Papers

Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial

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Abstract

Objectives To determine the effect of long term inhaled corticosteroids on lung function, exacerbations, and health status in patients with moderate to severe chronic obstructive pulmonary disease.

Design Double blind, placebo controlled study.

Setting Eighteen UK hospitals.

Participants 751 men and women aged between 40 and 75 years with mean forced expiratory volume in one second (FEV_1) 50% of predicted normal.

Interventions Inhaled fluticasone propionate 500 µg twice daily from a metered dose inhaler or identical placebo.

Main outcome measures Efficacy measures: rate of decline in FEV_1 after the bronchodilator and in health status, frequency of exacerbations, respiratory withdrawals. Safety measures: morning serum cortisol concentration, incidence of adverse events.

Results There was no significant difference in the annual rate of decline in FEV_1 (P = 0.16). Mean FEV_1 after bronchodilator remained significantly higher throughout the study with fluticasone propionate compared with placebo (P < 0.001). Median exacerbation rate was reduced by 25% from 1.32 a year on placebo to 0.99 a year on with fluticasone propionate (P = 0.026). Health status deteriorated by 3.2 units a year on placebo and 2.0 units a year on fluticasone propionate (P = 0.0043). Withdrawals because of respiratory disease not related to malignancy were higher in the placebo group (25% v 19%, P = 0.034).

Conclusions Fluticasone propionate 500 µg twice daily did not affect the rate of decline in FEV_1 but did produce a small increase in FEV_1. Patients on fluticasone propionate had fewer exacerbations and a slower decline in health status. These improvements in clinical outcomes support the use of this treatment in patients with moderate to severe chronic obstructive pulmonary disease.

Introduction

Chronic obstructive pulmonary disease is a leading cause of morbidity and mortality worldwide,[1][2] and its prevalence is rising.[3] It occurs predominantly in tobacco smokers and is characterised by an increase in the annual rate of decline of forced expiratory volume in one second (FEV_1).[4] As lung function deteriorates, substantial changes in general health occur.[5] Smoking cessation reduces the rate of decline in FEV_1 in people with this disease,[6] but no pharmacological intervention has been shown to modify the progression of disease or the associated decline in health status.

In at least 10% of patients with stable chronic obstructive pulmonary disease FEV_1 will increase significantly after oral prednisolone.[7] A large, retrospective, open study reported a reduction in the rate of decline of FEV_1 in those taking oral corticosteroids.[8] Recently, two studies over three years of inhaled budesonide 800 µg in mild to moderate chronic obstructive pulmonary disease found no effect of treatment on the rate of decline in FEV_1.[9][10] Clinical outcomes such as exacerbations, however, were infrequent and health status either showed no benefit of budesonide[9] or was not assessed.[10]

The inhaled steroids in obstructive lung disease in Europe (ISOLDE) study was designed to test the effect of inhaled fluticasone propionate 500 µg twice daily on the rate of decline of FEV_1 and other relevant clinical outcomes.

Participants and methods

Participants

Eighteen UK hospitals participated. Patients were current or former smokers aged 40-75 years with non-asthmatic chronic obstructive pulmonary disease. Baseline FEV_1 after bronchodilator was at least 0.8 litres but less than 85% of predicted normal, and the ratio of FEV_1 to forced vital capacity was less than 70%. Previous use of inhaled and oral corticosteroids was permitted. Patients were excluded if their FEV_1 response to 400 µg salbutamol exceeded 10% of predicted normal, they had a life expectancy of less than five years from concurrent diseases, or they used β blockers. Nasal and ophthalmic corticosteroids, theophyllines, and all other bronchodilators were allowed during the study.

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The protocol was approved by each centre's local ethical committee and patients provided written informed consent.

Trial design

Patients were recruited between 1 October 1992 and 31 March 1995. Eligible patients entered an eight week run-in period after withdrawal from any oral or inhaled corticosteroids. After clinic visits at 0, 4, and 8 weeks (visits 0, 1, and 2, respectively) patients were randomised to receive either fluticasone propionate 500 µg or an identical placebo twice daily administered from a metered dose inhaler and with a spacer device by using 10 tidal breaths after each of two actuations. We used a computer generated allocation schedule stratified by centre (block size of six). Patients were randomised sequentially from a list comprising treatment numbers only. Throughout the trial patients used salbutamol (100 µg/puff) or ipratropium bromide (40 µg/puff), or both, for symptomatic relief.

Before the double blind phase, and if not contraindicated, patients received oral prednisolone 0.6 mg/kg/day for 14 days, after which spirometry was performed. These data were used to test whether the acute corticosteroid response could predict those patients who would benefit from long term inhaled corticosteroids. During the three year double blind phase, participants visited a clinic every three months for spirometry, recording of exacerbations, and safety assessments.

The primary end point was the decline (ml/year) in FEV_1 after bronchodilator. About 450 patients with two or more measurements of FEV_1 during treatment were required to detect a treatment difference of 20 ml/year, assuming a linear decline and a SD of 75 ml/year, with 80% power. Other key end points were frequency of exacerbation, changes in health status, withdrawals because of respiratory disease, morning serum cortisol concentrations, and adverse events.

Measurements

Spirometry measurements were recorded by well trained staff using a standardised procedure on new Sensormedics 2130D spirometers. Quality control included a computer generated check against the ATS criteria[11] and a central manual check for acceptability and reproducibility for all measurements, resulting in standards comparable with the lung health study.[12] Visits were rescheduled to four weeks after any respiratory infections or exacerbations of the disease.

An exacerbation was defined as worsening of respiratory symptoms that required treatment with oral
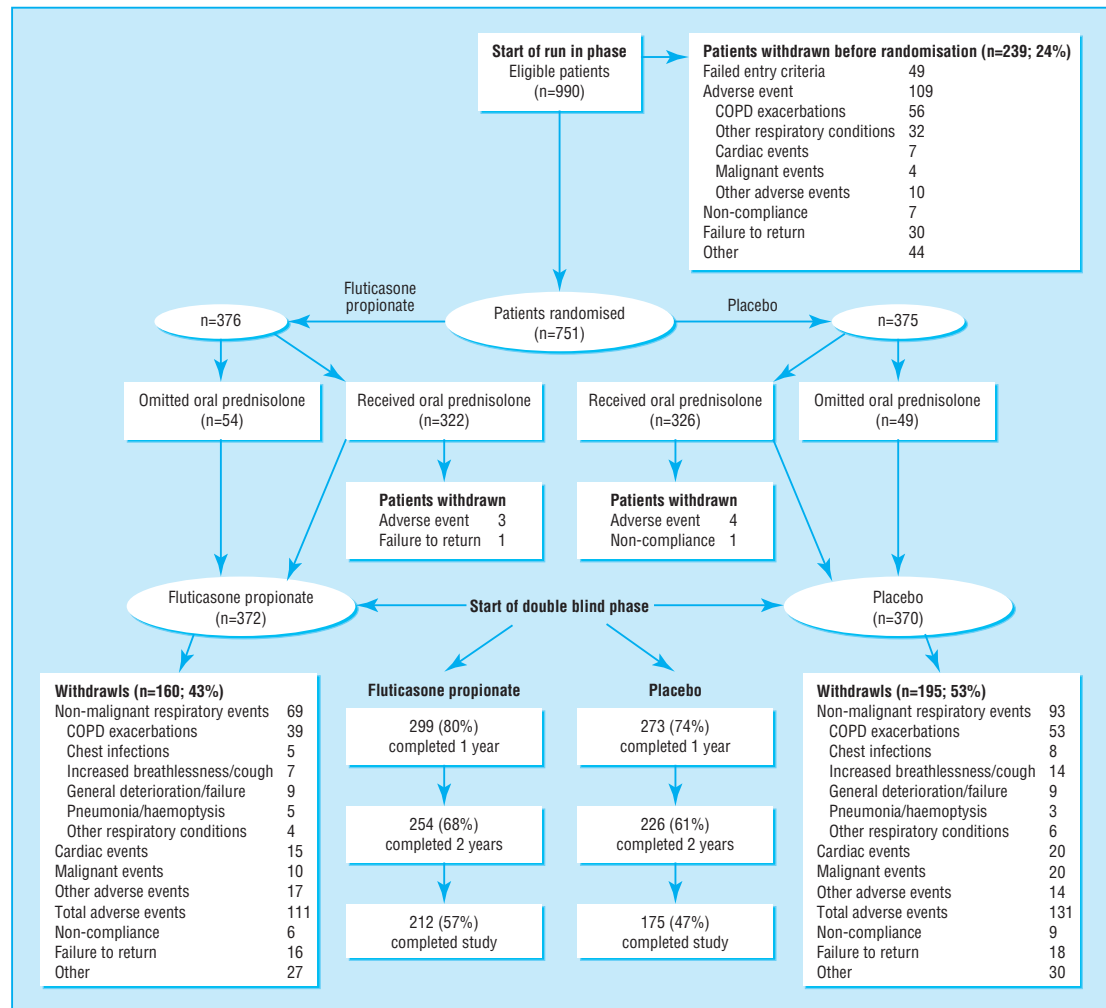

Fig 1 Profile of number of patients at each phase of study

corticosteroids or antibiotics, or both, as judged by the general practitioner; specific symptom criteria were not used. Patients were withdrawn from the study if the number of exacerbations that required corticosteroids exceeded two in any three month period.

Health status was assessed at baseline and six monthly thereafter by using the disease specific St George's respiratory questionnaire (SGRQ).[13] This questionnaire is sensitive to changes in treatment.[14] A change in total score of four or more units represents a clinically important change in the patient's condition.[5] Serum cortisol concentrations were measured before randomisation (baseline) and every six months during treatment. Samples were taken between 8 am and 10 am and were analysed with the ELISA-Boehringer Mannheim ES700 method.

At each visit patients were questioned about smoking status. Non-smoking was checked with exhaled carbon monoxide and urinary cotinine measurements. Self declared non-smokers were classified as smokers if cotinine was >40 ng/ml or carbon monoxide was >10 ppm at two visits. For analysis patients were categorised as continuous smokers, continuous former smokers, or intermittent smokers during the study.

Statistical analysis

Analyses for each parameter included all randomised patients with at least one valid measurement. To use all patient data we adopted the mixed models approach[15] for the primary analysis of FEV_1 and total score. This is the most suitable technique for estimating rates of change, with allowance for the correlation structure of repeated measures data. Regression estimates were adjusted for patient differences in the number of observations contributing to the model and for variances within patients.[16] Fixed effects were time and five covariates: baseline value centre, age, sex, and smoking status. Baseline FEV_1 was the mean at four and eight weeks of the run-in period—that is, at least four weeks after withdrawal of corticosteroids. Subject effects were assumed to be random. The treatment by time interaction tested for a differential treatment effect on the rate of change in FEV_1 or respiratory questionnaire score. The model for FEV_1 also included a treatment main effect to help to account for the early non-linear treatment changes. Measurements at the end of the prednisolone trial were excluded from the model of decline in FEV_1. FEV_1 was also compared by using analysis of covariance after 3, 6, 12, 24, and 36 months to investigate treatment differences over time.

Patient exacerbation rates were calculated as the exacerbation number per treatment days and extrapolated-interpolated to a number per treatment year. The Wilcoxon rank sum test,[17] stratified by centre, tested for treatment differences.

Fisher's exact test compared treatment withdrawals due to respiratory causes. These included any non-malignant lower respiratory diseases. Analysis of covariance compared data on log transformed serum cortisol concentration during treatment, adjusted for baseline. Tests were two sided, with a 5% significance level.

Results

Patient demographics

Of the 751 patients randomised, 376 received fluticasone propionate and 375 placebo (figure 1). During the double blind phase, 160 patients (43%) withdrew from the fluticasone propionate group and 195 patients (53%) from the placebo group, the commonest reason being frequent exacerbations of chronic obstructive pulmonary disease. Mean FEV_1 at visit two was 160 ml lower in patients who withdrew from placebo compared with those who did not withdraw (1.30 litre v 1.46 litre); patients who withdrew from fluticasone propionate had a 40 ml higher FEV_1 compared with those who did not withdraw (1.44 litre v 1.40 litre). Treatment groups were well matched at baseline (table 1).

Changes in FEV_1

There was a fall in mean FEV_1 after bronchodilator during the the run-in (placebo 75 ml, fluticasone propionate 65 ml) (fig 2). The effect was greater in patients who withdrew from inhaled corticosteroids at run-in (89 ml compared with 47 ml in the steroid naive group). After oral prednisolone there was a 60 ml (SD 170 ml) improvement in mean FEV_1 after bronchodilator in both treatment groups. Subsequently mean FEV_1 declined gradually in the fluticasone propionate group whereas in the placebo group it fell within three months to values before prednisolone treatment.

The annual rate of decline in FEV_1 was 59 ml/year in the placebo group and 50 ml/year in the fluticasone propionate group (P = 0.16) (table 2). This small difference in slopes was uninfluenced by smoking status, age, sex, or FEV_1 response to the oral corticosteroid trial. The predicted mean FEV_1 at three and 36 months in

Table 1 Baseline characteristics of randomised population. Figures are means (SD) unless stated otherwise

	Placebo	Fluticasone propionate
No of patients randomised	375	376
Age (years)	63.8 (7.1)	63.7 (7.1)
Women	97	94
Body mass index (kg/m²)	24.9 (4.7)	24.5 (4.8)
Evidence of atopy*	91	103
Smoked throughout trial	147	137
Former smoker throughout trial	172	176
Smoking pack years at randomisation†	44 (34)	44 (30)
Previous use of regular inhaled corticosteroids	214	192
Lung function at visit 0‡:		
After salbutamol (400 µg) FEV_1	1.40 (0.48)	1.42 (0.47)
As % predicted normal	50.0% (14.9%)	50.3% (14.9%)
Change in FEV_1 after salbutamol (400 µg)	0.13 (0.10)	0.13 (0.10)
As % predicted normal	4.4% (3.4%)	4.4% (3.5%)
After salbutamol (400 µg) FVC	3.29 (0.80)	3.37 (0.82)
After salbutamol (400 µg) FEV_1:FVC	43.0% (11.0%)	43.0% (12.0%)
Baseline (average of visit 1 and 2)§:		
FEV_1 before bronchodilator	1.23 (0.47)	1.25 (0.44)
FEV_1 after bronchodilator (salbutamol 400 µg and ipratropium bromide 80 µg)	1.40 (0.49)	1.42 (0.47)
Respiratory questionnaire total score¶	49.9 (17.4)	47.7 (17.6)

FEV_1=forced expiratory volume in one second in litres; FVC=forced vital capacity.
*Atopy was defined as being positive response to skin prick testing with common inhalant allergens. Missing data—placebo: 14; fluticasone propionate: 20.
†Missing data—placebo: 37; fluticasone propionate: 16.
‡Missing data—placebo: 4; fluticasone propionate: 3.
§Missing data—placebo: 1; fluticasone propionate: 0.
¶Score of zero indicates no health impairment and 100 represents worst possible score. Missing data—placebo: 8; fluticasone propionate: 7.
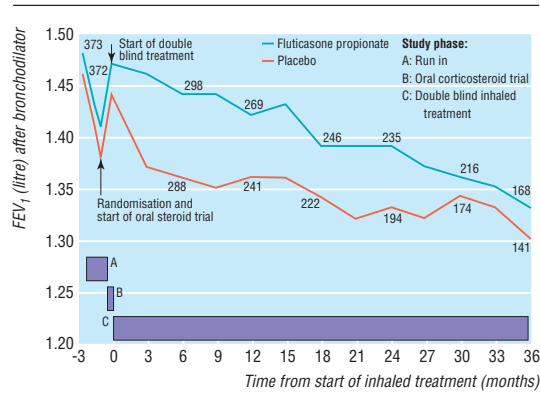
Fig 2 Mean FEV₁ (litres) after bronchodilator by time from start of double blind treatment. Numbers reflect patients with valid readings at each time point. Measurements within four weeks of exacerbation are excluded. Direct comparisons of FEV₁ means at each time point are not possible because fewer patients remained in the study as it progressed

the fluticasone propionate group was 76 ml and 100 ml higher, respectively, than in the placebo group (mixed effects model P < 0.001). The analysis of covariance showed that FEV₁ in the fluticasone propionate group was higher than in the placebo group by at least 70 ml at each time point (P ≤ 0.001). There was no significant relation between FEV₁ response to oral corticosteroid or fluticasone propionate (P = 0.056).

Exacerbations

The median yearly exacerbation rate was lower in the fluticasone propionate group (0.99 per year) compared with the placebo group (1.32 per year), a reduction of 25% in those receiving fluticasone propionate (P = 0.026).

Health status

At baseline the total respiratory questionnaire score was not significantly different between treatment groups (table 1), and it did not change significantly over the first six months of treatment (placebo: up 1.2 (SD 11.9); fluticasone propionate: down 0.5 (SD11.8); P = 0.09). Thereafter it increased (that is, health status declined) over time (figs 3 and 4). This increase was

linear (P < 0.0001). The respiratory questionnaire score worsened at a faster rate (P = 0.004) with placebo (3.2 units/year) than with fluticasone propionate (2.0 units/year).

Withdrawals

More patients in the placebo group than in the fluticasone propionate group withdrew because of respiratory disease that was not associated with malignancy (25% v 19%, respectively; P = 0.034).

Safety

Reported events were similar between treatments (table 3), except for a slightly higher incidence of events related to inhaled glucocorticoid in the fluticasone propionate group.

There was a significant (P ≤ 0.032) yet small decrease in mean cortisol concentrations with fluticasone propionate compared with placebo (table 4). No more than 5% of patients on fluticasone propionate had values below the normal range during the study at any time. No decreases were associated with any signs or symptoms of hypoadrenalism or other clinical effects.
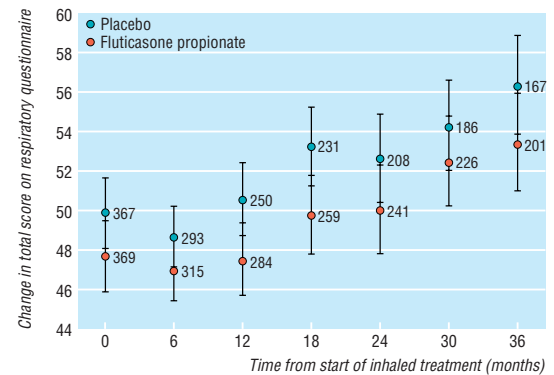

Fig 3 Effect of treatment on decline in health indicated by increasing total scores on respiratory questionnaire (means (95% confidence intervals) calculated from analyses of covariance). Numbers at each assessment indicate number of patients for whom measurements of health status were available at that visit. Direct comparisons of respiratory questionnaire scores at each time point are not possible because fewer patients remained in the study as it progressed

Table 2 Results from efficacy analyses. Mixed effects model analyses adjusted for covariates and Wilcoxon Mann-Whitney test adjusted for centre

Efficacy parameter	Placebo	Fluticasone propionate	Treatment difference between drug and placebo (95% CI)	P value
FEV₁ after bronchodilator:				
No of patients	325*	339*		
Mean change in FEV₁ ml/year (SE)	−59 (4.4)	−50 (4.1)	9 (6.0) (−3 to 20)	0.161
Predicted FEV₁ at 3 months	1.37	1.44	0.076 (0.056 to 0.097)	<0.001
Predicted FEV₁ at 3 years	1.20	1.30	0.100 (0.064 to 0.135)	<0.001
Health status:				
No of patients	291*	309*		
Mean change in questionnaire score (SE) (units/year)	3.17 (0.31)	2.00 (0.29)	−1.17 (0.40) (−1.95 to −0.39)	0.004
Annual exacerbation rate:				
No of patients	370	372		
Mean (SD) rates	1.90 (2.63)	1.43 (1.93)		
Median (range) rates	1.32 (0 to 30)	0.99 (0 to 26)	−0.3 (−0.4 to 0.0)†	0.026

FEV₁=forced expiratory volume in one second in litres.
*Numbers are smaller than randomised population for FEV₁ and health status because of patient withdrawals, missing assessments, or respiratory infections or exacerbations (affects FEV₁ only).
†Zero values are possible in 95% confidence intervals with non-parametric analyses that show P values ≤0.05 because method of calculation of confidence intervals differs from non-parametric test.
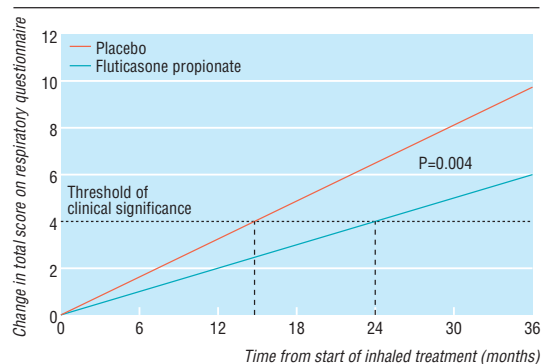
Fig 4 Weighted regressions from random coefficients (mixed) model (see text) to account for the effect of differences in the number of observations between patients, with adjustment for baseline covariates (baseline questionnaire score, age at entry, sex, centre, and smoking during the study)

Table 3 Number of patients with each category of adverse events during double blind period

	Placebo (n=370)	Fluticasone propionate (n=372)
Serious adverse events:		
Any event	148	141
Lower respiratory	101	87
Cardiovascular	44	40
Gastrointestinal	13	19
Deaths:		
Total	36	32
Non-malignant respiratory	6	9
Cardiovascular	12	10
Cancers	14	8
Other	4	5
Inhaled glucocorticoid-related events:		
Hoarseness/dysphonia	16	35
Throat irritation	27	43
Candidiasis of mouth/throat	24	41
Events possibly attributed to systemic absorption:		
Bruising*	15	27
Fractures	17	9
Cataracts	7	5

*Includes ecchymotic rash (1 placebo patient, 8 fluticasone propionate patients).

Discussion

Inhaled corticosteroids have been used widely in the United Kingdom for the empirical treatment of symptomatic chronic obstructive pulmonary disease, but evidence to support this practice is limited. Unlike early reports,[18][19] our study in moderate to severe chronic obstructive pulmonary disease found no effect of corticosteroids on the rate of decline in FEV_1—a finding consistent with two recent budesonide studies in mild disease.[9][10] Like Euroscop, a study in continued smokers,[10] we found a small improvement in FEV_1 after bronchodilator at three months, which was maintained throughout the study. The clinical significance of this change in airway function is unclear. Our study also showed no significant relation between corticosteroid trial response and response to long term inhaled corticosteroid.

The exacerbation rate for placebo was similar to that seen in previous reports,[20] but for fluticasone propionate it was 25% lower. Precise definition of an exacerbation is difficult in ambulant patients with chronic obstructive pulmonary disease, but, by using the operational approach adopted in ISOLDE, reductions in exacerbation severity were seen in another study of patients with moderately severe disease treated for six months with fluticasone propionate.[21] During the ISOLDE run-in we also observed that withdrawal of inhaled corticosteroids was associated with an increased likelihood of an exacerbation.[22] These observations suggest that inhaled corticosteroids do modify the risk of symptomatic deterioration in chronic obstructive pulmonary disease.

Assessment of of health status is recognised as an important additional measurement in patients with chronic respiratory disease and is a better predictor of admission to hospital and death within 12 months than FEV_1.[23] The baseline respiratory questionnaire score showed significant impairment, in keeping with other populations with similar reductions in FEV_1.[13][14] This study shows for the first time that, like FEV_1, health status declines at a measurable rate in patients with moderate to severe chronic obstructive pulmonary disease. Fluticasone propionate significantly reduced this rate of decline, delaying the average time for a clinically important reduction in health status from 15 to 24 months. As the respiratory questionnaire has only a weak correlation with FEV_1,[5] it must be reflecting other disease components other than airflow limitation.

Limitations

Several factors, including disease severity, comorbidity, and study duration, contributed to the high withdrawal rate. Patients were also actively withdrawn from the study and not subsequently followed up if they experi-

Table 4 Morning serum cortisol concentration (nmol/l) for patients who provided valid data (8 am to 10 am samples only) during double blind period

	Placebo (n=370)			Fluticasone propionate (n=372)		
Time point	Patients with valid samples	Geometric mean* serum cortisol (CV†)	No (%) of patients with values below normal range (150-700 nmol/l)	Patients with valid samples	Geometric mean * serum cortisol (CV†)	No (%) of patients with values below normal range (150-700 nmol/l)
Baseline	265	344 (33)	5 (2)	265	353 (31)	4 (2)
6 months	260	345 (33)	3 (1)	272	311 (42)	2 (1)
12 months	209	352 (34)	3 (1)	238	316 (45)	13 (5)
24 months	136	345 (34)	1 (1)	160	303 (44)	5 (3)
36 months	93	354 (33)	1 (1)	96	310 (35)	4 (4)
>1 point during double blind treatment	299	—	4 (1)	331	—	17 (5)

*Least squares means from analysis of covariance of log transformed serum cortisol concentrations were back transformed to give geometric means.
†CV=coefficient of variation (%).

What is already known on this topic

Inhaled corticosteroids are widely prescribed for patients with chronic obstructive pulmonary disease, although there are few studies to support this

A meta-analysis of three small studies showed improvements in FEV_1 with high dose beclomethasone dipropionate or budesonide but no benefit from medium dose treatment

In two recent large studies, budesonide in medium dose produced either no benefit or a small initial improvement in FEV_1

What this study adds

This study measured progressive decline in health status of patients with chronic obstructive pulmonary disease rather than just the FEV_1

In patients with moderate to severe disease, fluticasone propionate 1 mg daily resulted in fewer exacerbations, a reduced rate of decline in health status, and higher FEV_1 values than placebo treatment

Serious side effects were similar to placebo, topical side effects were increased

These data provide a rationale for the use of high dose inhaled corticosteroids in patients with moderate to severe chronic obstructive pulmonary disease

enced frequent exacerbations; this is an acknowledged limitation of the study. The effect of the differential rate of withdrawal from treatment is difficult to quantify, nevertheless it is likely to have led to a conservative estimate of benefit with fluticasone propionate.

Reports of adverse events for each treatment were generally similar, although the incidence of events related to glucocorticoids was slightly higher in the fluticasone propionate group. The incidence of fractures was low (2%) and similar to that reported in Euroscop.[10] No more than 5% of patients on fluticasone propionate had cortisol concentrations below the normal range at any time during treatment. Similar reassuring data have been reported from a two year placebo controlled study of fluticasone propionate 500 µg twice daily in adults with mild asthma.[24]

Conclusions

We found no benefit of fluticasone propionate on the rate of decline in FEV_1, although small improvements in FEV_1 were seen. Unlike the two studies in patients with milder disease, where other clinical outcomes were less measurable,[9] [10] we found that fluticasone propionate 500 µg twice daily significantly reduced exacerbations and the rate of decline in health status. These data provide a rationale for the current practice of using use of inhaled corticosteroids at this dose in patients with moderate to severe chronic obstructive pulmonary disease.

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Comparing health inequality in men and women: prospective study of mortality 1986-96

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Abstract

Objectives To study prospectively the differences in health inequality in men and women from 1986-96 using the Office for National Statistics' longitudinal study and new socioeconomic classification. To assess the relative importance of social class (based on employment characteristics) and social position according to the general social advantage of the household to mortality risk in men and women.

Design Prospective study.

Setting England and Wales.

Subjects Men and women of working age at the time of the 1981 census, with a recorded occupation.

Main outcome measures Mortality.

Results In men, social class based on employment relations, measured according to the Office for National Statistics' socioeconomic classification, was the most important influence on mortality. In women, social class based on individual employment relations and conditions showed only a weak gradient. Large differences in risk of mortality in women were found, however, when social position was measured according to the general social advantage in the household.

Conclusions Comparisons of the extent of health inequality in men and women are affected by the measures of social inequality used. For women, even those in paid work, classifications based on characteristics of the employment situation may give a considerable underestimate. The Office for National Statistics' new measure of socioeconomic position is useful for assessing health inequality in men, but in women a more important predictor of mortality is inequality in general social advantage of the household.

Introduction

Social variation in morbidity and mortality in women whose social position is measured according to their own occupation is often found to be less than that of men.[1–4] The extent of social inequality in women's health is known to be particularly sensitive to the way in which inequality is defined and measured.[1 5 6] When women's social position is classified according to the occupation of their male partners, male and female health gradients are more similar.[7 8] In estimates of health inequality there is comparatively little discussion of these apparent sex differences.

It is now possible to study sex differences in health inequality with distinct validated measures of social position and advantage, one based on relations and conditions of employment and the other on material cultural aspects of lifestyle outside the workplace. The Office for National Statistics (ONS) has recently adopted a new measure of social inequality: the ONS socioeconomic classification, for use in the 2001 census and official surveys.[9] This measure allocates occupations to social classes on the basis of aspects of the work situation, in particular the extent to which members of an occupation have control over their own work and that of others.

The other measure is the Cambridge scale, which is based on general social and material advantage and lifestyle as reflected in choices of friendship.[10–12] Both measures are being increasingly used in health studies and have been found to be related to mortality, morbidity, and health related behaviour.[13–18]

We aimed to determine whether social gradients in mortality in women in England and Wales during 1986-96 were less noticeable than in men, and whether this depended on the measure of social inequality used.

Subjects and methods

Sample

The ONS longitudinal study is an approximate 1% sample of the population of England and Wales. Sampling was begun at the time of the 1971 census when all those born on any one of four days in the year were entered into the dataset. The study is regularly updated to include new members born on any one of the four designated dates.[19] Vital events including mortality are

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Some occupations according to ONS classes and the Cambridge scale appear on the BMJ's website