A controlled trial of prednisone, in low dosage, in patients with chronic airways obstruction

J. A. Evans, I. M. Morrison, and K. B. Saunders

Departments of Medicine and of Thoracic Medicine, St. Thomas' Hospital, London SE1


All patients had breathlessness as their main complaint, and chronic cough with sputum for 2 to 30 years; five had evidence of emphysema on the chest radiograph. None had a personal or family history of asthma. For the group, mean forced expiratory volume in one second was 1.11 l, and mean forced vital capacity was 2.28 l. Six patients had abnormally high levels of arterial Pco₂, (46–52 mmHg).

When the 'placebo' and 'prednisone' measurements were compared there was no significant change in forced expiratory volumes, bronchodilator effect on forced expiratory volumes, or blood gas tensions. Inspiratory airways resistance measured by body plethysmography was significantly higher, or 'worse', on prednisone (mean 4.2 cmH₂O per 1/sec) than on placebo (mean 3.2).

The beneficial effect of corticosteroids in asthma is undoubted. In patients with chronic bronchitis, emphysema, or both, who have chronic airways obstruction with little or no response to inhaled bronchodilator drugs, the effect of corticosteroids is debatable.

Previous studies of this problem have come to widely differing conclusions (see Discussion). The most carefully conducted and controlled studies suggest that prednisone is not helpful.

Despite this evidence, it is common practice to give a trial of steroids to patients with severe dyspnoea not helped by bronchodilators. In the individual case it may be difficult to distinguish a moderate response to prednisone from spontaneous slow fluctuations in the disease. Nevertheless it was our impression that some patients do respond to steroids and also that they may respond to a small dose. We therefore designed a controlled double-blind cross-over trial of prednisone, 5 mg per day by mouth, in patients with chronic airways obstruction and used measurements of forced expiratory lung volumes, airways resistance, and blood gas tensions to assess the effect of the drug.

The patients were asked if they would take part in a trial of a drug which might be beneficial to them, and willingly agreed to participate. The study was approved by the hospital committee on ethical procedures. A short account of this work has been given previously (Evans, Morrison, and Saunders, 1973).

SUBJECTS

We studied 10 men with chronic diffuse airways obstruction and little or no response to bronchodilator therapy (Table 1). Their ages ranged from 50 to 72 (mean 62). All were smokers or ex-smokers. All had chronic cough with sputum (on most days for at least three months of the year, for at least two years) and in all the main complaint was of breathlessness. None had a family or personal history suggestive of atopy. Routine blood counts did not show an excess of eosinophils. Five had radiographic evidence of emphysema. No patient had electrocardiographic evidence of right ventricular hypertrophy. None had previously received steroid therapy. One subject only was receiving bronchodilator treatment (oral orciprenaline), and he continued this throughout the trial. No courses of antibiotics were required during the trial.
METHODS

The trial was conducted over the months January to April. Each patient took 2-5 mg prednisone twice daily for a week, and placebo tablets for a week, the order of administration being randomized and known only to the hospital pharmacist. Five subjects took placebo in the first week and prednisone in the second week and the other five took their tablets in the reverse order.

The lung function studies were carried out on three occasions, first immediately before starting the trial ('pre-trial') and again after the first and second weeks of treatment (placebo or 'prednisone').

The following measurements were made, in the same order, at each attendance, between 14.00 and 16.00 hours.

1. FORCED EXPIRATORY VOLUMES We measured forced expiratory volumes in 1 second (FEV
denotes container (Medihaler Iso Forte) and the measurements of FEV
FVC ratio with a dry spirometer (Collins, McDermott, and McDermott, 1964), obtained three technically satisfactory blows at approximately one minute intervals, and took the mean of the highest two values for each variable.

2. INSPIRATORY AIRWAYS RESISTANCE (Raw) and SPECIFIC CONDUCTANCE (SGaw) We used a constant volume whole body plethysmograph (Dubois et al., 1956a; Dubois, Botelho and Comroe, 1956b) with the patient in the semi-reclining position. Thoracic gas volume (TGV) was measured by the airway occlusion technique. The relation between alveolar pressure and flow was displayed on a storage oscilloscope (Tektronix 564B). Slope measurements for derivation of Raw were made on the inspiratory portion of the trace, the expiratory phase being widely looped in these patients. The means of three measurements of TGV and of Raw were taken, and SGaw was calculated as the conductance, or reciprocal of Raw, divided by TGV.

3. RESPONSE TO ISOPRENALE When the above measurements were completed the patient received two inhalations of isoprenaline aerosol from a metered-dose container (Medihaler Iso Forte) and the measurements of FEV
FVC, and FEV
FVC were repeated. Two patients (1 and 7) declined this part of the procedure because of previous side effects from similar therapy.

4. BLOOD GAS ANALYSIS Finally, a sample of blood was taken under local anaesthesia from the brachial artery and analysed for the partial pressure of oxygen (Pao2), carbon-dioxide (Paco2), and pH with Radiometer electrodes. Pao2 measurements were not obtained in patients 7 and 8.

RADILOGICAL ASSESSMENT The chest radiographs of all subjects were examined by an independent observer (Dr. J. W. Pierce) and assessed for the presence of emphysema with particular reference to the nature of peripheral vascular markings (Laws and Heard, 1962). The films were divided into three groups: (1) no evidence of emphysema; (2) probable evidence of emphysema; and (3) definite emphysema. Each film was assessed on two separate occasions, the observer being unaware of the results of lung function tests and, during the second assessment, of his previous grading of the film. In fact the only two patients initially graded as 'probable' (5 and 9) were on the second occasion thought to show no evidence of emphysema and have been graded as such. The other eight films were given the same grading on both occasions.

RESULTS

Table I shows the initial lung function assessment for each patient. All had clear evidence of airways obstruction of varying degree. Bronchodilator response was unimpressive (although useful in subject 6), and did not in any patient restore spirometric values to anywhere near normal. If the upper limit of normal Pac02 is set at 45 mmHg, six patients had mild respiratory failure with CO2 retention.
The effects of prednisone and placebo on lung function are shown in Table II. No significant differences were seen in forced expiratory volumes, bronchodilator effect on forced expiratory volumes, or blood gases. Inspiratory resistance was significantly higher (i.e., worse) and specific conductance lower on prednisone than on placebo (Fig. 1). This was also true if the prednisone measurements are compared with those immediately before prednisone treatment ('pre-trial' in five cases and 'placebo' in five). The statistical significance of the changes in Raw on prednisone is mainly due to large changes in two patients, 4 and 7. No particular characteristics otherwise distinguished them from the group as a whole.

Since the subjects had fortuitously fallen into two equal groups with and without evidence of emphysema on the chest film, they were tested for differences between means for each group, for all variables described above, using an unpaired two-tailed t test. No significant differences were found.

**DISCUSSION**

Whole body plethysmography provides a sensitive method of detecting small changes in airways resistance (Lloyd and Wright, 1963; Stein, Tanabe, Rege, and Khan, 1966). Since intrathoracic airways become wider on inspiration and narrower on expiration, the value for Raw obtained depends on the lung volume at which the measurement is made. We measured thoracic gas volume and found no significant differences in mean values on the three occasions of measurement. Hence these three measurements of airways resistance may fairly be compared. Since the relation between conductance (1/Raw) and thoracic gas volume is roughly linear (Briscoe and Dubois, 1958) many workers prefer to express their results as specific conductance, that is, conductance divided by the thoracic gas volume at which the measurement was made, in an attempt to obtain an index independent of lung volume. This assumes not only linearity of the conductance (TGV relation) but also that it passes through zero, which is not quite true for normal subjects (Briscoe and Dubois, 1958) and probably less so for patients with chronic lung disease. Detailed figures for Raw, SGaw, and TGV on placebo and prednisone are given in Table III. In all except one patient (4) the maximum variation in TGV was 0.71. In patient 4 a large increase in airways resistance occurred on prednisone despite an increase of 2.2 l. in TGV (which if acting alone would have been expected to be accompanied by a fall in resistance). In this patient also, FEV1 fell on prednisone from 0.97 to 0.68, and FVC from 2.39 to 1.50 l. Surprisingly, Paco2 in this patient was the highest in the group: 96 mmHg pre-trial, 100 mmHg placebo, 96 mmHg prednisone. Paco2 was 36 mmHg on all three occasions. He was aged 69, a smoker, had a 30-year history of chronic cough and sputum, and radiographic evidence of emphysema.

While we have expressed our results both as Raw and SGaw, the changes in one closely
TABLE II
MEAN RESULTS, WITH 1 STANDARD DEVIATION, FOR LUNG FUNCTION TESTS

|                      | Pre-trial       | Prednisone      | Placebo        | Comparisons                     
|----------------------|-----------------|-----------------|-----------------|-------------------------------
| FEV₁ (L)             | 1.11 (0.40)     | 0.99 (0.37)     | 1.03 (0.37)     | NS                            
| FVC(L)               | 2.28 (0.63)     | 2.20 (0.54)     | 2.22 (0.60)     | NS                            
| FEV₁/FVC (%)         | 49 (15)         | 46 (16)         | 47 (16)         | NS                            
| Change after         |                 |                 |                 |                               
| bronchodilator       |                 |                 |                 |                               
| in FEV₁(L)           | +0.09 (0.13)    | +0.15 (0.13)    | +0.10 (0.13)    | NS                            
| in FVC(L)            | +0.17 (0.28)    | +0.19 (0.29)    | +0.17 (0.36)    | NS                            
| Raw (cmH₂O per l/sec)| 3.38 (1.12)     | 4.24 (1.33)     | 3.19 (0.77)     | 0 < 2P < 0.02                 
| SGaw (cmH₂O⁻¹ sec⁻¹)| 0.051 (0.016)   | 0.039 (0.018)   | 0.050 (0.016)   | 0 < 2P < 0.01                 
| Pao₂ (mmHg)          | 72 (12)         | 74 (11)         | 74 (11)         | NS                            
| PacO₂ (mmHg)         | 45 (6)          | 47 (7)          | 47 (6)          | NS                            
| pH                   | 7.42 (0.02)     | 7.41 (0.02)     | 7.42 (0.01)     | NS                            

Comparisons between means are made by a two-tailed paired t test. In the 'before v after prednisone' comparison the results on prednisone are compared with the results immediately preceding the prednisone week—'placebo' in five cases, and 'pre-trial' in five cases. NS=not significant (2P > 0.05).

TABLE III
INDIVIDUAL VALUES FOR FEV₁, FVC, RAW, SGAW, AND TGV FOR 10 SUBJECTS ON PLACEBO AND PREDNISONE

<table>
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<th>Placebo</th>
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<tr>
<td>FEV₁ (L)</td>
<td>0.66</td>
<td>0.72</td>
<td>1.87</td>
<td>2.09</td>
<td>2.9</td>
<td>3.6</td>
<td>0.049</td>
<td>0.036</td>
<td>7.04</td>
<td>7.72</td>
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<td>FVC(L)</td>
<td>1.22</td>
<td>1.35</td>
<td>2.23</td>
<td>2.25</td>
<td>1.6</td>
<td>1.6</td>
<td>0.094</td>
<td>0.089</td>
<td>6.65</td>
<td>7.02</td>
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<td>Raw (cmH₂O per l/sec)</td>
<td>0.076</td>
<td>0.071</td>
<td>3.93</td>
<td>3.42</td>
<td>3.4</td>
<td>3.8</td>
<td>0.041</td>
<td>0.037</td>
<td>7.12</td>
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<tr>
<td>SGaw (cmH₂O⁻¹ sec⁻¹)</td>
<td>0.051</td>
<td>0.054</td>
<td>2.39</td>
<td>1.50</td>
<td>2.8</td>
<td>5.7</td>
<td>0.054</td>
<td>0.020</td>
<td>6.61</td>
<td>8.78</td>
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<td>TGV (L)</td>
<td>1.1</td>
<td>1.2</td>
<td>1.95</td>
<td>1.78</td>
<td>4.6</td>
<td>5.8</td>
<td>0.047</td>
<td>0.036</td>
<td>4.63</td>
<td>4.78</td>
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<td>0.73</td>
<td>0.73</td>
<td>2.15</td>
<td>2.18</td>
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<td>4.2</td>
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<td>0.030</td>
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<td>0.85</td>
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<td>1.52</td>
<td>1.53</td>
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<td>2.28</td>
<td>3.1</td>
<td>3.9</td>
<td>0.040</td>
<td>0.034</td>
<td>6.58</td>
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<td>3.8</td>
<td>0.033</td>
<td>0.034</td>
<td>8.41</td>
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followed changes in the other in individual patients, reflecting the fact that TGV was very similar on all three occasions when it was measured (with the one exception already mentioned).

We include figures for SGaw to allow comparison with the results of others (Oppenheimer, Rigatto, and Fletcher, 1968).

Previous studies of the effect of prednisone in chronic airways obstruction have given variable, and generally discouraging, results. Earlier studies (Franklin, Michelson, Lowell, and Schiller, 1958; Corazza, Morrow, and Chesney, 1961; Clifton and Stuart-Harris, 1962; Freedman, 1963; Fuleihan, Feisal, and Malouf, 1967) were not controlled. Moyes and Kershaw (1957) concluded that there was no significant symptomatic benefit to chronic bronchitics given tetracycline plus prednisone, 15 mg/day, as opposed to tetracycline alone. Lung function studies were limited to vital capacity measurements. Oppenheimer et al. (1968), in a controlled single-blind study using body plethysmography, found no significant benefit in patients given 20 mg prednisone for one week. Their patients had a mean FEV₁ of 1·47 l, mean VC of 2·91 l, and mean SGaw of 0·103 cmH₂O⁻¹ sec⁻¹, suggesting that, as a group, they had less severe obstruction than ours (mean FEV₁ 1·11 l, FVC 2·28 l, SGaw 0·051 cmH₂O⁻¹ sec⁻¹ in the pre-trial values). Indeed their mean value for SGaw of 0·103 falls not far below the lower limit of normal (0·13) obtained by Briscoe and Dubois (1958), with which observations in our laboratory agree.

There appear to be only three double-blind trials other than our own. Beere, Jick, and Tyler (1963) did not use body plethysmography and gave prednisone in high dosage (60 mg daily, decreasing to 20 mg on the third day, and continuing at that dose for two weeks in all). Marked improvement in FEV₁, was seen in two patients, but both had had episodes of wheezing since adolescence, which suggested an asthmatic basis for their symptoms. Beere and Vance (1971) showed some improvement in arterial blood gases and pulmonary diffusion capacity in patients with emphysema given 60 mg prednisone daily initially, decreasing to a maintenance dose of 20 mg daily for eight weeks.
Seven of the 23 patients in this study had obvious side effects of steroids. Morgan and Rusche (1964) did use body plethysmography in five of seven subjects, and gave betamethasone, 3-6 mg daily for three days, and 1-8 mg daily thereafter, equivalent to 24 and 12 mg prednisone respectively. All five patients showed deterioration in measurements of airways resistance while on the active preparation, not only on body plethysmography but also in measurements derived from spirometry. We have now reached a similar conclusion giving only 5 mg prednisone daily.

We did not systematically investigate symptoms. All patients said they 'felt better' on the tablets but, more to the point, did not distinguish between placebo and active treatment.

It may have been assumed in the past that if steroids, in low dose, were given to patients with chronic airways obstruction, they would do no harm, even if they did no good. Our findings, in conjunction with those of Morgan and Rusche (1964), suggest that this is not always the case.

It may be very difficult to distinguish clinically between a patient with chronic bronchitis, airways obstruction, and increasing dyspnoea, and a patient with chronic bronchitis and late-onset asthma. In such cases a trial of steroids may be justified. Clearly, the result of such a trial should be judged by careful and detailed assessment of lung function.

We are glad to record the assistance of Mr. Coles (Hospital Pharmacy), who controlled the randomization of the trial, and of Miss Valerie Arnold (Department of Clinical Physiology) who did the blood gas measurements. Dr. J. W. Pierce graded the chest radiographs and Dr. M. Webb-Peploe assessed the electrocardiograms.

The body plethysmograph was purchased by a grant from the St. Thomas' Hospital Endowments Committee and built by Vickers Ltd. (Medical Group), to whom we are indebted for advice and servicing facilities.

REFERENCES


Requests for reprints to: Dr. J. A. Evans, University College Hospital, Gower Street, London WC1.