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

S. M. HARDING AND S. FREEDMAN

From the West Middlesex Hospital, Isleworth, Middlesex and Enfield District Hospital, Enfield, Middlesex

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; Beereel et al., 1963; Freedman, 1963), some, subjective improvement only (Cullen and Reidt, 1960; Beereel 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
A comparison of oral and inhaled steroids in patients with chronic airways obstruction

expiratory volume in one second (FEV\textsubscript{1.0}) less than 70% predicted normal (Cotes, 1975) and/or FEV\textsubscript{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 \( \mu \)g per puff) and placebo tablets, and treatment 3 comprised placebo aerosol and predni-
sone 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\textsubscript{1.0} and peak expira-
tory 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 \( \mu \)g/day). After a further 7–10 days, the aerosol was dis-
continued, and the patients were given prednisol-
one, 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 assess-
ment on the last three mornings of the week. Two patients did not complete the third phase, predni-
solone 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 question-
naire 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\textsubscript{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 \( \geq 3 \) 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 in-
patients included response to isoprenaline (800 \( \mu \)g from a pressurised aerosol), grading of right ventric-
ular hypertrophy from ECG (Goodwin and Abdin, 1959), and, in most cases, measurement of arterial \( \text{PCO}_2 \) (\( \text{Paco}_2 \)) 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 measures-
ments of FEV\textsubscript{1.0}, FVC, and PEFR before and after the inhalation of 800 \( \mu \)g isoprenaline. In addi-
tion, daily sputum volume was measured. In four patients sputum collections were unsatis-
factory in the third week of the trial.

Results
Five patients differed from the rest by virtue of an unequivocal increase in FEV\textsubscript{1.0} or AFM readings on steroids. In addition, a sixth patient had a small but statistically significant improvement in FEV\textsubscript{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\textsubscript{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 eosino-
philia compared with three of 30 non-responders (\( \chi^2 \) 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 ventila-
tory capacity, as assessed by AFM readings or FEV\textsubscript{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
the largest variation in FEV₁₀, 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 FEV₁₀ and the subjective impression of variability of symptoms was poor (Fig. 2).

Analysis of the answers to the questionnaire

1 Full details of patients and results available from S. M. Harding 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,
sputum volume, grade of right ventricular hyper-
trophy, and PaCO₂, was also unhelpful. The re-
sponders 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 vol-
ume was variable. There was no correlation be-
tween 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 improve-
ment 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 indistinguish-
able clinically from those with typical chronic 
bronchitis who did not respond to steroids. Oppen-
heimer 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 pred-
sisone. It is impossible to tell from their data 
whether these four were included in those who 
had positive skin tests or blood or sputum eosino-
ophilia. 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 evi-
dence of improvement with steroids.

It is thus still not clear which patients with 
chronic bronchitis will respond to steroids, al-
though 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 ob-
jective assessment of ventilatory capacity, prefer-
ably 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, con-
sultant 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.

References

Beerel, F., Jick, H., and Tyler, J. M. (1963). A con-
trolled study of the effect of prednisone on air-flow 
obstruction in severe pulmonary emphysema. New 

treatment of stable pulmonary emphysema. Ameri-
can Review of Respiratory Disease, 104, 264–266.

Brewis, R. A. L., Lye, M. D. W., Dodds, W. R., and 
treatment with corticosteroids and cromoglycate in 
patients with chronic airways obstruction. Thorax, 
29, 610.
Medical Research Council (1965). Definition and classification of chronic bronchitis for clinical and epidemiological purposes. Lancet, 1, 775–779.
Medical Research Council (1966). Committee on Research into Chronic Bronchitis. Questionnaire on Respiratory Symptoms.

Requests for reprints to: Dr. S. M. Harding, Clinical Division, Glaxo Research Limited, Greenford, Middlesex UB6 0HE.
A comparison of oral and inhaled steroids in patients with chronic airways obstruction: features determining response.

S M Harding and S Freedman

Thoax 1978 33: 214-218
doi: 10.1136/thx.33.2.214