Evidence of prednisolone induced mood change ('steroid euphoria') in patients with chronic obstructive airways disease

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- 1 It is a clinical impression that some patients given oral corticosteroids develop a sense of wellbeing that is 'inappropriate' to improvements in physical health. This has been termed steroid 'euphoria', but unlike steroid-induced psychosis it has not been documented.
- 2 To test for the size and frequency of this phenomenon, 20 patients with severe chronic obstructive airways disease (mean FEV₁ 0.86 l) were given 30 mg of prednisolone for 14 days, after a period of placebo administration in a single-blind study.
- 3 Lung spirometry and arterial saturation during exercise were measured serially, together with established measures of mood state.
- 4 No changes in spirometry or arterial saturation during exercise were detected until 7 days of active therapy.
- 5 Mood state did not change during the placebo period, but small significant reductions in anxiety and depression were measured after 3 days of prednisolone and before any measurable improvement in lung function. Mood state did not then further improve, despite measurable improvements in lung spirometry.
- 6 This is evidence that prednisolone may produce a mild 'inappropriate' sense of wellbeing within a population receiving the drug, rather than as an occasional idiosyncratic response.

Keywords mood spirometry corticosteroids chronic airflow limitation euphoria

Introduction

Chronic obstructive airways disease is a major source of morbidity and physical disability. It is recommended clinical practice to give a therapeutic trial of oral corticosteroid to symptomatic patients who have not shown a good response to bronchodilators in the hope of improving airway function and producing a subsequent improvement in symptoms and disability (Editorial, 1981). Doses of prednisolone, in excess of 40 mg per day, are associated with major psychiatric disturbances, including euphoria, depression and psychosis (Ling *et al.*, 1981). Practising physicians also have anecdotal experience of mood changes in patients receiving lower doses of cortico-

steroids although the existence of this phenomenon has never been clearly established. Usually, but not invariably, this perceived change in mood is an improvement in sense of wellbeing. Within the context of chronic obstructive airways disease, this 'euphoria' may cause patients to report a symptomatic improvement in their disease state which cannot be explained by any measurable improvement in pulmonary function (Freedman, 1963).

In a study of patients with chronic obstructive airways disease receiving oral corticosteroids it was not possible to distinguish a euphoriant action of prednisolone from placebo effects (Mitchell *et*

al., 1984). To specifically test for the presence of any mild psychogenic effects of prednisolone, we have performed multiple sequential measurements of mood state and pulmonary function in a group of patients with chronic obstructive airways disease before and during treatment with placebo and active prednisolone.

Methods

Patients

Twenty patients (seven male) were studied. Their mean age was 64 (range 49–75) years. All suffered from severe chronic obstructive airways disease and were symptomatic, rating themselves as moderate to severely breathless on the Fletcher scale (Fletcher *et al.*, 1959).

Measurements

The forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) were measured using a dry spirometer. All measurements were made in triplicate after inhalation of salbutamol 200 µg. The highest value was used in the analysis.

Arterial saturation (S_aO₂) was measured during cycle-ergometer exercise using an ear oximeter (Hewlett Packard 47210a).

Mood state was assessed using three questionnaires completed by the patients. Four areas of emotion from the profile of mood state of McNair and Lorr were used (McNair & Lorr, 1964; McNair *et al.*, 1971). These were depression-dejection; tension-anxiety; fatigue-inertia; and vigour-activity. Depression and anxiety were further assessed using two additional scales, the Beck Depression Inventory (Beck *et al.*, 1961) and the Spielberger State Anxiety Index (Spielberger *et al.*, 1970). The same observer always presented the questionnaires in the same order and manner at a set place and time of day.

Protocol

Patients were admitted to hospital for 2 weeks during which they took their regular medication. At the end of the first week they received three daily treatments with placebo, following which they received active prednisolone for 14 days in a single morning dose of 30 mg day⁻¹. For the third week of the study the patients were seen as outpatients.

Measurements of FEV₁ and FVC were made for 3 consecutive days before the introduction of placebo. Measurements of FEV₁ and FVC, arterial saturation during exercise and mood

state scores obtained on the day before the administration of placebo were used as baseline measures. Subsequently, all measurements were repeated after 3 days of placebo and after 3, 7 and 14 days of active prednisolone. It should be noted that the measurements on day 3 of prednisolone were made around 50 h after the start of this therapy. All patients gave informed consent, but were not informed of the initial placebo period.

The results were analysed using appropriate analyses of variance and covariance (Glim 3.11, Royal Statistical Society, London).

Results

Baseline period

After salbutamol, FEV₁ was 0.86 ± 0.3 s.d. and FVC was 1.73 ± 0.5 l, showing the presence of severe airflow obstruction. There was no change over the last 3 days of the baseline period indicating that the patients were in a stable state. Arterial saturation at rest was $93 \pm 3\%$; the mean fall on exercise was $3 \pm 3\%$.

Baseline scores for mood state are shown in Table 1. The patients showed moderate levels of anxiety (Knight *et al.*, 1983) and the values for the Beck Depression Inventory fall within the range of borderline depression (Nielsen & Williams, 1980).

FVC, as a percentage of each patient's predicted normal, was negatively correlated ($P < 0.05$) with the Beck ($r = -0.438$) and McNair-Lorr ($r = -0.461$) measures of depression and the Spielberger anxiety score ($r = -0.433$). A negative correlation was also found between the FEV₁ (as percent predicted) and the McNair-Lorr depression score ($r = -0.480$; $P < 0.05$). The mood state scores also correlated significantly with each other ($P < 0.05$ or lower), with the exception that the index for vigour-activity failed to correlate significantly with any other measure of mood state.

Table 1 Baseline characteristics

	Mean	s.d.
FEV ₁ (l)	0.86	0.31
FVC (l)	1.73	0.51
Dyspnoea grade	3.6	0.8
Spielberger state anxiety	39.6	11.8
Spielberger trait anxiety	44.2	11.8
Beck depression	10.9	8.9
McNair-Lorr depression-dejection	12.5	5.7
McNair-Lorr tension-anxiety	7.7	3.1
McNair-Lorr vigour-activity	7.3	3.1
McNair-Lorr fatigue-inertia	8.6	2.9

Placebo period

Changes in all measured variables between the baseline and placebo periods were small (Figure 1 and Figure 2) and not statistically significant.

Figure 1 Change in FEV₁ (□) and FVC (■) compared with baseline, following administration of placebo and after 3, 7 and 14 days of prednisolone 30 mg day⁻¹. Error bars are standard errors. Significance of changes compared with baseline (paired *t*-test): * *P* < 0.05.

Prednisolone period

Changes in FEV₁ and FVC were small and did not improve significantly until after 7 days of active prednisolone (Figure 1). In two patients, S_aO₂ during exercise increased by 6.5 and 8% following prednisolone, but this did not occur until 7 or 14 days of therapy. In contrast, statistically significant changes occurred in nearly all measures of mood within three days of starting prednisolone. Figure 2 illustrates the changes in Beck depression score and Spielberger anxiety score with placebo and prednisolone. The fall in Beck score relative to baseline was significant after 3 days of prednisolone; between the placebo period and the third day of prednisolone, there were significant falls in both the Beck depression score (*P* < 0.05) and the Spielberger anxiety score (*P* < 0.01). There were also significant differences between the baseline and the third day of prednisolone in the McNair-Lorr scores for depression-dejection ($\Delta = -1.0 \pm 0.4$ (s.e. mean), *P* = 0.013 with paired testing), tension-anxiety ($\Delta = -0.9 \pm 0.3$, *P* = 0.02) and vigour-activity ($\Delta = 1.1 \pm 0.4$, *P* = 0.017). Beyond the third day of treatment, there was a little variability in these scores, but none of the changes reached statistical significance. In addition, there were no significant trends over time: between day 3 and day 14 of prednisolone therapy depression-dejection did not change, $\Delta = 0.0 \pm 0.09$

Figure 2 Changes in Beck depression score (□) and Spielberger state anxiety score (■) relative to baseline, following administration of placebo and after 3, 7 and 14 days of prednisolone 30 mg day⁻¹. Error bars are standard errors. Significance of changes compared with baseline (paired *t*-test): * *P* < 0.05; ** *P* < 0.01.

(s.e. mean) and the changes in tension-anxiety and vigour-activity were small; $\Delta = -0.1 \pm 0.4$ (s.e. mean) and 0.3 ± 0.5 respectively.

In response to prednisolone, significant correlations were found between changes in the Beck and McNair-Lorr depression indices ($r = 0.458$, $P < 0.05$) and between the Spielberger and McNair-Lorr anxiety scores ($r = 0.529$, $P < 0.02$). Changes in the McNair-Lorr index of fatigue were correlated with changes in both the Beck depression score ($r = 0.471$, $P < 0.05$) and the McNair-Lorr depression-dejection score ($r = 0.520$, $P < 0.02$). Changes in the fatigue index were negatively correlated with changes in vigour-activity score ($r = 0.524$, $P < 0.02$). No significant correlation was found between change in spirometry (FEV₁ and FVC) and change in any measure of mood.

Discussion

This study has shown that prednisolone may produce changes in mood state which precede any measurable improvement in lung function. The changes in mood state, which consisted of a reduction in depression, anxiety and fatigue and increase in vigour, were towards an improvement in sense of wellbeing or euphoria. As far as we are aware, this is the first demonstration that a population of patients receiving an oral corticosteroid may show a generalized improvement in mood state in the absence of improved physical health. The changes in mood were small and occurred on a background of anxiety and depression, which appeared to be related to the severity of the lung disease.

It is arguable that other changes in lung function may have occurred before spirometric improvement became apparent and these could have caused the early improvement in mood. We have previously reported two patients with chronic obstructive airways disease who demonstrated a clear improvement in arterial oxygen saturation during exercise following prednisolone, without any measurable change in spirometry (Swinburn *et al.*, 1986). In the current study, any improvements in arterial saturation clearly lagged behind the changes in mood. While it is still possible that there were other more subtle changes in lung function that caused the improvement in mood, such a hypothesis would need to explain why we observed no further improvement in mood state, despite subsequent measurable changes in lung function. This was not due to the total removal of anxiety and depression, since all the changes were small and all the patients had mood state scores that were well above zero while on prednisolone.

We recognized that a potential weakness of the study was the fact that the observer was not blind to the treatment. To prevent observer-induced bias, the questionnaires were presented to the patients in a highly standardized manner, with identical instructions being given on each occasion. The observer played no role in completing the forms and offered no guidance as to the most suitable reply. Furthermore, conversations between observer and patients concerning their health and the effectiveness of the medication were proscribed. No judgements were required of the observer in calculating the results. The questionnaires were therefore completed by the patients in a neutral and unbiased environment and although we cannot exclude subliminal observer-induced bias, the likelihood of this having occurred was very low. It is worth noting that we had not expected our findings.

The results appear to be at variance with those of Mitchell *et al.* (1984) who were unable to show any effect of prednisolone on mood state over and above a placebo effect. These workers observed a significant reduction in a number of aspects of mood state following both placebo and prednisolone and it is therefore possible that the small mood changes that we detected following prednisolone were masked by placebo effects in the earlier study. A 'Type 2' statistical error—failure to detect small differences because of measurement noise—may also have occurred in the study of Mitchell *et al.* (1984) because of their choice of mood state measure. These were single item visual analogue scores, and it is known that the repeatability of single items is often much less than the repeatability of the total score in a multiple-item questionnaire (Charlton *et al.*, 1983). In our study, the mood state measures were all of a comprehensive multiple item type and have been well validated. Finally, it is recognized that the mode and consistency of presentation have an important influence on the repeatability of the patients' responses to these types of measures. Different interviewers may achieve different results for example. We went to considerable lengths to ensure that, throughout the study, the questionnaires were presented to the patients in exactly the same manner and under identical conditions. This level of consistency was not possible in the study of Mitchell *et al.* (1984) (D. M. Mitchell, personal communication). We therefore conclude, that 'euphoriant' effects of prednisolone uncovered in our study were too small to be detected with the methods and design used by Mitchell *et al.* (1984).

Support for this conclusion comes from an earlier analysis of part of this data (Swinburn *et al.*, 1984), in which we did not detect the apparent

'euphoriant' effect. We suggest that the reason for this was that, like Mitchell *et al.* (1984), we concentrated on the changes in mood state spirometry and exercise performance at the end of the steroid treatment period, after there had been some improvement in airway function. In the presence of improved physical health it is difficult to separate any 'euphoriant' effects of the drug from wellbeing effects due to improved physical state. However, with our study design, we were able to detect short-term temporal differences in the responses to prednisolone and unmask the small degree of 'inappropriately' improved wellbeing. In this, we were probably aided by the generally poor spirometric response to prednisolone in our study population.

In conclusion, we have evidence to show that oral corticosteroids may produce a generalized

improvement in mood state in a population of patients receiving the drug. This confirms a long held, but previously undocumented clinical impression. We do not know whether this effect is related to the previously described idiosyncratic psychoses occasionally encountered with higher doses of steroids. The size of the mood change was small in our study population and may usually be insignificant or difficult to detect in the presence of other effects such as placebo responses and improved wellbeing due to improved disease state.

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