

Comparison of a low and high dose ACTH gel in the treatment of hay fever

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Summary

The present data show that in fourteen patients treated with 200 iu Acthar gel, hay fever symptoms were less during the period of peak pollen challenge during June, than those experienced by an equivalent group treated with 80 iu. Analysis of the data showed that in the seven worst sufferers in both groups the difference between treatments was statistically significant ($P=0.033$, estimated by analysis of covariance of the symptom scores over the period of peak pollen challenge). No serious side effects were noted in patients from either group.

Introduction

Hay fever (seasonal allergic rhinitis) in its milder forms is treated by a variety of means, but many clinicians treat the more refractory cases with oral steroids, depot steroid injections or corticotrophin (ACTH) depot injections. The use of ACTH is favoured by some over the synthetic oral steroids as there is less risk of suppressing the hypothalamic-pituitary-adrenal (HPA) axis. Other well known potential unwanted effects of steroids are also less common. Previously a regime of 80 iu Acthar gel (porcine adrenocorticotrophic hormone in gelatin base) given once or twice weekly has proved effective, giving protection for 3–7 days (Parr, 1976). However, a recent uncontrolled study (McMillin, 1978) has indicated that 200 iu Acthar gel provides protection for an extended period, thus overcoming the practical disadvantages of too frequent injections.

The use of Acthar gel as a single injection of 200 iu is accepted in the treatment of asthma and its safety in this dose is recognised (Glick & Friedman, 1969).

The present study was undertaken to confirm these findings by comparing the relative efficacy of 80 iu and 200 iu Acthar gel given once a fortnight.

Materials and methods

Patient selection

The patients were obtained from the Hay Fever Clinic at Llandough Hospital. All patients had a history of hay fever for at least two seasons and all gave a positive skin test to grass pollen. None had obtained complete or satisfactory relief from other treatments in previous years. One third of the patients also had asthma during the hay fever season.

None of the patients were found to have any contraindication to steroid therapy.

All patients were volunteers from whom informed consent was obtained before the start of the study.

Trial procedure

The trial started on 6 June 1978 and finished on 11 July 1978. During the trial period the patients kept a daily record (completed each evening) of their hay fever symptoms graded according to severity:

0 = no symptoms

1 = mild symptoms causing no inconvenience

2 = moderate symptoms causing some inconvenience but not affecting activities

3 = severe symptoms interfering with activities

The patients also recorded, at the same time, any symptoms of asthma and details of any other treatment taken, e.g. antihistamines, nasal sprays, eyedrops, and anti-spasmodics. The records were checked at each attendance for injection and at the end of the trial.

On 6 June all patients were given an i.m. injection of 2 ml of the gelatin component of ACTH gel (Acthar gel, Armour U.K.) in order to obtain baseline data under trial conditions, and to establish any sensitivity to gelatin. The patients were not aware that this was not an active injection.

Treatment started on 13 June with the patients being randomly allocated to one of the two treatment groups. Patients in one group received 80 iu ACTH gel in 2 ml and in the other, 200 iu in 2.5 ml. The injections were given i.m. in the thigh by the same nurse and were administered on 13 and 27 June. Neither the patients nor investigator were aware of the dose or even the volume (since this differed) of ACTH gel given. All patients were allowed to use symptomatic treatment if they found it necessary.

IgE and RAST estimations were made on blood samples taken one week prior to the start of the trial, midway through on 27 June and at the end of the trial on 11 July.

Experimental method

The skin prick tests were made using mixed grass pollen extract and control solutions (Bencard, U.K.).

Total IgE was determined using a Pharmacia PRIST kit. Results are expressed in international units per ml (iu/ml⁻¹).

RAST grades of allergen specific antibodies to Timothy grass and rye grass pollen were determined using a pharmacia RAST kit. Grades were expressed as 0 = negative, 1 = low, 2 = moderate, 3 = high and 4 = very high.

The daily pollen count was obtained from the Asthma Research Unit's Hirst Trap at the University College, Cardiff.

Analysis of data

In order to assess the effects of treatment the results have been considered for each group as a whole and for the seven patients in each group most severely affected during the treatment period, i.e. those with the highest scores. This was done as it was noted that in each group there were several patients who showed minimal symptoms throughout the trial. In an attempt to minimise possible differences between the two groups the hay fever symptom scores have been analysed by analysis of covariance (ANOCOVA) using the pretreatment week score as the covariate (Winer, 1971; Handelman *et al.*, 1977).

The incidence of mild/moderate/severe, or alternatively just moderate/severe hay fever symptoms is defined (Parr, 1976) as:

$$\text{incidence} = \frac{\text{the total no. of days patients were affected}}{\text{no. of patients} \times \text{no. of days}}$$

Results

Pre-treatment period

Of the twenty-nine patients first admitted to the trial one withdrew at the end of the preliminary pre-treatment week complaining of lassitude and oedema of the feet for 2 days following the gelatin injection. The remaining twenty-eight patients were randomly allocated to one of the two groups to receive 80 iu ACTH or 200 iu ACTH.

The two groups were reasonably homogenous—median ages of 31 years and 29.5 years, median duration of hay fever 13 years (range 4–33 yrs) and 15 years (range 4–38 yrs), eleven males and three females in the 80 iu group, and nine males and five females in the 200 iu group. There was no significant difference in the basic hay fever status between the two groups during the pre-treatment week, although the 80 iu group had a higher incidence of symptoms (0.90:0.82) and mean daily score (1.58, range 0.29–2.43:1.37, range 0.43–2.71), and incidence of moderate and severe symptoms (Table 1).

Treatment period

Figure 1 shows that the period of peak pollen challenge occurred between 16 and 20 June with smaller peaks on 29 June, 25 June and 4–6 July. In addition the figure also shows the number of patients on each day, in the two groups, who recorded moderate to severe hay fever symptoms. As far as can be judged in the absence of a placebo group, patients in either group responded favourably to the initial treatment injection given on the 13 June.

In the pre-treatment week both groups were similar but during the first three treatment weeks the 80 iu group almost invariably had the highest number of moderately or severely affected patients. This was particularly apparent in the second week of treatment, when the number in the 200 iu group was less than during the pre-treatment week. After the second ACTH injection on the 27 June the numbers of moderately or severely affected fell in both groups, this being more noticeable in the 200 iu group. Essentially the same pattern was found when the four symptom grades were assessed numerically to give a mean daily score for each group (Fig. 2).

During the full 4 weeks of treatment patients receiving 80 iu were, on average, symptom-free for 6.3 days compared to 10.9 days for patients in the 200 iu group

Table 1. Weekly average number of days when patients were symptom-free or almost so

	Pre-treatment week		1st week		2nd week		3rd week		4th week	
	80 iu	200 iu	80 iu	200 iu	80 iu	200 iu	80 iu	200 iu	80 iu	200 iu
Mean of the no. of days patients were symptom-free	0.7	1.3	0.5	1.8*	1.0	1.6	2.2	3.7	3.7	4.0
Incidence of symptoms	0.90	0.82	0.93	0.74	0.86	0.78	0.68	0.47	0.47	0.43
Average number of days each patient was symptom-free over the full four weeks of treatment:										
	In the 80 iu group:					In the 200 iu group:				
	mean = 6.3 days					mean = 10.9 days				
	median = 5.5 days					median = 8 days				
Mean of the no. of days patients recorded nil or mild symptoms	3.4	4.0	3.8	4.6	2.9	5.3*	5.5	6.5	6.4	6.1
Incidence of moderate and severe symptoms	0.51	0.43	0.46	0.34	0.59	0.24	0.21	0.07	0.09	0.12
Average number of days each patient recorded nil or mild symptoms over the full four weeks of treatment:										
	In the 80 iu group:					In the 200 iu group:				
	mean = 18.4 days					mean = 22.6 days†				
	median = 18 days					median = 23.5 days				

* Comparison of groups: $0.02 < P < 0.05$ (Mann-Whitney test)

† Comparison of groups: $0.05 < P < 0.10$ (Mann-Whitney test)

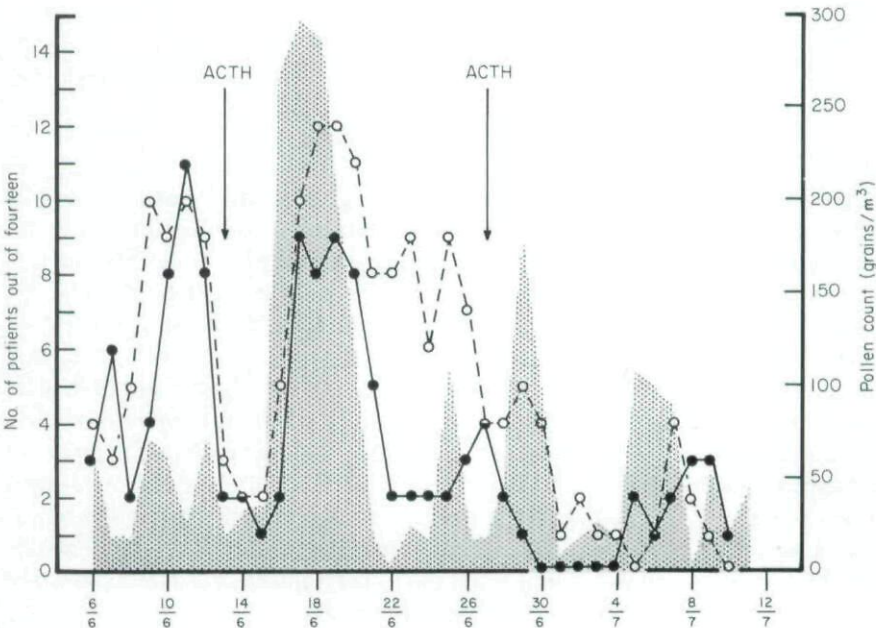


Fig. 1. The numbers of patients on each day recording moderate or severe hay fever symptoms. N.B. the number of patients in each group was fourteen. □, Pollen count; ○—○, 80 iu; ●—●, 200 iu.

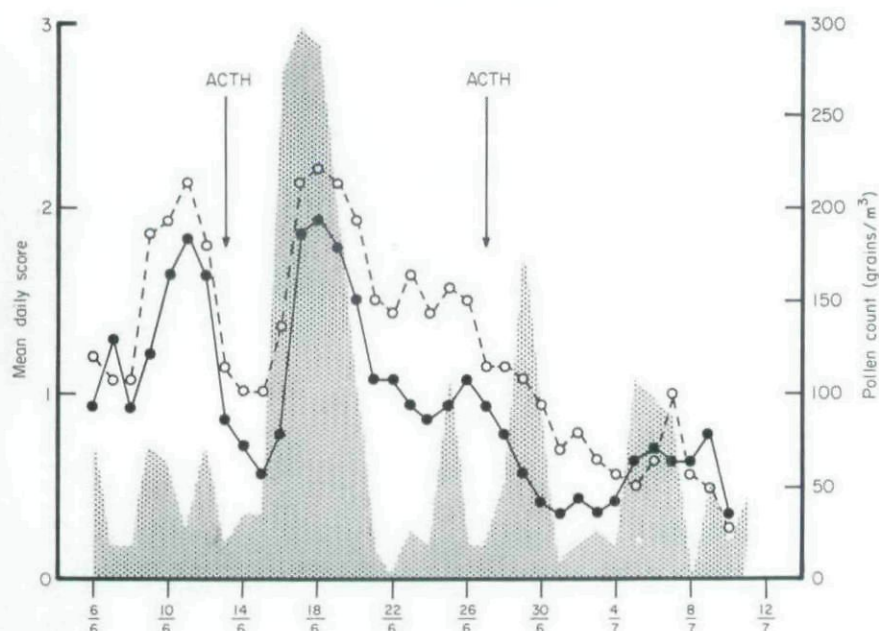


Fig. 2. Mean daily hay fever scores for patients in the two treatment groups, N.B. no symptoms score 0; mild score 1; moderate score 2; severe score 3. $\square$, Pollen count; $\circ$ — $\circ$, 80 iu; $\bullet$ — $\bullet$, 200 iu.

Table 2. Average daily hay fever symptom scores (with and without adjustment for variations in pretreatment week scores), and analysis of scores: (a) over the 4-week trial period, (b) over the first two weeks of treatment commensurate with the period of peak pollen challenge, and (c) specifically over week 2 of treatment

Average daily score during:					
	Pre-treatment week	Week 1	Week 2	Week 3	Week 4
80 iu $\bar{X}$	1.58	1.57	1.57	0.92	0.58
adj.	—	1.52	1.52	0.86	0.53
200 iu $\bar{X}$	1.37	1.20	1.06	0.55	0.60
adj.	—	1.26	1.12	0.61	0.66

Analysis of scores			
	Over weeks 1-4	Weeks 1-2	Week 2 only
ANOVA (d.f. 1, 24)	$F=2.52, P=0.125$	$F=3.85, P=0.061$	$F=3.86, P=0.060$
ANOCOVA (d.f. 1, 23)	$F=1.61, P=0.228$	$F=3.21, P=0.092$	$F=3.02, P=0.102$

ANOVA=analysis of variance (no adjustment made for variations in pretreatment score).

ANOCOVA=analysis of covariance (includes adjustment).

Table 3. Average daily hay fever symptom scores (with and without adjustment for variations in pretreatment week scores) for the seven top scorers in each group, together with an analysis of scores: (a) over the 4-week trial period, (b) over the first two weeks of treatment commensurate with the period of peak pollen challenge, and (c) specifically over week 2 of treatment

	Average daily score during:				
	Pre-treatment week	Week 1	Week 2	Week 3	Week 4
80 iu $\bar{X}$	1.88	1.98	2.10	1.32	0.82
adj	—	1.90	2.02	1.35	0.74
200 iu $\bar{X}$	1.67	1.63	1.43	0.88	1.00
adj	—	1.71	1.51	0.96	1.08

Analysis of scores			
	Over weeks 1 to 4	Weeks 1 and 2	Week 2 only
ANOVA (d.f. 1, 12)	F = 5.34, $P = 0.039$	F = 6.88, $P = 0.022$	F = 6.96, $P = 0.022$
ANOCOVA (d.f. 1, 11)	F = 4.72, $P = 0.065$	F = 6.76, $P = 0.033$	F = 5.97, $P = 0.042$

(Table 1). This difference was apparent in each individual week and is thus reflected also in the incidence of symptoms. When compared by the Mann-Whitney test, however, the only significant difference between the two groups was during the first treatment week.

The results of the analysis of the individual symptom scores (Table 2) showed that over the full 4 weeks of treatment there was little evidence of any significant difference between treatments. However, when attention is focussed on the scores over the period of peak pollen challenge, i.e. weeks 1 and 2, the differences are close to significance ($P = 0.061$ before and $P = 0.092$ after adjustment).

Re-analysis of the data for the seven worst sufferers in either group (Table 3) showed that even with the more conservative analysis of covariance there was a significant difference between groups during weeks 1 and 2 combined ($P = 0.033$). It was anticipated from the start of this study that any additional effect of 200 iu would most likely be in extending the period of protection from hay fever. This is supported by the results in Table 3; the mean (adjusted) daily score of the patients in the 80 iu group increasing from 1.90 in the first week to 2.02 in the second, whilst in contrast that for the patients in the 200 iu group decreased from 1.71 to 1.51. The difference between groups during this second week was statistically significant ($P = 0.042$).

Occurrence of summer asthma

During the period of the trial seven patients in the 80 iu and five patients in the 200 iu group reported symptoms of summer asthma. In either group there was a tendency for these to be among those exhibiting the more pronounced hay fever symptoms. Over the 5 weeks of the study symptom grades for asthma tended to follow symptom grades recorded for hay fever. With the exception of one patient the most severe symptoms experienced occurred at the time of peak pollen challenge, and by the end of the 4-week treatment period only one patient continued to record mild symptoms.

Additional medication

The taking of additional medication was not confined either to high or low scorers, though high scorers in either group including all but one of the patients recording asthma symptoms, took additional medication. During the 4 weeks of treatment eleven patients in the 80 iu group took additional medication (on average for 12 of the 14 days during the first 2-week period, and six during the second) compared to ten patients in the 200 iu group (on average for 10/14 and 8/14 days respectively).

Transeasonal changes in IgE

In most patients there was an increase in IgE levels during the trial period; this appeared to occur to an equal extent in both groups. The mean change at the mid trial sampling was +62% (s.d. 81%, d.f. 24, $P < 0.001$) and on completion of the trial +54% (s.d. 71%, d.f. 23, $P < 0.001$).

Within patients there was no apparent relationship between blood IgE content or percentage change and the severity and duration of hay fever symptoms during the period of peak pollen challenge.

Transeasonal changes in RAST grades

In seven of the twelve patients in the 80 iu group and seven of thirteen in the 200 iu group, there was an increase in RAST grades to either Timothy or rye grass. In both groups there was a tendency for RAST grades to rye grass to be higher than those to Timothy grass.

Side effects

Four patients in the 80 iu group reported side effects (two facial flushes; three, painful and stiff legs) and six in the 200 iu group (three facial flushes; six painful and stiff legs).

Discussion

The treatment of hay fever takes two forms—preseasonal hyposensitisation and seasonal suppressive treatment. Preseasonal hyposensitisation does not always give complete relief to all patients and in fact some gain no benefit at all. In addition, there is always the possibility of reactions. Seasonal treatments are also not uniformly successful and have drawbacks. Antihistamines may be soporific and cause nasal 'stuffiness'. Nasal sprays may cause irritation and depot corticosteroids the risk of suppressing adrenal functions.

Assessment of treatment presents difficulties. There are variations in pollen counts and patient activities from day to day and there is no objective measurement of hay fever severity. Treatment may be discredited, not because of lack of effectiveness, but because of side effects.

In a previous paper, intramuscular injections of 80 iu ACTH were shown to have a beneficial effect on hay fever for at least several days. A recent report has suggested that 200 iu ACTH has a longer duration of effect. This trial was undertaken to compare the efficacy of 80 iu and 200 iu ACTH given at fortnightly intervals.

There were marked variations in the pollen count during the trial period, demonstrating one of the difficulties in assessing treatment—a treatment given prior to a sudden fall in pollen count can give quite misleading results. Fortunately, in this trial, the first ACTH injections were given just prior to the major peak of the season and the second just prior to the next highest peak.

The general effect of the injections is shown in Figs 1 and 2. As far as can be judged in the absence of a placebo group, both groups successfully met the challenge of increased pollen count occurring after the first ACTH injection.

With regard to the incidence of hay fever symptoms this was less in patients given 200 iu ACTH than in those given 80 iu (Table 1). Over the full four weeks of treatment patients in the 200 iu group had on average 10.9 symptom-free days compared to 6.3 days for patients in the 80 iu group. Perhaps as important as the complete abolition of symptoms is the reduction in the severity of symptoms to a more tolerable and controllable level. As shown in Table 1 the incidence of moderate and severe symptoms was again less in the 200 iu than in the 80 iu group. When the symptoms were assessed as numerical scores and were analysed by analysis of covariance (the pretreatment week score for each patient being included as the covariate in order to adjust for any imbalance between groups) there was, in the comparison of the seven worst sufferers in the two groups, a significant difference between treatments in favour of 200 iu over the first two weeks of the trial ($P=0.033$). From examination of the mean scores it appeared that this difference was due to increased protection being afforded by the 200 iu dose during the second week.

As previously mentioned one patient complained of lassitude and oedema following injection of gelatin during the pretreatment week, and had to be withdrawn from the study. The most common complaint was of discomfort in the leg after the injection (gelatin alone or Acthar gel) and it is thought that this would have been less frequent if instead the patients had been given the injection in the buttock.

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