

# Time course of response to prednisolone in chronic airflow obstruction

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**ABSTRACT** Nineteen patients with chronic airflow obstruction measured their morning and evening peak expiratory flow (PEF) daily for 28 days. A placebo was taken for the first week and prednisolone 20 mg twice daily was taken for the last three weeks. The mean PEF in 13 patients who responded to prednisolone reached a maximum after eight days' treatment. The majority of the 19 patients had asthma and were thought to represent a typical cross section of patients who would be considered for a trial of oral corticosteroids. Most responsive patients will achieve a maximum response within eight days.

Patients with chronic airflow obstruction may improve with corticosteroid treatment and the idea of a trial of corticosteroids was introduced by Walsh and Grant.<sup>1</sup> The value of corticosteroids to patients with chronic airflow obstruction not thought to be caused by asthma is much more dubious.<sup>2</sup> However, in an individual patient it is usually impossible to predict the presence or absence of corticosteroid responsiveness and for this reason many will require a trial of corticosteroids. The time course of the response to oral corticosteroids has not been adequately defined and uncertainty exists about the optimum length of such a trial. For this reason we have undertaken a prospective trial of corticosteroids in 19 patients with chronic airflow obstruction to investigate the time course of the response. The airflow obstruction was caused by asthma in most of the patients and in the remainder asthma was thought to contribute in part to the airflow obstruction.

## Methods

Patients were selected for a trial of corticosteroids if they had airflow obstruction that had been present for at least three months and which had failed to respond adequately to bronchodilator therapy. None of the patients had previously been on long-term corticosteroids or had a short course of corticosteroids during the previous three

months. Details of the 19 patients are shown in the table.

Each patient was seen by one of us (JW) and shown how to use a peak flow gauge (Airmed Ltd). Three readings of peak expiratory flow (PEF) were recorded at approximately the same time each morning soon after rising and again before retiring each evening for four weeks. Most patients were using a salbutamol aerosol during the trial and they were asked not to use their aerosol for a minimum of four hours before recording their peak flow. Four bottles of tablets were given to the patient, marked week 1, 2, 3, and 4. Week 1 bottle contained placebo tablets, and weeks 2, 3, and 4 contained 5 mg prednisolone tablets. Four tablets (20 mg) were taken each morning and evening.

A graph of the PEF was plotted for each patient over the four-week period. The time taken to reach an improved level of PEF was assessed by eye by one of us (JW) and by an independent observer.

## STATISTICAL ANALYSIS

Initial inspection of the data revealed considerable differences in variability in each patient's PEF readings during the first week of the trial. A logarithmic transformation was found to stabilise the variance.

Differences in response to treatment at different times of day and over the four-week period of the trial were investigated using an analysis of vari-

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Table Clinical details of the 19 patients

Patient	Age	Sex	Cigarettes/history	Skin test	PEF % predicted	Diagnosis	% Response to prednisolone
1	59	M	60/day until age 52 yr when wheeze and dyspnoea began	-ve	62	CB, A	< 10
2	38	M	Non-smoker. Hayfever and asthma began at age 36 yr	+ve	56	A	75
3	67	M	20/day. Cough and sputum 25 yr. Wheezy since age 50 yr.	-ve	24	CB, A	18
4	62	M	25/day. "Chesty" as a child. Wheezy 5 yr.	+ve	55	A, CB	16
5	32	M	20/day. Asthma as a child and returned at age 28 yr.	+ve	68	A	20
6	41	M	20/day. Rhinitis and wheeze since age 26 yr.	-ve	59	A	23
7	36	M	20/day. Wheeze began at age 26 yr.	+ve	51	A	< 10
8	49	M	20/day. Dyspnoea since age 40 yr. Occasional wheeze.	+ve	46	E, A	10
9	54	M	Non-smoker. Asthma since age 14 yr.	+ve	51	A	27
10	52	M	15/day until age 50 yr. Asthma until age 11 yr and age 30 yr. until now.	+ve	36	A	77
11	71	F	40/day. Chronic wheezy dyspnoea for 10 yr.	-ve	47	CB, A	< 10
12	56	M	10/day. Wheezy dyspnoea since age 30 yr.	+ve	39	A, CB	20
13	56	M	20/day. Cough, sputum, and wheeze since age 40 yr.	-ve	41	CB, A, E	< 10
14	66	M	20/day. Cough, sputum, and wheeze since age 45 yr.	-ve	18	CB, A	34
15	66	M	15/day. Wheezy cough since age 30 yr.	+ve	24	A, CB	13
16	63	M	15/day. Chronic wheezy dyspnoea since age 55 yr.	-ve	53	CB, A	< 10
17	42	F	Non-smoker. Wheezy dyspnoea began age 31 yr.	+ve	34	A	16
18	31	F	10/day for three yr. Wheezy till age 10 and again age 17 yr.	+ve	74	A	< 10
19	30	F	Non-smoker. Asthma and rhinitis since age 21 yr.	+ve	55	A	36

PEF% predicted = mean of 14 PEF readings during week on placebo expressed as a percentage of the predicted PEF. A = asthma, CB = chronic bronchitis, E = emphysema. The order is determined by the disease process thought to be responsible for most of the airflow obstruction.

ance. In order to establish whether or not there was a placebo effect readings on day seven were compared with readings on day one using a paired *t* test. Response to treatment was measured by comparing the mean PEF readings during the third and fourth weeks of treatment with the mean PEF readings during the placebo week.

Response to corticosteroids was assessed firstly by using a 10% increase in PEF as a response criterion, and secondly by carrying out a *t* test on the untransformed data and taking a significance level of one per cent.

## Results

There was a considerable difference between morning and evening mean PEF readings over the four week period ( $p < 0.01$ ). The evening PEF measurement was, on average, 6% higher than the morning PEF measurement (95% confidence limits 5% and 8%), and this difference remained effectively constant throughout the four-week period.

There was no difference in PEF on days one and seven of the first week ( $p > 0.4$ ), nor between the mean PEF values during the third and fourth weeks ( $p > 0.8$ ). The mean improvement in PEF between the first week and the third and fourth weeks was 18% (95% confidence limits 15% and 21%).

Individual responses to treatment are shown in the table. The two criteria for determining individual response to treatment gave identical results in all patients. Thirteen patients showed an improvement in PEF of at least 10%. Their mean PEF readings throughout the four-week period are shown in fig 1. The maximum daily mean PEF occurred on the eighth day of treatment. The mean evening peak flow measurement was 10% higher than the mean morning peak flow measurement during the placebo weeks and 7% higher during the third and fourth weeks. This difference is not statistically significant ( $p > 0.1$ ).

The two observers' assessments of the time taken to respond to treatment in individual trials agreed to within one day in nine patients and to within three days in the remaining four patients (range for the two observers one to 11 days). The average of the assessments for each patient is shown in fig 2. In only one patient did the time taken to reach the improved PEF level exceed eight days.

## Discussion

The patients reported are thought to represent a typical cross-section of patients who would be considered for a trial of corticosteroids. Most of the patients selected had unequivocal asthma. However, some patients with chronic obstructive

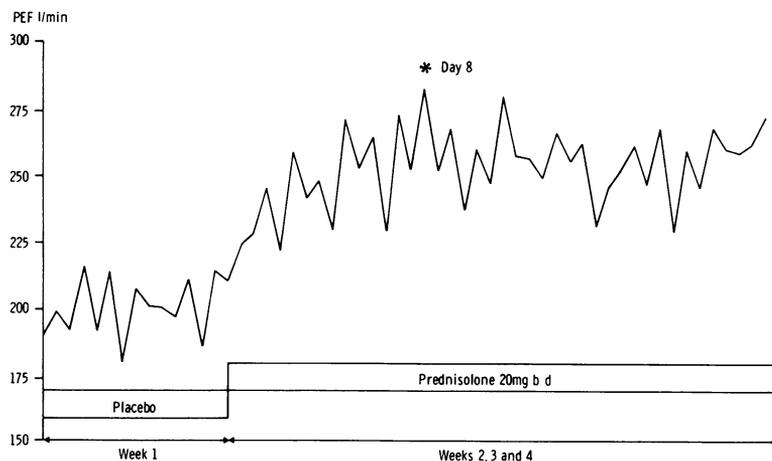


Fig 1 Mean PEF of 13 responsive patients throughout a one-month trial of corticosteroids.

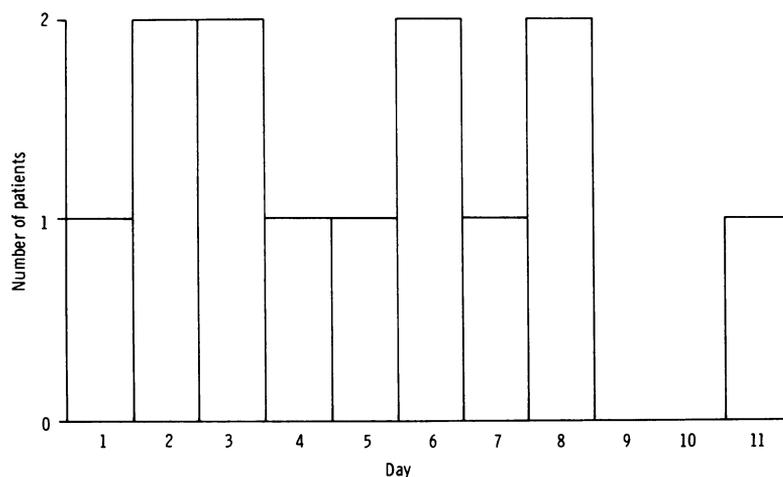


Fig 2 Time taken to reach the improved level of PEF in 13 responsive patients.

bronchitis and emphysema were included because it was not possible to exclude some degree of asthma contributing to their airflow obstruction.

The length of time required for a trial of corticosteroids will depend on the time taken to achieve a maximum response on a continuous dose of corticosteroids. Shenfield *et al*<sup>3</sup> demonstrated a "striking response" to corticosteroids in six patients with chronic asthma during a one-week course of prednisolone 40 mg/day. In five of the six patients, the best FEV<sub>1</sub> was obtained on the seventh and final day of the trial. Crompton,<sup>4</sup> in a group of 18 chronic asthmatic patients given a six-day course of 40 mg of prednisolone a day, showed that the mean FEV<sub>1</sub> for the 18 patients reached a maximum on the sixth and final day of

the trial. These patients might have continued to improve if the trials had continued longer. The results of the 13 patients who responded to corticosteroids in this study indicate that the maximum response occurred on the eighth day. This would suggest that the length of time for a trial of corticosteroids should be at least eight days. The dose of 40 mg/day used in our trials was arbitrary because the dose-response characteristics of airflow obstruction to corticosteroids has not been adequately defined.

The design of the trial should ideally incorporate a control period to establish a reliable baseline measurement. Ethically this control period cannot involve stopping treatment and so usual bronchodilator drugs should be continued during

this period. We found that the cheaper peak flow meters now available are ideal for use in out-patient trials of corticosteroids.

There are points of interest arising from some of the trials performed in the 19 patients. Two patients, numbers 7 and 18, aged 36 and 31 years, both had chronic "extrinsic" asthma with positive skin tests. There was no subjective or objective evidence of any change in respiratory function while on corticosteroids in either of them. Patient 7 was seen again in the chest clinic six months later, taking no treatment with a peak flow of 480 l/min. His peak flow had averaged approximately 290 l/min during treatment with prednisolone. This patient had moderate airflow obstruction when undergoing the trial of corticosteroids which failed to improve even though potential for considerable improvement was present. Failure to respond to corticosteroids was not the result of impaired absorption of prednisolone since his basal cortisol levels were depressed to 100 nm/l. The results from these two patients emphasise that not all asthmatic patients respond to corticosteroids. In contrast, three of the seven patients with airflow obstruction not thought to be caused predominantly by asthma responded to corticosteroids. This emphasises how difficult it is to predict which patient will respond to corticosteroids and explains why a group of patients selected for a trial of corticosteroids will inevitably include patients with different causes of airflow obstruction.

Diurnal variation in PEF is well recognised in asthma. The serum cortisol levels also drop in the early morning but continuous infusion of hydrocortisone does not abolish the dip in PEF.<sup>5</sup> The results in this study show that supraphysiological doses of corticosteroids do not influence diurnal variation in either the corticosteroid responsive or non-responsive patients when considered as a group.

None of the 19 patients experienced an exacerbation of asthma on withdrawal from prednisolone and there were no serious side-effects during or after the three-week trial of corticosteroids. The details of the effects of 40 mg of prednisolone daily for three weeks on the hypothalamic pituitary adrenal axis are reported elsewhere.<sup>6</sup>

In conclusion, we believe that the majority of patients with chronic airflow obstruction whose symptoms are not adequately controlled with bronchodilators should have a trial of corticosteroids lasting at least eight days. Not all patients with asthma respond to corticosteroids and a trial cannot be used as the sole criterion for diagnosis.

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