Upsala J Med Sci 106: 117–121, 2001

Inhibition of Carbonic Anhydrase in the Lens does not Induce Myopia in Cynomolgus Monkeys

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ABSTRACT

Refraction was measured in eyes of cynomolgus (*Macaca irus*) monkeys, before and during continuous intravenous infusion of large doses of the carbonic anhydrase (CA) inhibitors acetazolamide and ethoxzolamide.

No changes of refraction were seen.

Therefore, inhibition of CA in lens, cornea and retina does not appear to be the cause of the transient myopia and associated symptoms, occasionally observed in patients treated with CA inhibitors.

INTRODUCTION

Transient myopia evoked by chemotherapeutic sulfonamides was first reported in 1939 by Fredrik Berg at the Uppsala University Hospital Eye Clinic (cited by Carlberg (2)). The myopia is seen occasionally (<1/1000) also in patients treated with sulfonamide carbonic anhydrase (CA) inhibitors, such as acetazolamide (6,9,11) and ethoxzolamide (1). It usually amounts to 5 (range 0.5–8) diopters, and is observed mostly in young women and often during pregnancy (11). It is some times associated with edema of the retina (1,4), seen as retinal corrugations or central radial folds. Conjunctival chemosis, aqueous flare, corpuscles in the aqueous humor, concentric restriction of the visual field and, choroidal detachment, have also been reported (4). In addition, the anterior chamber may become shallower with an anterior displacement of the lens (6,11).

The myopia may occur in a dramatic fashion within 15 min after intake of the inhibitor, but usually appears after 1 to 2 days. The effect typically subsides 2–3 days after cessation of the drug (1).

The mechanisms behind these symptoms are not well understood (see the Discussion). However, we hypothesized that certain patients could be highly sensitive to the effects of inhibition of CA in ocular tissues, causing electrolyte disturbances and swelling of the lens, cornea and perhaps retina which in turn could induce myopia. We tested this by measuring the refraction in monkeys given very large doses of acetazolamide and ethoxzolamide, which would ensure maximal inhibition of CA in the eye.

METHODS

Animals

The experiments were approved by the local Ethics Committee for animal experimentation. Two adult female cynomolgus monkeys (*Macaca irus*), weighing 2.1 and 2.5 kg, respectively, were used. They were sphincterotomized to facilitate objective refraction. Two months postoperatively, the anterior chambers were free of cells and flare, and the lenses were clear on slit lamp examination.

Refraction readings

The animals were anaesthetized with 15 mg/kg of sodium methohexital (Brietal®, Lilly), given intramuscularly. The animal lay prone on a board with its head fixed by an holder. The body temperature was maintained with an heat pad. Catheters were introduced into the leg veins.

Monkey, no.1, was given one drop of 1% homatropine in both eyes at 30 min before the measurements started.

Refraction was performed with a Thorner refractometer, as described by Törnqvist (14). The standard deviation of a single reading was ±0.33 diopters.

After five min of readings, one monkey was infused intravenously (i.v.) with acetazolamide (Diamox®, Lederle), and another with ethoxzolamide (Cardrase®, Upjohn) for 20 min (Fig.1). Thereafter, the refraction in both eyes was measured every min for 10 min, and then every 10 min for still another 50–60 min.

RESULTS AND DISCUSSION

The monkeys were given 2–3 times larger doses of acetazolamide and ethoxzolamide, than the highest recommended for patients. These inhibitors have a Ki of @10 nM against CA isozymes CAII and CAIV (17), found in lens epithelium, corneal endothelium, and retinal pigment epithelium (16). Moreover, they are lipid soluble, ethoxzolamide in particular, and will cross the blood-eye barriers to reach the aqueous humor and retina soon after an i.v. injection. Acetazolamide is known to reduce aqueous humor flow within sec after an i.v. injection, as a result of >99% inhibition of CAII and CAIV in the ciliary epithelium (17)**.** Also**,** the effects of inhibition of CA in cornea, lens and retina, as described below, were recorded within min after administration of the inhibitors (cf.16). We assume therefore that fluid transport in the ocular tissues was rapidly reduced, also in our monkeys.

However, the inhibitors did not change the refraction in the monkey eyes during 90 min of observation (Fig.1).

Since the results were negative in spite of maximal CA inhibition, we felt that there was no sense in extending the studies to more monkeys.

CAII and CAIV are both involved in electrolyte and fluid transport, and their inhibition in corneal endothelium causes corneal swelling (16). It is therefore of interest that a topical CA inhibitor, dorzolamide, recently introduced in the treatment of glaucoma, may give a slight, but significant thickening of the human cornea (15). However, it is inconceivable that such an effect on cornea would explain the myopia.

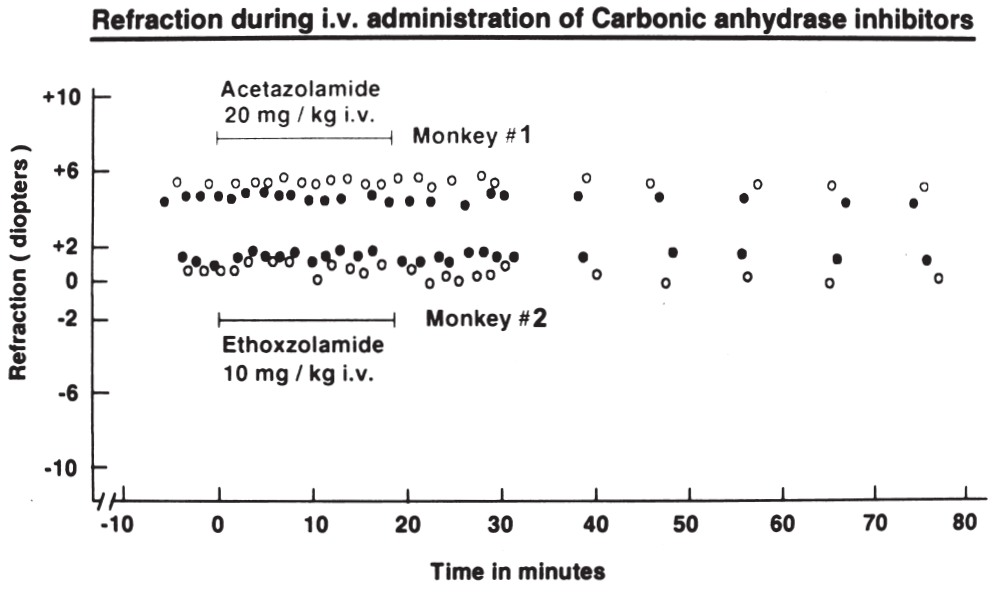

Fig. 1. Refraction values in eyes of cynomolgus monkeys during continuous intravenous infusion of the carbonic anhydrase inhibitors acetazolamide and ethoxzolamide. Homatropine, 1%,was given to both eyes of monkey no. 1, at 30 min before refraction readings were started. Open and filled circles are right and left eyes, respectively.

Transient myopia has been attributed to edema of the retina (5). Such an effect is improbable, however, since, if anything, edema is known to cause hyperopia. Actually, CA inhibitors have been shown instead to reduce edema of the retina, due to inhibition of CA in the pigment epithelium (3). It is therefore unlikely that the retinal folds, observed (1) during the myopic episodes, are caused by inhibition of retinal CA.

A shallow chamber and anterior displacement of the lens has been noted by some authors (9). A shallower chamber, due to a swollen lens, could in itself increase the refractive power of the eye, but not to the extent that would explain the large changes, usually seen in transient myopia (7).

Swelling of the lens is the only reasonable mechanism behind the transient myopia observed after acetazolamide and ethoxzolamide. Such a swelling, in synchrony with the myopia, also has been recorded echographically after intake of chemotherapeutic and diuretic sulfonamides (8,13). However, the present results indicate that the thickening of the lens after administration of CA inhibitors, is not due to inhibition of CAII and CAIV in the lens (16). Instead, we must conclude that the mechanism behind the development of transient myopia is the same for CA inhibitors and many other types of drugs.

Several authors (cf.8) have suggested that sulfonamides and other drugs may induce allergic reactions in the eye with ciliary body edema. This in turn could relax the zonule of Zinn and thereby thicken the lens (4,5). Topically applied chemotherapeutic sulfonamides are known to cause allergic reactions. One would expect there-

fore, that some patients using topical CA inhibitors for glaucoma, eventually would experience transient myopia. However, no such case has as yet been reported.

The allergy theory requires an initial sensitization by the drug in question, but there are many cases (10), where the patient has experienced transient myopia at the first exposure to the drug. Therefore, Krieg & Schipper (8) suggested that the drugs instead might increase directly the levels of leucotrienes, including prostaglandins, in the affected tissue. It has been shown that sulfonamides may stimulate the synthesis of prostaglandin E_2, and histamine release (12). This could cause edema and perhaps contraction of smooth muscles in the ciliary body. However, the problem with this theory is that transient myopia, in most cases, occurs without signs of inflammation in the eye. Therefore, the mechanism for the intriguing side effect of transient myopia and associated symptoms, is as yet obscure and needs further investigation.

ACKNOWLEDGEMENTS

The work was supported by the Swedish Medical Research Council, grant nr. 2874. I thank Mrs. Ingalill Wersäll for performing the refraction measurements.

REFERENCES

Beasley, F.J.: Transient myopia and retinal edema during ethoxzolamide (Cardrase) therapy. Arch Ophthalmol 68: 490–491, 1962.

Carlberg, O.: Zur Genese der Sulfonamidmyopie. Acta Ophthalmol 20: 275–284, 1942.

Cox, S.N., Hay, E.& Bird, A.C.: Treatment of chronic macular edema with acetazolamide. Arch Ophthalmol 106: 1190–1195, 1988.

Fan, J.T., Johnson, D.H. & Burk, R.R.: Transient myopia, angle-closure glaucoma and choroidal detachment after oral acetazolamide. Am J Ophthalmol 94: 99–102, 1993.

Gailey, W.W.: Transient myopia from sulfanilamide. Am J Ophthalmol 22: 1399–1400, 1939.

Galin, M.A., Baras, I. & Zweifach, P.: Diamox-induced myopia. Am J Ophthalmol 54: 237–243, 1962.

Jampolsky, A.J. & Flom, B.: Transient myopia associated with anterior displacement of the crystalline lens. Am J Ophthalmol 36: 81–85, 1953.

Krieg, P.H. & Schipper, I.: Drug-induced ciliary body oedema: a new theory. Eye 10: 121–126, 1996.

Kronning, E.: Transient myopia following the use of acetazolamide. Acta Ophthalmol 35: 478–484, 1957.

Mattson, R.: Transient myopia following the use of sulphonamides. Acta Ophthalmol 30: 385–398, 1952.

Muirhead, F.J. & Scheie, G.H.: Transient myopia after acetazolamide. Arch Ophthalmol 63: 315–318, 1960.

O'Donnell, W.J., Rosenberg, M., Niven, R.W., Drazen, J.M. & Israel, E.: Acetazolamide and furosemide attenuate asthma induced by hyperventilation of cold dry air. Am Rev Resp Dis 146: 1518–1523, 1992.

Pallin, O. & Ericsson, R.: Ultrasound studies in a case of hygroton induced myopia. Acta Ophthalmol 43: 692–696, 1965.

Törnqvist, G.: Comparative studies of the effect of pilocarpine on the pupil and on the refraction in two species of monkey (Cercopithecus ethiops and Macaca irus). Investigative Ophthalmol 3: 388–398, 1964.

Wilkerson, M., Cyrlin, M.N., Lippa, E.A., Esposito, D., Deasy, D., Panebianco, D., Fazio, R., Yablonski, M. & Shields, B.: Four-week safety and efficacy study of dorzolamide, a novel, active topical carbonic anhydrase inhibitor. Arch Ophthalmol 111: 1343–1350, 1993.

Wistrand, P.J.: Carbonic anhydrase inhibition in ophthalmology: Carbonic anhydrases in cornea, lens, retina and lacrimal gland. In: The Carbonic Anhydrases. New Horizons (ed. W.R.Chegwidden, N.D.Carter & Y.H.Edwards), pp. 413–424. Birkhäuser Verlag, Basel, 2000.

Wistrand, P.J. & Lindqvist, A.: Design of carbonic anhydrase inhibitors, and the relationship between the pharmacodynamics and pharmacokinetics of acetazolamide. In: Carbonic Anhydrase: From Biochemistry and Genetics to Physiology and Clinical Medicine (ed. F.Botré, G.Gros & B.T.Storey), pp.352–378. VCH Verlagsgesellschaft mbH, Weinheim, 1991.

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