Thorax 1986;**41**:606–610

Value of serial peak expiratory flow measurements in assessing treatment response in chronic airflow limitation

D M MITCHELL, P GILDEH, A H DIMOND, J V COLLINS

From Brompton Hospital, London, and Benenden Hospital, Kent

ABSTRACT A double blind, randomised, placebo controlled, crossover trial of prednisolone (40 mg/day for 14 days) was carried out in 33 patients with chronic airflow limitation (mean age 62 years, mean FEV_1 1·01 litres, mean FEV_1/FVC ratio 44%), to assess the value of serial peak expiratory flow (PEF) measurements, taken five times daily in evaluating treatment response by comparison with other objective measurements and with measurements of symptoms. The mean serial PEF after a one week run in period was 189 l min^{-1}, during the second week of placebo 193 l min^{-1}, and during the second week on prednisolone 231 l min^{-1}. The difference in mean PEF values between placebo and prednisolone was significant ($p < 0·01$). With regard to the response to steroids of the individual patients, 13 of the 33 had a detectable trend of improvement on visual inspection of serial PEF measurements during prednisolone treatment but only one during placebo administration. Of all the objective measurements made after the run in and after each treatment phase (12 minute walking distance, FEV_1, forced vital capacity (FVC), serial PEF), the serial PEF chart provided the best discrimination between placebo and prednisolone treatment. There was no statistically significant association between steroid induced improvement in serial PEF measurements and in breathlessness, partly because of placebo improvements in symptoms in those who had no improvement in serial PEF values. This study indicates the importance of making objective measurements to identify a genuine steroid response rather than relying on symptomatic improvement alone. The best simple measurement to make is serial PEF during steroid trials. This is more sensitive in detecting a steroid response than are the 12 minute walking distance, FEV_1, or FVC, and is also less likely than these measurements to show spurious placebo responses.

Serial peak expiratory flow (PEF) measurements are of established value in the study of patterns in asthma and of responses to treatment[1–3] It is usual to measure PEF serially in patients with chronic airflow limitation both during the treatment of acute exacerbations of disease in hospital and in the assessment of response to bronchodilators or corticosteroids in patients with stable disease. The value of this practice has not been established, although an improvement in the serial PEF measurements is generally assumed to be correlated with clinical improvement. The amplitude of changes in serial PEF after treatment with bronchodilators or corticosteroids is usually much smaller in patients with chronic airflow limitation than in asthmatic patients, and may also be less than the natural diurnal variation seen in these patients over a period of time.[4]

The present study was done to assess the value of serial PEF measurements in patients with chronic airflow limitation during a double blind crossover controlled trial of oral corticosteroids when compared with changes in symptoms and with other commonly used objective measurements of response.

Address for reprint requests: Dr D M Mitchell, University College Hospital, London WC1E 6AU.

Accepted 16 December 1985

Methods

We studied 33 (26 male) patients aged 48–77 (mean 61·7) years with moderate to severe chronic airflow limitation (mean FEV_1/forced vital capacity (FVC)) ratio 44%, 58% predicted. The mean FEV_1 was 1·01 l (36% predicted; range 0·44–1·77%) and the mean FVC was 2·29 l (63% predicted). All patients had had

progressive breathlessness on exertion for at least five years, and all had been closely followed at a chest clinic for at least two years. None of the patients was known to have asthma in that there was no history of episodic wheeze, cough, or breathlessness. FEV_1 measurements had not varied by more than 20% at clinic visits in any patient, nor had any of the patients had a 20% or greater improvement in peak expiratory flow (PEF), FEV_1, or FVC after inhalation of 400 μg salbutamol by aerosol. One patient had sputum eosinophilia. All patients were clinically stable before and during the study in that there had been no recent variation in breathlessness and no infective exacerbation. None had previously received oral corticosteroids and none was taking inhaled steroids. All had smoked (mean 26·2 cigarettes a day for 34·7 years) but most had stopped some time before the study. Most patients were taking oral or inhaled β_2 adrenergic agonists and some were taking oral methylxanthines. Medication was not altered during the trial.

A double blind, controlled and randomised cross-over trial design was used to compare the effect of oral prednisolone 40 mg/day for 14 days with visually identical placebo tablets for 14 days. Patients' consent was obtained. After a seven day run in period baseline measurements were obtained and patients received prednisolone or placebo in random order. After 14 days measurements were repeated and patients immediately received the alternative treatment for 14 days, at the end of which the final measurements were made. Fifteen patients received prednisolone first and 18 received placebo first. All patients were admitted to hospital for the study. The best of three measurements of PEF (Wright peak flow meter) at 6 and 10 am and at 2, 6, and 10 pm were recorded on a serial PEF chart for each patient during the run in and both treatment phases. All PEF measurements were made before routine aerosol bronchodilators had been given.

PEF measurements were supervised and recorded by a nurse trained in the correct use of the meter. After the run in period and after each phase of treatment the following measurements were made. Breathlessness was assessed in terms of a simple breathlessness score (1–5)[5] and oxygen cost diagram.[5] Each patient completed a 10 cm visual analogue line self assessment rating for feelings of general well being. After each treatment patients were asked whether they felt better, worse, or unchanged. Exercise performance was measured on the basis of the 12 minute walking distance.[6] Each patient did a practice walk several hours before the baseline 12 minute walk was performed. All measurements were made at the same time of day for each patient before routine bronchodilators had been taken. An improvement in a measurement after treatment was arbitrarily taken as a 20% or greater increase when compared with the baseline value. Any visually detectable positive gradient in the serial PEF chart after the run in period or either treatment phase was scored as an improvement. This was assessed before the randomisation code was broken. The overall mean PEF for each patient and the mean PEF at 6 am were calculated for the baseline period of one week, for the second week of the placebo period, and for the second week of the prednisolone period. The following indices of variability in PEF readings during each period were also calculated. The difference between the minimum and maximum PEF readings during the weekly period was expressed as a percentage of the mean PEF for the week. The mean diurnal variation was calculated from the minimum and maximum of each day's PEF values during each weekly period and expressed as a percentage of the mean PEF for the week. Results were analysed by χ^2 test with Yates's correction. The mean PEF values calculated from the serial charts were compared using Wilcoxon's signed pairs rank sum test.

Results

The numbers of patients showing an improvement (> 20% increase) in each measurement after prednisolone only, after placebo only, and after both prednisolone and placebo are shown in table 1. Visual inspection of the serial PEF charts of the 33 patients for the five week study period showed that improvement occurred solely during the prednisolone phase in 13. No improvements were seen during any phase (run in, placebo, or prednisolone period) in 15 patients; in four patients serial PEF measurements improved during both placebo and prednisolone periods and in the final patient improvement was seen during the run in and placebo periods but not during prednisolone treatment. Nearly as many patients showed improvements in terms of breathlesssness and exercise tolerance (12 minute walk) after placebo as after prednisolone, but there were fewer placebo responses seen in FEV_1, FVC, and the serial PEF chart. The placebo responses were not due to a carry over effect of prednisolone into the placebo period, for when data on patients receiving placebo after prednisolone were analysed separately from data on those receiving placebo first there was no excess of placebo improvements for any measurement in the first group.

A comparison between improvements in serial PEF charts and improvements in the other measurements is made in table 2. There were no statistically significant associations between improvements on the PEF chart and any other measurement (χ^2 tests with

Table 1 *Numbers of patients (total 33) who improved (≥20%) from the baseline during treatment with prednisolone or placebo*

Index of improvement	*Prednisolone only*	*Placebo only*	*Both prednisolone and placebo*
Breathlessness score	6	4	11
Oxygen cost	7	5	6
General well being	8	4	7
12 minute walk	6	1	13
FEV_1	9	2	4
Forced vital capacity	7	0	3
Serial PEF chart*	13	1	4

*Improvement defined as a visually detectable trend of improvement (positive gradient) in serial peak expiratory flow (PEF) measurements during the 14 day treatment periods.

Table 2 *Relationships between improvements in peak expiratory flow (PEF) and other indices**

Change in other indices after prednisolone	*Improvement in PEF chart†*	*No improvement in PEF chart*
Felt better	11	7
no change or worse	2	8
Breathlessness score, oxygen cost, or general well being improved (≥20%)	6	5
not improved	7	10
12 min walk improved	5	1
not improved	8	14
FEV_1 improved	6	2
not improved	7	13
Forced vital capacity improved	5	1
not improved	8	14

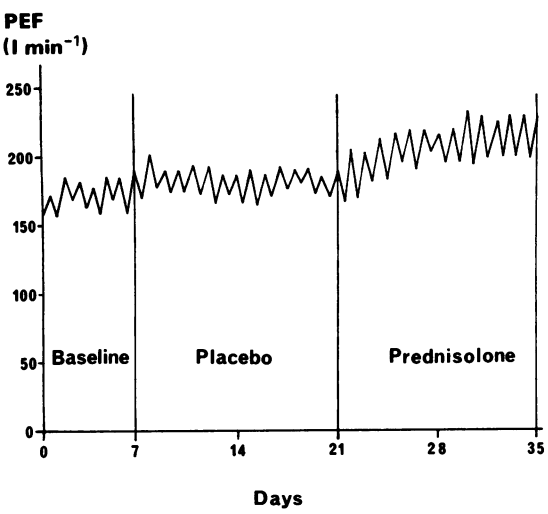
*Twenty eight patients; the five who showed improvements on the serial PEF chart with both placebo and prednisolone or with placebo alone are not shown.
†There was no significant association between improvements on the PEF chart and improvement in any other measurement (χ^2 with Yates's correction).

Table 3 *Mean peak expiratory flow (PEF) after the baseline week and each treatment phase and indices of variability*

	Predicted	*Baseline*		*Placebo*		*Prednisolone*
Mean (SD) PEF ($l\ min^{-1}$)	543 (53)	189 (73)	*	193 (74)	†	231 (78)
Mean PEF at 6 am ($l\ min^{-1}$)	—	169		181		202
Min and max PEF (% mean)	—	42		46		49
Mean diurnal variation (% mean)	—	24		20		22

Significance of differences between means: *non-significant; †$p < 0.01$.

Yates's correction). In objective measurements, however (12 minute walk, FEV_1, FVC), only one or two patients improved their performance without also showing improvements on their PEF chart, whereas larger numbers had improvements in symptoms without improvement in PEF. Of the 13 patients with improvements in their PEF charts during prednisolone treatment, those with a less than 20% improvement in FEV_1 showed smaller improvements on their PEF charts than those with a greater than 20% improvement in FEV_1. The mean PEF values during the baseline week, the second week of placebo, and prednisolone treatment are shown in table 3. A small increase in mean PEF occurred with placebo and this was not significant. A greater increase occurred with prednisolone and this was significantly more than the placebo response ($p < 0.01$). The mean PEF at 6 am was consistently lower than the mean PEF for the whole day (five PEF readings) for each period and indices of variability in PEF readings were similar for each period. There was no detectable relationship between diurnal variation or difference between minimum and maximum PEF for any individual during the baseline week and subsequent improvement on the serial PEF chart with prednisolone. Of the 13 patients who had a visually detectable trend of improvement in serial PEF readings during prednisolone treatment, all had a 20% or greater increase in mean PEF value for the second week of prednisolone over the mean PEF value for the baseline week, except for two patients whose increases were 13% and 15% respectively. Of the 15 patients with no visually detectable improvement, eight had no increase in mean PEF during this period and in the other seven the increases were all very small (less than 10 $l\ min^{-1}$). The mean 6 am and 6 pm PEF



Mean peak expiratory flow (PEF) readings at 6 am and 6 pm for 33 patients during baseline run in, placebo, and prednisolone periods.

readings for all 33 patients during both treatment phases are shown in the figure.

Discussion

Trials of oral corticosteroids produce a beneficial effect in a proportion of patients with severe chronic airflow limitation.[7-9] The present study was done to assess the value of serial PEF measurements during steroid trials by comparison with other measurements used for determining response. A placebo effect was seen in symptomatic improvement and exercise tolerance (12 minute walk) but was far less with FEV_1, FVC, and serial PEF chart. All patients were admitted to hospital for the study. Any improvement due simply to this was minimised by having a run in period before baseline measurements were obtained. The placebo effect was probably not due to a carry over of prednisolone induced improvement in those who had received prednisolone before placebo, as separate analysis of those receiving placebo first and those receiving placebo second did not show an excess of responders for any measurement in the latter group. Mean maximum improvements have been shown to occur eight days after the start of prednisolone in patients with chronic airflow limitation[10] and the hypothalmic pituitary-adrenal axis to return to normal within three days of stopping prednisolone (40 mg/day) taken for three weeks.[11] However, it is possible that steroid induced benefit could persist for as long as 14 days after stopping steroid treatment when placebo measurements were taken. As the study was double blind the most probable explanation is that the placebo effect was genuine. It could still be argued that the placebo effect resulted from the study being done on inpatients rather than outpatients. However, it is common practice to admit patients to hospital for steroid trials so that responses can be accurately monitored and hazardous side effects detected early. The present study was designed to test assumptions related to this practice. It is noteworthy that the placebo effect was most marked with symptoms, as the prime aim of treatment is to relieve breathlessness, yet symptomatic improvement in the absence of some objective improvement in pulmonary function may be purely due to a placebo or euphoriant effect of prednisolone.

Trends of improvement or deterioration in serial PEF measurements are often assessed by visual inspection alone, and mathematical procedures such as cusum analysis for exposing more subtle trends are unlikely to be of clinical relevance[12]—indeed, cosinor analysis is helpful only in exposing diurnal variation.[3] In this study visual inspection of PEF charts, although a relatively crude method of assessment, was remarkable in its discriminative power in that it showed a considerable difference between placebo and prednisolone treatment. Of all the measurements used, the serial PEF chart was the most sensitive way of detecting a steroid response (table 1). This may simply be related to the large number of measurements of PEF made, which increased the signal to noise ratio; whereas symptoms, exercise tolerance, FEV_1, and FVC were measured only at the end of the run in and of each treatment phase. The better discrimination of the PEF chart is less likely to have been due to a positive trend that was evident with very small percentage increases in mean values between baseline and prednisolone, while other measurements were scored as an improvement only if there had been a 20% or greater increment. Of the 13 patients with a positive trend on the peak flow chart, all but two had a mean PEF value in the second week of prednisolone that was 20% or more above the baseline mean.

Steroid induced improvements in serial PEF measurements were not necessarily accompanied by improvements in symptoms, exercise tolerance, FEV_1, or FVC, and such associations as there were did not reach statistical significance, perhaps because numbers were small. It was, however, noteworthy that only one or two subjects without improved PEF measurements after taking steroids showed improvements in other objective measurements, whereas larger numbers had improved symptoms in the face of no improvement in PEF measurements. This, taken together with the observation that the PEF chart was the best discriminator between placebo and prednisolone, would indicate that the

PEF chart was the most sensitive index of steroid responsiveness of all the measurements made. If only FEV_1 and FVC had been measured some potentially useful improvements on steroids might have been missed.

These results emphasise the difficulty of assessing a steroid response in chronic airflow limitation and the dilemma over which measurements should be used, given that the aim of the treatment is to relieve breathlessness. If this can be achieved with a placebo, then steroids become redundant. Steroid trials in clinical practice should perhaps have a placebo phase to select out this group of patients.

This study shows that oral corticosteroids decrease airflow limitation as measured by serial PEF in about 30% of patients with chronic airflow limitation. Placebo effects make symptom measurement alone unreliable and an objective measurement is required to detect a genuine response. Serial PEF measurements provided the best discrimination between prednisolone and placebo and may be the most sensitive way of detecting a steroid response.

References

1 Turner-Warwick M. On observing patterns of airflow obstruction in chronic asthma. *Br J Dis Chest* 1977;**71**:73–86.

2 Hetzel MR, Clark TJH. Comparison of normal and asthmatic circadian rhythms in peak expiratory flow rate. *Thorax* 1980;**35**:732–8.

3 Hetzel MR. The pulmonary clock. *Thorax* 1981;**36**: 481–6.

4 Dawkins KD, Muers MF. Diurnal variation in airflow obstruction in chronic bronchitis. *Thorax* 1981;**36**: 618–21.

5 Fletcher CM, Elmes PC, Fairbairn AS, Wood CH. The significance of respiratory symptoms and the diagnosis of bronchitis in a working population. *Br Med J* 1959;ii:257–66.

6 McGavin CR, Artvinli M, Haoe H, McHardy GJR. Dyspnoea, disability and distance walked: comparison of estimates of exercise performance in respiratory disease. *Br Med J* 1978;ii:241–3.

7 Sahn SA. Corticosteroids in chronic bronchitis and pulmonary emphysema. *Chest* 1978;**73**:389–96.

8 Harding SM, Freedman S. Comparison of oral and inhaled steroids in patients with chronic airways obstruction: features determining response. *Thorax* 1978;**33**:214–8.

9 Mendella LA, Manfreda J, Warren CPW, Anthonisen NR. Steroid response in chronic obstructive pulmonary disease. *Ann Intern Med* 1982;**96**:17–21.

10 Webb J, Clark TJH, Chilvers C. Time course of response to prednisolone in chronic airflow limitation. *Thorax* 1981;**36**:18–21.

11 Webb J, Clark TJH. Recovery of plasma corticotrophin and cortisol levels after a 3 week course of prednisolone. *Thorax* 1981;**36**:22–4.

12 Mitchell DM, Collins JV, Morley J. An evaluation of cusum analysis in asthma. *Br J Dis Chest* 1980;**74**: 169–74.