

A comparison of oral and inhaled steroids in patients with chronic airways obstruction: features determining response

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Harding, S. M., and Freedman, S. (1978). *Thorax*, 33, 214–218. **A comparison of oral and inhaled steroids in patients with chronic airways obstruction: features determining response.** Two trials comparing aerosol and oral steroid treatment were carried out in patients with chronic airways obstruction. All patients had a history of chronic productive cough and an FEV₁ less than 70% predicted but did not have episodic or seasonal breathlessness with wheezing. One trial involved 18 outpatients, the other 18 inpatients. Both studies involved three consecutive treatment periods, the first with placebo aerosol, the second with active aerosol (betamethasone valerate, 800 µg/day), and the third with oral prednisone or prednisolone (30 mg/day). Six patients showed a significant improvement in ventilatory capacity on steroids. Initial assessment included a comprehensive history using a questionnaire, skin tests, blood and sputum eosinophil counts, and chest radiography. In addition, for the inpatients, response to isoprenaline, daily sputum volume, and PaCO₂ were measured. Only blood eosinophilia and variability in ventilatory capacity during the placebo period seemed indicative of a likely response to steroids. However, there was a large overlap between various features on assessment in the responders and non-responders, and the management of every patient with chronic airways obstruction should include a controlled trial of steroids. The steroid aerosol produced a good improvement in ventilatory capacity in the responsive patients who were hospitalised and this was thought to be helped by supervision of aerosol technique. Such an aerosol could therefore be used for a steroid trial although oral steroids were found to give a more definitive response.

Betamethasone valerate and beclomethasone dipropionate aerosols have been shown to be effective in the treatment of asthma while being devoid of the side effects of systemic steroids. They have not previously been used in patients with 'irreversible' airways obstruction associated with chronic bronchitis, although a short report on the use of triamcinolone acetonide aerosol has indicated that some will respond to this route of corticosteroid administration (Matlin, 1976). Oral corticosteroids, however, have been used in several studies with some investigations claiming objective improvement (Franklin *et al.*, 1958; Clifton and Stuart-Harris, 1962; Beerel *et al.*, 1963; Freedman, 1963), some, subjective improvement only (Cullen and Reidt, 1960; Beerel and Vance, 1971), and others no benefit (Morgan and Rusche, 1964; Oppenheimer *et al.*, 1968; Evans *et al.*, 1974).

Detailed data of individual patients have not always been given in these studies, and it has therefore not been possible to determine which patients are most likely to respond. Hence, we wished to try to define the clinical and physiological characteristics which might be associated with a response to steroids and in addition to see if the response is as good with a steroid aerosol as with prednisolone.

Methods and patients

Two groups of patients were studied—18 outpatients at Isleworth and 18 inpatients at Enfield. All but one were long-standing cigarette smokers and all had chronic bronchitis as defined by the Medical Research Council (1965) as well as spirometric evidence of airways obstruction (forced

expiratory volume in one second ($FEV_{1.0}$) less than 70% predicted normal (Cotes, 1975) and/or $FEV_{1.0}$ /vital capacity ratio less than 0.6). We excluded patients with a present or past diagnosis of asthma and patients with a history of wheezing or breathlessness which was episodic or seasonal. Outpatients were referred specifically for assessment and possible entry to the study by their general practitioners. Inpatients were admitted if they suffered an exacerbation of their chronic bronchitis or if they were severely limited by chronic respiratory symptoms as outpatients.

DRUGS

Outpatients were given three packs, each containing material for 10 days' treatment, which was taken on a single-blind basis. Each pack contained a pressurised aerosol, two puffs to be inhaled four times a day and tablets, one to be taken three times a day. Treatment 1 comprised placebo aerosol (propellants only) and placebo tablets (lactose), treatment 2 comprised active aerosol (betamethasone valerate, 100 μ g per puff) and placebo tablets, and treatment 3 comprised placebo aerosol and prednisone tablets (10 mg per tablet). One patient was given 10 mg prednisone/day and another 20 mg/day because of coexisting medical problems.

Inpatients were given a placebo aerosol for an initial 7–10 days. When $FEV_{1.0}$ and peak expiratory flow rate (PEFR) readings were judged to be stable over a three-day period, the aerosol was changed, without the patient's knowledge, to one containing betamethasone valerate (800 μ g/day). After a further 7–10 days, the aerosol was discontinued, and the patients were given prednisolone, 30 mg/day for one week. In nine patients, this third week was completed on an outpatient basis, the patients coming up to hospital for assessment on the last three mornings of the week. Two patients did not complete the third phase, prednisolone being withdrawn after two days because of severe dyspepsia.

Other drugs, such as diuretics or antibiotics, were given as indicated clinically during the trial, and the patient's dose of oral bronchodilators was kept constant.

INITIAL ASSESSMENT

Before beginning the trial the patients were assessed by the completion of a detailed questionnaire about respiratory symptoms based on the Medical Research Council (1966) questionnaire and which included smoking habits and past occupational and family history. In addition, a chest radiograph was taken, $FEV_{1.0}$ and forced vital capacity (FVC) were measured using a dry spi-

rometer (Vitalograph) and also peak expiratory flow rate (PEFR) using the Wright peak-flow meter. Skin (prick) tests to 13 common allergens were carried out, a wheal >3 mm being regarded as positive. Sputum was examined for eosinophils by wet eosin or Leishman's stain and recorded as positive if more than occasional such cells were seen. Blood eosinophilia was recorded if more than 500 cells were seen on a differential count of a stained smear. Additional observations on the inpatients included response to isoprenaline (800 μ g from a pressurised aerosol), grading of right ventricular hypertrophy from ECG (Goodwin and Abdin, 1959), and, in most cases, measurement of arterial PCO_2 ($Paco_2$) within a few days of admission.

FOLLOW-UP

Throughout the trial outpatients filled in a diary card of symptoms and twice daily measurements with an Airflometer (AFM), a portable device for quantitating airways obstruction (Friedman and Walker, 1975). Inpatients had twice daily measurements of $FEV_{1.0}$, FVC, and PEFR before and after the inhalation of 800 μ g isoprenaline. In addition, daily sputum volume was measured. In four patients sputum collections were unsatisfactory in the third week of the trial.

Results

Five patients differed from the rest by virtue of an unequivocal increase in $FEV_{1.0}$ or AFM readings on steroids. In addition, a sixth patient had a small but statistically significant improvement in $FEV_{1.0}$.

Of the patients who responded to steroids, the inpatients did almost as well on inhaled steroid, but the outpatient responders had much better responses to oral prednisone (Fig. 1). A low initial $FEV_{1.0}$ did not prevent a response to the steroid aerosol. The outpatient responders improved more during the placebo period than did the inpatients. Three of the six responders had blood eosinophilia compared with three of 30 non-responders ($P < 0.05$, by χ^2 analysis). Sputum eosinophilia was present in two of the four specimens obtained from responders. Personal or family history of allergy and positive skin tests did not help to predict a response. The only other feature which came close to separating the steroid-responders from the others was that of variability of ventilatory capacity, as assessed by AFM readings or $FEV_{1.0}$ measured during the placebo period. Thus, in the outpatients, of the three with the largest measured variation in AFM units, two were steroid responders; in the inpatient group, of the six with

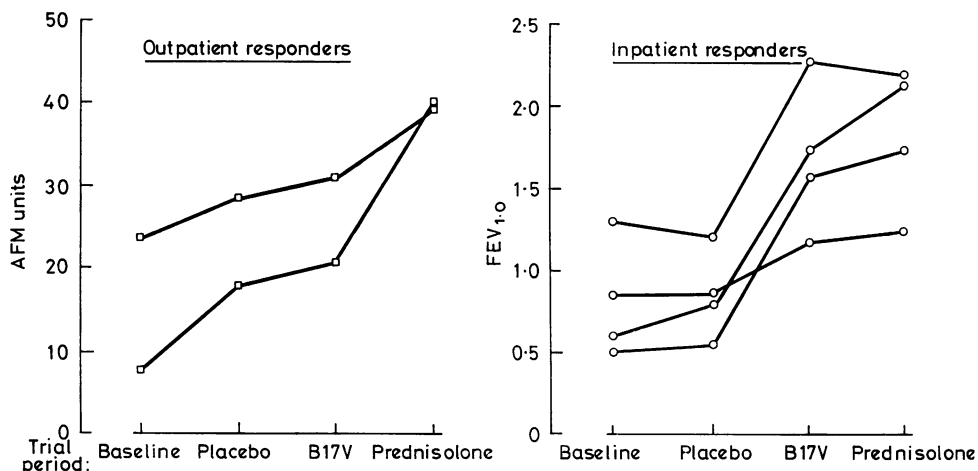


Fig. 1 Changes in ventilatory capacity with steroids. AFM and FEV_{1.0} readings are the average of 3-6 readings at the beginning (baseline) and last three days (treatment period) of trial period.

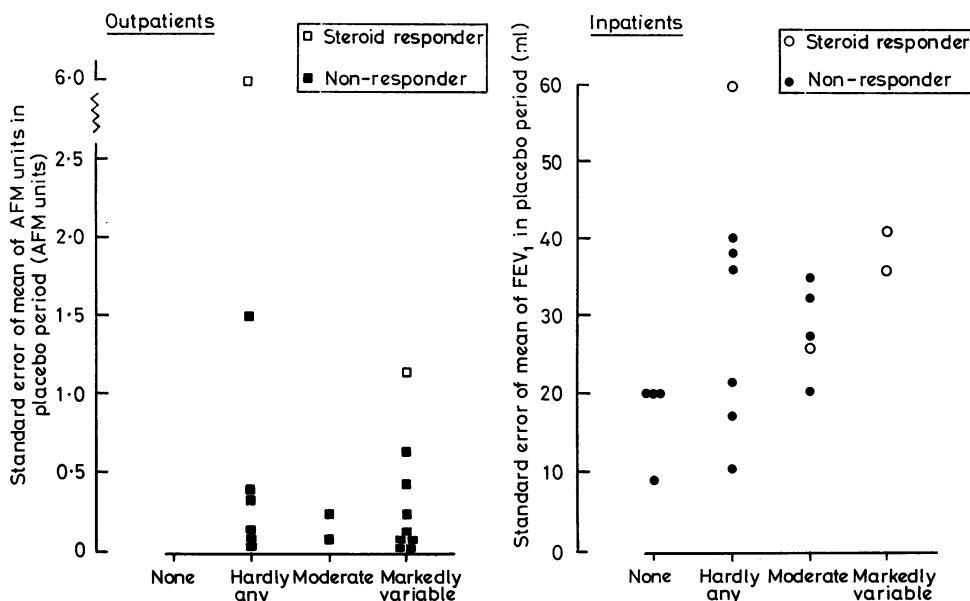


Fig. 2 Measured and subjective variability of ventilatory capacity (pre-treatment). Questionnaire reply about variation in chest symptoms day to day.

the largest variation in FEV_{1.0}, three were steroid responders (Fig. 2). Patient 6 could not be distinguished from the group as a whole. Correlation between the measured variation in AFM or FEV_{1.0} and the subjective impression of variability of symptoms was poor (Fig. 2).

Analysis of the answers to the questionnaire¹

failed to reveal a pattern of symptoms which would discriminate between steroid-responders and the others. All the responders excepting one had chest radiographs which were within normal limits. Overinflation (Hodson *et al.*, 1974) was not a feature and occurred in 13 of the 30 non-responders.

The additional information which was available only for inpatients, ie, response to isoprenaline,

¹Full details of patients and results available from S. M. Harding

sputum volume, grade of right ventricular hypertrophy, and Paco_2 , was also unhelpful. The responders did not demonstrate greater reversibility to isoprenaline during the placebo period than the non-responders and neither did oral or inhaled steroid produce an increase in reversibility. The effect of steroids, oral or aerosol, on sputum volume was variable. There was no correlation between changes in $\text{FEV}_{1.0}$ and sputum volume, and in one patient a large daily sputum volume did not prevent a good response to inhaled steroids.

Discussion

Five of 36 patients who had apparently irreversible airways obstruction had a clear measured improvement in ventilatory capacity after treatment with corticosteroids while one other patient had a smaller increase. Three had blood eosinophilia while variability in ventilatory capacity, as judged by a large standard error of the mean of AFM or $\text{FEV}_{1.0}$ readings during the placebo period, was a feature of the five clear responders. This raises the question whether these patients really had asthma.

Similarly, other studies have shown that steroid-responders frequently have features suggestive of asthma. Freedman (1963) studied 26 patients with chronic airways obstruction and found that the six who showed an appreciable response to steroids had personal or family histories of allergy. Beerel *et al.* (1963) found that two of their 10 patients with 'stable pulmonary emphysema' responded to steroids—both had asthmatic symptoms starting before the age of 20 and personal histories of allergy. More recently, Brewis *et al.* (1974) and Matlin (1976) have found response to steroids to be associated with blood eosinophilia. However, Clifton and Stuart-Harris (1962) found a 'striking' improvement in forced expiratory tests after one week on steroids in seven of their 28 patients, and, of these, only two were thought to have 'asthmatic bronchitis'; the remaining five were indistinguishable clinically from those with typical chronic bronchitis who did not respond to steroids. Oppenheimer *et al.* (1968) used criteria similar to ours for selection of patients and concluded that none of their 26 patients had a good response to steroids, although in fact four patients had a greater than 20% improvement in $\text{FEV}_{1.0}$ on prednisone. It is impossible to tell from their data whether these four were included in those who had positive skin tests or blood or sputum eosinophilia. Of the remaining trials—including that of Cullen and Reidt (1960), who deliberately selected patients with 'bronchospasm' and included five

patients with a possible diagnosis of allergic asthma—none has demonstrated objective evidence of improvement with steroids.

It is thus still not clear which patients with chronic bronchitis will respond to steroids, although it appears that the presence of features usually associated with asthma indicate a possible response. The report of the Working Group on the Definition of Asthma (1971) concluded that asthma could not be defined separately from chronic obstructive bronchitis and recommended that authors provide as much detailed information as possible about their patients. We would agree with this report since we were not able usefully to separate 'responders' from 'non-responders'.

Therefore the concept still stands that every patient with 'irreversible' airways obstruction, whatever features present on assessment, deserves a trial of steroids. A suggested protocol for such a trial is as follows: Firstly, there should be objective assessment of ventilatory capacity, preferably by several measurements rather than a single one at the end of the treatment period. Secondly, there should be a placebo period either before or after the active treatment. Thirdly, the treatment period should last at least 10 days. Fourthly, the dose should be adequate. A steroid aerosol can be substituted for prednisolone where systemic steroids are contraindicated, but, in general, especially for outpatients, oral steroids will be found to give a more definitive response. A steroid aerosol could then be substituted if there is a response and careful supervision of the technique of aerosol administration carried out.

We should like to thank Dr. R. P. K. Coe, consultant physician, West Middlesex Hospital, Dr. D. K. Suri, clinical assistant at Enfield District Hospital, and Dr. R. V. Mummery, Department of Bacteriology, Enfield District Hospital, for their help in this study. Glaxo Laboratories Limited, Greenford, Middlesex, supplied the drugs for this study and also financial assistance.

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