



Twenty-four-hour efficacy of the brinzolamide 1%/brimonidine 0.2% fixed combination: what does the new evidence tell us?

Anastasios G. Konstas^{1,2}, Andreas Katsanos³

¹1st University Department of Ophthalmology, ²3rd University Department of Ophthalmology, Aristotle University of Thessaloniki, Thessaloniki, Greece; ³Ophthalmology Department, University of Ioannina, Ioannina, Greece

Correspondence to: Prof. Anastasios G. Konstas. 1st University Department of Ophthalmology, Aristotle University of Thessaloniki, Thessaloniki, Greece. Email: konstas@med.auth.gr.

Comment on: Weinreb RN, Bacharach J, Fechtner RD, *et al.* 24-Hour Intraocular Pressure Control with Fixed-dose Combination Brinzolamide 1%/Brimonidine 0.2%: A Multicenter, Randomized Trial. *Ophthalmology* 2018. [Epub ahead of print].

Received: 06 February 2019; Accepted: 28 February 2019; Published: 04 March 2019.

doi: 10.21037/aes.2019.02.02

View this article at: <http://dx.doi.org/10.21037/aes.2019.02.02>

The importance of 24-hour intraocular pressure (IOP) assessment has increasingly being recognized in recent years (1-4). In cardiology, 24-hour blood pressure monitoring is widely employed to accurately characterize a patient's blood pressure profile and to guide management. Similarly, in glaucoma care 24-hour IOP assessment can delineate a patient's true pressure characteristics and guide stepwise decision-making (1,5). Nevertheless, the precise predictive value of a short-term 24-hour untreated, or treated curve upon the long-term prognosis of glaucoma remains to be elucidated. There is some evidence suggesting that those patients with fluctuating 24-hour IOP characteristics manifest greater degrees of ocular damage and functional deterioration than those with stable pressures (1,6-8). Consequently, notwithstanding practicality issues, monitoring untreated 24-hour IOP characteristics can provide important evidence to tailor more precisely target pressure requirements and optimize therapy selection. In treated glaucoma patients, 24-hour IOP monitoring determines the quality of IOP control and detects detrimental predictive features such as high peak and 24-hour IOP wide fluctuation. This evidence greatly influenced the management of progressive glaucoma patients on medical therapy with "apparently good IOP control" as determined by single IOP measurements in the clinic (3,4).

Beyond patient management, 24-hour studies have enabled researchers to better describe the true 24-hour efficacy of many novel therapeutic options over the last

2 decades (6,7). This is more crucial with available medical therapy options as most medications lower IOP more during the day than during the night (5-7). Controlled 24-hour efficacy evidence over the years has unveiled the true magnitude of IOP-lowering provided by several antiglaucoma medications and directly impacted their adoption and popularity in clinical practice. For example, a key reason for the adoption of prostaglandins as first option therapy worldwide was their superior 24-hour efficacy (6-7). In contrast, the reduced efficacy of timolol and brimonidine during the night reduced their appeal in glaucoma management. Published 24-hour studies have delineated efficacy results which would have remained unknown if only daytime assessment had been performed (9-11).

In view of the key role played by 24-hour IOP monitoring in the evaluation of a novel antiglaucoma medication, the recently published study by Weinreb and coworkers (12) is a welcome addition to the existing literature. This is especially so because the authors evaluated a relatively new therapeutic option, the brinzolamide 1%/brimonidine 0.2% fixed combination (BBFC), which represents the first commercially available beta blocker-free antiglaucoma fixed combination. As such, BBFC may prove a valuable option for patients in whom topical beta-blockers are contraindicated due to systemic conditions such as asthma or bradycardia.

In their study, Weinreb *et al.* (12) present the results of a 4-week, prospective, multicenter, double-masked, placebo-controlled trial in 16 academic and non-academic sites in

the USA. Following an appropriate wash-out period and a baseline 24-hour IOP curve, 125 subjects with either open-angle glaucoma, or ocular hypertension were randomized 1:1 to either BBFC or placebo, each dosed 3 times daily for 4 weeks. A treated 24-hour IOP curve was repeated at the end of the 4-week period with IOP readings performed every 2 hours in the habitual position (sitting IOP between 08:00 and 20:00 and supine IOP readings between 22:00 and 06:00). The IOP was evaluated with a pneumotonometer in 16 overnight facilities with controlled lighting conditions. The authors reported that BBFC significantly reduced mean 24-hour IOP compared to placebo [least squares mean difference (95% confidence interval): -2.5 (-3.3 to -1.7)]. Therapy with BBFC reduced mean IOP from baseline by 14–22% during the daytime period, and by 6–9% during the nocturnal period. The frequency of adverse events was similar between the 2 groups during this 4-week trial.

Consequently, it appears that despite the thrice-daily dosage, the overall efficacy of BBFC was modest. Moreover, the nocturnal reduction in least squares mean IOP of 1.2 mmHg with BBFC *vs.* placebo did not achieve statistical significance in the full analysis set (12). This is consistent to some extent with previous 24-hour evidence showing reduced efficacy of brimonidine at night (11,13,14). It is more surprising though with regard to the second component of the fixed combination: brinzolamide. A meta-analysis of 24-hour studies (15) reported that dorzolamide (a carbonic anhydrase inhibitor just like brinzolamide) was the only glaucoma medication working better during the night (21%) than during the day (16%). If carbonic anhydrase inhibitors are the only class of antiglaucoma medications working better during the night than during the day (6,7,15) the intriguing question then is why this efficacy was not observed in the study with BBFC? Although this pattern of enhanced night-time efficacy relies on dorzolamide studies (no published studies exist as yet with brinzolamide) it should be noted that satisfactory night-time efficacy has been previously recorded in 24-hour studies with other fixed combinations: the timolol/dorzolamide (16) and timolol/brinzolamide (17) fixed combinations. We can only hypothesize that the lower magnitude of 24-hour IOP reduction documented here with BBFC may be due to variations in study design, patient selection and relatively low baseline pressures.

The study by Weinreb *et al.* (12) has certain methodological strengths. With 123 completed patients it is the largest 24-hour study ever performed and obviously is more than adequately powered. Its design (double-

masked, placebo-controlled study) is optimal and it should be highlighted that few controlled studies to date have included a placebo arm in assessing the efficacy of a therapy option. Indeed, to the best of our knowledge this is the first 24-hour study, which is placebo-controlled. Finally, the present study has been conducted in strictly regulated conditions of a sleep laboratory.

On the other hand, as with all studies there are limitations. First, IOP measurements in several of the participating overnight facilities were performed by trained, but inexperienced personnel. Indeed, many of the participating sites established their overnight facilities specifically for this study. Secondly, the rigorously controlled conditions and the IOP and blood pressure monitoring every 2 hours may impact the routine circadian activity of some study patients. Inherent problems with all 24-hour monitoring studies are that IOP measurements may be influenced by factors such as the stress of waking, and the precision of tonometry in low-light conditions. An important methodological consideration is that by employing a pneumotonometer to evaluate IOP, the results of the present study do not reflect the Goldmann gold standard employed in clinical practice and the evidence accumulated with Goldmann technology in many other previous 24-hour studies.

The study by Weinreb *et al.* (12) represents a significant contribution to the available evidence on the 24-hour efficacy of the recently introduced BBFC (18). Several issues with regard to BBFC need to be addressed in the future. In Europe BBFC is mostly prescribed twice daily. It remains to be seen what the 24-hour efficacy of BBFC is when dosed twice daily. This issue is clinically relevant as it will influence 24-hour efficacy, long-term tolerability and adherence (5,19,20). Another question is to what extent BBFC causes delayed hypersensitivity reactions similar in frequency and severity to those of brimonidine monotherapy (21). Long-term clinical studies and cumulative clinical experience are desirable to better understand the safety and tolerability profile of this novel combination. Future studies should determine the comparative 24-hour efficacy of this medication versus that of more established therapy options (22).

It should not be overlooked that the real efficacy profile of all available anti-glaucoma medications would not have been detected without a complete 24-hour IOP evaluation. How this evidence reflects upon real life efficacy, popularity and long-term prognosis remains to be elucidated. Nevertheless, Weinreb and colleagues (12) should be applauded for evaluating the 24-hour efficacy of BBFC

in a large controlled study and for establishing the true IOP-lowering characteristics of this novel fixed combination for the first time, as well as setting the bar for future investigations of this nature.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Eye Science*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/aes.2019.02.02>). Professor AG Konstas has received research support from Allergan, Bayer Hellas, Pharmathen Hellas S.A. and Santen as well as honoraria from Allergan, Novartis, Santen and had congress expenses covered by Allergan, Bayer Hellas, Santen and Vianex. Assistant Professor A Katsanos has received honoraria from Allergan, Laboratoires Théa, Novartis, Vianex and had congress expenses covered by Laboratoires Théa and Vianex.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

1. Quaranta L, Katsanos A, Russo A, et al. 24-hour intraocular pressure and ocular perfusion pressure in glaucoma. *Surv Ophthalmol* 2013;58:26-41.
2. Asrani S, Zeimer R, Wilensky J, et al. Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma. *J Glaucoma* 2000;9:134-42.
3. Barkana Y, Anis S, Liebmann J, et al. Clinical utility of intraocular pressure monitoring outside of normal office hours in patients with glaucoma. *Arch Ophthalmol* 2006;124:793-7.
4. Hughes E, Spry P, Diamond J. 24-hour monitoring of intraocular pressure in glaucoma management: a retrospective review. *J Glaucoma* 2003;12:232-6.
5. Konstas AG, Kahook MY, Araie M, et al. Diurnal and 24-h Intraocular Pressures in Glaucoma: Monitoring Strategies and Impact on Prognosis and Treatment. *Adv Ther* 2018;35:1775-804.
6. Konstas AG, Quaranta L, Bozkurt B, et al. 24-h Efficacy of Glaucoma Treatment Options. *Adv Ther* 2016;33:481-517.
7. Konstas AG, Katsanos A, Quaranta L, et al. Twenty-four hour efficacy of glaucoma medications. *Prog Brain Res* 2015;221:297-318.
8. Konstas AG, Mantziris DA, Stewart WC. Diurnal intraocular pressure in untreated exfoliation and primary open-angle glaucoma. *Arch Ophthalmol* 1997;115:182-5.
9. Konstas AG, Quaranta L, Katsanos A, et al. Twenty-four hour efficacy with preservative free tafluprost compared with latanoprost in patients with primary open angle glaucoma or ocular hypertension. *Br J Ophthalmol* 2013;97:1510-5.
10. Konstas AG, Mikropoulos DG, Embeslidis TA, et al. 24-h Intraocular pressure control with evening-dosed travoprost/timolol, compared with latanoprost/timolol, fixed combinations in exfoliative glaucoma. *Eye (Lond)* 2010;24:1606-13.
11. Liu JHK, Medeiros FA, Slight JR, et al. Diurnal and nocturnal effects of brimonidine monotherapy on intraocular pressure. *Ophthalmology* 2010;117:2075-9.
12. Weinreb RN, Bacharach J, Fechtner RD, et al. 24-Hour Intraocular Pressure Control with Fixed-dose Combination Brinzolamide 1%/Brimonidine 0.2%: A Multicenter, Randomized Trial. *Ophthalmology* 2018. [Epub ahead of print].
13. Konstas AG, Stewart WC, Topouzis F, et al. Brimonidine 0.2% given two or three times daily versus timolol maleate 0.5% in primary open-angle glaucoma. *Am J Ophthalmol* 2001;131:729-33.
14. Quaranta L, Gandolfo F, Turano R, et al. Effects of topical hypotensive drugs on circadian IOP, blood pressure, and calculated diastolic ocular perfusion

- pressure in patients with glaucoma. *Invest Ophthalmol Vis Sci* 2006;47:2917-23.
15. Stewart WC, Konstas AG, Nelson LA, et al. Meta-analysis of 24-hour intraocular pressure studies evaluating the efficacy of glaucoma medicines. *Ophthalmology* 2008;115:1117-22.e1.
 16. Konstas AG, Quaranta L, Yan DB, et al. Twenty-four hour efficacy with the dorzolamide/timolol-fixed combination compared with the brimonidine/timolol-fixed combination in primary open-angle glaucoma. *Eye (Lond)* 2012;26:80-7.
 17. Konstas AG, Holló G, Haidich AB, et al. Comparison of 24-hour intraocular pressure reduction obtained with brinzolamide/timolol or brimonidine/timolol fixed-combination adjunctive to travoprost therapy. *J Ocul Pharmacol Ther* 2013;29:652-7.
 18. Seibold LK, DeWitt PE, Kroehl ME, et al. The 24-Hour Effects of Brinzolamide/Brimonidine Fixed Combination and Timolol on Intraocular Pressure and Ocular Perfusion Pressure. *J Ocul Pharmacol Ther* 2017;33:161-9.
 19. Baudouin C, Labbé A, Liang H, et al. Preservatives in eyedrops: the good, the bad and the ugly. *Prog Retin Eye Res* 2010;29:312-34.
 20. Tsai JC, McClure CA, Ramos SE, et al. Compliance barriers in glaucoma: a systematic classification. *J Glaucoma* 2003;12:393-8.
 21. Watts P, Hawksworth N. Delayed hypersensitivity to brimonidine tartrate 0.2% associated with high intraocular pressure. *Eye (Lond)* 2002;16:132-5.
 22. Riva I, Katsanos A, Floriani I, et al. Long-term 24-hour intraocular pressure control with travoprost monotherapy in patients with primary open-angle glaucoma. *J Glaucoma* 2014;23:535-40.

doi: 10.21037/aes.2019.02.02

Cite this article as: Konstas AG, Katsanos A. Twenty-four-hour efficacy of the brinzolamide 1%/brimonidine 0.2% fixed combination: what does the new evidence tell us? *Ann Eye Sci* 2019;4:11.