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Azathioprine in active chronic iridocyclitis

A double-blind controlled trial

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Active chronic iridocyclitis is a suspected autoimmune disease, although specific autoantibodies to uveal or lens tissue are not demonstrable. The condition may respond to corticosteroid drugs, but these seldom effect a "cure" (Duke-Elder and Perkins, 1966). Hence we decided to assess whether the immunosuppressive drug, azathioprine, would induce remissions of active chronic iridocyclitis, and if so, whether such remissions would be permanent. This to our knowledge has been the first fully controlled double-blind assessment using objective criteria of any form of immunosuppressive therapy in man.

Methods

Patients

Adult patients with diagnoses of active iritis or iridocyclitis were admitted to the trial from the Department of Ophthalmology. The patients were told that they were to be subjects of a research study and that they might receive a new drug or a "dummy" tablet for 3 months. All agreed to participate. The hospital pharmacist arranged for the patients to be allocated randomly, in approximately equal numbers, to a "treatment" group or a "control" group. Patients in the "treatment" group were given 100 mg. azathioprine twice daily for 3 months and patients in the "control" group received identical inert tablets. At monthly intervals blood examinations were made and the patients were seen in both the Ophthalmology Clinic and in the Medical Clinic. The patient, the ophthalmologists (J.B. and B.C.), and the supervising physician (I.M.) were unaware of which preparation was supplied. Systemic or local corticosteroid preparations and other standard treatments were maintained (or added) as necessary for uveitis, or for complicating systemic disease or glaucoma.

Assessment of response

The effect of the treatment, azathioprine or placebo, was assessed by the patient's subjective impressions and by a semi-quantitative recording of the following indices: visual acuity, intraocular pressure, and, by slit-lamp, "flare" and cells in the anterior chamber. Although disease was unilateral in some patients, both eyes were assessed at each examination. The scoring system shown in Table I was arranged so that an increase in score indicated an improvement in the particular index, *i.e.* better visual acuity, decreased intraocular pressure, or decreased flare or cells in the anterior chamber.

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Table I *Grading of objective parameters of disease activity*

Parameter	*Score*						
	1	2	3	4	5	6	7
A. Visual acuity	6/60	6/36	6/24	6/18	6/12	6/9	6/6
B. Cells in anterior chamber*	>15	5–15	>5	0	·	·	·
C. Flare	Severe	Moderate	Mild	Absent	·	·	·
D. Intraocular pressure†	⩾30	27–29	24–26	21–23	18–20	15–17	<15

* seen in finest slit-lamp beam
† mm. Hg Schiötz tonometer

Statistical analysis

Admission of new patients to the trial was stopped when a sequential "t" test of increments in score indicated that there was unlikely to be a significant difference between the progress of the two groups of patients (Armitage, 1960). At this time, the 3-month course of treatment was completed for those patients remaining in the trial and the results were analysed retrospectively by Fisher's exact method for 2 × 2 contingency tables (Fisher, 1950).

Results

Sixteen patients completed a 3-month course of treatment with azathioprine or placebo, and three patients completed a course of the placebo and later received a course of azathioprine, the results of which were included in the analysis; thus the nineteen completed courses included eleven with azathioprine and eight with placebo.

One of eight control patients and five of eleven treated patients claimed improvement in symptoms after 3 months of treatment: this difference in favour of treatment was not significant statistically.

As the arbitrary "scores" of the various indices of activity of disease (Table I) cannot be assumed to be either independent or additive, the definitive analysis of the effect of therapy on the ocular signs (acuity, pressure, cells, and flare) was based on a consideration of the proportion of patients from each group with disease which could be classified as *improved*, *unchanged*, or *deteriorated* at the completion of the 3-month course of treatment. This analysis was performed for each eye, for each index of activity, and after 1, 2, or 3 months of treatment. No significant effect of azathioprine on any of the indices of disease was found, even when data from both eyes were pooled (Table II shows the results at 3 months, the findings at 1 and 2 months being similar). Improvement in visual acuity and flare was not more frequent in the treated group (where 3 of 21 and 3 of 22 eyes showed improvement) than in the control group (where 3 of 16 and 3 of 16 eyes showed improvement). Similarly, for intraocular pressure, the frequency of improvement in the treated group ($6/22 = 27$ per cent.) did not differ significantly from that in the control group ($4/16 = 25$ per cent.). With respect to reduction of cells in the anterior chamber, there was an apparent advantage for the treated group 3 months after starting treatment ($9/22 = 41$ per cent., compared with $4/16 = 25$ per cent. for controls), but the difference was not significant statistically.

Table II *Results after 3 months of treatment*

Parameter	*Eye**	*Number of cases*					
		Azathioprine			*Placebo*		
		Improved	*Unchanged*	*Worse*	*Improved*	*Unchanged*	*Worse*
Visual acuity†	First	1	8	2	2	4	2
	Second†	2	5	3	1	6	1
	Total	3	13	5	3	10	3
Cells	First	5	4	2	3	3	2
	Second	4	6	1	1	6	1
	Total	9	10	3	4	9	3
Flare	First	2	7	2	2	4	2
	Second	1	9	1	1	7	—
	Total	3	16	3	3	11	2
Intraocular pressure‡	First	4	3	4	3	3	2
	Second	2	5	4	1	3	4
	Total	6	8	8	4	6	6
All parameters pooled	First	12	22	10	10	19	8
	Second	9	25	9	4	22	6
	Total	21	47	19	14	41	14

* First eye – the eye more affected at first examination (or right eye if both were equally affected)
Second eye – less affected eye (or left eye)
† One eye of a patient receiving azathioprine was not assessed for acuity at first examination
‡ mm. Hg, Schiötz tonometer

For each patient there was a tendency for the indices of ocular function in each eye to increase or decrease together over each time interval. This tendency was statistically significant only when data from treated and control groups were pooled (*e.g.* $n = 19$; $r = 0{\cdot}56$; $P < 0.05$ for cells). There was no simple correlation between activity as measured by one index, and activity as measured by another, with the possible exception that changes in cells were significantly correlated with changes in flare for the azathioprine group ($n = 11$; $t = 2{\cdot}8$; $P < 0{\cdot}05$). There was no correlation between the symptomatic benefit claimed by the patient and the changes in disease activity assessed by any of the objective indices.

One patient developed a transient neutropenia while receiving azathioprine.

Discussion

Although there may have been benefit to some of the patients who received azathioprine, we were unable to demonstrate that any differences in favour of the drug were statistically significant. Temporal fluctuations in the parameters of activity of disease tended to be similar in the two eyes of each patient. This finding suggests that completely random variation was not responsible for such fluctuations. Although these fluctuations could result from systematic biases in the ophthalmological assessment, they are more reasonably interpreted as being due to true changes in activity of a bilateral disease process. The results from both the treated and control groups indicate that there was difficulty and

ambiguity in the quantitative assessment of activity of uveal tract disease. Changes in cellularity and flare (presumably the more acute manifestations of activity) did not correlate with the subjective evaluation of symptoms. The reasons for this are not known. The lack of correlation of the more acute signs (cellularity and flare) with visual acuity and intraocular pressure could be because the latter indices reflect, at least in part, established ocular damage due to chronicity of the uveitis with associated glaucoma and cataract.

Diagnostic heterogeneity and the relatively small number of patients in this trial would have made it difficult to detect even a significant benefit in a minority of patients. With a much larger series of patients, the effect of azathioprine in reducing cellularity of the aqueous humour could have become statistically significant, but there are no objective data from this trial to indicate that such an effect would be matched by improvement in symptoms or in visual acuity.

Summary

A double-blind controlled trial was made of azathioprine as an adjunct to the conventional treatment of active chronic iritis and iridocyclitis. Subjective improvement was claimed by five of eleven patients receiving azathioprine and by one of eight patients receiving placebo, and a decrease in cellularity of the anterior chamber was more frequent in the treated group; neither of these changes was statistically significant. Changes in visual acuity, in intraocular pressure, and in flare, were similar for both treated and control groups of patients. The subjective assessment of benefit by patients could not be correlated with changes in any of the objective indices of disease activity.

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