Reduction of macular oedema by acetazolamide in patients with chronic iridocyclitis: a randomised prospective crossover study

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Abstract

Thirty patients with cystoid macular oedema secondary to chronic iridocyclitis were enrolled in a two period, prospective, randomised, double masked, crossover study that compared sustained release acetazolamide (500 mg twice a day) with a placebo to measure the effects on the reduction of cystoid macular oedema and improvement of visual acuity. All patients were treated for 1 month with either acetazolamide or placebo, received no treatment for 1 month, and were then treated for 1 month with the other medication. Statistically significant improvement in visual acuity was seen at 14 and 28 days in the treated patients. No improvement was seen when patients received placebo. Improved visual acuity was not associated with race or sex. However, younger patients (under age 55 years) were more likely to benefit from treatment. Results of vitreous fluorophotometry, obtained at baseline and 4 weeks, demonstrated an improvement in posterior vitreous penetration ratios and mid vitreous penetration ratios after treatment with acetazolamide but not with placebo.

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Patients with uveitis suffer from a variety of ocular signs, including cystoid macular oedema (CMO). In 1988, Cox *et al*¹ reported that CMO in three of six patients with chronic uveitis responded favourably to the administration of acetazolamide. Complete resolution of CMO was demonstrated angiographically in two patients, whereas partial resolution of CMO was seen angiographically in the third patient. Furthermore, acetazolamide has been shown in animals to increase the rate of fluorescein clearance from the vitreous² and the rate of subretinal fluid resorption.³

Since CMO is a major cause of decreased vision in patients with chronic uveitis, a randomised clinical trial was undertaken to determine if acetazolamide reduces macular CMO in these patients.

Patients and methods

Patients with chronic iridocyclitis who were seen in the uveitis clinic at the University of Illinois at

Chicago Eye Center from September 1989 to January 1992 were enrolled in a two period, prospective, randomised, double masked, crossover study. The diagnosis of chronic iridocyclitis was made by the presence of persistent anterior and posterior chamber inflammation for over 2 months unaccompanied by fundus lesions. All patients were screened with a recent chest x ray, and were tested for the angiotensin converting enzyme, serum lysozyme, and fluorescent treponema antibody absorption. They were considered to have idiopathic iridocyclitis if these tests were negative, there was no obvious cause for their uveitis, and they fitted no syndrome such as Fuchs' heterochromia.

Inclusion criteria were (1) age of 18 years or more; and (2) the presence of CMO and a visual acuity of 20/40 to 20/200, documented by fluorescein angiography on two visits separated by at least 2 weeks. Exclusion criteria were (1) a history of liver or kidney disease, cardiovascular disease (except hypertension), chronic obstructive pulmonary disease, insulin-dependent diabetes mellitus, abnormal serum electrolyte levels, or hypersensitivity to sulphonamides; (2) pregnancy; or (3) having received systemic or periocular corticosteroids during the previous month. The use of topical corticosteroids between one and four times daily was permitted throughout the study. Informed consent was obtained in each patient.

The assignment to receive acetazolamide or placebo during the first month of the study was determined randomly. (Both the acetazolamide and the placebo tablets were provided by Storz Ophthalmic Pharmaceutical Research & Development, and repackaged and labelled by one of the principal investigators (MDF).) All other investigators and the patients were masked. She was the only person who knew which medication each patient received, and the patients were told to contact her if they experienced medication side effects.

The patients randomised to receive acetazolamide for the first month were asked to take two tablets of sustained release acetazolamide, 500 mg daily, one after breakfast and the second before bedtime. The patients randomised to the control group were placed on the same regimen with the use of placebo tablets which appeared identical to the acetazolamide tablets.

For the second month (the washout period),

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patients received no acetazolamide or placebo. For the third month, patients who had been randomised to acetazolamide were given placebo tablets, and patients who first had received placebo were given acetazolamide.

Before enrolment a complete ocular examination was performed by one of us (HHT or SL), including slit-lamp biomicroscopy and direct and indirect ophthalmoscopy. At baseline and at each follow up visit (fortnightly) thereafter, best corrected visual acuities were measured with the modified Bailey-Lovie logarithmic visual acuity charts at a distance of 4 metres, and at 1 metre as well if visual acuity was worse than 20/100. All measurements of visual acuity were made by one of us (AC) in the same lane with the same lighting conditions. Applanation tonometry, blood pressure measurements, tablet counts to determine compliance, and a complete blood cell count and blood chemistry study were also performed at the baseline and at each follow up visit.

Visual acuity was analysed by means of the logMAR score developed by Ferris *et al.*⁴ The logMAR score is derived by taking the logarithm

(base 10) of the fraction of Snellen visual acuity. A score of 0.0 is equivalent to a visual acuity of 20/20 on the Snellen acuity chart, whereas a score of +1.0 is equivalent to 20/200.

Vitreous fluorophotometry measurements were performed at baseline, 4 weeks, 8 weeks, and 12 weeks by one of us (MMR). Vitreous fluorophotometry was performed with a fluorophotometer (Fluorotron Master, Coherent Medical, Palo Alto, CA, USA) which has been described in greater detail elsewhere.⁵⁻¹⁰ The pupils were dilated with one drop each of 10% phenylephrine and 1% tropicamide. Before a 14 mg/kg injection of 25% fluorescein sodium, fluorophotometric scans of both eyes were obtained. Scanning was repeated at 2 to 5 minutes, 11 to 15 minutes, and 60 minutes after the injection. The scans started posteriorly over the macula and then proceeded anteriorly through the cornea. A 2 mm to 4 mm area in front of the chorioretinal peak (an average of five locations) was used to obtain the posterior vitreous fluorescence values, and an 8 mm to 10 mm area was used for the mid vitreous values.

Finger prick blood samples were taken 10 minutes and 1 hour after injection, and plasma fluorescence was determined. The posterior vitreous penetration ratio (PVPR) and mid vitreous penetration ratio (MVPR) were determined with the aid of the computer software program 'log log plasma' (Coherent Medical). These ratios reflected the amount of fluorescein that enters the posterior and mid vitreous for a specific amount of fluorescein that has circulated in the blood over time.

Statistical methods for analyses included the χ^2 test (with Yates' correction) for association between discrete variables and Fisher's exact test (two tailed) when the sample size was not adequate for the χ^2 test. We also used Student's paired *t* test to compare mean values.

A sample size of 30 subjects was selected based on the expected improvement in visual acuity if acetazolamide proved to be an effective treatment. Therefore, the protocol required 30 patients to complete both arms of the study. Since seven patients dropped out before completing their treatment, seven additional patients were chosen to participate in the clinical trial.

Results

Thirty seven patients were initially enrolled in the study. A list of all patients who enrolled is shown in Table 1, and includes an explanation for why seven patients discontinued their medication. Also shown in Table 1 is the baseline and 4 week visual acuities of each participant.

Table 2 Characteristics of subjects

Age (years)	
Mean (SD)	50.1 (13.05)
Range	26-76
Sex, No (%)	
Male	7 (23)
Female	23 (77)
Race, No (%)	
White	19 (63)
Black	9 (30)
Other	2 (7)
Diagnosis of iridocyclitis, No (%)	
Idiopathic	25 (83)
Sarcoid	5 (17)

Table 1 Visual acuity measurements, by treatment group

Patient No	Race, sex/age	Acetazolamide group			Placebo group		
		Baseline	4 Weeks	Change	Baseline	4 Weeks	Change
01*	WF/29	20/63	20/63	0	20/40	20/80	-
	She halved her medication after 1 week						
02*	BF/35	20/80	20/63	+	20/40	20/32	+
04*	WF/57	20/125	20/125	0	20/200	20/250	-
06	BF/50	20/100	20/63	+	20/63	20/100	-
07	WF/54	HM	HM	0	20/250	20/320	-
08*	BF/28	20/100	20/100	0	20/100	20/125	-
09*	WM/46	20/80	20/50	+	20/63	20/50	+
11*	BF/58	20/80	20/40	+	20/50	20/63	-
12	WF/44	20/40	20/40	0	20/63	20/40	+
13*	WF/76	20/80	20/80	0	20/80	20/63	+
14*	BF/33	20/160	20/125	+	20/125	20/100	+
15*	BF/50	20/40	20/16	+	20/16	20/16	0
16	WF/62	20/16	20/16	0	20/40	20/25	+
17*	WF/73	20/63	20/80	-	20/80	20/80	0
18	WF/51	20/40	20/32	+	20/50	20/50	0
19	WM/43	20/160	20/100	+	20/160	20/160	0
	He had a medication reaction after 2½ weeks; his second treatment visual acuity was taken at 2 weeks						
20*	WF/57	20/40	20/40	0	20/50	20/50	0
21	WF/58	20/40	20/40	0	20/40	20/50	-
22	WM/40	20/40	20/32	+	20/40	20/32	+
24	FF/55	20/25	20/32	-	20/40	20/32	+
25	BF/64	20/100	20/100	0	20/125	20/100	+
	She halved her medication after 2 weeks						
26*	WM/37	20/100	20/50	+	20/50	20/63	-
28	BM/56	20/50	20/80	-	20/160	20/63	+
29	WF/46	20/63	20/50	+	20/40	20/63	-
30*	WF/26	20/125	20/63	+	20/40	20/50	-
32	OM/50	20/80	20/80	0	20/50	20/50	0
34*	WF/68	20/200	20/200	0	20/160	20/200	-
35*	BF/37	20/100	20/80	+	20/80	20/80	0
36*	WM/63	20/40	20/63	-	20/40	20/40	0
37*	WF/59	20/40	20/20	+	20/32	20/25	+
Not eligible or discontinued medication							
03*	BF/35	20/32					
	Ineligible due to a visual acuity better than 20/40						
05*	BF/54	20/40					
	She took one capsule; she had a reaction to fluorescein and dropped out						
10*	WF/65	20/63					
	She took four capsules; combined with digoxin (Lanoxin) and frusemide (Lasix) that she was taking, she had severe diuresis						
23	BM/44	20/80			20/200	20/125	+
	He completed his placebo treatment, but stopped acetazolamide after 2 days complaining of haematuria (he had Reiter's syndrome)						
27	WF/46	20/40			20/40	20/40	0
	She completed her placebo treatment, but stopped acetazolamide after 2 days complaining of severe fatigue and muscle cramps						
31*	WF/35	20/80					
	She halved her medication after 1 week and stopped after 2 weeks complaining of severe fatigue						
33	WF/76	20/32			20/40	20/30	+
	She discontinued medication after 4 days complaining of severe fatigue and a body rash						

*Patients who received placebo first and acetazolamide second.

WM=white male; BM=black male; OM=oriental male; WF=white female; BF=black female; FF=Filipino female.

Of the 30 patients who completed the study, one woman had to reduce her medication by half after 1 week, and another halved her medication after 2 weeks. The first woman complained of excessive paraesthesia in her extremities, nausea, and drowsiness, and the second woman suffered from weight loss and chronic fatigue. One man had to discontinue the acetazolamide after 2½ weeks owing to a mild cutaneous allergic reaction all over his body, and moderate swelling of his extremities.

Seventeen patients were randomised to the acetazolamide group during the first month, with the remaining 13 patients receiving placebos during this period.

The 30 patients completing the study are described in Table 2. The mean age of the patients was 50.1 years (range 26 to 76 years); and 23 (77%) were female; 19 (63%) of the patients were white, nine (30%) were black, one was oriental, and one was Filipino. The 30 patients were diagnosed as having idiopathic chronic iridocyclitis (25 (83%)) or chronic granulomatous sarcoid disease (5 (17%)).

The mean (SD) baseline logMAR score for the 17 patients randomised to receive acetazolamide during the first month was 0.60 (0.22) and the score for 13 patients randomised to treatment during the third month was 0.52 (0.47). This is less than 1 Snellen line, and was not statistically significant (two tailed independent Student's *t* test, $p=0.59$). Similar results were seen for those randomised to receive placebos first (logMAR 0.54 (0.28)) and second (logMAR score 0.48 (0.27); $p=0.59$). Since there appeared to be no order effect, we combined data for patients taking acetazolamide and for those taking placebos.

No differences were noted between the acetazolamide and placebo groups (Table 3). However, when comparisons were made within groups, the mean visual acuity at 14 days improved by 12% and at 28 days improved by 14% in the acetazolamide group, compared with 4% and 2% at 14 and 28 days, respectively, in the

Table 3 Mean logMAR visual acuity measurements (SD) at baseline, 14, and 28 days*

Day	LogMAR scores	
	Acetazolamide group	Placebo group
Baseline	0.57 (0.34)	0.51 (0.28)
14	0.50 (0.35) [-12]†	0.53 (0.30) [4]†
28	0.49 (0.36) [-14]†	0.50 (0.30) [2]†

*All data represent mean (SD) visual acuity logMAR scores (logMAR 0.50=Snellen 20/63; logMAR 0.60=Snellen 20/80; as the score decreases, the vision improves).

†Numbers in square brackets represent per cent reduction from baseline. No significant differences noted between the two groups ($n=30$).

Table 4 Mean differences between logMAR visual acuity measurements at baseline, 14, and 28 days

Day	Acetazolamide group			Placebo group		
	Difference from baseline			Difference from baseline		
	Mean	95% CI	p Value	Mean	95% CI	p Value
14	0.060	-0.101 to 0.221	0.02	-0.017	-0.076 to 0.042	NS
28	0.073	-0.018 to 0.129	0.01	0.003	-0.049 to 0.056	NS

CI=confidence interval; NS=not significant. Data are for 30 subjects, except for one missing value at 14 days for placebo. All data represent visual acuity logMAR scores.

Table 5 Visual acuity results by age, sex, and race*

Variable	Acetazolamide group		Placebo group	
	Improvement	No change or worse	Improvement	No change or worse
Age				
<55	12	5	5	12
55+	2	11	6	7
p Value		0.004		NS
Sex				
Male	4	3	3	4
Female	10	13	8	15
p Value		NS		NS
Race				
White	8	11	6	13
Black	6	3	4	5
p Value		NS		NS

*Improvement of 0.1 on the logMAR scale, equivalent to one line on the Snellen visual acuity chart; p values were determined by Fisher's two tailed exact test; NS=not significant.

placebo group. The mean differences from baseline are shown in Table 4. In the acetazolamide group, the improvement in vision was statistically significant at both 14 days ($p=0.02$), and 28 days ($p=0.01$). No statistically significant improvement in vision was noted after the patients took placebo.

A comparison of treatment results by age, sex, and race showed that only age was a significant variable for improvement in visual acuity, and only after patients took acetazolamide. Patients under the age of 55 years during treatment did significantly better than patients aged 55 years or older ($p=0.004$) (Table 5).

The PVPR was not measured in five patients who had poor or irregular dilatation of the pupil and in four patients who had undergone cataract extraction and intraocular lens implantation before entering the study. Seven patients did not complete all measurements.

The PVPR at baseline and after 28 days was available for 14 patients. The mean (SD) PVPR at baseline for treated patients was 15.9 (12.0); at 4 weeks it was 10.5 (6.9), for a mean change of 5.5 (7.6), which was statistically significant ($p<0.02$). When patients were given placebos, their mean PVPR was 17.1 (12.0) at baseline and it was 16.3 (12.6) at 4 weeks, for a mean change of 0.8 (5.1) (not statistically significant).

The MVPR at baseline and 28 days was available for 18 patients. The mean (SD) MVPR at baseline for the treated patients was 16.6 (16.1); at 4 weeks it was 12.8 (13.5), for a mean change of 3.9 (5.7), which was statistically significant ($p<0.02$). When patients were given placebo, their baseline MVPR was 16.3 (16.2); at 4 weeks it was 16.3 (17.8), for a mean change of -0.04 (4.3) (not statistically significant).

Discussion

The results of our study support the observations of Cox *et al*¹ concerning the benefits of acetazolamide for some patients with uveitic CMO. Visual acuity improved significantly after 14 and 28 days of acetazolamide therapy. No similar improvement was noted when these same patients received placebo.

Our results also showed that patients younger than age 55 years responded significantly better after being treated with acetazolamide than did those older than 55 years. The increased benefit

of acetazolamide in younger patients may be due to the fact that younger maculas may have more reserve or be more resilient to damage from CMO.

It is believed that CMO occurs as a consequence of the breakdown of the blood-retinal barrier. In our study, vitreous fluorophotometry also demonstrated a significant decrease in leakage of fluorescein into the posterior vitreous and mid vitreous in some patients who were treated with acetazolamide. These findings suggest that acetazolamide has therapeutic effects in decreasing leakage through the blood-retinal barrier.

We did not obtain fluorescein angiography after the initial diagnostic test because of logistics of performing fluorophotometry at the same time. Further, studies have indicated a poor correlation between leakage on angiography and visual acuity.^{11 12}

Our study had two shortcomings. The first is that systemic side effects caused by acetazolamide and reported by many patients essentially unmasked the study for these patients. The second is that all patients in our study started with the same dosages of oral acetazolamide (500 mg orally twice daily). Some of our patients developed side effects; some dropped out of the study, and in some the dosages had to be decreased. A better therapeutic approach might have been to adjust the dose according to the patients' body weight or to titrate the dose according to the side effect profile.

Our study did not address the long term use of acetazolamide in the treatment of CMO. In a condition such as CMO, which may vary spontaneously in severity, the amount of acetazolamide should be titrated according to the visual acuity and the amount of CMO. According to Cox *et al.*,¹ a dose of 125 or 250 mg once daily often appeared to work as well as the 500 mg dose taken twice daily, and so far our clinical experience supports this.

In summary, acetazolamide appears to improve visual acuity in patients with chronic iridocyclitis, especially in patients younger than age 55 years. Our data on vitreous fluorophotometry provide objective support for its efficacy in reducing CMO. We believe that acetazolamide is of value in the treatment of CMO associated with chronic iridocyclitis.

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- 1 Cox SN, Hay E, Bird AC. Treatment of chronic macular edema with acetazolamide. *Arch Ophthalmol* 1988; **106**: 1190-5.
- 2 Tsuboi S, Pederson J. Experimental retinal detachment X: effect of acetazolamide on vitreous fluorescein disappearance. *Arch Ophthalmol* 1985; **103**: 1557-8.
- 3 Marmor MF, Megi A. Pharmacologic modifications of sub-retinal fluid absorption in the rabbit eye. *Arch Ophthalmol* 1986; **104**: 1674-7.
- 4 Ferris FL III, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. *Am J Ophthalmol* 1982; **94**: 91-6.
- 5 Zeimer RC, Blair NP, Cunha-Vaz JG. Vitreous fluorophotometry for clinical research. I. Description and evaluation of a new fluorophotometer. *Arch Ophthalmol* 1983; **101**: 1753-6.
- 6 Blair NP, Elman MJ, Rusin MM. Vitreous fluorophotometry in patients with cataract surgery. *Graefes Arch Clin Exp Ophthalmol* 1987; **225**: 441-6.
- 7 Cunha-Vaz JG, Gray JR, Zeimer RC, Mota MC, Ishimoto BM, Leite EC. Characterization of the early stages of diabetic retinopathy by vitreous fluorophotometry. *Diabetes* 1985; **34**: 53-9.
- 8 Cunha-Vaz JG, Mota CC, Leite EC, Abreu JR, Ruas MA. Effect of sulindac on the permeability of the blood-retinal barrier in early diabetic retinopathy. *Arch Ophthalmol* 1985; **103**: 1307-11.
- 9 Rusin MM, Fishman GA, Larson JA, Gilbert LD. Vitreous fluorophotometry in carriers of choroideremia and X-linked retinitis pigmentosa. *Arch Ophthalmol* 1989; **107**: 209-12.
- 10 Zeimer RC, Blair NP, Cunha-Vaz JG. Vitreous fluorophotometry for clinical research. II. Method of data acquisition and processing. *Arch Ophthalmol* 1983; **101**: 1757-61.
- 11 Nussenblatt RB, Kaufman SC, Palestine AG, Davis MD, Ferris RL. Macular thickening and visual acuity. Measurement in patients with cystoid macular edema. *Ophthalmology* 1987; **94**: 1134-9.
- 12 Jennings T, Rusin MM, Tessler HH, Cunha-Vaz JG. Posterior sub-Tenon's injections of corticosteroids in uveitis patients with cystoid macular edema. *Jap J Ophthalmol* 1988; **32**: 385-91.