A trial of corticotrophin gelatin injection in acute optic neuritis

A. N. BOWDEN, P. M. A. BOWDEN, A. I. FRIEDMANN,
G. D. PERKIN, AND F. C. ROSE

From the Royal Eye Hospital Medical Ophthalmology Unit, Lambeth Hospital, London

SYNOPSIS The effect of a 30 day course of corticotrophin gelatin injections on the natural history of acute unilateral optic neuritis in 27 patients is reported. A further 27 patients received inert injections in a double-blind control. Measurements were made on visual acuity, visual field, macular threshold, and colour vision, and the development of optic atrophy and other neurological episodes was recorded. No significant differences were found between treated and control groups at intervals up to two years from the start of the trial. The criteria for inclusion of patients are given and it is concluded that corticotrophin has no effect on the natural history of the condition as defined.

The prognosis for vision in untreated acute optic neuritis is good. A recent survey found that by one and six months after the attack, 50% and 75% respectively of patients had regained normal vision (Bradley and Whitty, 1967). Corticotrophin (ACTH) is widely used in the treatment of acute optic neuritis, though the evidence that it favourably affects the natural history comes from one trial in which (1) only patients presenting within 10 days of the onset of visual blurring were included; (2) the only measure of visual function used was acuity for near vision; and (3) significant benefit was shown only in the first month of treatment with corticotrophin gel (Rawson *et al.*, 1966, 1969). However, many patients with acute optic neuritis are not seen within 10 days of the onset of visual impairment, and, though their vision may be improving when they are first seen, it is important to know whether to use ACTH. Again, visual field defects and abnormal colour vision may reduce the quality of vision irrespective of visual acuity. These are easily measured and should be considered when assessing improvement.

In the present double-blind trial 54 consecutive patients presenting with acute optic neuritis were treated with either corticotrophin gel injection or an inert control and several parameters of visual function were used to assess progress.

PATIENTS

Patients were referred to a medical ophthalmology unit by ophthalmologists. Fifty-four consecutive patients with acute unilateral optic neuritis who were admitted between July 1967 and July 1969 agreed to enter the trial. The criteria for inclusion were: (1) recent sudden onset of visual impairment in one eye; (2) reduced visual acuity with a central or paracentral scotoma and abnormal colour vision in the affected eye; (3) no evidence of retinal disease or of a compressive lesion of the optic nerve.

Blood tests, radiographs of skull and optic foramina, and lumbar puncture were performed in all patients.

METHODS

Treatment consisted of daily subcutaneous injections of 1 ml corticotrophin gel for 30 days, given at home by the local district nurse. Allocation of active (Acthar Gel, Armour, 40 i.u. per ml) or inactive gel was randomized and double blind. The hospital pharmacist kept the key to the distribution of active and inactive gel.

Progress was followed in the outpatients department. Patients were seen weekly during the 30 days' treatment, then at two, six, 12, and 24 months after entry into the trial. At each visit the following measurements were made:

(1) *Visual acuity* on Snellen chart, using previous correction if any.

(2) *Visual field*: this was recorded on the Friedmann analyser, a perimeter which measures the white light thresholds at 46 static points in the central 25° of vision in the dark adapted eye (Friedmann, 1966). The thresholds were used to calculate a score representing the extent and intensity of the central field loss. The normal score is 20 (arbitrary units), and -4 represents complete loss of the central 25° of the visual field; between these limits central and paracentral scotomas could be assessed quantitatively and followed in time;

(3) *Macular threshold*: this was measured on the Friedmann analyser as the white light threshold at the fixation point, and was expressed in units from 28 (normal) to 0 (no perception of light). Macular function could be followed quantitatively in this way.

(4) Colour vision.

(5) Blood pressure and body weight during treatment.

(6) The appearances of both optic discs were noted and fundus photographs taken. While patients were receiving injections side-effects were sought. Specific inquiry and routine neurological examina-

tion were used to detect neurological disturbance at follow-up.

The results were tested statistically as follows. For each functional subgroup at each follow-up time (see Tables 1 and 2) the difference in percentages of treated and control patients was divided by its standard error and a quotient greater than 2 was accepted as significant—that is, $P < 0.05$. The validity of this test is doubtful in those subgroups containing very small numbers of patients.

RESULTS

Twenty-seven patients were found to have received ACTH (treated) and 27 inactive gel (control). The female:male ratio was 1.0 in the treated group and 2.0 in the control group. The mean age in both groups was 34 years. The mean number of days between onset of visual deterioration and first examination was 16.7 in the treated group and 18.5 in the control group. Eighteen treated and 13 control patients were seen within two weeks of onset of visual deterioration.

TABLE 1a
NUMBERS OF PATIENTS IN VISUAL ACUITY, VISUAL FIELD, AND MACULAR THRESHOLD GROUPS
UP TO TWO YEARS AFTER ENTRY INTO TRIAL

	Time after entry into trial (months)													
	0		½		1		2		6		12		24	
	T	C	T	C	T	C	T	C	T	C	T	C	T	C
Total no. of patients	27	27	27	27	27	27	24	26	21	23	16	19	8	6
Visual acuity														
6/6	0	0	3	4	13	12	17	17	14	20	11	17	6	6
6/9	2	4	2	5	3	4	1	3	0	1	0	0	0	0
6/12	1	4	3	1	2	0	0	4	0	2	0	2	0	0
6/18	2	1	4	1	1	5	1	1	2	0	1	0	0	0
6/24	1	1	1	4	1	3	1	1	0	0	1	0	0	0
6/36	2	2	4	4	1	3	0	0	0	0	0	0	0	0
6/60	7	3	2	3	2	0	2	0	2	0	1	0	2	0
< 6/60	12	12	8	5	4	0	2	0	3	0	2	0	0	0
Visual field score														
20	0	0	1	1	3	3	6	6	4	7	4	7	1	4
14-18	5	6	4	8	11	15	13	13	12	14	8	10	4	1
8-12	4	4	9	6	9	4	2	6	3	2	2	2	1	1
2-6	4	5	4	8	2	5	3	0	1	0	2	0	2	0
-4-0	14	12	9	4	2	0	0	1	1	0	0	0	0	0
Macular threshold														
28	1	0	2	0	3	2	6	4	5	6	4	6	1	1
22-26	0	2	3	4	8	12	8	12	7	11	5	11	4	4
16-20	4	4	5	4	4	5	5	8	5	5	4	1	1	1
10-14	6	4	5	5	6	1	2	2	0	1	0	1	0	0
4-8	1	3	2	5	4	3	1	0	1	0	1	0	0	0
0-2	15	14	10	9	2	4	2	0	3	0	2	0	2	0

T: Treated. C: Control.

TABLE 1b

NUMBERS OF PATIENTS, SEEN WITHIN TWO WEEKS OF ONSET OF VISUAL DETERIORATION, IN VISUAL ACUITY, VISUAL FIELD, AND MACULAR THRESHOLD GROUPS UP TO TWO YEARS AFTER ENTRY INTO TRIAL

	Time after entry into trial (months)													
	0		½		1		2		6		12		24	
	T	C	T	C	T	C	T	C	T	C	T	C	T	C
Total no. of patients	18	13	18	13	18	13	15	13	13	11	9	9	3	3
Visual acuity														
6/6	0	0	2	2	8	8	10	11	9	11	7	9	3	3
6/9	0	2	2	3	2	1	1	1	0	0	0	0	0	0
6/12	1	3	2	0	1	0	0	1	0	0	0	0	0	0
6/18	2	0	1	0	1	2	1	0	1	0	1	0	0	0
6/24	1	1	0	2	1	1	1	0	0	0	0	0	0	0
6/36	1	1	3	3	1	1	0	0	0	0	0	0	0	0
6/60	3	1	1	1	1	0	1	0	1	0	1	0	0	0
< 6/60	10	5	7	2	3	0	1	0	2	0	0	0	0	0
Visual field score														
20	0	0	1	0	3	1	4	3	3	3	3	3	1	1
14-18	4	2	3	4	6	7	8	7	8	6	4	4	2	1
8-12	2	1	4	0	6	1	1	2	1	2	2	2	0	1
2-6	0	2	2	6	1	4	2	0	0	0	0	0	0	0
-4-0	12	8	8	3	2	0	0	1	1	0	0	0	0	0
Macular threshold														
28	1	0	2	0	3	1	6	3	5	4	4	4	1	0
22-26	0	1	2	3	4	8	3	7	3	5	2	4	2	2
16-20	2	2	3	3	2	1	2	2	2	1	2	0	0	0
10-14	3	2	1	1	4	0	2	1	0	1	0	1	0	1
4-8	0	3	2	2	3	1	0	0	0	0	1	0	0	0
0-2	12	5	8	4	2	2	2	0	3	0	0	0	0	0

T: Treated. C: Control.

Twenty patients had noticed some improvement in vision of the affected eye before starting the trial.

From their previous history seven patients had definite multiple sclerosis and a further two patients had unequivocal evidence of multiple sclerosis on first examination. Four of these patients were in the treated group, five in the control group. One of the treated patients had had a previous episode of optic neuritis in the other eye. Three females (one treated, two control) were on an oral contraceptive at the time of onset of the optic neuritis. Papillitis, indicated by blurring of the disc margins or definite oedema of the optic disc, was present in 35 patients: 21 treated, 14 control.

The visual acuities, visual field scores, and macular thresholds in treated and control groups before starting injections are given in Table 1. There are no significant differences between the percentages of treated and control patients in the various functional categories.

TABLE 2

PERCENTAGES OF PATIENTS ACHIEVING NORMAL VISUAL ACUITY, VISUAL FIELD SCORE, AND MACULAR THRESHOLD AT INTERVALS AFTER ENTRY INTO TRIAL

Time after entry into trial (months)		Percentages of patients with normal			Total no. of patients
		Visual acuity	Visual field score	Macular threshold	
½	T	11 (11)	4 (6)	7 (11)	27 (18)
	C	15 (15)	4 (0)	0 (0)	27 (13)
1	T	48 (44)	11 (17)	11 (17)	27 (18)
	C	44 (61)	11 (8)	7 (8)	27 (13)
2	T	67 (61)	26 (28)	22 (33)	27 (18)
	C	63 (84)	27 (23)	15 (15)	27 (13)
6	T	74 (72)	26 (28)	22 (33)	27 (18)
	C	78 (100)	37 (46)	26 (15)	27 (13)
12	T	78 (78)	30 (33)	26 (33)	27 (18)
	C	85 (100)	37 (46)	26 (15)	27 (13)
24	T	78 (78)	30 (33)	26 (33)	27 (18)
	C	85 (100)	37 (46)	26 (15)	27 (13)

T: Treated. C: Control.
Numbers in parentheses: patients seen within two weeks of onset of visual deterioration.

The mean follow-up in treated patients was 12.1 months and in control patients 12.3 months. Fifty patients were followed for longer than one month, 14 for two years. Of the 40 patients who had defaulted by two years, 32 had achieved normal visual acuity in the affected eye.

SIDE-EFFECTS These were mild in all but two patients. Of the 27 treated patients, 25 gained weight, 20 developed facial mooning and ankle oedema, and five developed acne. Blood pressure remained normal. One treated patient developed a severe depressive reaction, and one a local cutaneous reaction at the site of ACTH injection followed by a generalized maculopapular eruption which responded to chlorpheniramine.

VISUAL ACUITY The visual acuities at follow-up are given in Table 1. There are no significant differences between the percentages of treated and control patients with 6/6 vision at any of the follow-up times (Table 2).

VISUAL FIELD SCORE The scores are given in Table 1. Again, there are no significant differences between treated and control groups, nor between the percentages of patients achieving a normal field score at any of the follow-up times (Table 2). The percentages of patients with a normal score are consistently lower than those of patients with a normal visual acuity at each follow-up time (Table 2). At one year after the attack only one-third of treated and control patients had a normal field score.

MACULAR THRESHOLD Again there are no significant differences between treated and control groups (Tables 1 and 2). The findings for macular threshold correspond fairly closely with those for visual field score. Only one quarter of patients had achieved a normal macular threshold one year after the attack.

OPTIC ATROPHY Thirty-eight patients, 21 treated and 17 control, developed definite pallor of the optic disc in the affected eye during follow-up. This difference between treated and control groups is not significant.

COLOUR VISION Information on the affected eye was available in 44 patients, 21 treated and 23

control. Normal colour vision returned in seven treated and 12 control patients in mean times of 3.8 and 8.4 months respectively. These differences are not significant. Colour vision remained abnormal in 14 treated and 11 control patients after mean follow-up periods of 10.6 and 13 months respectively.

RECURRENCE OF OPTIC NEURITIS One treated and one control patient had subsequent episodes of optic neuritis in the same eye one and two years respectively after the initial attack. Two further control patients had subsequent attacks in the other eye 10 and 12 months after the initial attack.

OTHER NEUROLOGICAL EPISODES Four control patients developed signs of definite multiple sclerosis during follow-up.

FAILURE TO IMPROVE Three treated patients had visual acuities of 6/60 or worse one year or more after the initial attack. All had visual acuities of less than 6/60 when first seen and all developed optic atrophy. One of these patients was taking an oral contraceptive at the onset of the attack.

WITHIN GROUP FACTORS HAVING A POSSIBLE EFFECT ON PROGNOSIS The percentages of patients reaching normality were calculated for visual acuity, visual field score, and macular threshold, in those patients (1) seen within two weeks of onset of visual deterioration (Table 2); (2) with initial visual acuity less than 6/36; and (3) with papillitis in the initial attack. Again, there were no significant differences between treated and control groups at any follow-up time.

DISCUSSION

The presenting features and follow-up findings in the present series of patients with acute unilateral optic neuritis are essentially the same as those reported in the literature for untreated patients (Wybar, 1952; Lynn, 1959; Hyllested and Moller, 1961; Bradley and Whitty, 1967; Rawson *et al.*, 1966, 1969). The only significant difference is the high incidence of residual central visual field defects in the present series, which probably reflects the greater sensitivity of the

method used for analysing the central visual field.

Treated and control groups happen to have been reasonably well matched. Although there were more males, more patients seen within two weeks of onset of deterioration of vision, and more patients with an initial visual acuity less than 6/36 and with papillitis in the treated group, these differences do not achieve statistical significance and, apart from the sex inequality, were shown to have no effect on the response to ACTH gel.

We could find no significant differences between treated and control groups at any time within the two years of follow-up using several measurable parameters of visual function. These conclusions are contrary to general opinion and to the conclusions reached in other trials, which have been that ACTH speeds recovery in acute episodes of multiple sclerosis (Miller *et al.*, 1961; Rinne *et al.*, 1968) including acute optic neuritis (Rawson *et al.*, 1966, 1969).

The only results that are strictly comparable with the present findings are those of Rawson *et al.* (1966, 1969), who found a significantly greater percentage of patients with normal near vision in the first month after starting treatment with ACTH gel in 25 patients compared with 25 controls given inert gel, over a follow-up period of one year. The main differences between the present series and that of Rawson *et al.* are that all of the patients in the latter series were seen within 10 days of onset of visual deterioration and were not improving, and two-thirds had evidence of multiple sclerosis at the time of onset of optic neuritis. The treatment regimen was the same in both series. When only those patients in the present series who were seen within 14 days of onset of visual deterioration are considered there are still no significant differences between treated and control groups.

Critical assessment of the trials of ACTH in multiple sclerosis shows that its value is not unequivocally proven. In a disease with many features each of which may show marked natural fluctuation and which are difficult to assess quantitatively, large numbers of treated patients with suitably matched and managed controls are necessary to enable the effects of any treatment to be analysed satisfactorily. This is especially true of acute episodes which show a natural

tendency to remit. Controlled trials of ACTH were said to show more treated patients achieving greater improvement in acute exacerbations of multiple sclerosis (Miller *et al.*, 1961; Rinne *et al.*, 1968) but the total number of patients in both series was only 76, and in the series of Miller *et al.* the controls were poorly matched. Although the results of the Cooperative Study (1970) in the U.S.A. tended to support this, the benefits over placebo were marginal and it was concluded that, for the individual patient with an acute exacerbation of multiple sclerosis, there is 'little evidence to justify the enthusiastic administration of ACTH'. The value of ACTH in chronic multiple sclerosis is even more doubtful, benefit being claimed by some (Alexander and Cass, 1963) and denied by others (Rinne *et al.*, 1968; Millar *et al.*, 1967).

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