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CLINICAL STUDY

Evaluation of the effect of acetazolamide on cystoid macular oedema in patients with Behcet's disease

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Abstract

Aim **To study the effect of acetazolamide on cystoid macular oedema (CMO) in patients with Behcet's disease.**

Patients and methods **A total of 67 eyes of 35 Behcet's patients with chronic, but well-controlled uveitis, and CMO were randomised into a double-masked, crossover trial comparing the effect of acetazolamide *vs* placebo. The patients received an initial 4-week course of either 250 mg acetazolamide twice daily (b.i.d.) or placebo, followed by a 4-week washout period. They then received a 4-week course of the reverse study medication. An improvement in visual acuity and fundus fluorescein angiographic findings was assessed.**

Results **In total, 29 patients (55 eyes) completed the trial and were available for analysis. Of the 29, 16 men and 13 were women. The age range was 13–50 years (mean 33.6 years). Patients on acetazolamide showed a slightly better improvement of angiographic signs (at least by one grade improvement) over that of placebo (12 *vs* five eyes). They also had less deterioration of angiographic signs over that of placebo (three *vs* seven eyes). However, these findings were not statistically significant ($P = 0.99$). Acetazolamide had no statistically significant effect ($P = 0.53$) on the improvement of visual acuity of patients over that of placebo (13 *vs* eight eyes), nor on the deterioration of visual acuity (three *vs* 11 eyes).**

Conclusion **Despite seemingly favourable results, the 4-week course of acetazolamide (250 mg b.i.d.) has no statistically significant effect on the improvement of the visual acuity and the fluorescein angiographic findings in Behcet's patients with CMO.**

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Introduction

Cystoid macular oedema (CMO) is a major cause of reduction of the visual acuity (VA) in patients with uveitis.[1–3] Different measures such as nonsteroidal anti-inflammatory drugs, corticosteroids, other immunosuppressive agents, grid laser photocoagulation, and pars plana vitrectomy are proposed for the treatment of CMO.[1,2,4,5] Although Cox *et al*[6] have reported favourable results after the introduction of acetazolamide for CMO, there has been little evidence on the treatment of CMO in Behcet's disease. Therefore, we conducted a randomised, double-masked, crossover trial of acetazolamide for CMO in patients with controlled, chronic posterior uveitis.

Patients and methods

During a 42-month period (1996–2000), 35 patients fulfilling the international study group criteria for complete Behcet's disease were enrolled. They had clinically controlled chronic posterior uveitis with minimal vitritis and vasculitis. They were not on any immunosuppressive agents such as steroid. Some remained on nonsteroidal anti-inflammatory agents. Other inclusion criteria were a minimum age of 12 years and best corrected visual acuity (BCVA) of 6/7.5 (20/25) or worse in at least one eye. Exclusion criteria

were receiving acetazolamide as part of the current therapeutic regimen, history of hypersensitivity to acetazolamide, sulphonamides and fluorescein, significant hazy media that obscured fundus fluorescein angiography (FFA), macular ischaemia, and macular lesion including macular hole or scar.

After obtaining informed consent, all patients had baseline ocular examination including measurement of BCVA by Snellen's chart, slit-lamp biomicroscopy, applanation tonometry, and dilated pupil examination by 90-dioptre lens and indirect ophthalmoscopy. They were, then, assigned randomly to receive acetazolamide 250 mg or placebo orally every 12 h for 4 weeks (course A). Every other patient was enrolled to the same regimen.

A multivitamin tablet was manufactured in the same shape as acetazolamide by Iran-Darma Company and was used as placebo. After completing course A, the patients were examined and then, there was a 4-week washout period where no study medication was administered. At the end of the washout period, the patients were examined again and then received a 4-week course of the opposite study medication that they were assigned in course A (course B). At the end of course B, the patients were examined again (12th week examination). Standard FFA was performed at the start of the study and then was repeated at week 4, 8, and 12. Late frames were obtained at 5 min during each FFA.

Both patients and investigators were masked to randomisation except one ophthalmologist who monitored patients' compliance and drug-adverse reactions. All patients continued their nonsteroidal anti-inflammatory medications during the study course and all were recorded at each visit. Fluorescein angiograms were graded, using a modification of a grading system proposed by Miyake[7] and Fishman *et al*.[8]

In brief, grading consists of grade O (no leakage), GIA (trace, murky leakage), GIB (mild leakage not petalloid in appearance nor exceeding 1/2 to 3/4 disc diameter (DD)), GIIA (either partial or complete stellate pattern not exceeding 1/2 to 3/4 DD), GIIB (complete stellate pattern measuring 3/4 but less than $1^{1/3}$ DD), GIIIA (complete stellate pattern equal or greater than $1^{1/3}$ DD) and GIIIB (diffuse leakage throughout the posterior pole beyond $1^{1/3}$ DD) (Figures 1–3). Transparent templates were used for grading of CMO, and were read by two masked ophthalmologists in random order. Angiograms were studied again for interobserver variations by the same two ophthalmologists. For the third and final time, they studied all the angiograms. This time they were studied in the date order for every patient. One grade change in FFA reading was determined as significant. A masked optometrist under standard conditions checked VA. A clinically significant change in VA was defined as a two scale or greater difference in BCVA using Snellen's chart acuity converted to standardised consecutive Log Mar scales. Senn's[9] approach and SPSS software (spss / win 10.1) were used for statistical analysis.

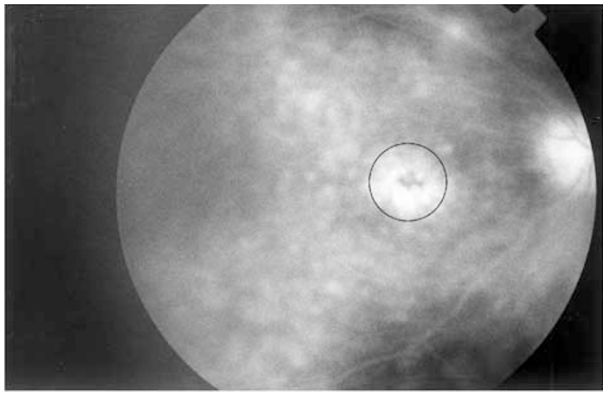

Figure 1 Grade IIIA: complete stellate pattern of fluorescein leakage extending more than $1\frac{1}{3}$ DD horizontally.

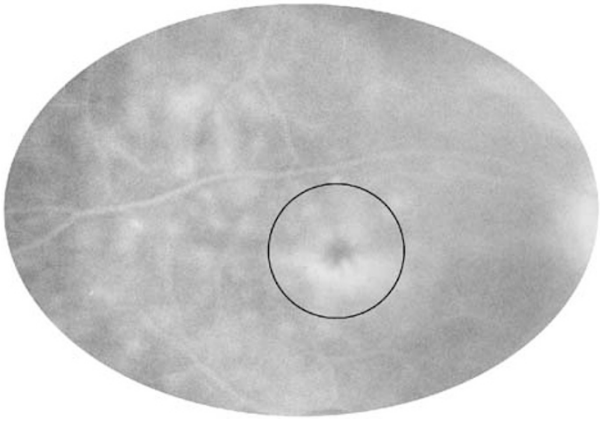

Figure 2 Grade IIB: complete stellate pattern of fluorescein leakage extending from 3/4 to $1\frac{1}{3}$ DD horizontally.

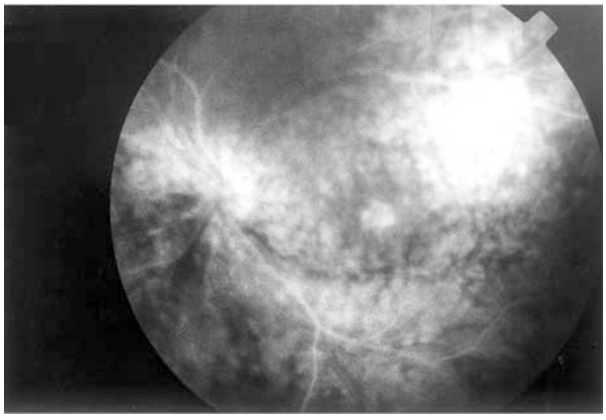

Figure 3 Grade IIB: diffuse fluorescein leakage throughout the posterior pole.

Results

A total of 35 eligible patients were randomised into the study. Of these, 29 patients (55 eyes) completed the trial and were available for analysis; 16 were men and 13 were women. Their mean age was 33.6 years (range 13–50 years). The duration of the disease was 1.5–25 years (mean: 4.6). No important complication, which interrupted the course of acetazolamide, or placebo use, occurred. Few patients reported mild nausea and pins and needles in the extremities but continued with medication. VA changes following the use of acetazolamide and placebo are shown in Table 1. With acetazolamide, VA improved in 13 eyes but deteriorated in three eyes. Overall, 16 patients reported subjective improvement in their VA, while one patient reported subjective deterioration of his acuity. However, in placebo group, eight eyes had an improvement of VA, while 11 eyes had decreased VA. Two patients had subjective improvement in their VA. Independent *t*-test shows no significant effect of acetazolamide on VA of patients ($P = 0.53$), neither on the time effect ($P = 0.64$) nor on the carryover effect ($P = 0.45$).

All patients had minimal vasculitis. FFA changes following the use of acetazolamide and placebo are shown in Table 2. Acetazolamide showed an improvement of CMO in 12 eyes and worsening of the CMO in three eyes. In the placebo group, five eyes showed improved CMO, while seven eyes had worsening of the CMO. Independent *t*-test shows no significant effect of acetazolamide on CMO ($P = 0.99$), neither on the time effect ($P = 0.42$) nor on the carryover effect ($P = 0.48$).

In all 13 eyes that had improved vision after acetazolamide, angiographies had either improved (10 eyes) or not changed (three eyes). In all three eyes, in which the VA had deteriorated after acetazolamide, FFAs were unchanged. In eight eyes, in which VA had improved after placebo, FFA was improved in seven, while unchanged in one. In 11 eyes, in which VA had

Table 1 Effect of acetazolamide on VA

	Treatment sequence			
	Day 1	*Week 4*	*Week 8*	*Week 12*
	Before placebo	After placebo	Before drug	After drug
BCVA	0.430	0.430	0.537	0.448
Range (Log Mar)	0.1–1.5	0.1–1.5	0.1–1.5	0.1–1.5
No. of eyes	27	27	27	27
	Before drug	After drug	Before placebo	After placebo
BCVA	0.632	0.604	0.596	0.626
Range (Log Mar)	0.1–1.5	0.1–1.5	0.1–1.5	0.1–1.5
No. of eyes	28	28	28	28

BCVA = best-corrected visual acuity.

Table 2 Effect of acetazolamide on CMO

	Treatment sequence			
	Day 1	*Week 4*	*Week 8*	*Week 12*
	Before placebo	After placebo	Before drug	After drug
CMO grading	1.643	1.714	1.892	1.678
Range	0–4	0–4	0–4	0–4
No. of eyes	27	27	27	27
	Before drug	After drug	Before placebo	After placebo
CMO grading	2.429	2.321	2.5	2.535
Range	1–6	0–6	1–6	1–6
No. of eyes	28	28	28	28

CMO = cystoid macular oedema.

worsened after placebo, FFAs were unchanged in eight, deteriorated in two, and improved in one.

Records of six noncompliant patients showed 11 eyes with CMO ranging GIA to GIIB and one eye being GIIB to GIIIA at different intervals. The distribution of signs was the same as the compliant patients.

Discussion

Cox *et al*[6] and other investigators[2,8,10] demonstrated that acetazolamide could be of some benefit in reducing the CMO in uveitis patients. While the exact mechanism by which acetazolamide decreases CMO remains unclear, several mechanisms of action are proposed. These include regulation of ion transport in the retinal pigment epithelium,[2,11] inhibition of membrane-bound carbonic anhydrase,[12] change in chloride flux and the resting potential of the retinal pigment epithelium,[13] and reduction in subretinal fluid.[14] However, the clinical effectiveness of acetazolamide in reducing CMO of patients with uveitis has been controversial.[2,15] Various factors might alter the final outcomes of acetazolamide therapy for CMO such as severity of vasculitis, macular ischaemia, age of patients, chronicity of CMO, and role of prostaglandin.[16,17].

To our knowledge, this is the first study on the evaluation of the effect of acetazolamide on CMO in Behcet's patient. Acetazolamide improved the BCVA and FFA of some of the Behcet's patients. The improvement failed to be statistically significant following the 4-week course of its use.

Our study has been conducted with a fixed dosage of acetazolamide and rather short duration of treatment with acetazolamide. The exact duration of CMO in our patients was unclear and limited numbers of eligible cases have reduced the power of our study. Some patients continued with their nonsteroidal anti-inflammatory treatment. Some patients felt the systemic effect of acetazolamide. These might have compromised the unbiased analysis of the data.

We feel that future studies should address the following issues: detection of the duration of the CMO, trial of various different dosage of acetazolamide with different courses of treatment, selection of more accurate subjective VA measurement charts,[18,19] and new objective measures for better evaluation and quantification of CMO such as capillary blood flow velocity measurement,[20] optical coherence tomography (OCT),[21] and retinal thickness analyser. These in combination with fluorescein angiography will provide more reliable results. Our study, however, has shown that administration of acetazolamide has little place, if any, in the treatment of Behcet's patients with CMO.

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