

OCULAR HYPERTENSION IN CHILDREN TREATED WITH BRIMONIDINE 0.2%. A CLINICAL STUDY

TRATAMIENTO DE LA HIPERTENSIÓN OCULAR INFANTIL CON COLIRIO DE BRIMONIDINA 0,2%

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ABSTRACT

Purpose: To evaluate the safety and efficacy of topical brimonidine 0.2% use in children.

Materials and methods: A descriptive study of twelve successive children (21 eyes) who needed topical treatment of intraocular hypertension, and where the use of b-blockers was contraindicated.

Results: During treatment we observed an average decrease of IOP of 5 SD 1.8 mmHg (21% of basal IOP), but found more common local symptoms, with stinging being complained of in 52.4% of cases. Somnolence was also complained of in two cases (*Arch Soc Esp Ophthalmol 2006; 81: 155-160*).

Key words: Ocular hypertension, glaucoma, paediatric, brimonidine.

RESUMEN

Objetivos: Se ha valorado la seguridad y eficacia de uso del colirio de brimonidina 0,2% en niños.

Método: Se estudiaron doce niños con hipertensión ocular (21 ojos) y contraindicación del uso de beta-bloqueantes. Se realiza estudio descriptivo de casos sucesivos de niños que necesitaban tratamiento médico tópico por hipertensión ocular.

Resultados: En cuanto a la eficacia del tratamiento se observa un descenso medio de la PIO de 5 DE 1,8 mmHg (21% de la PIO basal) y en cuanto a la seguridad en el uso del medicamento se encontró con síntomas más frecuentes a nivel local el escozor en un 52,38% de los casos y a nivel sistémico la aparición de somnolencia en dos casos.

Palabras claves: Hipertensión ocular, glaucoma infantil, brimonidina.

INTRODUCTION

Orally administered acetazolamide is the commonly accepted indication for the medical treatment of eye hypertension in extreme cases and for short periods of time due to the multiple undesira-

ble effects which take place at the systemic level. A reasonable alternative would be to utilise topical carbon anhydrase inhibitors, but in our experience we have not obtained good results because its application in children is difficult and inefficient due to the irritation it produces. In addition, the use of

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topical beta-blockers for prolonged periods of time was the only available option, but its application as a compassionate medication is also limited due to its highly relevant undesirable effects.

As an alternative to the above, other IOP-reducers are available: alpha-2 adrenergics, which can be utilised in children due to their improved systemic tolerance. However, their use may be contraindicated after the emergence of some secondary isolated effect of systemic alteration (1-3) and depression of the central nervous system (4,5) after their use in children.

Glaucoma is one of the most common causes of blindness and the second cause of bilateral blindness (6). It affects about 13 million people all over the world (7), which is only the prevalence of primary congenital glaucoma of 1:10.000 live births. To this figure we should add all the forms of secondary childhood glaucoma.

Brimonidine, Clonidine and Apraclonidine are alpha-2 adrenergic agonists. Due to their chemical composition, they have an increased sensitivity for alpha-2 receptors, potentially reducing allergic reactions. This is even more so for Brimonidine (8), which is more stable than Apraclonidine. In comparison with prostaglandines (Latanoprost 0.005%), it seems to have a smaller effect in reducing IOP although it produces less hyperemia (9). Brimonidine tartrate 0.2% has a similar effect as Dorzolamide 2%, although it is better tolerated (6) and greater than timolole maleate 0.5% (7,10).

Alpha-2 adrenergic agonists reduce the production of aqueous in the ciliary body and increase the drainage thereof - through the uveo-scleral path - (10) by the activation of said adrenergic receptors in the tissues (8). Their action is fast, reducing IOP two hours after application, with a mean duration of twelve hours. In addition, they enhance retinal blood flow (11). Their effect can be detected two weeks after discontinuing use (12) and can be utilised in association with other IOP reducing agents (10). Brimonidine is more selective and powerful than Clonidine and Apraclonidine (10).

The topical use of Brimonidine seems to improve sensitivity to contrast (13), prevents post-laser IOP increases after YAG laser iridectomy, capsulotomy (14) and argon trabeculoplasty (15); it appears to have less secondary effects than other alpha-2 agonists (Clonidine, Apraclonidine) (8) due to its likely oxidative stability (16); 7-15% have some type of allergic conjunctivitis, allergic blepharitis,

follicular conjunctivitis and anterior uveitis, which appears after 6-9 months of use and disappearing after discontinuing use (16). The literature describes feelings of sleepiness and fatigue (16,18) and isolated skin reactions (19), although others have not found any addiction related to the need of increasing the dosage (12).

SUBJECTS, MATERIAL AND METHODS

Description of the study group

The study comprised 21 eyes of twelve children with intraocular hypertension where the use of Beta-blockers was contraindicated. Eight subjects were boys and four were girls, with ages between 5 and 14 (10 SD 4.81); nine of these children suffered congenital glaucoma and had previously received surgical (three of them on two occasions - goniotomy and trabeculectomy) and medical treatment (beta-blockers). In 3 other subjects, treatment was established due to high IOP and myopia. In all subjects, the use of beta-blockers had been contraindicated, in most cases due to breathing problems and one due to heart problems.

Inclusion criteria

A retrospective study of children with childhood glaucoma and eye hypertension with myopia who had been previously treated with beta-blockers, based on compassionate use of medication criteria. The study included all the children who had been treated with Brimonidine in order to avoid the undesirable effects of beta-blockers in the past two years in the Paediatric Ophthalmology Department of the Ophthalmology Service. The treatment was not applied to any child under 5 with known neurological pathology or any patients with associated systemic pathology.

The treatment comprised Brimonidine tartrate eye drops 0.2% (Alphagan; Allergan, Inc., Irvine, CA) administered at 12-hour intervals, instructing the parents to reduce as much as possible the volume which may filter through to lacrimal pathways. Before beginning the treatment, a washing period of at least 48 hours was established after which the IOP and cardio-respiratory condition of the child was

assessed. If the subject fulfilled the inclusion criteria, the treatment with Brimonidine was established.

The safety of the treatment was assessed jointly with the paediatric cardiology department on the same date of treatment initiation, one week and one month later. When it was necessary to treat both eyes, we always started treating only one and, if no undesirable effects arose, the other eye was added to the treatment.

All the adverse reactions which were considered as possibly related to the use of Brimonidine eye drops (at the local as well as systemic level) were registered. In addition, the efficiency of the treatment was assessed by applanation tonometry (Perkins tonometer), evaluating the reduction of IOP vis-a-vis the baseline values measured before beginning the treatment in the above described conditions, and assessing its efficiency as a substitute treatment for beta-blockers (Betaxolol or Timolol 0.25%). The data were registered in mmHg one week, one month and three months after beginning the treatment (except the subjects who gave up the treatment) and the percentage of this reduction vis-a-vis the IOP baseline of the children after said 48-hour cleaning period.

For analysing the results, descriptive data of the group were taken into account, utilising arithmetic mean figures and standard deviations. For assessing IOP the paired «t for Student» was applied. The statistical analysis was carried out utilising the SPSS 11.0 system (SPSS inc., Chicago, United States).

RESULTS

Twenty-one 21 eyes of ten children with 10 SD 4,81 years of age were studied, 66.66% were boys (eight patients) and 33.33% girls (4 patients). Nine children (75%) had congenital glaucoma and 25% (three children) had intraocular hypertension and myopia. Of the 21 eyes, 17 (80.95%) corresponded to children with congenital glaucoma, and four (19.40%) to children with IOP and myopia. Of the nine children with congenital glaucoma, 66.66% (6 patients) had been intervened on one occasion and 33.33% (three patients) on two occasions.

Safety

Local tolerance: 52.38% (11 eyes) felt more stinging than with previous eye drops during the first

week, which persisted only in 20% (four eyes) after three months. Three subjects (14.28%) referred dryness in the mouth, which disappeared in successive controls. In addition, two subjects had blurred vision which disappeared after the first months of treatment and could not be confirmed with visual acuity measurements.

Systemic tolerance: three patients gave up the treatment, two after 15 days due to persistent sleepiness and the third due to unclassified loss of appetite. The latter was given a substitute treatment by parental request. One subject had relative asthenia which improved and made it unnecessary to interrupt treatment. Two subjects had some headaches which gradually disappeared after a few days. No breathing or heart alterations were evidenced in any of the patients of the study.

Efficacy

The baseline IOP was 25 SD 4 mmHg in the group of children with glaucoma and/or intraocular hypertension. In all subjects the IOP reduced in 5 SD 1.8 mmHg with respect to the starting values, and a maximum reduction of 9 mmHg (45%). This reduction was established in the second control (treatment day 8) and remained stable throughout the three months or more (in two subjects it was maintained for one year). The reduction of IOP represents 21% of the baseline value (fig. 1).

DISCUSSION

The study was made in order to assess the safety and pressure-reducing efficacy of topical Brimonidine 0.2% in children with intraocular hypertension as a substitute treatment for other anti-glaucoma drugs which reduce IOP, particularly beta-blockers, a rather frequent situation in paediatric ophthalmology due to the undesirable effects of these drugs on the cardiorespiratory system of children (20). At present, beta-blockers are the most utilised treatment for topical application and as «compassionate use of medication», because none of the topical anti-glaucoma drugs on the market are indicated for childhood glaucoma (recently, the US Paediatric Ophthalmology Medical Association recommends in first place the IAC's and secondly beta-blockers) and we have a large amount of experience consider-

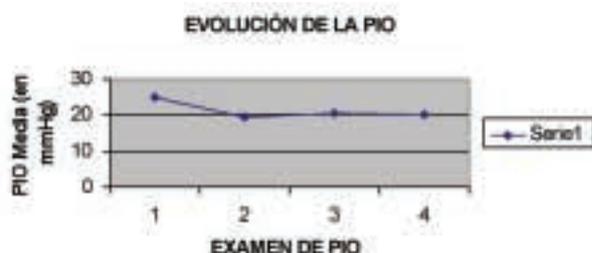


Fig. 1: IOP control:

Nº 1: Exploration before beginning the treatment.

Nº 2: Exploration at treatment day 7

Nº 3: Exploration at treatment day 30.

Nº 4: Exploration at treatment day 90.

ring the efficacy and tolerance of beta-blockers in this type of patients.

In what concerns efficacy, we can say that 0.2% Brimonidine reduced pressure about 21% in all analysed cases. These values were established after 48 hours of initiating treatment and remained stable all the time, in two subjects over one year without complications. In only subjects, the pressure reducing efficacy was equal of greater than the beta-blockers it substituted.

In what concerns safety, considering the existence of two clinical cases published in the literature referring serious depression of the central nervous system in children treated with Brimonidine 0.2%, it was determined that in no case this treatment should be applied to children under five or having known neurological pathologies. Said two cases were low-weight lactating infants, one was a premature baby weighing 860 g and therefore with a high degree of neurological immaturity and a disproportionate dosage/body weight ratio, and therefore it was reasonable to exclude such treatment beforehand.

In the group of the study no serious adverse reactions were detected, excepting two cases of persistent sleepiness leading to abandoning the treatment, one case of unclassified appetite loss and two cases of headaches which gradually disappeared after the first week of treatment.

In principle, the most reasonable treatment for these subjects should have been carbon anhydrase inhibitors, currently available in topical application, above all if we consider that Acetazolamide is the only authorised medical treatment for childhood glaucoma, but the two preparations on the market

which we tested did not demonstrate efficiency and were unbearably irritating for the children, a factor having a decisive influence in the efficacy of this medication.

Even though there are other options which could be utilised in children needing IOP reducing treatment, nowadays there is a debate about the use of Brimonidine in children and therefore we thought it would be interesting to publish our experience. Although in the future this treatment may not be the choice for these cases, we believe it is a possibility which should be considered for childhood eye hypertension.

REFERENCES

1. Korsch E, Grote A, Seybold M, Soditt V. Systemic adverse effects of topical treatment with brimonidine in an infant with secondary glaucoma. *Eur J Pediatr* 1999; 158: 685.
2. Berlin R, Sing K, Lee U, Steiner R. Toxicity from use of brimonidine ophthalmic solution in an infant and reversal with naloxone. *J Toxicol Clin Toxicol* 1997; 35: 506.
3. Enyedi LB, Freedman SF. Safety and efficacy of brimonidine in children with glaucoma. *J AAPOS* 2001; 5: 281-284.
4. Carlsen JO, Zabriskie NA, Kwon YH, Barbe ME, Scott WE. Apparent central nervous system depression in infants after the use of topical brimonidine. *Am J Ophthalmol* 1999; 128: 255-256.
5. Berlin RJ, Lee UT, Samples JR, Rich LF, Tang-Liu DD, Sing KA, et al. Ophthalmic drops causing coma in an infant. *J Pediatr* 2001; 138: 441-443.
6. Bateman DN, Clark R, Azuara-Blanco A, Bain M, Forrest J. The effects of new topical treatments on management of glaucoma in Scotland: an examination of ophthalmological health care. *Br J Ophthalmol* 2002; 86: 551-554.
7. Katz LJ. Brimonidine tartrate 0.2% twice daily vs timolol 0.5% twice daily: 1-year results in glaucoma patients. *Brimonidine Study Group. Am J Ophthalmol* 1999; 127: 20-26.
8. Derick RJ, Robin AL, Walters TR, Barnebey HS, Choplin N, Schuman J, et al. Brimonidine tartrate: a one-month dose response study. *Ophthalmology* 1997; 104: 131-136.
9. Stewart WC, Day DG, Stewart JA, Schuhr J, Latham KE. The efficacy and safety of latanoprost 0.005% once daily versus brimonidine 0.2% twice daily in open-angle glaucoma or ocular hypertension. *Am J Ophthalmol* 2001; 131: 631-635.
10. LeBlanc RP. Twelve-month results of an ongoing randomized trial comparing brimonidine tartrate 0.2% and timolol 0.5% given twice daily in patients with glaucoma or ocular hypertension. *Brimonidine Study Group 2. Ophthalmology* 1998; 105: 1960-1967.
11. Rolle T, Cipullo D, Vizzeri GM, Triggiani A, Brogliatti B. Evaluation and comparison between the effects on intraocular pressure and retinal blood flow of two antiglaucomatous drugs administered in monotherapy: brimonidine

- and latanoprost. Preliminary results. *Acta Ophthalmol Scand Suppl* 2000; 232: 50-52.
12. Stewart WC, Holmes KT, Johnson MA. Washout periods for brimonidine 0.2% and latanoprost 0.005%. *Am J Ophthalmol* 2001; 131: 798-799.
 13. Sponsel WE, Paris G, Trigo Y, Pena M, Weber A, Sanford K, et al. Latanoprost and brimonidine: therapeutic and physiologic assessment before and after oral nonsteroidal anti-inflammatory therapy. *Am J Ophthalmol* 2002; 133: 11-18.
 14. Chen TC, Ang RT, Grosskreutz CL, Pasquale LR, Fan JT. Brimonidine 0.2% versus apraclonidine 0.5% for prevention of intraocular pressure elevations after anterior segment laser surgery. *Ophthalmology* 2001; 108: 1033-1038.
 15. Kasahara N. Brimonidine 0.2% to prevent post laser IOP elevation (letter). *Ophthalmology* 2002; 109: 828-829.
 16. Byles DB, Frith P, Salmon JF. Anterior uveitis as a side effect of topical brimonidine. *Am J Ophthalmol* 2000; 130: 287-291.
 17. Stewart WC, Stewart JA, Jackson AL. Cardiovascular effects of timolol maleate, brimonidine or brimonidine/timolol maleate in concomitant therapy. *Acta Ophthalmol Scand* 2002; 80: 277-281.
 18. Stewart WC, Sharpe ED, Harbin TS Jr, Pastor SA, Day DG, Holmes KT, et al. Brimonidine 0.2% versus dorzolamide 2% each given three times daily to reduce intraocular pressure. *Am J Ophthalmol* 2000; 129: 723-727.
 19. Scruggs JT, Whiteside-Michel J, Brodsky MC. The tear-drop sign: a rare dermatological reaction to brimonidine. *Br J Ophthalmol* 2000; 84: 671-672.
 20. Zimmerman TJ, Koener KS, Morgan KS. Safety and efficacy of timolol in pediatric glaucoma. *Surv Ophthalmol* 1983; 28: 262-264.