A Randomized, Masked, Cross-over Trial of Acetazolamide for Cystoid Macular Edema in Patients with Uveitis

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Purpose: To study the effect of acetazolamide on cystoid macular edema in patients with uveitis.

Methods: Forty patients with chronic intermediate, posterior, or panuveitis associated cystoid macular edema were randomized into a masked, cross-over trial comparing acetazolamide versus placebo. Patients received an initial 4-week course of either acetazolamide or placebo (course A) followed by a 4-week washout period. They then received a 4-week course of the opposite study medication (course B). Primary endpoints included area of cystoid macular edema measured on late-phase views of fluorescein angiography and visual acuity.

Results: Thirty-seven patients completed the trial and were available for analysis; 17 (46%) were randomized to receive acetazolamide and 20 (54%) to receive placebo during course A. Acetazolamide resulted in a 0.5-disc area (25%) decrease in cystoid macular edema over that of placebo ($P = 0.01$; estimated treatment effect = −0.5 disc areas; 95% confidence interval, −0.9 to −0.1). However, there was no statistically significant effect of acetazolamide on visual acuity ($P = 0.61$; estimated treatment effect = 0.6 letters; 95% confidence interval, −2 to 3).

Conclusions: A 4-week course of acetazolamide therapy results in a statistically significant but small decrease in cystoid macular edema in patients with chronic uveitis, and does not improve visual acuity. In contrast to previous studies in the literature, acetazolamide may have a more limited clinical benefit in patients with long-standing cystoid macular edema associated with chronic uveitis.

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Cystoid macular edema (CME) is a major cause of decreased visual acuity in patients with uveitis. Smith et al[1] noted CME in 75% of eyes in patients with intermediate uveitis with visual acuity of 20/40 or worse. Treatment with corticosteroids, immunosuppressive agents, and nonsteroidal anti-inflammatory drugs all have been used to treat uveitic CME[2,3]; however, many patients are resistant or intolerant of these treatments. Pars plana vitrectomy appeared to decrease CME in patients with uveitis,[4–7] but additional surgery was required in as many as 50% of the patients,[5] and some investigators noted a recurrence of the CME after surgery.

In 1988, Cox et al[8] reported a prospective cross-over study of acetazolamide for CME. Sixteen of 41 patients with documented CME showed a reproducible response to acetazolamide; there was no response to placebo. Six of the 41 patients had uveitis; half of these responded to therapy with decreased CME on fluorescein angiography and improvement of visual acuity. In a randomized, cross-over study of 37 patients with chronic iridocyclitis, Farber et al[9] showed a small but statistically significant improvement in visual acuity soon after acetazolamide therapy

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but not after placebo administration. The authors also showed decreased leakage of fluorescein into the posterior vitreous after acetazolamide; however, measurements were available on less than half the enrolled patients, and fluorescein angiography was not performed. In addition, 7 of the 37 patients discontinued their medications. Several other reports suggested a therapeutic benefit of acetazolamide for uveitic CME,[2,10,11] but a randomized clinical trial to study the effects of acetazolamide on visual acuity and CME measured on fluorescein angiography has not been performed on a large group of patients with uveitis. The National Eye Institute, therefore, conducted a randomized, masked, cross-over trial of acetazolamide for CME in patients with chronic uveitis.

Patients and Methods

Patients with intermediate uveitis, posterior uveitis, or panuveitis and visual acuity of 20/40 or worse in at least one eye with CME documented on fluorescein angiography were eligible for enrollment. The diagnosis of intermediate uveitis required the presence of vitritis, CME, and either peripheral retinal vascular disease, cellular debris in the inferior vitreous "vitreous snowballs," exudate on the pars plana, or peripheral retinal infiltrates. The diagnosis of posterior uveitis required the presence of vitritis, CME, and infiltrative retinal lesions involving the posterior pole of the eye. The diagnosis of panuveitis required the finding of anterior segment inflammation, vitritis, and infiltrative retinal lesions. Additional inclusion criteria included age of at least 8 years and weight of at least 35 kg. Patients receiving systemic or topical anti-inflammatory therapy for their uveitis were eligible for the study. Patients receiving acetazolamide or another carbonic anhydrase inhibitor were not eligible for the trial. Additional exclusion criteria included a history of hypersensitivity reactions to acetazolamide, sulfonamides, or fluorescein and evidence of marked renal or hepatic dysfunction or hyperchloremic acidosis based on serum electrolyte values and liver function tests. Eyes were ineligible for the study if they had hazy media due to cataract or vitreous opacity that would obscure fluorescein angiography (vitreous haze $\geq$ 2+ based on standard photography),[12] a macular hole, or choroidal neovascularization. Each patient was required to have at least one eligible eye for the study.

Study Design

An investigational new drug application to use acetazolamide to treat CME in patients with uveitis was obtained from the Federal Drug Administration. The study protocol was approved by the institutional review board of the National Eye Institute at the National Institutes of Health.

Sample Size Calculation

This study was designed to assess the efficacy of acetazolamide compared with placebo in treating CME secondary to uveitis. Previous studies suggested that the event rate, defined as a statistically significant change in CME in the acetazolamide-treated group,[8] would be approximately 50%, and the event rate in the placebo-treated group would be less than 10%. Using a two-sided statistical test with an alpha error of 0.05 and a beta error of 0.2, we calculated that a sample size of 40 patients would be needed for a two-armed study. The cross-over design, where each patient receives acetazolamide and placebo therapy in succession, gives additional statistical power to this study. Therefore, the sample size of 40 patients was believed to be a conservative estimate of the number of patients needed for the proposed design.

Randomization and Study Protocol

After signing an informed consent, patients received a baseline examination that included measuring the visual acuity with the patient's current correction and after manifest refraction using a logarithmic visual acuity chart under standard conditions,[13] slit-lamp biomicroscopy, measurement of intraocular pressure using a Goldmann tonometer, and dilated fundus examination by masked observers. Fluorescein angiography then was performed under a standard protocol. Complete blood counts, serum electrolytes, and liver function test results also were obtained. The clinical examination, fluorescein angiography, and laboratory tests were repeated at the 4-, 8-, and 12-week visits.

If eligibility was confirmed after the baseline examination outlined above, patients were assigned randomly to receive acetazolamide sodium (500-mg sequel) or placebo orally every 12 hours for 4 weeks (course A). If patients had severe adverse effects attributed to the study medication, the dose was decreased to 500 mg once daily or the study medication was discontinued. Investigators involved in study measurements were masked to side effects and changes in the dosages of study medications. A randomization schedule was generated from a random number chart in blocks of 6. Both patients and investigators were masked to randomization. Acetazolamide and placebo were placed in identical capsules by the Pharmacy Department of the Warren G. Magnuson Clinical Center at the National Institutes of Health.

After completing 4 weeks of the course A medication, patients were examined as outlined above. There was then a 4-week washout period where no study medication was administered. At the end of the washout period, patients again were examined (second baseline examination) as outlined above and then received a 4-week course of the opposite study medication to which they were assigned during course A. Patients randomly assigned to receive acetazolamide during course A received placebo during course B and vice versa. At the end of course B, patients again were examined (12-week examination) as outlined above. At the examinations after courses A and B, patients were asked if they had side effects associated with therapy, including numbness or tingling in an extremity, change in appetite, lethargy, nausea, or increased urinary frequency. If side effects during one of the courses of therapy

became intolerable, the dose of the study medication was decreased from every 12 hours to once daily. Patients continued their anti-inflammatory medications during the study. No change in these medications was made unless a sight-threatening exacerbation of the underlying uveitis occurred. All medications were recorded at each study visit. Changes in serum electrolytes during acetazolamide therapy were used as an indicator of patient compliance with the study protocol.

Study Endpoints

The primary endpoints of the study were the amount of CME measured on fluorescein angiography and best-corrected visual acuity. Fluorescein angiograms were graded by two masked observers. The initial study protocol stated that the degree of CME on fluorescein angiography would be quantified by measuring the height of the macular edema as previously detailed.[14] However, many patients had small pupils secondary to posterior synechiae, and it was technically impossible to obtain stereoscopic fluorescein angiograms on a number of these patients. Therefore, before the fluorescein angiograms were read by the masked observers, a decision was made to quantify the degree of CME according to the Macular Photocoagulation Study.[15] A transparent template was placed over a late frame of the angiogram, when no further accumulation of fluorescein was noted (Fig 1). The extent of late leakage was determined by placing the best fit over this area. The 2-disc-area circle measured 3.5 mm^2; the 3.5-disc-area circle measured 6.2 mm^2; the 4-disc-area circle measured 7.1 mm^2; and the 6-disc-area circle measured 10.6 mm^2. Fluorescein angiograms were read by two masked ophthalmologists in random order. Disagreement in the grading of more than 0.5 disc area occurred on less than 5% of the angiograms. These angiograms were reviewed, and the differences were adjudicated.

A clinically significant change in visual acuity was defined as a three-line (15-letter) or greater difference in visual acuity using a logarithmic eye chart and a standardized protocol for measuring best-corrected visual acuity. Because few patients had a three-line or greater change in visual acuity after either acetazolamide treatment or placebo administration, the change in visual acuity measured in number of letters also was examined. Secondary endpoints of the study included intraocular pressure, complete blood count, and serum potassium level.

Statistical Analysis

The effect of acetazolamide on visual acuity and CME was analyzed by comparing the difference in the measurements before and after acetazolamide and the difference in the measurements before and after placebo. Therefore, the outcome measure was the difference in differences. The analysis followed the approach of Senn,[16] where regressing the outcome variable on a treatment period indicator adjusts for period effects (the effect of time on the outcome variable). The treatment effect then is estimated by the intercept term of the model.

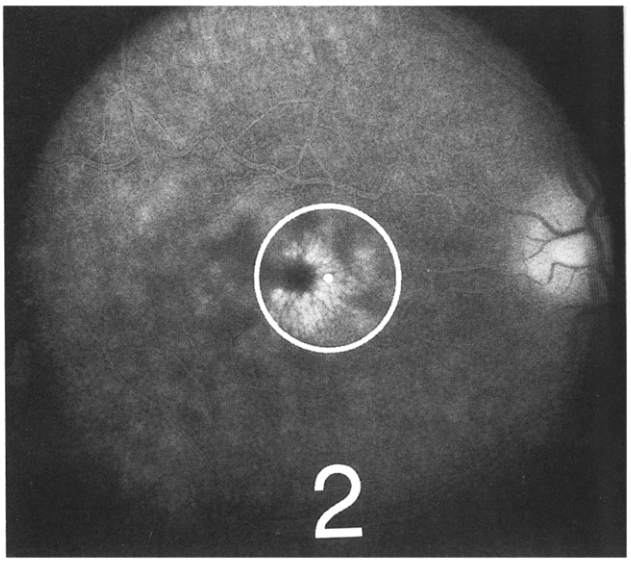

Figure 1. Late frame of the fluorescein angiogram shows the use of a standardized grid to quantify the amount of cystoid macular edema as the number of disc areas of fluorescein leakage.

At the time of enrollment into the study, 14 patients had both eyes eligible and 26 patients had only one eligible eye. The additional data from having two eligible eyes were analyzed in two ways for the primary endpoints: (1) by averaging the two eyes in the regression analyses and (2) by using both measurements in a repeated measures model. The results of the two analyses were similar, and we only report the former. For the secondary endpoints, only the former analysis was performed.

Subgroup analyses also were performed to determine whether the treatment effect of acetazolamide was related to duration of uveitis, systemic anti-inflammatory medications, or previous cataract surgery. This was analyzed by fitting separate regression models to the two levels of each covariate. For example, separate regression models were fitted for patients taking systemic anti-inflammatory medications and for patients not receiving systemic anti-inflammatory medications. Approximate z tests were used for the statistical comparisons, and P values corresponding to the approximate z tests are presented for each subgroup analysis. In some patients, only one of two eligible study eyes had undergone previous cataract extraction. In this case, the two eyes were treated as independent variables, although in a strict sense, they were not statistically independent.

Results

Forty patients were randomized into this study. Thirty-seven patients completed the trial and were available for analysis. Case 8 had a subfoveal choroidal neovascular membrane in her only eligible eye. Since a choroidal neo-

vascular membrane was an exclusion criterion for the study, the patient was removed from the analysis. Case 23 had a history of depression, which worsened several days after starting course A therapy with acetazolamide, and dropped out of the study. In case 37, a retinal detachment developed in an area of pre-existing chorioretinal atrophy soon after randomization to course A with acetazolamide, and this patient was removed from the study.

The demographic and clinical characteristics of the 37 analyzed patients are shown in Table 1. Twenty-one patients had intermediate uveitis, 11 had posterior uveitis, and 5 had panuveitis. Most of these patients had noninfectious causes of their uveitis; two patients had persistent CME after receiving treatment for *Propionibacterium acnes* endophthalmitis. Most patients in the study had chronic uveitis with long-standing CME. The mean duration of uveitis was 6.6 years; only two patients had uveitis for less than 1 year. At the start of the study, 17 patients (46%) were receiving systemic anti-inflammatory agents, 6 (16%) were receiving topical anti-inflammatory medications alone, and 14 patients (38%) were receiving no anti-inflammatory medications.

Of the 37 patients available for analysis, 17 (46%) were randomized to receive acetazolamide during course A, and 20 (54%) were randomized to receive placebo during course A. Visual acuity data were available for all 37 patients for all visits. Fluorescein angiography data were available for 145 (98%) of the 148 study visits. The fluorescein angiogram could not be graded for one visit for the only eligible eye for case 14 and for one of the two eligible eyes of case 34. In case 11, a rash developed during course B with acetazolamide, and the patient stopped taking the study medication. She was examined 2 weeks after starting course B, and, although visual acuity data are available for this visit, a fluorescein angiogram was not performed.

The effect of acetazolamide on CME is shown in Table 2. There was a statistically significant decrease in CME after acetazolamide therapy when compared with placebo ($P = 0.01$; estimated treatment effect = −0.5 disc area; 95% confidence interval, −0.9 to −0.1). The mean area of CME at the start of therapy was 2.0 disc areas; therefore, a 0.5-disc-area reduction represented approximately a 25% decrease in CME as measured by fluorescein angiography. The confidence interval suggests that treatment with acetazolamide resulted in a 4-week reduction in CME as much as 0.9 disc area, or as little as 0.1 disc area over that of placebo. Only five patients had a 50% or greater reduction in CME after acetazolamide therapy (Fig 2).

The effect of acetazolamide on visual acuity is shown in Table 3. There was no statistically significant effect of acetazolamide on visual acuity ($P = 0.61$; estimated treatment effect = 0.6 letter; 95% confidence interval, −2 to 3). The confidence interval suggests that the average 4-week change in visual acuity is estimated to range from two letters worse to three letters better for acetazolamide compared with placebo. In the five patients with a 50% or greater reduction in CME after acetazolamide therapy, visual acuity actually decreased by three and four letters

Table 1. Patient Characteristics

Sex	
Females	22
Males	15
Race	
White	26 (70%)
African Ameriican	7 (19%)
Hispanic	2 (5%)
Asian	1 (3%)
Native American	1 (3%)
Age (yrs)	
Mean ± SD	41.0 ± 14.4
Range	13-74
	No. of Patients (n = 37)
Type of uveitis	
Intermediate	21
Idiopathic	19
Associated with multiple sclerosis	2
Posterior	11
Behçet disease	3
Idiopathic	3
Vogt-Koyanagi-Harada disease	2
Birdshot retinochoroiditis	1
Sarcoidosis	1
Multifocal choroiditis	1
Panuveitis	5
Propionibacterium acnes endophthalmitis	2
Idiopathic	2
Sarcoidosis	1
Duration of uveitis (yrs)	
Mean ± SD	6.6-6.6
Range	0.5-34
Anti-inflammatory medications	
Systemic medications	17
Cyclosporine	3
Cyclosporine + prednisone	6
Cyclosporine + prednisone + azathioprine	1
Prednisone	6
Prednisone + cyclophosphamide	1
Topical medications	11
Alone	6
With systemic immunosuppression	5
Topical corticosteroids	11
Topical NSAIDs	1
No medications	14
	No. of Eligible Eyes (n = 51)
Previous cataract surgery	
Phakic	40 (78%)
Pseudophakic	6 (12%)
Aphakic	5 (10%)

SD = standard deviation; NSAIDs = nonsteroidal anti-inflammatory drugs.

Table 2. Effect of Acetazolamide on Cystoid Macular Edema

	Treatment Sequence			
	First Baseline	*After Acetazolamide*	*Second Baseline*	*After Placebo*
Area of CME*	2.2	2.0	2.0	2.0
Range	0.8–20.0	0.8–20.0	0.2–20.0	1.0–20.0
No. of eligible eyes	21	19	21	21
	First Baseline	*After Placebo*	*Second Baseline*	*After Acetazolamide*
Area of CME*	2.1	2.0	2.1	1.5
Range	0.5–20.0	1.0–10.0	0.0–20.0	0.0–5.0
No. of eligible eyes	30	30	30	27

CME = cystoid macular edema.

* Data presented as the number of disc areas (mean ± standard deviation) of CME.

in two patients, improved by two letters in two patients, and improved by ten letters in one patient.

Subset analyses were performed to determine whether the treatment effect of acetazolamide on CME or visual acuity differed: (1) in patients with uveitis for 4 years or more versus patients with uveitis for less than 4 years, (2) in patients taking systemic anti-inflammatory medications at the start of the trial versus patients not taking systemic medications, and (3) in eyes with previous cataract surgery versus eyes without previous cataract surgery (Table 4). Although the numbers in each group were small and the study was not designed for subgroup analyses, no significant interaction was noted between these covariates and the treatment effect of acetazolamide.

The treatment effect of acetazolamide on intraocular pressure, hemoglobin levels, and serum potassium values also was analyzed. In the 34 patients who had intraocular pressure measurements for all four study visits, there was no significant treatment effect on intraocular pressure ($P = 0.11$; estimated treatment effect = −1.3 mmHg; 95% confidence interval, −2.9 to 0.3). In the 25 patients with complete hematology data, there was no treatment effect of acetazolamide on hemoglobin level ($P = 0.77$; estimated treatment effect = 0.1 g/dl; 95% confidence interval, −0.4 to 0.5). Similarly, in the 23 patients with complete serum chemistry data, there was no treatment effect of acetazolamide on serum potassium level ($P = 0.54$; estimated treatment effect = −0.1 mmol/l; 95% confidence interval, −0.3 to 0.2).

The adverse drug reactions reported during acetazolamide and placebo therapy are listed in Table 5. Possible adverse drug reactions were reported by 34 (92%) of the 37 patients during acetazolamide therapy. In contrast, at least one adverse drug reaction was reported in only 5 (14%) of 37 patients during placebo therapy. Of the three patients excluded from analysis, one had nausea and diarrhea, one had worsening of her depression, and one had nervousness while taking acetazolamide. Nevertheless, in most patients, the side effects were not severe enough to warrant cessation of therapy. Thirty-five (95%) of the 37 patients analyzed continued taking acetazolamide at the prescribed dose of 500 mg twice daily. Two patients decreased their dose to 500 mg once daily. The patient in whom a rash developed during the study had her course of acetazolamide shortened by 2 weeks, but the rash subsequently was related to her underlying disease and not to acetazolamide therapy. One of the three patients not available for analysis was removed from the study because of exacerbation of a previously diagnosed depression, possibly related to acetazolamide therapy.

When possible, patients' anti-inflammatory medications were not changed immediately before or during the trial. There were no changes in the dosages of cyclosporine, azathioprine, or cyclophosphamide during the study. Prednisone dosage was constant throughout the study in 10 of the 15 patients taking the drug and varied by no more than 5 mg daily in three other patients with stable ocular inflammation. Four patients had exacerbation of their underlying uveitis during the study and required increased anti-inflammatory medication. Cases 21 and 35 received a periocular injection of 40 mg triamcinolone to the right eye after measurements were taken at the end of course A. Both eyes were eligible for the study for these two patients. After the washout period, both patients were believed to have stable ocular inflammatory disease; case 21 then received acetazolamide and case 35 received placebo during course B. Case 13 had an exacerbation of uveitis during course B with placebo; therefore, prednisone was increased from 20 to 80 mg daily 3 weeks before the last study visit. Case 16 had an exacerbation of uveitis during course A with placebo and was started on prednisone during the washout period. At the second baseline examination, the patient was taking 30 mg prednisone daily and had stable ocular inflammation.

Discussion

We demonstrated that acetazolamide therapy results in a statistically significant but small decrease in CME in patients with chronic intermediate, posterior, and panuveitis. Acetazolamide therapy resulted in a 0.5-disc-area (25%)

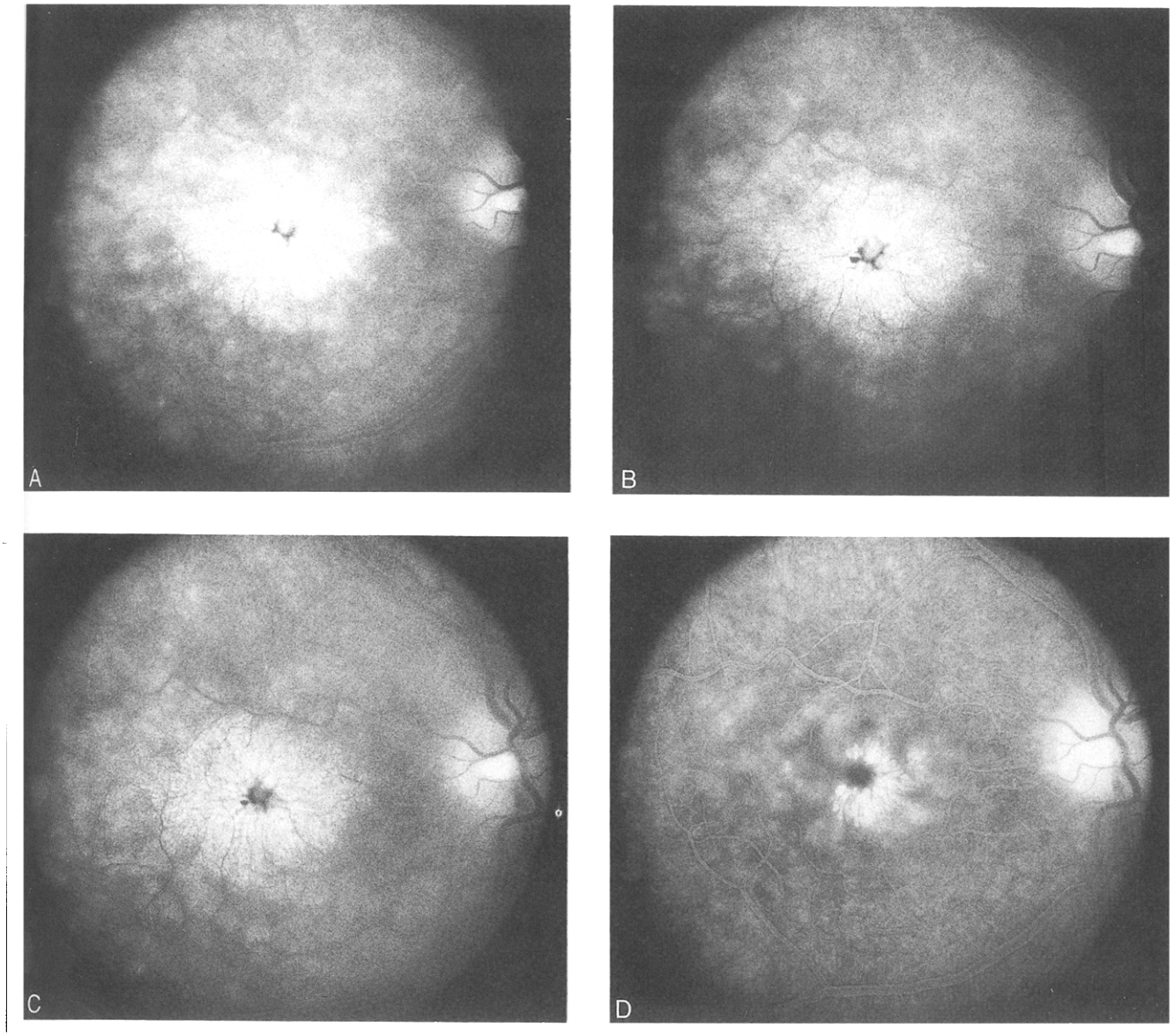

Figure 2. Late frames of the fluorescein angiograms from case 32, a 33-year-old man with bilateral intermediate uveitis for 6 months' duration. **A,** substantial cystoid macular edema is shown at baseline (visual acuity = 69 letters). **B,** no significant change is seen in the amount of cystoid macular edema after placebo (visual acuity = 69 letters). **C,** fluorescein angiogram after the 4-week washout period shows cystoid macular edema similar to the level at baseline (visual acuity = 65 letters). **D,** significant reduction in cystoid macular edema is shown after a 4-week course of acetazolamide therapy (visual acuity = 75 letters).

reduction in CME over that of placebo, and there was no treatment effect on visual acuity.

These results suggest that the short-term effect of acetazolamide on CME may be less clinically important than previously thought. Farber et al[9] showed statistically significant improvement of visual acuity 14 and 28 days after treatment with acetazolamide when compared with baseline but no improvement after treatment with placebo. However, statistical analyses comparing change in visual acuity after acetazolamide compared with the change after placebo showed no significant difference between the two groups. Cox et al[8] showed improvement in both visual acuity and CME in three of six patients with uveitis treated with acetazolamide; however, this was not a placebo-controlled trial, and the improvement in patients with uveitis was based on a subgroup analysis in a small number of patients.

Uveitis remains an important cause of visual loss. In one study, uveitis accounted for 10% of the severe vision loss in the United States,[17] and CME is the cause of decreased vision in most of these patients.[1] Cystoid macular edema is a common condition that also causes visual loss in diabetic retinopathy, retinal degenerations such as retinitis pigmentosa, vascular occlusive disease, and after cataract extraction. Studies have shown that acetazolamide may decrease CME causes by a number of these conditions.[2,8] However, some data suggest that acetazolamide is not effective for treating all forms of this con-

Table 3. Effect of Acetazolamide on Visual Acuity

	Treatment Sequence			
	First Baseline	*After Acetazolamide*	*Second Baseline*	*After Placebo*
Visual acuity*	48 (20/100−2)	48 (20/100−2)	49 (20/100−1)	51 (20/100+1)
Range	15-70	8-72	8-76	15-78
No. of eligible eyes	21	21	21	21
	First Baseline	*After Placebo*	*Second Baseline*	*After Acetazolamide*
Visual acuity*	60 (20/63)	58 (20/63−2)	60 (20/63)	62 (20/63+2)
Range	4-70	3-76	8-80	20-79
No. of eligible eyes	30	30	30	30

* Data presented as the median number of correct letters read after manifest refraction. The corresponding Snellen visual acuity is presented in parentheses for reference.

dition. Pinckers et al[18] showed that acetazolamide was not effective therapy for CME in dominant cystoid macular dystrophy. Therefore, the results of this study should not be generalized to conditions other than uveitis.

The mechanism by which acetazolamide decreases CME remains unclear. Deturgescence of the retina is related partly to the movement of fluid from the retina to the choroid. A number of studies indicate that this movement of fluid is dependent on active transport of ions by the retinal pigment epithelium from its apical to basal surface.[19,20] Similar to the ciliary body[21] and cornea,[22] the carbonic anhydrase system is considered to be important in regulating ion transport in the retinal pigment epithelium. Other researchers have demonstrated carbonic anhydrase in retinal cells (retinal pigment epithelium, Müller cells, photoreceptors, and vascular endothelium) in laboratory animals and in humans.[23,24] Acetazolamide also has been shown to change chloride flux and the resting potential of the retinal pigment epithelium.[25,26] In addition, Tsuboi and Pederson[27] showed that carbonic anhydrase inhibitors increase the rate of fluorescein disappearance from the vitreous. Also, acetazolamide increases resorption of subretinal fluid in rabbits with experimentally induced rhegmatogenous retinal detachment.[28] Some researchers hypothesized that acetazolamide decreases CME by diminishing macular blood flow, but a recent report showed a small but insignificant increase in blood flow after acetazolamide therapy.[29]

Several limitations of this study should be noted. The trial was designed as a double-masked study, but since the majority of patients had side effects while receiving acetazolamide, many were effectively unmasked to their treatment. However, ophthalmic technicians who measured visual acuity remained masked to patients' therapy, and the area of CME was graded by masked reviewers.

Table 4. Interaction of Treatment Effect and Covariates*

Covariate	Change in CME	Change in Visual Acuity
Systemic medications (yes versus no)	0.26	0.65
Duration of uveitis (yrs) <4 versus ≥4	0.47	0.15
Previous cataract surgery (yes versus no)	0.33	0.43

CME = cystoid macular edema.

* Data are presented as the *P* value for the interaction of the treatment effect of acetazolamide and the listed covariate.

Table 5. Possible Adverse Drug Reactions*

Adverse Drug Reaction	Acetazolamide (n = 37)	Placebo (n = 37)
Parasthesias	25	2
Fatigue	10	2
Altered taste	8	0
Nausea	5	0
Diarrhea	4	0
Polyuria	4	1
Joint pain/arthralgias	4	1
Drowsiness	2	0
Headache	2	2
Nervousness	1	1
Dry mouth	1	0
Heartburn	1	0
Back pain	1	0
Leg cramps	1	0
Rash	1	0
Stomach cramps	1	0
Weight loss	1	0
Retinal detachment	1	0

* One patient withdrew from the study after a worsening of a pre-existing depression, possibly related to acetazolamide.

The patient population in this study tended to have severe, chronic uveitis. Seventeen patients were receiving systemic immunosuppressive therapy for their disease. Thirty-five of the 37 patients had uveitis for more than 1 year. In fact, the one patient with at least a 50% decrease in CME and better than a one-line improvement in visual acuity after acetazolamide had the shortest duration of uveitis (6 months). Therefore, these results may not be generalizable to patients with less-severe uveitis with CME for short duration, and additional studies are needed to assess whether acetazolamide has a greater therapeutic effect in these patients.

Although great care was taken to maintain immunosuppressive therapy constant through the trial, changes in disease activity warranted some alteration in the doses of these medications. Fortunately, changes in anti-inflammatory medications were relatively rare. Only 4 of the 37 patients analyzed had substantial changes in immunosuppressive therapy during the study. In addition to underlying uveitis, cataract surgery was performed in 11 (22%) of 51 eligible eyes. Theoretically, CME in this subset of patients may respond differently to acetazolamide, but treatment effects did not differ significantly in patients with or without previous cataract surgery. Similarly, subgroup analysis showed that duration of uveitis or the need for systemic anti-inflammatory medications did not significantly alter the treatment effect of acetazolamide on CME or visual acuity.

The cross-over design may lead to additional statistical power over a two-sample study, but its analysis and conclusions depend on a lack of carry-over effect between the two courses of therapy.[16] Previous studies suggested that the therapeutic effect of acetazolamide occurs rapidly, and that a 4-week washout period is sufficient to prevent a carry-over effect[8,9]; however, it is difficult to rule out the possibility of a small carry-over effect of acetazolamide after the 4-week washout period. A longer washout period was considered, but this would increase the chance of an exacerbation of uveitis occurring during the trial, and the need for change in immunosuppressive medication that could alter the results of the study.

Although treatment with acetazolamide was not associated with a significant improvement in visual acuity, this study did not address the long-term effects of acetazolamide therapy. It is possible that even a small reduction in CME could moderate visual loss over time in patients with chronic uveitis. Also, it may take longer than 1 month for visual acuity to improve from acetazolamide therapy, although previous studies suggested that improvement in vision occurred by 28 days of therapy. In addition, other measures of visual function, such as color vision or contrast sensitivity, were not assessed and may have been more sensitive in showing a therapeutic benefit of acetazolamide. Additional studies are in progress to determine whether visual acuity or other measures of visual function improve after several months of treatment.

Although this study suggests only a small treatment effect from acetazolamide for uveitis CME, other treatments for chronic CME in patients with uveitis are limited. Systemic or periocular injections of corticosteroids can reduce CME in patients with uveitis, but are associated with a number of side effects.[30] Immunosuppressive agents, such as cyclosporine and azathioprine, also can decrease uveitis CME, but, again, these agents are associated with substantial adverse drug effects.[31] In addition, uveitic CME often is resistant to these treatments. Topical corticosteroids and nonsteroidal anti-inflammatory drugs have been reported to decrease angiographic CME after cataract surgery,[32,33] but the effect of these medications was ephemeral, and visual acuity did not improve. A single trial[34] showed resolution of chronic aphakic and pseudophakic CME and improvement in visual acuity after treatment with ketorolac tromethamine, but results have not been confirmed. Some investigators have suggested that vitreous traction may be a cause for chronic CME after surgery and in patients with uveitis.[35] The Vitrectomy-Aphakic Cystoid Macular Edema Study found a statistically significant improvement in visual acuity in patients undergoing vitrectomy surgery for chronic CME after surgery,[35] but randomized trials in patients with CME and chronic uveitis have not been performed.

Although the overall treatment effect of acetazolamide is small, there may be a role for this medication, possibly in combination with other anti-inflammatory agents, to treat CME in patients with uveitis. In this study, however, we show that acetazolamide is rarely a cure for chronic CME, and in contrast to previous reports, clinicians should expect only a limited short-term therapeutic benefit from this medication. We currently would recommend acetazolamide therapy for treating chronic CME associated with uveitis only if other medications are ineffective. Additional studies, however, are needed to determine whether acetazolamide has a greater therapeutic effect in patients with CME for shorter duration. In addition, because acetazolamide therapy is associated with adverse drug reactions, if improvement is not noted after several months of therapy, acetazolamide should be discontinued.

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Discussion
by
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Cystoid macular edema (CME) is a highly relevant clinical problem because it is responsible for most of the visual disabilities in intermediate, posterior, and panuveitis. Current treatment strategies aim at maximal suppression of intraocular inflammation; no specific "magic bullet" exists for CME. Ironically, diuretic treatment often is proposed by the patients who, upon being told that the retina is "wet," ask for a pill to "dry it up." From the physician's perspective, slow deturgescence of the retina by manipulation of the ionic currents in the retinal pigment epithelium seems an indirect and weak substitute for the desired self-guided, long-range missile. However, it is clear that even small amounts of improvement will benefit some patients. Whitcup and associates have tried to quantitate those benefits in a carefully designed, randomized, controlled clinical trial.

Although basic science research may eventually decode the pathophysiology of CME, clinical trials with humans are virtually the only way to assess its treatment because no adequate animal model exists. The participants selected for this trial had uveitis

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for more than 6 months and had the usual heterogeneity of diagnoses; approximately half of these patients had idiopathic intermediate uveitis. The duration of CME was not noted, and it is possible that some patients had had CME for years—a factor that might reasonably be expected to lessen the response to any treatment. Acetazolamide was used as an adjunctive treatment. Primary treatment with anti-inflammatory medications was given to the majority of patients during the trial but was not altered except for sight-threatening indications. The patients, diagnoses, and primary treatments are as homogenous as could be expected in a single-center clinical trial in uveitis. In addition, the cross-over design probably minimizes the effects of heterogeneity because each patient's data during the treatment phase are paired statistically with data taken from that patient in the placebo phase.

One disadvantage of crossover design is that it reduces the amount of time that study subjects spend on the treatment being studied. This may be particularly important in a chronic condition such as CME which is presumed to respond slowly to treatment. Concern is expressed that lack of an adequate "washout" period may confound results; however, the opposite is also true: inadequate treatment time may stunt the response before it is fully developed. This may be particularly true for visual recovery which may lag for some time after the deturgescence of the retina has been achieved. The results of the study may support this view since a statistically significant decrease in the amount of leakage was detected, yet improvement in visual acuity was not confirmed.

Outcome variables in CME pose some difficulties. Accurate visual acuity measures were possible with calibrated eye charts and standard testing protocols, but fluorescein leakage had to be estimated by the appearance of a photograph because no better method exists. This measure should be considered semiquantitative. Subjective contrast sensitivity[1] or objective capillary blood flow[2] are two other quantitative methods that could be used to assess outcomes in future studies. Other aspects of data analysis also deserve scrutiny. Patients with two eligible eyes had both entered into the study. The two-eye data were handled by averaging the response of the two eyes. Because many patients with uveitis may have one eye that is more severely affected than the other, this may have diluted some treatment effect in the better eye, although no bias was apparent when the results were analyzed by a repeated measures test. Subgroup analyses concentrated on the most important variables of systemic treatment for uveitis, duration of uveitis, and prior cataract surgery. No significant interactions were noted, although the small sizes of the subgroups limits the power to draw any conclusions regarding these factors. Treatment effects on intraocular pressure, hemoglobin, and serum potassium also were negligible. However, other investigators have reported that increased intraocular pressure after corticosteroid use is associated with improvement in CME in pseudophakic and aphakic eyes[3]; therefore, it would be interesting to know whether the "insignificant" fall in intraocular pressure after acetazolamide had any interaction with outcomes in this trial.

Duration of treatment with acetazolamide may be critically important. It would be interesting in future trials to see whether visual acuity would improve more if treatment were carried out until maximal reduction in the amount of angiographically detectable edema was achieved. The authors' conclusions regarding the usefulness of acetazolamide for treating CME in chronic uveitis are limited to the treatment regimen used in the current trial. Acetazolamide may yet prove to be a valuable adjunct in managing chronic CME in uveitis.

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