Effect of Acetazolamide on the Differential Threshold

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• **Following the oral administration of three 250-mg doses of acetazolamide sodium to nine patients with glaucomatous visual-field defects, a statistically significant improvement in the differential threshold was observed, whereas in 16 glaucoma suspects, no change could be detected. The greatest improvements following acetazolamide administration occurred in younger patients and in those with the greatest disturbances of the visual field.**

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The most important sign of chronic open-angle glaucoma is the slowly progressive visual field defect. It is generally assumed that a substantial reduction in intraocular pressure halts or slows the progression of these defects. It is probable but less well established that some field defects can be completely reversed or improved by appropriate therapy. In an individual patient, such a reversibility in the field defects must be differentiated from long-term fluctuation of the field by examination of a number of visual fields prior to and following any treatment. Paterson[1] reported an improvement of both absolute and relative scotomata on a Goldmann perimeter 30 minutes after the intravenous administration of 500 mg of acetazolamide sodium. The reversibility varied greatly from patient to patient, but younger patients showed greater improvements. Heilmann[2] noted a pronounced improvement of the differential threshold on the Tübinger perimeter in his patients two hours after administration of 250 mg of acetazolamide sodium (in tablet form). He noticed a diminution in the size of scotomata and a small improvement in the mean threshold of those visual fields that were without a localized disturbance. No improvement of the visual field occurred following a reduction of IOP with clonidine hydrochloride administration, which simultaneously lowers the BP. He concluded that an improvement in perfusion pressure was the determining factor in producing the improvements. The return of the IOP to pretreatment levels resulted in a deterioration of the visual fields that was smaller than was the improvement following pressure reduction. He concluded, therefore, that the damage caused by high IOP took place more slowly than the reversal. Greve et al[3] described a slow improvement in visual-field defects following surgical intervention.

All of these studies were carried out by means of manual perimetry, which does not exclude the risk of bias introduced inadvertently by the examiner who is carrying out the field evaluations. The present study, using computerized perimetry, employed acetazolamide as the pressure-reducing agent (as it has previously been used in similar studies).

Acetazolamide is a carbonic anhydrase inhibitor that probably lowers IOP through the reduction in aqueous production.[4] It has a diuretic effect, which occurs later than the IOP reduction[5] and produces a fall in BP.[6-8] The diuretic effect diminishes with time, due to compensatory mechanisms,[9] but the induced acidosis remains.[10] Acetazolamide is no longer used for its diuretic effects because of the existence of more effective agents.

The aim of the present study was (1) to examine the effect—measured by automatic perimetry—of acetazolamide therapy on the visual field, (2) to study the effect of acetazolamide therapy while the BP was reduced, and (3) to evaluate factors that might enable us to predict possible reversibility.

PATIENTS AND METHODS

Twenty-five eyes of 25 patients were examined. All of them had undergone numerous previous manual visual-field examinations, which were used in deciding that nine had open-angle glaucoma and 16 were suspected of having glaucoma. The mean age, BP, retinal sensitivity, and IOP of the group are shown in Table 1. We decided not to use placebo controls (as we

Table 1.—Mean Threshold, Intraocular Pressure, BP, and Age in 25 Patients With Glaucoma or Suspected Glaucoma

Characteristic	Patients Suspected of Glaucoma* (N = 16)*	Patients With Open-Angle Glaucoma* (N = 9)*
Threshold, dB	26 ± 1.8	17 ± 5.8
IOP, mm Hg	25 ± 7	25 ± 9
Mean BP, mm Hg	97 ± 20	98 ± 12
Age, yr	56 ± 11	63 ± 16

*Mean ± SD.

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had in a study of ours that had just been concluded in which 26 eyes were subjected to placebo; no change in the differential threshold was found).[11] Each eye was examined without and following acetazolamide therapy. Examinations were conducted one week apart, and, to exclude a systematic error, the sequence of baseline or post-therapy tests was alternately assigned. The treatment consisted of 250 mg of acetazolamide sodium (in tablet form) administered three times during the 12-hour period prior to examination, the last tablet being taken two hours prior to the examination. The IOP, BP, and pulse were measured with the patient in the sitting position, while the visual field was tested by means of special experimental program JO[12] on the Octopus perimeter, which determines thresholds of 49 locations within 30° of fixation. The point of fixation and one peripheral point were measured ten times, whereas in the remaining 47 locations, thresholds were measured twice.

RESULTS

In the 16 patients with elevated IOP alone, acetazolamide did not alter the mean differential threshold (Fig 1), while the group of eyes with chronic open-angle glaucoma underwent a significant improvement in the differential threshold following acetazolamide therapy ($P < .05$) (Fig 2). The main improvement in the threshold occurred in defective areas. The relationship between the change noted in the differential threshold following acetazolamide therapy and the differential threshold observed in the pretreated stage (Fig 3) shows that improvement in the mean of the two threshold determinations of the individual points tested was greater the denser the visual-field defect. This relationship also includes the effects of the regression to the mean, which, when observed in placebo-treated patients from other studies and in those who were merely tested twice, was much smaller than the effect produced by acetazolamide administration.

The IOP drop was significant (Table 2), amounting to a mean fall of 8.2 mm Hg ± 7.4 mm Hg SD in the patients with elevated IOP alone and 8.9 mm Hg ± 6.4 mm Hg SD in the open-angle glaucoma group. There was the expected negative correlation between the IOP without treatment and the fall in IOP following therapy ($r = -.9$). The mean BP was also reduced in both groups. Those with elevated IOP alone had a mean reduction of 4 mm Hg ± 7.4 ($P > .05$), and the glaucoma group showed a fall of 9.4 mm Hg ± 15.6 (not significant). The elevation in perfusion pressure (mean BP minus IOP) was only minor in patients with elevated IOP alone and was unchanged in the group with open-angle glaucoma. There was no correlation between the changes in the differential threshold and the fall in BP or IOP or between the changes in the differential threshold and the changes in perfusion pressure.

Using multiple regression analysis

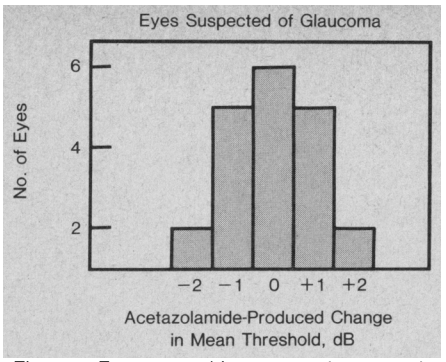

Fig 1.—Frequency histogram of acetazolamide-produced change in mean threshold (49 points) for eyes suspected of glaucoma, disclosing no change in mean. Differences have normal distribution around 0.

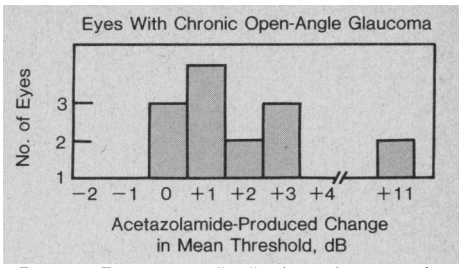

Fig 2.—Frequency distribution of acetazolamide-produced change in mean threshold of points tested in patients with open-angle glaucoma. A few patients show no change in threshold, but majority shows improvement.

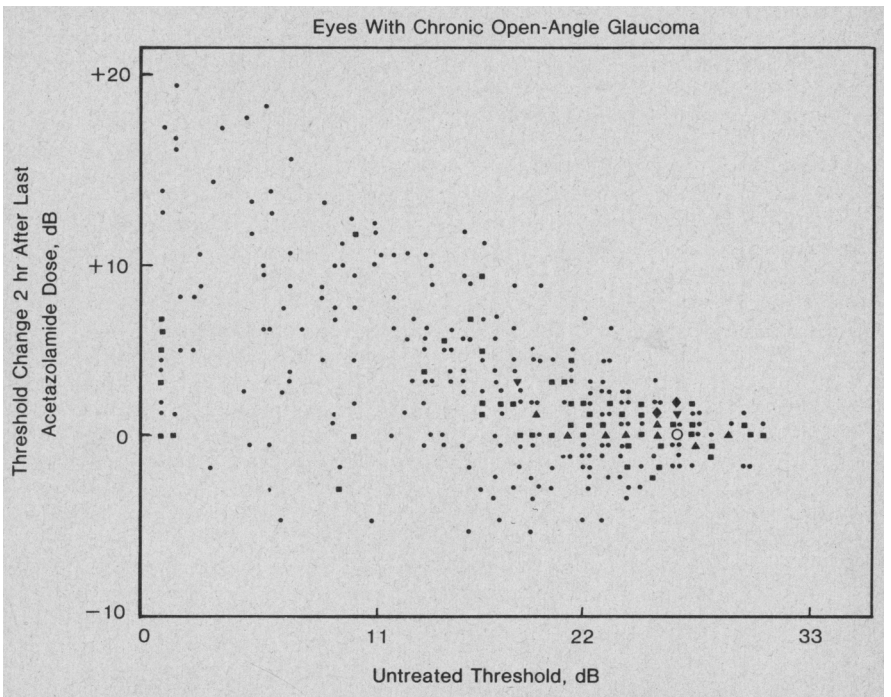

Fig 3.—Scattergram showing relationship between change in threshold two hours following acetazolamide administration and untreated threshold in patients with suspected glaucoma. Dots represent one point; squares, two to ten points; right-side-up triangles, 21 to 30 points; upside-down triangles, 31 to 40 points; diamonds, 41 to 50 points; and the open circle, 51 points or more.

Table 2.—Effect of Acetazolamide Administration on Mean Ocular Function Values in Patients With Glaucoma or Suspected Glaucoma

Characteristic	Patients Suspected of Glaucoma*	Patients With Open-Angle Glaucoma*
Differential Threshold, dB	+0.02 ± 0.9	+2.4 ± 3.2†
Intraocular Pressure, mm Hg	−8 ± 7†	−9 ± 6†
Mean BP, mm Hg	−4 ± 7	−9 ± 16
Perfusion pressure (mean BP minus IOP), mm Hg	+4 ± 10	0 ± 20

*Mean ± SD.
†$P < .05$.

Table 3.—Multiple Regression Analysis of Changes in Overall Mean Threshold in Patients With Open-Angle Glaucoma Treated With Acetazolamide*

Independent Variable†	Slope	F Value	P Value
Age	−0.17	16.6	.005
Untreated differential threshold	−0.17	11.7	.008
Perfusion pressure (BP minus intraocular pressure)	+0.02	7.0	.03

*Constant = 15.4; multiple r = .90.
†Mean values.

(Table 3), with drug-produced changes in the differential threshold taken as the dependent variable, the age of the patient, the changes in the perfusion pressure, and the mean threshold without therapy were interpreted as significant. The more depressed the untreated differential threshold, the greater the improvement of the differential threshold following acetazolamide therapy. The younger the patient the greater was the improvement. The greater the change in the perfusion pressure, the greater was the improvement of the differential threshold following acetazolamide administration. The scatter of the threshold, the reaction time, and the false-positive and false-negative responses were not related to the acetazolamide therapy.

COMMENT

The ingestion of 750 mg of acetazolamide sodium during a 12-hour period produced a significant ($P < .05$) partial reversibility in the glaucomatous visual-field defects. This confirms some previous reports,[1,2] but we found no changes in patients with elevated IOP alone.[2] Younger patients showed a greater reversibility, a finding that has also been shown by Paterson[1] and Phelps.[13] Strongly disturbed parts of the visual field showed a relatively greater improvement than did less-disturbed areas.

We confirmed Heilmann's[2] findings of the lack of correlation between the change in the visual field and the IOP reduction. The pronounced reduction of BP in our patients contradicts Heilmann's concept, however, that the improvement of the visual field is principally due to an improvement in the perfusion pressure. The multiple regression analysis suggests a possible relationship between the change in the visual field and the perfusion pressure. The change in perfusion pressure cannot be the principal cause for the improvement in the visual field, as the mean perfusion pressure in the group with chronic open-angle glaucoma—which showed the field improvement—had not changed.

The question arises, then, whether acetazolamide produces improvement in the visual field through a pharmacologic mechanism other than the IOP reduction. Acidosis is a constant and lasting effect of the drug. Respiratory acidosis, as well as acetazolamide-produced acidosis, causes an increase in the blood flow of brain and choroid.[13-17] In monkeys, the choroidal blood flow increases by 75% after acetazolamide administration. One can assume that the increased blood flow caused by acetazolamide is produced by acidosis.[18] It is therefore possible that the improvement in visual function can be produced by an improved blood flow to the optic nerve, which might result, not from changes in the perfusion pressure, but from a decreased vascular resistance. (It is also possible that acidosis might have a direct effect on the functionally damaged axons.) The acidosis following a single oral dose of acetazolamide lasts longer than the reduction in IOP; this might explain Heilmann's[19] findings that the deterioration of the visual function following the return of the IOP to the pretreated level was less pronounced than the improvement of the visual function produced by the fall in IOP. The improvement of visual function in the glaucomatous field defect following acetazolamide administration seems to be substantiated, but the mechanism underlying it remains unconfirmed.

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