Methazolamide 1% in Cyclodextrin Solution Lowers IOP in Human Ocular Hypertension

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PURPOSE. To formulate aqueous eye drops containing methazolamide 1% in cyclodextrin solution and to evaluate their effect on intraocular pressure (IOP) in a double-blind randomized trial in humans. Methazolamide, a carbonic anhydrase inhibitor (CAI), has been used in oral doses in the treatment of glaucoma but hitherto has not been successfully formulated in eye drops. In this study the effects of methazolamide are compared with those of dorzolamide (Trusopt).

METHODS. Methazolamide 1% was formulated in a 2-hydroxypropyl-β-cyclodextrin with hydroxypropyl methylcellulose in aqueous solution. Eight persons with ocular hypertension were treated with the methazolamide-cyclodextrin eye drops and eight persons with dorzolamide (Trusopt), both groups at dosages of three times a day for 1 week. IOP was measured before treatment was begun and on days 1, 3, and 8 at 9 AM (peak) and 3 PM (trough).

RESULTS. After 1 week of treatment, the peak IOP in the methazolamide group had decreased from 24.4 ± 2.1 mm Hg (mean ± SD) to 21.0 ± 2.0 mm Hg, which is a 14% pressure decrease (P = 0.006). In the dorzolamide group, the peak IOP decreased from 23.3 ± 2.1 mm Hg to 17.2 ± 3.1 mm Hg, which is a 26% pressure decrease (P < 0.001). On average, the IOP declined 3.4 ± 1.8 mm Hg after methazolamide administration and 6.1 ± 3.6 mm Hg after dorzolamide.

CONCLUSIONS. Through cyclodextrin complexation, it is possible to produce topically active methazolamide eye drops that lower IOP. This is the first double-blind clinical trial that demonstrates the efficacy of the classic CAIs in eye drop formulation. (Invest Ophthalmol Vis Sci. 2000;41:3552–3554)

Carbonic anhydrase inhibitors (CAIs) were invented during the middle of the 20th century, and acetazolamide and methazolamide were used as systemically administered glaucoma drugs for the latter half of the century. Numerous attempts to formulate these drugs as eyedrops were unsuccessful, and it was thought by many that their formulation in eye drops was impossible.1,2 With the help of a cyclodextrin-based drug delivery system we have successfully formulated acetazolamide, methazolamide, and ethoxyzolamide in eye drops and tested these in experimental animals and in an open pilot study in humans.3–5 We now report a double-blind randomized clinical trial comparing the effect of methazolamide in a cyclodextrin eye drop formulation to dorzolamide eye drops (Trusopt; Merck Inc., Whitehouse Station, NJ).

Methazolamide is nearly insoluble in water and aqueous tear fluid, and this has made formulation of methazolamide eye drops impossible until now.5 A drug molecule in eye drops must be water soluble, at least to some degree, to be dissolved in the aqueous tear film and also somewhat lipid soluble to be able to penetrate the lipophilic barriers of the cornea.6 Few drugs fulfill both criteria. However, cyclodextrin can serve as a vehicle that carries a hydrophobic drug in aqueous solution. Eight persons with ocular hypertension were treated with the methazolamide-cyclodextrin eye drops and eight persons with dorzolamide (Trusopt), both groups at dosages of three times a day for 1 week. IOP was measured before treatment was begun and on days 1, 3, and 8 at 9 AM (peak) and 3 PM (trough).

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The purpose of this study was to formulate eye drops containing methazolamide 1% in cyclodextrin solution and to evaluate its effect on IOP in humans with ocular hypertension and to compare it with dorzolamide in a double-blind randomized clinical trial.

**Materials and Methods**

The institutional review board of Landspitali University Hospital and the State Committee on Pharmaceuticals in Reykjavík approved the protocol, which conformed to the tenets of the Declaration of Helsinki. Methazolamide eye drops were formulated in an aqueous solution of HPβCD with HPMC. One gram of methazolamide was added to 100 ml of an aqueous solution containing 23 g HPβCD (Encapsin; Janssen Biotech, Beerse, Belgium), 0.1 g HPMC, 0.01 g benzalkonium chloride, and 0.05 g EDTA. The solution was heated in an autoclave at 121°C for 40 minutes to promote the complexation between HPβCD and methazolamide. The resultant solution was filtered through a 0.45-μm nylon membrane and aseptically divided into eye drop vials. Finally, the eye drop vials and their contents were sterilized in an autoclave at 121°C for 20 minutes.

Patients with ocular hypertension (IOP >21 mm Hg) were recruited. Inclusion criteria included no previous treatment to lower ocular pressure and no concurrent ocular therapy other than the study drug. Informed consent was obtained from each subject. Sixteen persons were included, 5 men and 11 women. The trial was randomized and double blind. We chose the eye in each patient with the higher IOP for the study. If both eyes had the same IOP, we chose the eye with the worse visual acuity to be the study eye.

Dorzolamide and methazolamide eye drops were placed in identical bottles and were numbered in sequence and randomized for containing either dorzolamide or methazolamide. Eight persons self-administered the methazolamide-cyclodextrin eye drops and eight persons dorzolamide (Trusopt) eye drops three times a day in the study eye for 1 week, at 7 AM, 3 PM, and 11 PM. There were no treatments of the other eye. The baseline IOP was measured on day 0 before treatment began at 9 AM and at 3 PM. The pressure was then measured on days 1 and 3 and after 1 week after treatment at 9 AM, (peak: 2 hours after the first drop) and 3 PM (trough: just before the second drop). We compared IOP at 9 AM on the study days with the baseline value at 9 AM on the baseline day 0, and a similar comparison was made for the 3 PM measurements, which were compared with the 3 PM measurement on day 0.

The IOP was measured by Goldmann applanation tonometry two times at each measurement point, and the mean value recorded. Possible toxic effects were monitored throughout the study with evaluation of symptoms, best corrected Snellen visual acuity, and slit lamp examinations at all time points on study days. Student’s t-test was used for statistical analysis of the data.

**Results**

Table 1 shows the IOP data. Data are expressed as means ± SD. After 1 week of treatment, the peak IOP in the methazolamide group had decreased from 24.4 ± 2.1 to 21.0 ± 2.1 mm Hg, which is a 14% pressure decrease (P = 0.006). In the dorzolamide group, the peak IOP decreased from 25.3 ± 2.1 to 17.2 ± 3.1 mm Hg, which is a 26% pressure decrease (P < 0.001). On average, the IOP declined 3.4 ± 1.8 mm Hg after methazolamide administration and 6.1 ± 3.6 mm Hg after dorzolamide. The difference between the methazolamide and dorzolamide groups did not reach statistical significance (P = 0.07).

Figure 1 shows the effect of methazolamide and dorzolamide on peak IOP. Looking at the trough effect (IOP at 3 PM, just before the administration of the second drop) the IOP in the methazolamide group decreased from 23.2 ± 2.4 to 17.2 ± 1.5 mm Hg, which is a 26% pressure decrease (P < 0.001). Lowering of IOP also occurred in the other eye that received no treatment, with IOP lowering at 9 AM from 22.6 ± 5.0 to 21.3 ± 4.3 mm Hg in the methazolamide group, which is a 6% pressure decrease and in the dorzolamide group from 21.3 ± 3.1 to 19.9 ± 3.8 mm Hg, which also is a 6% pressure decrease.

The methazolamide-cyclodextrin eye drops were well tolerated, and slit lamp examination of anterior segment revealed no adverse effects of the drug. All persons in the methazolamide group mentioned a mild burning sensation on instillation but no other symptoms. In the dorzolamide group, all but one person reported a mild burning sensation on instillation and one person experienced transient (1–2 minutes) problems of focusing after 1 week of treatment.
there is currently considerable interest in the possible involvement of the formation of aqueous humor. This may still be the case, but CA IV is membrane bound. CA isoenzymes vary in different organs. The ciliary body is rich in CA II, and there are at least four isoenzymes of CA, and their concentrations differ in different organs. The ciliary body is rich in CA II, and CA IV is also present in the ciliary body. CA II is found in the cellular cytoplasm, but CA IV is membrane bound. CA isoenzyme II was traditionally viewed as the critical isoenzyme in the formation of aqueous humor. This may still be the case, but there is currently considerable interest in the possible involvement of CA isoenzyme IV. Dorzolamide and methazolamide have different affinity and ability to inhibit human CA isoenzymes II and IV.

IC₅₀ is the concentration at which a drug inhibits 50% of enzyme activity, therefore lower IC₅₀ values indicate higher drug inhibitory activity. Dorzolamide has an IC₅₀ for CA II of 0.18 nM and 6.9 nM for CA IV, whereas methazolamide has an IC₅₀ for CA II of 8.1 nM and 80.3 nM for CA IV. This indicates that dorzolamide is a 45 times and 12 times more potent inhibitor of the CA isoenzymes II and IV, respectively, than methazolamide. If we take into account that 1% methazolamide was compared with 2% dorzolamide, the cyclodextrin drug delivery system would have had to be 90 times more effective in drug delivery than the Trusopt system to equal the effect on CAI II. Acetazolamide has an IC₅₀ value for CA II of 3.4 nM and 14.7 nM for CA IV. Thus, acetazolamide would be expected to be more effective than methazolamide but less effective than dorzolamide. In our study the mean IOP decrease 2 hours after instillation of the drops was 14% in the methazolamide group and 26% in the dorzolamide group. In our earlier study in which acetazolamide was formulated in cyclodextrin solution, the mean IOP decrease 2 hours after instillation was 15.6%. If we combine data from these studies on methazolamide, dorzolamide, and acetazolamide we conclude that there seems to be a correlation between the affinity of the CAIs for the isoenzymes and their IOP-lowering effect.

Our study shows for the first time in a double-blind randomized trial that one of the classic CAIs, methazolamide, is effective in an eye drop formulation based on HPβCD and HPMC. This has not been possible with any other drug delivery system, even though attempts have been made over several decades to formulate the classic CAIs into eyedrops.

**References**