The Acute Effect of Oral Acetazolamide on Macular Blood Flow

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Acetazolamide has been shown to be beneficial in the treatment of macular edema. To investigate whether this effect is associated with changes in the retinal circulation, the acute effect of oral acetazolamide on macular blood flow was studied in 20 healthy volunteers. The blue-field simulation technique, a noninvasive method enabling the quantitation of the number (N) and mean velocity (Vm) of leukocytes flowing in the subject's own macular capillaries was used in this study. On two different occasions, separated by 3 or more days, 20 subjects adjusted Vm and N of computer-simulated leukocytes moving on a video screen to match those of their own entoptically perceived leukocytes before and 3 hr after a double-blind, randomized administration of 500 mg acetazolamide or placebo capsules. Ten trials were done, and the velocities were averaged. After acetazolamide ingestion, there was a nonsignificant average change from baseline in Vm (2.5 ± 23% [± one standard deviation]; P > 0.1, by paired student t-test) and N (6.9 ± 25%, P > 0.1). After placebo ingestion, the average changes from baseline in Vm and N also were not statistically significant (−1 ± 18% and 14.9 ± 30.3%, respectively). Furthermore, when compared with the changes measured after placebo intake, acetazolamide ingestion was associated with a nonsignificant 4.3 ± 28.7% change in Vm (P > 0.1) and a −8 ± 30.9% change in N (P > 0.1). With 20 subjects tested, the calculated average minimum change in leukocyte velocity that could have been detected with this technique (P < 0.05, by paired student t-test) is about 9%. Acetazolamide, therefore, does not affect macular leukocyte velocity, or presumably blood flow, by more than this amount in the normal eye. Invest Ophthalmol Vis Sci 33:504-507, 1992

Acetazolamide is the most commonly used carbonic-anhydrase inhibitor in the management of glaucoma.1 Recent studies have shown that chronic administration of acetazolamide has a clinically beneficial effect on patients with macular edema.2,3 The mechanism of this effect is unknown. We investigated whether acetazolamide affects the retinal macular circulation. Such an effect could be associated with the clinical improvement observed in patients with macular edema.

Materials and Methods

Twenty normal volunteers with no history of hypertension, diabetes, or other systemic diseases participated in this study. Their ages ranged from 18–51 yr (mean ± standard deviation, 30.9 ± 9.0). There were 11 men and 9 women. All eyes studied had a best-corrected visual acuity of 6/6 or better, normal intraocular pressure (IOP), clear media, and normal fundi. The right eye was studied in all subjects except three. In three subjects, the left eye was used because the best-corrected visual acuity in the right eye was less than 6/6. No volunteers had received any systemic or ocular medication within 1 week of the study, nor did they ingest any caffeine within 24 hr before the study. Informed consent was obtained from each volunteer after the nature of the study was explained.

The subjects were seated in a darkened room in front of a blue-field simulator (Occulix, Berwin, PA). This instrument provides a diffuse and uniform Maxwellian illumination of the retina at a wavelength of 430 nm. When this illumination is centered at the fovea, optimal entoptic visualization of the leukocytes flowing in the subject's own macular capillaries is obtained. The diameter of the illuminated field is approximately 24°, and the intensity level needed to observe this phenomenon is well below the maximal permissible level of retinal irradiance.4

In the macular microcirculation, where capillaries measure 7–10 μm in diameter, the velocity of leukocytes is equal (within a few percent) to the mean velocity of whole blood.5 This velocity can be assumed to represent flow because these capillaries probably have a constant diameter.6–9
Quantitation of the mean velocity ($V_m$) and number ($N$) of these leukocytes was done using the blue-field simulation (BFS) technique in which the subjects adjusted the number and the velocity of computer-simulated leukocytes moving on a video screen to match those of their own entoptically perceived leukocytes.10

A BFS trial consisted of matching $V_m$ and $N$ of a simulated set of particles on a video screen to those of the entoptically observed leukocytes using two potentiometers. During the first baseline trial and the first trial done 3 hr after drug ingestion, the subjects adjusted $V_m$ and $N$ by alternately looking at their entoptic phenomenon and the simulation. During all subsequent trials, the velocity was scrambled by the computer, but $N$ was unchanged, and the subjects only adjusted the velocity.

The subjects were asked to match a computer simulation of the blue field to a standard simulation five times. In this way, the accuracy of the subjects could be assessed. All subjects who participated in this study were able to adjust $V_m$ of the simulated blue field to within 20% of the standard.

The subjects then did five practice BFS trials followed by a 10-min relaxation period. In the next phase of the experiment, the subject’s brachial artery pressure (BP) and heart rate (HR) were measured twice using an automated sphygmomanometer (Datascoppe Accutorr, Paramus, NJ), and the means were determined. This was followed by ten BFS trials to obtain a baseline $V_m$ and $N$. The subjects adjusted both $V_m$ and $N$ for the first trial in each set. For subsequent trials, however, they only adjusted $V_m$ because the computer provided the same $N$ as used in the first trial. Both BP and HR were measured again as described while the subject remained seated. Goldmann applanation tonometry was done on the study eyes. The subjects then were given a 500-mg acetazolamide-containing or placebo capsule (1000 mg of lactose powder) in a randomized, double-masked manner. The order in which drug or placebo were given was chosen randomly, and both subjects and investigators were masked as to the identity of the drug. After 3 hr, the entire protocol was repeated (without the five familiarization trials). Three or more days later, the experimental procedure was repeated with the other capsule.

Mean BP ($BP_m$) was calculated according to the formula

$$BP_m = BP_d + \frac{1}{3}(BP_s - BP_d)$$  

(1)

where $BP_s$ and $BP_d$ are the brachial artery systolic and diastolic pressures. Perfusion pressure (PP) for the study eye was determined according to the formula

$$PP = \frac{1}{3}BP_m - IOP$$  

(2)

We used student paired t-test and correlation analysis in the statistical evaluation of the results.

Results

Our experimental results are summarized in Tables 1 and 2. After acetazolamide ingestion, there was a significant average $15.5 \pm 13.1\%$ ($\pm 1$ standard deviation) decrease in HR and a significant average $14.5 \pm 13.1\%$ decrease in IOP. The mean arterial blood pressure ($BP_m$) and perfusion pressure 3 hr after acetazolamide (A) and placebo (P) ingestion are also shown.

### Table 1. Percentage changes from baseline in heart rate (HR), intraocular pressure (IOP), mean arterial blood pressure ($BP_m$), and perfusion pressure 3 hr after acetazolamide (A) and placebo (P) ingestion

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tion, $P < 0.05$) decrease in IOP and a 6.1 ± 11.2% ($P < 0.05$) increase in PP from baseline. There were no significant changes in IOP (5.4 ± 15.8%, $P > 0.1$) or PP (2.1 ± 11.2%, $P > 0.1$) after placebo ingestion. By comparison with the changes associated with placebo intake, there was a significant 20.9 ± 23.7% ($P < 0.001$) decrease in IOP and a nonsignificant 4.0 ± 16.2% ($P > 0.1$) in PP after acetazolamide intake.

A significant decrease in HR was observed after both acetazolamide and placebo intake (8.9 ± 8.7% and 7.7 ± 8.2%, respectively, $P < 0.05$, Table 1). However, by comparison with changes in HR associated with placebo intake, there was no significant change in HR after acetazolamide intake (1.5 ± 9.4%, $P > 0.1$).

After acetazolamide ingestion, there was a nonsignificant average increase in $V_m$ by 0.01 ± 0.16 mm/sec. This corresponded to a 2.5 ± 23% change from baseline ($P > 0.1$). After placebo ingestion, there was a nonsignificant average decrease in $V_m$ of 0.05 ± 0.16 mm/sec, corresponding to a 1.0 ± 18.0% change ($P > 0.1$, Table 2). Compared with the placebo effect, acetazolamide was associated with a nonsignificant average increase in $V_m$ of 3.5 ± 28.8% ($P > 0.1$).

A nonsignificant average increase in N of 2.8 ± 32.0 particles per field of view corresponding to an increase of 6.9 ± 25% ($P > 0.1$) was observed after acetazolamide ingestion. After placebo ingestion, N increased by an average of 14.0 particles per field of view, corresponding to an average increase of 14.9 ± 30.3% ($P > 0.1$, Table 2). Compared with the effect that followed placebo intake, acetazolamide was not associated with a significant change in N (8.0 ± 30.9%, $P > 0.1$).

A nonsignificant average increase in $BP_m$ of 0.2 ± 7.6% ($P > 0.1$) was observed after acetazolamide ingestion and of 2.6 ± 7.6% ($P > 0.1$) after placebo ingestion (Table 1). Compared with placebo, there was a nonsignificant 2.4 ± 10.0% ($P > 0.1$) decrease in $BP_m$. The HR also did not change significantly after acetazolamide or placebo intake (−8.9 ± 8.7% and −7.7 ± 8.2%, respectively, $P > 0.1$). There were no correlations between the changes in $V_m$ or N and the changes in either IOP, $BP_m$, PP, or HR after acetazolamide or placebo.

### Discussion

Our results show that, in the normal eye, acetazolamide ingestion is not associated with a significant change in $V_m$ or N. Therefore, macular blood flow does not appear to be affected acutely by this drug.

The significant changes in IOP and PP produced by acetazolamide in our normal subjects were not associated with significant changes in $V_m$ or N. This may be a result of the autoregulatory capacity of the normal retinal circulation, which maintains an unchanged blood flow despite changes in PP or IOP.9,11−13 A normal autoregulatory response may have masked any possible effects of acetazolamide on
macular blood flow. Whether this occurs in patients with diabetic macular edema that have abnormal retinal vascular regulatory responses remains to be investigated further. It is possible that, in such patients, the autoregulatory response may not mask a possible effect of acetazolamide on the retinal circulation.

It also is important to evaluate the effect of acetazolamide on the macular circulation of patients with macular edema from other causes, such as retinitis pigmentosa, aphakia, and uveitis, because the most beneficial effects of this drug have been reported in these patients. The HR decreased significantly after both acetazolamide and placebo ingestion. Because the decrease after acetazolamide ingestion did not differ significantly from the change associated with placebo ingestion, we cannot conclude that this change in HR was a result of the drug. This decrease in HR could be explained by the fact that the subjects may have been more relaxed and familiar with the experimental procedure after the 3-hr waiting period following capsule ingestion and thus may have been less nervous.

Because we did not find any significant changes in Vm after acetazolamide ingestion, it is important to discuss the sensitivity of our technique. We estimated that the minimum percentage change in Vm that would have been detected with our technique was about 9%. This figure was calculated from the following equation:

$$\frac{\Delta V_m}{V_m} (%) = \frac{SD \cdot T_{19,0.05}}{20 \cdot V_m} \cdot 100$$ \hspace{1cm} (3)

which was derived from the formula used to calculate t for paired observations. The Vm represents the normalized mean leukocyte velocity, with SD as the standard deviation of the difference in normalized mean leukocyte velocity for the 20 subjects, t_{19,0.05} as the t value for 19 degrees of freedom at a significance level of P < 0.05 (two tailed), and 20 as the number of subjects. Acetazolamide, therefore, does not seem to affect Vm (or presumably blood flow) by more than this amount in normal eyes.

Key words: acetazolamide, blue-field simulation, leukocyte velocity, macular edema, retinal blood flow

References