected so that target-pressure is attained throughout the 24-h cycle. Further, there is evidence to suggest that specific 24-h IOP characteristics such as mean, fluctuation, or maximum can influence the long-term prognosis of glaucoma patients (Asrani et al., 2000; Bergea et al., 1999; Konstas et al., 2012a; Quaranta et al., 2013b; Wilensky et al., 1987). There is no consensus as yet however which 24-h parameter is of greater importance in glaucoma management. There is also the possibility that the various pressure characteristics may play different roles in each form of glaucoma and their influence may vary in the different stages of glaucomatous damage. For example, 24-h fluctuation of IOP may not be as important in early glaucoma as in advanced, or end-stage glaucoma. Consequently, the efficacy of all therapeutic options and their modifying effect in each 24-h parameter should be recorded and taken into account in formulating the most successful glaucoma treatment algorithm in the future.

The key 24-h characteristics are: (a) the mean 24-h IOP, (b) the 24-h IOP range, or fluctuation, and (c) the peak 24-h IOP. As yet the precise value of 24-h IOP testing in the long-term prognosis of glaucoma remains largely unproven. However, there is preliminary convincing evidence suggesting that those patients with the worst untreated 24-h characteristics tend to show the greatest deterioration overtime. In a comparative 24-h IOP study (Konstas et al., 1997b) between 40 age-matched pairs with XFG and primary open-angle glaucoma (POAG), those with XFG had a higher untreated mean fluctuation of 24-h IOP (13.5 vs. 8.5 mm Hg for POAG) and a significantly higher untreated mean peak 24-h IOP (mean 38.2 vs. 26.9 mm Hg for POAG).

A subsequent 24-h IOP study (Konstas et al., 1997a) confirmed a strong linear correlation between untreated peak 24-h IOP in XFG ($r=0.71$) and POAG ($r=0.44$) and mean visual field defect at the time of diagnosis. The mean 24-h IOP was also strongly associated with untreated mean visual field loss in both XFG ($r=0.77$) and POAG ($r=0.28$) (Konstas et al., 1997a). Hence, it appears that in open-angle glaucoma the worse 24-h IOP characteristics account for the faster deterioration and the worse 24-h characteristics in XFG account for the worse prognosis in this glaucoma in comparison with POAG.

As indicated before, a pressure curve aids evaluation of the quality of treated IOP control. Here, some evidence suggests that a reduced IOP fluctuation is important in helping to prevent long-term progression of visual field loss (Asrani et al., 2000; Wax et al., 2002; Wilensky, 1991). However, it should be borne in mind that there is a significant correlation between fluctuation and peak 24-h IOP (Wilensky, 1991); hence, it is difficult to know if it is fluctuation, or peak 24-h IOP that play a key role in progression. Interestingly, a recent 5-year retrospective study demonstrated that peak 24-h IOP was the only independent factor for visual field progression in POAG patients (Konstas et al., 2012a).

This review summarizes 24-h efficacy data of the currently used antiglaucoma medications as highlighted in selected published evidence.

2 24-HOUR EFFICACY OF MONOTHERAPIES

2.1 PROSTAGLANDINS

Prostaglandin analogues (latanoprost, travoprost, bimatoprost, and tafluprost) are the most potent topical antiglaucoma agents, achieving a relatively uniform 24-h IOP reduction ranging between 24% and 29% (Russo et al., 2008; Stewart et al., 2008, 2010). This class of medications exerts its pharmacological effect by predominantly enhancing aqueous humor outflow through the uveoscleral pathway and to a lesser extent through the trabecular meshwork. This effect is facilitated through extracellular matrix remodeling (Weinreb et al., 1997; Winkler and Fautsch, 2014). All currently available prostaglandins are dosed once daily. Although studies have generally shown that peak prostaglandin efficacy occurs 8–12 h after administration, their ocular hypotensive effect is fairly uniform throughout the circadian cycle (Orzalesi et al., 2000, 2006; Quaranta et al., 2006, 2008a,b; Stewart et al., 2008; Yildirim et al., 2008). Still, cumulative evidence suggests that with evening administration prostaglandin effectiveness is greater during the daytime (Konstas et al., 1999a, 2006b, 2009b, 2010a; Quaranta et al., 2013b). The advantages of convenient dosing and superior 24-h efficacy have made prostaglandins a popular first choice glaucoma monotherapy.

Latanoprost, the prototype member of this class was first marketed in 1996. It is a prostaglandin F2α isopropyl ester prodrug, which is hydrolyzed by corneal esterases to the biologically active latanoprost acid (Russo et al., 2008). The efficacy of

latanoprost has been compared to that of other commonly used antiglaucoma medications. In a crossover study, Orzalesi et al. (2000) evaluated the 24-h IOP efficacy of latanoprost in patients with POAG or ocular hypertension (OH). Latanoprost was more efficacious than the prototype β-blocker timolol at 3 AM, 6 AM, 9 AM, 12 PM, 9 PM, and at midnight. The prostaglandin was also more effective than the topical carbonic anhydrase inhibitor dorzolamide at 9 AM, 12 PM, 3 AM, and 6 AM. Quaranta et al. (2006) reported similar 24-h effectiveness in POAG patients: compared to timolol, latanoprost exhibited superior night-time (10 PM to 6 AM) efficacy. On the other hand, timolol and latanoprost had similar day-time efficacy for the period between 8 AM and 8 PM, while dorzolamide was as effective as latanoprost at night (10 PM to 6 AM).

The peak efficacy of latanoprost is generally reported to occur approximately 8–12 h following instillation (Konstas et al., 1999a). In a 6-month diurnal, double-masked, randomized, multicenter study with three parallel groups (timolol administered twice-daily, morning-dosed latanoprost, and evening-dosed latanoprost), Alm and Stjernschantz (1995) observed that the mean diurnal IOP reduction for timolol, morning-dosed latanoprost, and evening-dosed latanoprost were 27%, 31%, and 35%, respectively. The diurnal pressure curves indicated that evening-dosed latanoprost was more efficacious than either morning-dosed latanoprost or timolol administered twice daily ($p < 0.001$). Subsequently, the complete 24-h efficacy of morning- versus evening-dosed latanoprost was investigated by Konstas et al. (1999a) in a crossover study. The authors reported that both regimens were efficacious over the 24-h curve, but morning instillation provided a statistically lower pressure at 10 PM, while evening instillation provided a statistically lower IOP at 10 AM. Both dosing regimens were equally efficacious at the critical 6 AM time point, when IOP is often high in glaucoma patients. The authors concluded that evening administration may be preferable for the majority of patients, but clinicians can select the optimal instillation time depending on each patient's idiosyncratic IOP profile.

An 8 weeks, crossover, double-masked trial, evaluated the quality of 24-h IOP control between morning- and evening-dosed travoprost in POAG patients (Konstas et al., 2006b). The untreated mean 24-h IOP was 23.6 ± 2.0 mm Hg. There were no significant mean 24-h IOP differences between morning (17.5 ± 1.9 mm Hg) and evening (17.3 ± 1.9 mm Hg) dosing ($p = 0.7$). At 10 AM, evening dosing provided a statistically lower IOP than morning dosing (17.2 ± 2.1 vs. 19.1 ± 2.5 mm Hg; $p = 0.02$). Importantly, evening dosing demonstrated a statistically lower 24-h IOP fluctuation than morning dosing (3.2 ± 1.0 vs. 4.0 ± 1.5 mm Hg; $p = 0.01$). This study suggests that travoprost is effective in reducing 24-h IOP when administered either in the morning or evening. However, evening administration may offer better quality of 24-h IOP control.

The relative 24-h efficacy of each prostaglandin analogue has been the subject of a number of investigations to date. In a controlled 1-month, double-masked, crossover trial the 24-h efficacy of latanoprost, travoprost, and bimatoprost was evaluated in 44 patients with POAG or OH (Orzalesi et al., 2006). All three medications significantly reduced 24-h IOP compared to untreated baseline. Among the three

prostaglandins, there was no statistically significant difference in terms of 24-h efficacy. Yildirim et al. (2008) investigated the circadian efficacy of these medications in an 8-week, parallel, randomized, assessor-masked study including 48 patients. Although the mean treated 24-h IOP is not reported, the authors reported similar efficacy for all three prostaglandins for all measurements except the 8 AM and 10 AM time points. At these time points, travoprost-treated patients had statistically greater IOP reduction (8.7 and 8.1 mm Hg, respectively) compared to latanoprost-treated patients (4.8 and 5.3 mm Hg, respectively) and bimatoprost-treated patients (5.5 and 4.9 mm Hg, respectively). In a double-masked, crossover 24-h study, Konstas et al. (2005c) compared the 24-h efficacy of latanoprost versus that of bimatoprost in POAG patients and reported that bimatoprost provided statistically superior 24-h efficacy, although the overall difference between groups was small (16.7 ± 2.4 vs. 17.3 ± 2.8 mm Hg; $p = 0.01$). A more recent crossover study compared the 24-h efficacy of preservative-free tafluprost versus branded, preserved latanoprost in patients with POAG or OH (Konstas et al., 2013c). Both prostaglandins significantly lowered the mean untreated 24-h IOP (24.9 mm Hg). When directly compared, the mean 24-h efficacy of preservative-free tafluprost was found to be identical to that of latanoprost (17.8 vs. 17.7 mm Hg; $p = 0.417$). With regard to specific 24-h characteristics, preservative-free tafluprost obtained significantly lower 24-h fluctuation (3.2 vs. 3.8 mm Hg; $p = 0.008$), whereas latanoprost showed significantly lower 24-h trough IOP (15.9 vs. 16.3 mm Hg; $p = 0.041$).

More recently, Seibold and Kahook (2014) examined the 24-h efficacy of SofZia-preserved travoprost in a 4-week, open label, sleep laboratory study with 40 subjects with open-angle glaucoma or OH. This trial established that SofZia-preserved travoprost significantly lowered mean diurnal and nocturnal pressures from untreated baseline. Additionally, the authors investigated the maintenance of efficacy after three doses were omitted. They reported that mean IOP was maintained significantly below baseline both at daytime and nighttime. Contrary to previous 24-h studies, in this trial SofZia-preserved travoprost was only modestly efficacious in reducing the habitual day-time (16%), night-time (6%), and mean 24-h IOP (12%). This could be explained conceivably by the relatively low baseline pressures in the study cohort (day-time sitting IOP: 18.1 ± 3.9 mm Hg, night-time supine IOP: 20.6 ± 3.6 mm Hg).

Although the overall efficacy of prostaglandins in most studies is found to be statistically similar, some evidence suggests that travoprost and bimatoprost may offer more uniform 24-h IOP reduction than latanoprost (Aptel et al., 2008; Aptel and Denis, 2011; Dubiner et al., 2004; Stewart et al., 2008; Walters et al., 2004). It remains to be determined whether such differences in the quality of 24-h IOP control are clinically important. On the other hand, it should be noted that large trials employing single pressure measurements have indicated that the risk of glaucoma progression may be reduced by 10–20% for each mm Hg of further IOP reduction (Chauhan et al., 2008; Leske et al., 2007). To date, the precise level of long-term protection for each mm Hg of further 24-h reduction remains to be elucidated. Nevertheless, considering available evidence, it can be hypothesized that obtaining lower target pressures over the complete 24-h period will enhance the possibility of favorable long-term prognosis.

The 24-h efficacy of the recently available formulation of bimatoprost solution 0.01% has been investigated by Tung et al. (2012) in a small cohort of patients with either POAG ($n=3$) or OH ($n=13$) who were housed in a sleep laboratory. The new formulation of bimatoprost has been developed with the aim of reducing the occurrence and severity of ocular hyperemia while largely maintaining the efficacy of the standard bimatoprost 0.03% solution. The new formulation was manufactured with a higher concentration of the preservative benzalconium chloride (0.2 mg/ml) compared to the standard bimatoprost 0.03% formulation (0.05 mg/ml) to optimize corneal penetration and intraocular bioavailability of the active ingredient. Although the mean 24-h efficacy of bimatoprost 0.01% was not reported in this study (Tung et al., 2012), the authors have reported a mean habitual IOP reduction of 21.7% during the day and 10.2% during the night.

Few 24-h studies have investigated the efficacy of prostaglandins in other glaucomas than POAG. The 24-h efficacy of latanoprost was considered in normal tension glaucoma patients by Ishibashi et al. (2006). These authors reported that although latanoprost achieved a statistically significant mean 24-h IOP lowering (12.5%), this was rather small. It should be borne in mind, however, that this cohort of patients had a relatively low baseline pressure (mean baseline 24-h IOP: 13.9 mm Hg). In agreement to this study, Costagliola et al. (2008) reported that latanoprost was effective throughout the 24-h cycle in normal tension glaucoma patients. It should be noted, however, that this study included patients with IOP values greater than 21 mm Hg at certain time points. An investigator-masked, crossover, 24-h study with previously untreated normal tension glaucoma patients showed that evening-dosed latanoprost and bimatoprost demonstrated similar albeit reduced efficacy (16% reduction from baseline) for each measurement time point and for the full 24-h cycle (Quaranta et al., 2008b). More recently, in an 8-week, crossover trial, Shin et al. (2014) assessed the 24-h efficacy of travoprost versus that of tafluprost in 41 normal tension glaucoma patients. Both prostaglandins significantly lowered IOP from the untreated baseline, but travoprost achieved statistically lower pressures at three time points (4, 6, and 8 PM) as well as for the 24-h curve.

As glaucoma is a lifelong disease, with subtle functional deterioration occurring over several years, suboptimal long-term IOP control may increase the chances of disease progression (Heijl et al., 2002; Holló et al., 2012; Musch et al., 2011; Konstas et al., 2012a; Stewart et al., 2000). Consequently, knowledge of the long-term 24-h efficacy of antiglaucoma medications would be of particular value in long-term glaucoma care. In the first study of its kind, Riva et al. (2014) recently described the long-term 24-h efficacy of travoprost monotherapy in a group of 34 previously untreated POAG patients who underwent annual 24-h measurements over a period of 5-year. This trial demonstrated a consistent pattern of long-term 24-h IOP lowering (27.8–28.6%). Further, a predetermined individualized target IOP reduction between 20% and 30% was reached and sustained by a significant proportion of study patients (82%). Interestingly, this evidence of long-term 24-h efficacy compares well with the previously published picture of short-term 24-h efficacy of travoprost monotherapy (Stewart et al., 2008).

2.2 TIMOLOL MALEATE

Timolol is a β-adrenergic blocker that has been successfully employed for the reduction of IOP for more than 30 years. It is available both as an ophthalmic solution (0.25% or 0.5%) typically administered twice daily and as a hydrogel formulation (0.1% or 0.5%) administered once daily. It exerts its ocular hypotensive effect by inhibiting the sympathetically driven part of aqueous humor production by the ciliary epithelium (Coakes and Brubaker, 1978).

In a 24-h study, Konstas et al. (1997a) investigated newly diagnosed, previously untreated XFG and POAG patients who were treated with timolol solution 0.5% administered twice daily. These authors recorded an IOP reduction varying between 10% and 25% at different time points. In a subsequent trial, Orzalesi et al. (2000) evaluated the 24-h efficacy of timolol 0.5% solution administered twice daily in patients with POAG and OH and reported that the nocturnal efficacy of timolol was about half the day-time efficacy. In agreement with these two trials, most, but not all, 24-h studies support the notion that despite its reduced nocturnal efficacy timolol achieves clinically meaningful IOP reduction throughout the 24-h cycle (Konstas et al., 1997a, 1999b; Lee et al., 2010; Quaranta et al., 2006, 2012). Because timolol exerts its ocular hypotensive effect by inhibiting aqueous humor production, its relatively low nocturnal efficacy has been attributed to the circulating catecholamine-induced reduction of aqueous humor synthesis normally observed at night (Maus et al., 1996; Reiss et al., 1984; Topper and Brubaker, 1985). Quaranta et al. (2006) showed that the efficacy of twice-daily administered timolol 0.5% is greater at daytime and smaller, but still significant, at nighttime. A subsequent meta-analysis of 24-h efficacy studies has confirmed that timolol 0.5% solution obtains a mean circadian IOP reduction of 19–24% from untreated baseline (Stewart et al., 2008).

Timolol gel-forming solutions may offer certain advantages. Firstly, the gel formulation allows a longer exposure of the active ingredient upon the ocular surface, and by doing so enhances ocular absorption and bioavailability. This allows a once-daily administration regimen to be sufficient. Secondly, the increased level of local absorption of timolol diminishes systemic absorption and improves its systemic safety profile. Lastly, the once-daily instillation may be advantageous in that it reduces exposure to preservatives and it improves patient adherence. In a 24-h comparison of the evening-dosed 0.5% gel-forming timolol solution versus the standard timolol 0.5% solution administered twice daily, Konstas et al. (1999b) reported almost equivalent 24-h efficacy in previously untreated patients with XFG, or POAG. Liu et al. (2004) used an open label, crossover design to compare the 24-h efficacy of latanoprost versus once-daily timolol 0.5% gel-forming solution in patients with OH or early glaucoma. In this study, both medications exhibited similar diurnal efficacy, but unlike latanoprost, timolol did not reduce the nocturnal IOP from untreated baseline. More recently, Quaranta et al. (2012) reported comparable 24-h efficacy between timolol 0.5% solution administered twice-daily and morning-dosed timolol 0.1% ophthalmic gel.

2.3 TOPICAL CARBONIC ANHYDRASE INHIBITORS

This class of antiglaucoma medications includes two members with essentially identical efficacy and tolerability profile: dorzolamide hydrochloride 2% solution and brinzolamide 1% suspension (Sall, 2000; Wilkerson et al., 1993). The ocular hypotensive effect of these medications is exerted via the inhibition of carbonic anhydrase, a key enzyme of the ciliary epithelial cells that is involved in aqueous humor formation (Maren, 1995). When used as monotherapy, dorzolamide is generally dosed three times daily and brinzolamide twice daily. As discussed in the following section, however, these molecules are often combined with timolol in the form of a fixed combination and then both dorzolamide and brinzolamide are administered twice daily. Dorzolamide monotherapy has been shown to lower circadian IOP by 15–23% when dosed three times daily (Orzalesi et al., 2000; Quaranta et al., 2006; Stewart et al., 2008). Importantly, there is evidence to suggest that contrary to other medications dorzolamide (and presumably brinzolamide) maintain their efficacy at night. For example, in a crossover trial with POAG and OH patients treated with latanoprost, timolol, and dorzolamide, Orzalesi et al. (2000) found that dorzolamide was equally efficacious with timolol over the 24-h period, but less efficacious than latanoprost. Importantly, dorzolamide was more efficacious than timolol at midnight and at 3 AM, whereas timolol was more efficacious than dorzolamide at 3 PM. A subsequent trial (Quaranta et al., 2006) confirmed that dorzolamide exhibits significant nocturnal efficacy. In fact, this investigation (Quaranta et al., 2006) observed that dorzolamide was equally efficacious with latanoprost during the night (10 PM to 6 AM) but less effective than either latanoprost or timolol during the day (6 AM to 8 PM). In another 24-h investigation (Konstas et al., 2000), dorzolamide was added to timolol in patients with POAG or XFG. Dorzolamide as adjunctive therapy to timolol significantly reduced IOP ($p < 0.05$) at all time points in patients with either type of glaucoma (Konstas et al., 2000). Finally, a meta-analysis performed by Stewart et al. (2008) confirmed that carbonic anhydrase inhibitors may be the only class of medications available today that exerts better night-time than day-time efficacy (21% vs. 16% IOP lowering from baseline, respectively).

2.4 BRIMONIDINE

Brimonidine is a highly selective α_2-adrenergic agonist and has been commercially available since 1996. It exerts its IOP-lowering effect via a dual mechanism: by inhibiting the enzyme adenylate cyclase, it reduces aqueous humor synthesis, while at the same time it moderately enhances outflow through the trabecular and the uveoscleral pathways (Reynolds, 2015). Although brimonidine has been approved in the United States for three times a day instillation, in Europe, it is often administered twice daily. The mean day-time efficacy of brimonidine 0.2% dosed twice daily was shown to be 14–19% (Serle, 1996; Whitson et al., 2004). In a 24-h crossover study with 20 POAG or OH patients, Orzalesi et al. (2003) established that brimonidine dosed twice daily reduced the mean 24-h IOP by 17.3%, but did not reduce

night-time IOP from baseline. In a subsequent 24-h study also with POAG patients, Quaranta et al. (2006) showed that the diurnal efficacy (8 AM to 8 PM) of brimonidine was similar to that of dorzolamide, while its night-time efficacy (10 PM to 6 AM) was reduced and similar to that of timolol. Subsequently, an open label, 24-h study performed in a sleep laboratory with 15 patients with open-angle glaucoma or OH (Liu et al., 2010) reported that even when administered three-times-daily brimonidine reduced the mean day-time IOP by 12.5%, but had virtually no nocturnal efficacy.

In a trial with POAG patients measured from 8 AM until midnight, Konstas et al. (2001) compared the efficacy of brimonidine 0.2% dosed twice or three times daily versus that of timolol 0.5% dosed twice daily. The mean 16-h efficacy for brimonidine dosed twice daily, three times daily and for timolol was 19.2, 18.0, and 17.7 mm Hg, respectively. All three regimens yielded statistically significant differences from untreated baseline. Moreover, pair-wise comparisons showed that three-times-daily brimonidine and twice-daily timolol were more effective than twice-daily brimonidine at every time point after 10 AM. In contrast, three-times-daily brimonidine and twice-daily timolol were equally efficacious over the 16-h period measured and for each time point except at 4 PM, when timolol was significantly more effective (Konstas et al., 2001). The authors observed that compared to twice-daily administration, brimonidine dosed three-times-daily exhibited superior efficacy at late afternoon and early nighttime.

3 24-HOUR EFFICACY OF COMBINED THERAPY

To date, there is limited evidence on the overall efficacy and predominantly the 24-h efficacy of combined therapy beyond the level of a single fixed combination. This despite the fact that cumulative evidence from large controlled clinical trials shows that most glaucoma patients need combined therapy to reach a predetermined target IOP level clinically deemed safe for them in the long term. Indeed, data from the Collaborative Initial Glaucoma Treatment Study suggested that about 75% of patients needed at least two medications to reach a 35% predetermined target pressure reduction (Lichter et al., 2001). Compared to the concomitant administration of separate medications, fixed combinations of antiglaucoma agents offer numerous advantages such as decreased exposure to preservatives, greater convenience, improved adherence, and the elimination of the washout phenomenon (Dunker et al., 2007). Several studies have compared the efficacy and safety of the concomitant use of individual medications versus that of fixed dose combinations of the same medications. Unfortunately, the majority of published studies only describe the daytime, rather than the complete 24-h efficacy of these regimens.

This section reviews available evidence on the 24-h efficacy of both fixed and unfixed combination regimens. Pilocarpine-containing regimens are not reviewed here, as they have become obsolete and are barely used today. From the following paragraphs, it becomes apparent that few trials have been conducted with the explicit objective of evaluating the 24-h efficacy of unfixed combinations, except when these

are compared with the respective fixed combination regimens. Similarly, although there are meta-analyses examining the efficacy of combination therapies (Cheng et al., 2012; Quaranta et al., 2013a; Webers et al., 2010), to date only one meta-analysis has dealt in part with the 24-h efficacy of fixed combination therapies (Stewart et al., 2008).

4 COMBINATIONS OF PROSTAGLANDIN ANALOGUES WITH β-BLOCKERS

4.1 LATANOPROST AND TIMOLOL

In the first 24-h study on a fixed combination product the latanoprost/timolol fixed combination (LTFC) was evaluated by Larsson (2001) in a 24-h, placebo-controlled, crossover study with 20 participants with OH followed-up for 1 month. The LTFC dosed in the morning was more efficacious than placebo both over the diurnal and the nocturnal period (differences vs. placebo: 5.6 and 3.1 mm Hg, respectively). In a crossover trial, Konstas et al. (2006a) compared the 24-h efficacy of LTFC with evening administration versus that of timolol dosed twice daily in 34 POAG patients treated for 2 months. Compared to timolol, LTFC was significantly more efficacious at all time points measured. The mean 24-h IOP was significantly reduced from 25 mm Hg at baseline to 19.3 and 16.4 mm Hg with timolol and LTFC, respectively. This difference (2.9 mm Hg) in favor of LTFC was statistically significant. A similarly designed 24-h trial evaluating both IOP and systemic blood pressure with evening-dosed LTFC versus timolol administered twice daily confirmed these results in eyes with POAG or OH (Konstas et al., 2009a).

Another 2-month, 24-h crossover trial with 37 POAG patients investigated the ocular hypotensive effect of the evening-dosed concomitant administration of latanoprost and timolol versus that of evening-dosed latanoprost (Konstas et al., 2005a). In this trial the mean untreated 24-h IOP was significantly reduced from 24.2 to 19.2 and 16.7 mm Hg, respectively, with latanoprost and the combination. When directly compared, the concomitant administration of latanoprost and timolol resulted in significantly lower pressures than latanoprost monotherapy both for the complete 24-h period and the individual time points. In another 3-month, parallel-arms, randomized 24-h clinical trial, Rossetti et al. (2007) compared the efficacy of bimatoprost monotherapy versus that of LTFC administered in the morning in a group of patients with POAG or OH. Both regimens demonstrated comparable efficacy and no significant difference was detected either in day-time or night-time pressures. In a meta-analysis of 24-h efficacy studies, the LTFC has been reported to achieve a mean circadian IOP reduction of 33% (Stewart et al., 2008).

4.2 TRAVOPROST AND TIMOLOL

A 4-month crossover study compared the efficacy of morning- versus evening-dosed travoprost/timolol fixed combination (TTFC) in 32 patients with POAG or XFG (Konstas et al., 2009b). Both dosing schemes of TTFC were efficacious in reducing

pressures at all time points and for the mean 24-h IOP (untreated baseline of the study was 27.7 mm Hg). The evening administration of TTFC however provided lower mean 24-h IOP (18.4 vs. 19.2 mm Hg) and lower 24-h fluctuation of IOP (3.8 vs. 5.1 mm Hg) in comparison with the morning administration of TTFC. More recently, an observer-masked, crossover, 3-month study, examined the 24-h efficacy of branded BAK-preserved LTFC and Polyquad-preserved TTFC in a cohort of 42 open-angle glaucoma patients inadequately controlled with latanoprost monotherapy (day-time IOP > 20 mm Hg on two separate occasions) (Konstas et al., 2014). The mean 24-h latanoprost-treated IOP was 21.5 ± 1.6 mm Hg. Both fixed combinations provided significantly better efficacy at each time point and for the mean, peak, and fluctuation of 24-h IOP. However, Polyquad-preserved TTFC provided significantly lower IOP at 6 PM (18.6 ± 2.5 vs. 19.5 ± 2.7 mm Hg; $p < 0.001$) and significantly lower mean 24-h IOP (18.9 ± 2.2 vs. 19.3 ± 2.3 mm Hg; $p = 0.004$).

4.3 BIMATOPROST AND TIMOLOL

A 3-month crossover trial evaluated the 24-h efficacy of the morning- or evening-dosed bimatoprost/timolol fixed combination (BTFC) in 60 patients with XFG (Konstas et al., 2010a). Study patients were treated with bimatoprost monotherapy for 6 weeks first before they were switched to the morning- or evening-dosed BTFC. The mean untreated 24-h IOP in this study was 29.0 mm Hg. The mean 24-h efficacy with morning- and evening-dosed BTFC was 10.2 and 9.8 mm Hg, respectively ($p = 0.005$). Both the morning and evening administration of BTFC were more efficacious than bimatoprost monotherapy at all time points evaluated. In a subsequent investigator-masked, 3-month, crossover trial, the 24-h efficacy of evening-dosed BTFC was compared with that of latanoprost when used as first choice therapy. Altogether, 37 at-risk exfoliation patients with high baseline IOP were enrolled in this trial (Konstas et al., 2013b). The mean untreated 24-h IOP was 31.1 mm Hg. As expected, BTFC achieved significantly better 24-h IOP control than latanoprost (18.9 vs. 21.2 mm Hg; $p < 0.001$). Compared to latanoprost, BTFC was significantly more efficacious at every time point, for the mean trough and peak 24-h IOP ($p < 0.001$).

5 COMBINATIONS OF CARBONIC ANHYDRASE INHIBITORS WITH β-BLOCKERS

5.1 DORZOLAMIDE AND TIMOLOL

The first 24-h study to investigate the efficacy of the dorzolamide/timolol fixed combination (DTFC) was a 6-week, crossover trial (Konstas et al., 2003) which compared DTFC versus latanoprost in 33 patients with POAG or OH. Both medications significantly reduced the mean untreated circadian IOP (25.8 ± 1.4 mm Hg). However, DTFC was found to be statistically more efficacious than latanoprost over the 24-h period (15.3 ± 2.0 vs. 15.9 ± 2.3 mm Hg; $p = 0.05$). There was no statistically

significant differences at individual time points between the two treatments except at the 10 PM time point, when DTFC was significantly more efficacious than latanoprost (14.6 ± 2.7 vs. 16.6 ± 3.1 mm Hg; $p = 0.006$). A subsequent 6-week, crossover trial investigated the 24-h efficacy of DTFC versus that of latanoprost as initial therapy in 27 previously untreated POAG patients (Quaranta et al., 2008a). In this study, there was a statistically significant difference in terms of 24-h efficacy between treatments of 1.3 mm Hg in favor of DTFC.

The DTFC has been reported to achieve an overall mean 24-h reduction of 26% in a meta-analysis that investigated the 24-h efficacy of IOP-lowering medications (Stewart et al., 2008). A randomized, parallel-arms 24-h trial compared the ocular hypotensive effect of DTFC versus timolol in a sample of 232 patients with open-angle glaucoma or OH (Feldman et al., 2008). After 2 months of therapy, both DTFC and timolol significantly reduced IOP from baseline at all time points. When the two therapies were directly compared, DTFC was found to achieve lower mean day-time pressure and superior efficacy at 10 AM and 2 PM.

In another crossover trial that included 53 patients with POAG or OH, Konstas et al. (2008b) compared the short-term (2 months) and mid-term (6 months) 24-h efficacy of DTFC versus that of latanoprost. Both medications significantly reduced the mean 24-h untreated baseline IOP (25.2 mm Hg) at month 2 and 6. When the two treatments were directly compared, after 2 months, DTFC was significantly more efficacious than latanoprost for the mean 24-h IOP, as well as the peak and trough 24-h IOP. Interestingly, the superiority of DTFC over latanoprost was not confirmed at the mid-term 6-month comparison. The reason for this therapeutic equivalence between the two therapies at 6 months was explained by the slight increase of efficacy (0.3 mm Hg) seen with latanoprost at 6 months. Consequently, it was concluded that although DTFC reaches its maximal efficacy at 2 months, latanoprost (and conceivably all prostaglandins) may exhibit a further increase in efficacy beyond the first 2–3 months.

Orzalesi et al. (2003) in a 1-month crossover study evaluated the 24-h IOP characteristics of 20 patients with POAG or OH who were treated with DTFC, latanoprost, or brimonidine. The effectiveness of DTFC was superior to that of latanoprost at 9 AM and that of brimonidine at 3 AM, 9 AM, 3 PM, and 6 PM. In a more recent double-masked, 6-week, crossover study on 33 POAG patients, Eren et al. (2012) compared the 24-h efficacy of DTFC versus that of LTFC. The untreated baseline 24-h IOP was 25.1 mm Hg. In this study, LTFC was more efficacious in lowering the mean 24-h IOP (16.3 vs. 17.3 mm Hg; $p = 0.001$) and the peak 24-h IOP (18.5 vs. 19.9 mm Hg; $p = 0.002$).

5.2 BRINZOLAMIDE AND TIMOLOL

An observer-masked, crossover study with POAG and XFG patients compared the 24-h IOP reduction achieved with the brinzolamide/timolol or the brimonidine/timolol fixed combination when added to travoprost (Konstas et al., 2013a). The investigators reported that brinzolamide/timolol fixed combination resulted in

a significantly lower mean 24-h IOP (17.2 mm Hg) than brimonidine/timolol fixed combination (18.0 mm Hg) when added to eyes inadequately controlled with travoprost monotherapy. More specifically, lower pressures in late afternoon and night (6 PM until 2 AM) were observed with the adjunct use of the brinzolamide/timolol fixed combination compared to the adjunct use of the brimonidine/timolol fixed combination in travoprost-treated eyes ($p \leq 0.036$).

6 COMBINATIONS OF CARBONIC ANHYDRASE INHIBITORS WITH A PROSTAGLANDIN ANALOGUE

6.1 COMBINATION OF DORZOLAMIDE OR BRINZOLAMIDE AND LATANOPROST

Three studies have evaluated the 24-h efficacy of dorzolamide when used as an adjunctive therapy to latanoprost. First, a double-masked, crossover study with 31 POAG patients (Konstas et al., 2005b) examined the 24-h IOP-lowering effect of dorzolamide versus that of brimonidine purite when added to latanoprost. The mean latanoprost-treated 24-h IOP (19.0 mm Hg) in this trial was significantly reduced to 16.9 and 16.8 mm Hg following the addition of brimonidine purite and dorzolamide, respectively. Second, in a crossover trial with 36 POAG patients treated with latanoprost, Tamer and Oksuz (2007) reported an additional ocular hypotensive effect of 3.2 mm Hg with dorzolamide when employed as adjunctive therapy over the 24-h period. The respective additional 24-h effect of timolol added to latanoprost was 2.6 mm Hg. Considering individual time points, the additive effect of dorzolamide was found to be superior to that of timolol in 5 of the 8 measurement time points. Third, a 1-month crossover trial on 20 POAG, ocular hypertensive, or chronic angle-closure glaucoma subjects evaluated the adjunctive 24-h efficacy of dorzolamide dosed twice, or three times daily versus brinzolamide dosed twice daily when added to latanoprost (Nakamura et al., 2009). Compared to the latanoprost-treated baseline 24-h IOP (20.0 mm Hg), both twice-daily and three times daily dosed dorzolamide (16.1 and 15.8 mm Hg, respectively) and brinzolamide (16.4 mm Hg) significantly reduced 24-h IOP. When directly compared, the three regimens were found equally efficacious.

7 COMBINATION OF AN ALPHA-2 AGONIST AND A β-BLOCKER

7.1 COMBINATION OF BRIMONIDINE AND TIMOLOL

The 24-h efficacy of the brimonidine/timolol fixed combination versus the concomitant administration of the individual constituents was evaluated in a 3-month, crossover trial that included 28 patients with POAG or OH (Konstas et al., 2008a). Both the fixed and the unfixed combination significantly lowered the untreated baseline 24-h IOP (24.6 mm Hg) by 22% to identical levels (19.2 mm Hg).

8 COMBINATION OF AN ALPHA-2 AGONIST AND A CARBONIC ANHYDRASE INHIBITOR

The first fixed combination without a β-blocker (brinzolamide 1%/brimonidine tartrate 0.2% ophthalmic suspension, Simbrinza™, Alcon) has recently been approved in the United States and Europe for the treatment of open-angle glaucoma or OH. The new fixed combination is labelled for three times a day administration in the United States and twice a day administration in Europe. Conceivably, this medication may provide uniform overall 24-h efficacy by containing targeted day/night constituents with brimonidine being effective during the day and brinzolamide being more efficacious during the night. Nevertheless, the 24-h efficacy of this new fixed combination remains to be elucidated. Of interest may also be the comparison between the two dosing regimens (twice and three times a day).

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