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
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[Text continues with a discussion of the comparison study, including the methods, results, and conclusions regarding the effectiveness of oral and inhaled steroids in patients with chronic airways obstruction.]
the largest variation in $\text{FEV}_{1.0}$, three were steroid responders (Fig. 2). Patient 6 could not be distinguished from the group as a whole. Correlation between the measured variation in $\text{AFM}$ or $\text{FEV}_{1.0}$ and the subjective impression of variability of symptoms was poor (Fig. 2).

Analysis of the answers to the questionnaire\(^1\) 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 \textit{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,

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\(^1\)Full details of patients and results available from S. M. Harding
sputum volume, grade of right ventricular hypertrophy, and PacO₂, 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 FEV₁₀ 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 FEV₁₀ 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 FEV₁₀ 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.

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