Intraocular pressure reduction of fixed combination timolol maleate 0.5% and dorzolamide 2% (Cosopt) administered three times a day

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Purpose: To evaluate the safety and efficacy in intraocular pressure (IOP) reduction of increasing Cosopt dosage from twice to three times a day.

Methods: The study included patients with primary open-angle glaucoma or ocular hypertension. After a washout period, IOP was measured at baseline, after 4 weeks of treatment with Cosopt twice a day, and after another 4 weeks of treatment with Cosopt three times a day. Blood pressure, heart rate, and oxygen saturation levels were also recorded.

Results: Twenty-nine eyes of 29 patients were included. Increasing Cosopt dosage resulted in a statistically significant ($P_{0.001}$) additional reduction in IOP of 2.2 ± 1.58 mmHg (10.69% ± 7.49% of the baseline IOP values). There were no local or systemic adverse effects.

Conclusion: Treatment with Cosopt three times a day was more effective in reducing IOP than twice a day, with no effect on safety.

Keywords: Cosopt, timolol, dorzolamide, glaucoma, intraocular pressure, dosage

Introduction

Primary open-angle glaucoma (POAG) is a chronic progressive disease, characterized by painless intraocular pressure (IOP) elevation, optic nerve damage, and visual field loss. POAG is the most common adult-onset type of glaucoma in the western world, and incidence increases with age. It is one of the most common causes of chronic visual impairment and the second leading cause of blindness in the world.

Large scale clinical studies have demonstrated the importance of early IOP reduction in order to prevent optic nerve damage and visual loss. Specifically, the Early Manifest Glaucoma Trial has shown that every 1 mmHg reduction in IOP is important, and is associated with approximately 10% reduction in the risk of disease progression.

First-line treatment typically consists of monotherapy with a single agent, and if the IOP reduction is insufficient treatment is switched to an alternative monotherapy or combination with a second agent. In patients requiring treatment with more than one agent, combination therapy is usually preferred since it is associated with increased compliance. However, it has been shown that in reality, combination therapy is often administered as first-line therapy for patients diagnosed with POAG or ocular hypertension (OHT).
A common combination treatment for glaucoma is Cosopt® (Merck & Co, Inc, Whitehouse Station, NJ), which is a fixed single dose combination of maleate timolol 0.5% (a nonselective beta-blocker) and dorzolamide 2.0% (a carbonic anhydrase inhibitor). Combination therapy with Cosopt has been consistently proven to be more effective in IOP reduction than monotherapy with either timolol or dorzolamide. It has also been demonstrated that treatment with Cosopt has been more effective in IOP reduction than monotherapy with either timolol or dorzolamide. Cosopt has been consistently proven to be more effective (a carbonic anhydrase inhibitor). Combination therapy with 0.5% (a nonselective beta-blocker) and dorzolamide 2.0% increased to three times a day for another 4 weeks. Patients were then followed for another 4 weeks and then the dosage was increased to three times a day for another 4 weeks.

IOP was measured in all patients at baseline, after 4 weeks of treatment with Cosopt twice a day, and after another 4 weeks of treatment with Cosopt three times a day. Baseline measurements were made after a 4 week washout period with Cosopt twice a day, to eliminate any effect of previous treatment. All measurements were made by Goldmann applanation tonometry, and were performed by a single ophthalmologist. All measurements were taken between 8–10 am, prior to instillation of the morning drop of Cosopt.

At each time point heart rate, blood pressure, and blood oxygen saturation levels were measured. Heart rate and blood pressure were measured by an automatic device and oxygen saturation was measured by a pulse oximeter. All measurements were made by the same physician at the time of IOP measurement.

The study protocol was reviewed and approved by the Institutional Review Board, and a written informed consent was obtained from all participants.

Descriptive statistics including the mean and standard deviation (SD) were produced for all continuous study variables. The statistical significance of the changes in IOP, systolic and diastolic blood pressure, heart rate, and oxygen saturation levels between time points was assessed by Student’s t-test for paired observations. The statistical significance level was set at 0.05. Data were analyzed using SPSS for Windows (version 17.0; SPSS Inc, Chicago, IL).

Results
Twenty-nine eyes of 29 patients were included in the study. Patients included 17 men (58.7%) and 12 women (41.3%), with a mean age of 71.1 years ± 7.9 (SD) (range 59–85 years).

At baseline, mean IOP levels were 21.11 ± 3.14 mmHg (range 13–27 mmHg). Mean systolic and diastolic blood pressure values were 146.31 ± 14.45 mmHg and 76.55 ± 10.87 mmHg, respectively. Mean heart rate was 75.06 ± 10.95 bpm, and mean oxygen saturation levels were 98.17% ± 1.31%.

After 4 weeks of treatment with Cosopt twice a day, mean IOP levels were 15.34 ± 12.86 mmHg (range 10–20 mmHg). Mean systolic and diastolic blood pressure values were 142.96 ± 12.07 mmHg and 72.82 ± 10.44 mmHg, respectively. Mean heart rate was 71.62 ± 12.86 bpm, and mean oxygen saturation levels were 97.96% ± 1.20%.

Methods
Twenty-nine patients with POAG or OHT were included in this study. All patients were 18 years or older, and were diagnosed with POAG or OHT by a glaucoma specialist after undergoing detailed ophthalmologic examination including evaluation of glaucomatous optic disc damage and gonioscopy, IOP measurements by applanation tonometry, and automated perimetry. Patients with advanced glaucoma (mean deviation lower than −12 dB or presence of central scotoma) were not included.

Exclusion criteria included closed-angle glaucoma or secondary open-angle glaucoma, such as pseudoexfoliation or pigment-dispersion syndrome. Also excluded were patients receiving systemic treatment with beta-blockers or carbonic anhydrase inhibitors for any reason, and patients with systemic conditions that may be adversely affected by timolol or dorzolamide, such as asthma, hypotension, bradycardia, cardiac arrhythmia, impaired kidney function, or impaired hepatic function. Patients who had previously undergone surgery or laser treatment to reduce IOP were also excluded. All patients had visual acuity of 20/80 or better. Only one eye of each patient was included in the study. If both eyes of a patient met the inclusion criteria, the left eye was routinely chosen arbitrarily.

All patients were previously treated only by either dorzolamide or timolol, and treatment was switched to Cosopt twice a day for a washout period of 4 weeks. Patients were then followed for another 4 weeks and then the dosage was increased to three times a day for another 4 weeks.
After another 4 weeks of treatment with Cosopt three times a day, mean IOP levels were 13.17 ± 1.81 mmHg (range 9–17 mmHg). Mean systolic and diastolic blood pressure values were 145.51 ± 15.75 mmHg and 74.93 ± 12.46 mmHg, respectively. Mean heart rate was 71.20 ± 12.16 bpm, and mean oxygen saturation levels were 98.06% ± 0.96%. Data are presented in Table 1.

Comparison of IOP values after 4 weeks of treatment with Cosopt twice a day and after another 4 weeks of Cosopt three times a day revealed an additional reduction of IOP that varied between 0–6 mmHg. The higher dosage resulted in a mean additional reduction of 2.2 ± 1.58 mmHg in IOP, which corresponded with a change of 10.69% ± 7.49% of the baseline IOP values. This reduction was statistically significant (P < 0.001). Data are presented in Figure 1.

Changes in systolic and diastolic blood pressure, heart rate, and oxygen saturation levels between all three time points were minimal and of no statistical significance. No patient complained of ocular surface irritation, and no patient suffered any systemic or local adverse effect that required cessation of Cosopt therapy.

Discussion

In this study, treatment with Cosopt twice a day caused a mean IOP reduction of 25.90% ± 10.37%, comparable to the results of previous studies of its efficacy.11,13,14,16,17,19–25 This effect on IOP was expected, as most patients included in this study did not receive previous treatment. After another 4 weeks of treatment with an increased dosage of Cosopt three times a day, IOP had decreased by another 2.2 ± 1.58 mmHg, corresponding to an additional reduction of 10.69% ± 7.49% of the baseline IOP value. The increased dosage was not associated with any significant systemic adverse effect or any change in blood pressure, heart rate, or oxygen saturation. It was also not associated with any local adverse effects or tolerability.

The strengths of this study include its prospective nature, exclusion of patients with any glaucoma other than POAG/OHT, and its open label design emulating the real life clinical setting. Potential limitations of this study include its relatively small cohort size and short treatment duration. However, the purpose of the study was to assess the effect on IOP of increasing Cosopt dosage from twice to three times a day, and the study was designed for this comparison, which revealed statistically significant results.

This study is the first to evaluate Cosopt administered three times a day. Our results indicate that increasing Cosopt dosage from twice to three times a day is associated with increased efficacy in IOP reduction, with no change in its safety profile. The additional reduction in IOP was considerable and statistically significant. This new finding is of clinical importance, as it has been demonstrated that every
1 mmHg reduction in IOP is associated with approximately 10% reduction in the risk of glaucoma progression. Since dorzolamide by itself is usually administered three times a day, it may be possible that it does not exert its full effect when given only twice a day as a component of Cosopt.

In conclusion, we found that Cosopt administered three times a day is more effective and as safe as when administered twice a day. Based on our results, we suggest that increasing Cosopt dosage to three times a day may be useful clinically in POAG/OHT patients in which a small yet significant additional reduction in IOP is required. Instead of changing or adding other antiglaucoma agents, this treatment may be a safe and simple way to achieve the target IOP. We also believe that increasing the dosage will not adversely affect patients’ compliance. It is possible that in POAG/OHT patients treated with Cosopt in which further IOP reduction is required, increasing the dosage to three times a day may be considered before other medications or surgery. Further large scale studies are required to corroborate our findings and establish their place in clinical practice.

Disclosure
No author has any proprietary interest in the publication of this report. No funds or grants were issued to support this study.

References
1. Sommer A, Tielsch JM, Katz J, et al. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore eye survey. Arch Ophthalmol. 1991;109:1090–1095.
2. Rouland JF, Berdeaux G, Lafuma A. The economic burden of glaucoma and ocular hypertension: implications for patient management. Drugs Aging. 2005;22:315–321.
3. Lee AG, Beaver HA. Visual loss in the elderly – Part I: Chronic visual loss: what to recognize and when to refer. Clinical Geriatrics. 2003;11:46–53.
4. Kingman S. Glaucoma is second leading cause of blindness globally. Bull World Health Org. 2004;82:887–888.
5. Leske MC, Heijl DK, Hussein M, et al. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. Arch Ophthalmol. 2003;121:48–56.
6. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120:701–713.
7. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2002;120:1268–1279.
8. Leske MC, Heijl A, Hyman L, Bengtsson B, Komaroff E. Factors for progression and glaucoma treatment: the Early Manifest Glaucoma Trial. Curr Opin Ophthalmol. 2004;15:102–106.
9. European Glaucoma Society. Terminology and Guidelines for Glaucoma. 3rd ed. Savona, Italy: Editrice Dogma S.r.l.; 2004.
10. Remo SJ, Wang-Pui S. Comparison of latanoprost with fixed combination dorzolamide and timolol in adult patients with elevated intraocular pressure: an eight week, randomized, open-label, parallel-group, multicenter study in Latin America. Clin Ther. 2004;26:755–756.
11. Gugleta K, Orgul S, Flammer J. Experience with Cosopt, the fixed combination of timolol and dorzolamide, after switch from free combination of timolol and dorzolamide, in Swiss ophthalmologists’ offices. Curr Med Res Opin. 2003;19:330–335.
12. Crocchioni AC, Harasymowycz P, Hutnik CM, et al. Effectiveness of dorzolamide–timolol (COSOPT) in patients who were treatment naïve for open-angle glaucoma or ocular hypertension: the COSOPT first-line study. J Ocul Pharmacol Ther. 2010;26:503–511.
13. Clineschmidt CM, Williams RD, Snyder E, Adamsons IA. A randomized trial in patients inadequately controlled with timolol alone comparing the dorzolamide-timolol combination to monotherapy with timolol or dorzolamide. Dorzolamide-Timolol Combination Study Group. Ophthalmology. 1998;105:1952–1959.
14. Boyle JE, Ghosh K, Gieter DK, Adamsons IA. A randomized trial comparing the dorzolamide-timolol combination given twice daily to monotherapy with timolol and dorzolamide. Ophthalmology. 1998;105:1945–1951.
15. Toris CB, Zhan GL, Yablonski ME, Camras CB. Effects on aqueous flow of dorzolamide combined with either timolol or acetazolamide. J Glaucoma. 2004;13:210–215.
16. Strohmaier K, Snyder E, Dubiner H, Adamsons I. The efficacy and safety of the dorzolamide-timolol combination versus the concomitant administration of its components. Dorzolamide-Timolol Study Group. Ophthalmology. 1998;105:1936–1944.
17. Francis BA, Du LT, Berke S, Ehrenhaus M, Minkler DS; Cosopt Study Group. Comparing the fixed combination dorzolamide-timolol (Cosopt) to concomitant administration of 2% dorzolamide (Trusopt) and 0.5% timolol – a randomized controlled trial and a replacement study. J Clin Pharm Ther. 2004;29:375–380.
18. Hutzelmann J, Owens S, Shadden E, Adamsmons I, Vargas E. Comparison of the safety and efficacy of the fixed combination of dorzolamide/timolol and the concomitant administration of dorzolamide/timolol: a clinical equivalence study. International Clinical Equivalence Study Group. Br J Ophthalmol. 1998;82:1249–1253.
19. Henderer JD, Wilson RP, Moster MR, et al. Timolol/dorzolamide combination therapy as initial treatment for intraocular pressure over 30 mmHg. J Glaucoma. 2005;14:267–270.
20. Renieri G, Führer K, Scheithe K, Lorenz K, Pfeiffer N, Thieme H. Efficacy and tolerability of preservative-free eye drops containing a fixed combination of dorzolamide and timolol in glaucoma patients. J Ocul Pharmacol Ther. 2010;26:597–603.
21. Shadden A, Adamsmons IA, Getson AJ, et al. Comparison of the efficacy and tolerability of preservative-free and preservative-containing formulations of the dorzolamide/timolol fixed combination (COSOPT™) in patients with elevated intraocular pressure in a randomized clinical trial. Graefes Arch Clin Exp Ophthalmol. 2010;248:1757–1764.
22. Hutnik C, Neima D, Ibrahim F, et al. Tolerability and effectiveness of preservative-free dorzolamide-timolol (preservative-free COSOPT) in patients with open-angle glaucoma or ocular hypertension. Clin Ophthalmol. 2010;4:581–590.
23. Jothi R, Ismail AM, Senthamarai R, Pal S. A comparative study on the efficacy, safety, and cost-effectiveness of brimonopro/timolol and dorzolamide/timolol combinations in glaucoma patients. Indian J Pharmacol. 2010;42:362–365.
24. Frampton JE, Perry CM. Topical dorzolamide 2%/timolol 0.5% ophthalmic solution: a review of its use in the treatment of glaucoma and ocular hypertension. Drugs Aging. 2006;23:977–995.
25. Sall KN, Greff LJ, Johnson-Pratt LR, et al. Dorzolamide/timolol combination versus concomitant administration of brimonidine and timolol. Ophthalmology. 2003;110:615–624.
Intraocular pressure reduction by Cosopt 3 times a day