ORIGINAL ARTICLE

Carbonic anhydrase inhibitors as fourth drug in primary glaucomas: Is it worth it?

Verena Ribeiro Juncal, MD,[*] Felipe Abdo Jorge, MD,[*] Augusto Paranhos Jr, MD, PhD,[*] Tiago Santos Prata, MD, PhD[*,†]

ABSTRACT • RÉSUMÉ

Objective: To evaluate the effectiveness of carbonic anhydrase inhibitors as the fourth drug regarding intraocular pressure (IOP) control in patients with primary glaucomas.

Design: Single-centre, prospective study.

Participants: Twenty-five eyes from 25 patients with primary glaucomas treated concomitantly with a topical prostaglandin analogue, a β-blocker, an α-adrenergic agonist, and a carbonic anhydrase inhibitor.

Methods: Patients followed at the Federal University of São Paulo were enrolled from August to November 2013 and were initially submitted to an ophthalmologic examination where the IOP was measured at 8 AM, 10 AM, and 12 PM. Afterward, patients underwent a 15-day washout of the carbonic anhydrase inhibitor and had their IOP measured again.

Results: Most patients were female, white, and with a mean age of 66.4 ± 9.7 years. The removal of the fourth drug had a statistically significant effect on the IOP peak (increase of 1.20 mm Hg, $p < 0.01$) and mean (increase of 1.23 mm Hg, $p < 0.01$), but it did not interfere significantly with morning fluctuation of the IOP ($p = 0.83$). After discontinuation of the fourth drug, the IOP increased ≥2 mm Hg in 32% of the patients, and there was a significant increase of the IOP (defined as an IOP change ≥20%) in only 5 patients (20%). Age older than 60 years was associated with 20% of the documented IOP change ($R^2 = 0.19$, $p = 0.03$).

Conclusions: The removal of a fourth medication does not appear to have a clinically significant impact on IOP control in most patients with glaucoma. However, 32% of the patients experienced an IOP increase ≥2 mm Hg, with age older than 60 years being the only significant predictive factor.

Objet : Évaluer l'efficacité d'inhibiteurs de l'anhydrase carbonique comme quatrième médicament dans le contrôle de la pression intraoculaire (PIO) chez des patients souffrant de glaucome primaire.

Nature : Étude prospective unicentrique.

Participants : 25 yeux de 25 patients souffrant de glaucome primaire traités concomitamment avec un analogue de prostaglandine topique, un bêta-bloquant, un agoniste alpha-adrénergique et un inhibiteur de l'anhydrase carbonique.

Méthodes : Des patients suivis à la Federal University de São Paulo ont été recrutés d'août à novembre 2013 et ont d'abord subi un examen ophtalmologique où la PIO a été mesurée à 8 h, à 10 h et à 12 h. Après 15 jours de lavage avec l'inhibiteur de l'anhydrase carbonique, on a repris les mesures de la PIO.

Résultats : La plupart des patients étaient de sexe féminin et de race blanche. L'âge moyen était de 66,4 ± 9,7 ans. Le retrait du quatrième médicament a eu un effet statistiquement significatif sur la PIO de pointe (accroissement de 1,20 mmHg; $p < 0,01$) et sur la PIO moyenne (accroissement de 1,23 mmHg; $p < 0,01$), mais il n'a pas interféré significativement avec la fluctuation en avant-midi de la PIO ($p = 0,83$). Après l'arrêt du quatrième médicament, la PIO a augmenté de ≥2 mmHg chez 32 % des patients, et on a noté une hausse significative de la PIO (définie comme une variation de la PIO de ≥20 %) chez 5 patients (20 %) seulement. La variation documentée de la PIO était attribuable à l'âge dans environ 20 % des cas ($R^2 = 0,19$; $p = 0,03$).

Conclusions : Le retrait d'un quatrième médicament ne semble pas avoir un impact significatif, du point de vue clinique, sur le contrôle de la PIO chez la plupart des patients glaucomateux. Cependant, la PIO a augmenté de >2 mmHg chez 32 % des patients, et l'âge supérieur à 60 ans était le seul facteur prédicteur significatif.

Glaucoma is the most important cause of irreversible blindness in the world, and elevated intraocular pressure (IOP) remains the main known risk factor for the development and progression of the disease.[1,2] The main therapeutic goal is to preserve visual function by reducing the IOP, which is the key modifiable risk factor.[3]

Medical therapy is the initial approach for most cases of primary glaucoma, due to the fact that the visual outcomes are similar compared with initial surgical treatment and the latter offers more risks to patients.[4] Four categories of topical medications are mainly used for glaucoma treatment: prostaglandin analogues, β-blockers, α-adrenergic agonists, and carbonic anhydrase inhibitors.[5] Although response to each medication may vary significantly, carbonic anhydrase inhibitors seem to be the least effective among the 4 classes, as previous studies have shown an average percentage of IOP reduction of 10% to 23%.[6–14] For instance, in the European Glaucoma Prevention Study, the mean IOP reduction in the dorzolamide group was comparable with the placebo group.[14]

From the [*]Glaucoma Service, Department of Ophthalmology, Federal University of São Paulo; and [†]Hospital Medicina dos Olhos, São Paulo, Brazil

Correspondence to Tiago Santos Prata, MD, PhD, Associate Professor of Ophthalmology Glaucoma Service, Department of Ophthalmology, Federal University of São Paulo, Rua Botucatu, 821, Vila Clementino, São Paulo 04023-062, Brazil; tiagoprata@ig.com.br

The study was presented at the 2014 Arvo meeting, on May 4, at the city of Orlando, FL.

Originally received Aug. 13, 2014. Final revision Mar. 13, 2015. Accepted Mar. 22, 2015

Can J Ophthalmol 2015;50:297–301

http://dx.doi.org/10.1016/j.jcjo.2015.03.009

In many cases, monotherapy does not reach the target IOP and adjunctive therapy is required to adequately reduce IOP, eventually resulting in more adverse reactions, higher cost, and poor treatment adherence.[5,6,8,14,15] In addition, it is known that the medications' effectiveness as adjuvants are lower than when used as monotherapy.[4,16–18]

Because the need for adjunctive therapy is common in clinical practice, it is important to determine which strategies actually lead to a successful outcome. The benefit of associating a fourth drug to glaucoma therapy is questionable, and there are no data reporting the effectiveness of a fourth adjuvant medication to support such a widely performed practice among ophthalmologists. Therefore, in this study, we sought to investigate how effective the fourth drug is (based on carbonic anhydrase inhibitor effect) regarding IOP control in patients with primary glaucomas.

Methods

Patients

This prospective study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board. Written, informed consent was obtained from all patients.

We prospectively enrolled consecutive patients older than 18 years with primary glaucomas (glaucomatous optic neuropathy and reproducible visual field loss) treated concomitantly in 1 or both eyes with a topical prostaglandin analogue, a β-blocker, an α-adrenergic agonist, and a carbonic anhydrase inhibitor followed at the Department of Ophthalmology of the Federal University of São Paulo. Initially, all participants underwent an ophthalmologic examination. Exclusion criteria included history of ocular trauma or surgical procedures other than uneventful cataract extraction or glaucoma surgeries, secondary glaucomas, ocular diseases other than glaucoma, and noncompliance to treatment. It was not required that both eyes meet eligibility criteria. Therefore, if the patient fulfilled inclusion criteria but 1 of the eyes had any exclusion factor, the other eye could still be used for the study.

Characteristic glaucomatous optic neuropathy was defined as a vertical cup-to-disc ratio (CDR) ≥ 0.6, asymmetry of CDR ≥ 0.2 between eyes, and the presence of localized retinal nerve fiber layer defects and/or neuroretinal rim defects in the absence of any other abnormalities that could explain such findings.[19] A glaucomatous visual field defect in the standard automated perimetry (Humphrey Swedish Interactive Threshold Algorithm Standard 24–2; Carl Zeiss Meditec, Dublin, Calif.) was defined as ≥ 3 points in clusters with a probability less than 5% (excluding those on the edge of the field or directly above and below the blind spot) on the pattern deviation plot, a pattern SD index with a probability less than 5%, or a glaucoma hemifield test with results outside the normal limits.[20]

Procedures and data acquisition

Patients were recruited from August 2013 to November 2013 for a first evaluation and were submitted to a complete ophthalmologic examination, including visual acuity measurement with a Snellen chart, slit-lamp biomicroscopy, tonometry, fundoscopy, and ultrasound pachymetry (the average of 3 measurements was considered for analysis). Using Goldmann applanation tonometry, a single investigator measured IOP one at a time at 8 AM, 10 AM, and 12 PM; the investigator performed both the IOP measurement and the reading. Afterward, patients underwent a 15-day washout of the carbonic anhydrase inhibitor and were recruited for a second visit,[21] during which they had their IOP measured again at 8 AM, 10 AM, and 12 PM by another examiner (masked to patients' previous IOP measurements and clinical data) using the same device and methodology. Patients were instructed to use their medications accordingly before each visit. Our main outcome measurements were the comparison of the following IOP-related parameters before and after the washout period: mean IOP, IOP peak, and morning fluctuation.

Statistical analysis

Descriptive analysis was used to present demographic and clinical data. D'Agostino–Pearson test was performed to determine whether the data had a normal distribution. Because it accepted normality, paired samples t test was used to compare continuous variables (before and after discontinuation of the fourth drug). Categorical data were compared using χ^2 test. Regression analysis was used to evaluate the association between patients' characteristics and magnitude of IOP change. The mean IOP change was chosen as the clinical parameter for sample-size calculation. Considering a hypothesized IOP difference of 2 mm Hg as clinically significant and an SD of the means of 2.5 mm Hg, it would be necessary to have a total of 25 patients to reach a statistical power of 80% (using an α-error of 0.05). Statistical significance level was set at p less than 0.05. Computerized analysis was performed using MedCalc software (MedCalc Inc, Mariakerke,

Table 1—Demographic and ocular characteristics of study patients

Parameters	Patients (n = 25)
Mean age ± SD, y	66.4 ± 9.7
Male/Female sex, %	36/64
Race: white/black/other, %	60/36/4
POAG/PACG diagnosis, %	80/20
History of ocular surgery, %	52
Mean central corneal thickness ± SD, μm	511 ± 31.7
Visual field mean deviation ± SD, dB	–6.5 ± 7.3
Mean vertical cup-to-disc ratio ± SD	0.85 ± 0.14

POAG, primary open-angle glaucoma; PACG, primary angle-closure glaucoma.