The presence of emphysema does not affect the systemic bioactivity of inhaled fluticasone in severe chronic obstructive pulmonary disease

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Aims

To assess the systemic bioactivity of fluticasone propionate (FP) 2000 µg daily on sensitive adrenal and bone markers in severe chronic obstructive pulmonary disease (COPD) patients with or without significant emphysema.

Methods

Ten patients without emphysema (COPD group: age 55 years, FEV₁ 51% predicted and DL_{CO} 83% predicted) and 10 patients with emphysema (COPDE group: age 59 years, FEV₁ 43% predicted and DL_{CO} 49% predicted) received FP 2000 µg daily via a spacer for 2 weeks. There was a 1-week washout period prior to FP treatment where patients were given salmeterol and oxitropium, after stopping their usual inhaled corticosteroids for the duration of the study. Measurements including overnight 10 h urinary cortisol excretion corrected for creatinine (OUCC) and serum osteocalcin concentrations were performed at baseline following washout and after 2 weeks of FP.

Results

Values for OUCC and serum osteocalcin concentrations pre- and post-FP were not significantly different between the COPD and COPDE groups. There was significant suppression of OUCC (nmol mmol⁻¹) by FP treatment within the COPD group ($P = 0.03$): 7.86 vs 4.64 (95% CI on the difference 0.47, 5.98), and within the COPDE group ($P = 0.006$): 7.13 vs 4.27 (95% CI on the difference: 1.03, 4.69). Likewise, there was significant suppression of osteocalcin concentration (nmol l⁻¹) by FP treatment within the COPD group ($P = 0.04$): 7.24 vs 6.34 (95% CI on the difference: 0.01, 1.78), and within the COPDE group ($P = 0.03$): 6.92 vs 5.72 (95% CI on the difference: 0.12, 2.29).

Conclusions

Severe COPD patients who are receiving high dose FP are susceptible to the development of systemic adverse effects, irrespective of the presence of emphysema.

Introduction

The effects of fluticasone propionate (FP) in the treatment of patients with chronic obstructive pulmonary disease (COPD) are well recognized. FP 1000 µg daily

has been shown to be associated with a slow down in declining health status, along with a reduction in disease exacerbation, predominantly in patients with moderate to severe COPD [1, 2]. In addition, the discontinuation

of FP 1000 µg daily in COPD patients has been found to be related to a more rapid onset of disease exacerbation and a significant deterioration in quality of life [3]. However, the systemic bioactivity of FP in COPD is less well documented. FP 1000 µg daily is associated with a significant suppression of spot morning serum cortisol concentration and an increased incidence of skin bruising in patients with moderate to severe COPD over a 3-year follow up period [1], suggesting a propensity for FP to produce systemic adverse effects at high doses [4]. A recent study showed that FP 1000 µg daily taken for 7 days using a spacer inhaler caused less suppression of mean serum cortisol concentration over 12 h in severe COPD patients compared with healthy controls [5]. Furthermore, a study of patients with severe asthma also showed significantly lower systemic bioavailability of FP compared with healthy controls [6]. Thus the available data would indicate that the systemic effects of FP should be assessed in patients with airflow obstruction and not in healthy subjects.

It is unclear whether the presence of emphysema would decrease the alveolar absorption and systemic bioactivity of FP in severe COPD. Therefore we conducted a study in severe COPD patients with or without emphysema to evaluate further the effects of the maximum recommended dose of FP 2000 µg daily taken for 2 weeks, using a primed spacer inhaler for optimal lung delivery. We assessed the systemic bioactivity of FP, using the overnight 10 h urinary excretion of cortisol, corrected for creatinine (OUCC) and the serum osteocalcin concentration, sensitive markers of adrenal and bone function, respectively.

Methods

Patients

Eligible patients, who were all long-term smokers of at least 20 pack years, had stable severe COPD [7] without a significant component of emphysema (designated the COPD group) or with a significant component of emphysema (designated the COPDE group), and an FEV₁ reversibility of less than 15% following 200 µg of salbutamol. The presence of significant emphysema was confirmed by at least two clinicians who had previously seen the patients, and on the basis of an impaired carbon monoxide diffusing capacity (DL_{CO}) of less than 60% predicted, along with the presence of dependent airway closure on an expiratory flow volume loop, reduced breath sounds on auscultation, evidence of upper lobe hyperlucency and lower zone marker vessels on plain chest X-ray or alveolar destruction seen on high resolution computer tomography scan. None had received

a course of oral corticosteroids or antibiotics during the preceding 6 months. The maximum daily dose of inhaled corticosteroids (ICS) permitted was up to 2000 µg of beclomethasone dipropionate (BDP)/budesonide or 1000 µg of FP. All gave informed consent and the study was approved by the Tayside Committee on Medical Research Ethics.

Study design

The study was conducted in a parallel group open label fashion. Patients had their usual ICS stopped for a 1-week washout period, the longest considered to be safe given the severity of the disease in the patients, and for the duration of the study. This was thought to be long enough for the effects of FP to have dissipated [17]. During the washout period, patients were treated with salmeterol 50 µg (Serevent 50 Accuhaler®, Allen & Hanburys Ltd, Uxbridge, UK) two puffs twice daily and oxitropium 100 µg (Oxivent 100 Autohaler®, Boehringer Ingelheim Ltd, Bracknell, UK) two puffs twice daily, which was withheld for 48 h prior to their study visit. After washout, patients received FP 250 µg (Flixotide 250 Evohaler®, Allen & Hanburys Ltd, Uxbridge, UK) four puffs twice daily via a primed 750 ml Volumatic® plastic spacer (Allen & Hanburys Ltd, Uxbridge, UK) for 2 weeks. Patients had measurements at baseline after washout and at 12 h following the last dose of FP. All subjects were instructed on the correct use of the spacer and shown to inhale using single puffs without delay.

Measurements

Spirometry Spirometry was performed according to the American Thoracic Society criteria [8] using a Micro Medical SuperSpiro® (Micro Medical Ltd, Rochester, UK).

Gas transfer DL_{CO} was measured using a Vmax Series® analyser (SensorMedics BV, Bithoven, Netherlands).

Urinary cortisol Subjects attended the laboratory at 07.30 h and rested in a supine position for 30 min. Following this, subjects had blood samples taken for osteocalcin analysis at 08.00 h, and voided their bladder. Thus this urine sample was collected over a 10 h period (22.00 h–08.00 h), the subjects having last emptied their bladder at 22.00 h the previous night, and having had the last dose of FP at 20.00 h. After recording of the urinary volume, aliquots were retained for the assays of cortisol and creatinine. A commercial radioimmunoassay kit (DiaSorin Ltd, Workingham, UK) was used to measure urinary cortisol concentration, and the method

did not cross react with FP. The within assay and between assay coefficients of variation for the method were 7.7% and 7.3%, respectively.

Urinary creatinine A Cobas Bio® autoanalyser (Roche Products Ltd, Welwyn Garden City, UK) and kit (Sigma-Aldrich Co Ltd, Poole, UK) were used to measure the urinary creatinine concentration. The within assay and between assay coefficients of variation were 3.0% and 5.0%, respectively.

Serum osteocalcin Determination of 08.00 h serum osteocalcin concentrations was performed using a radio-immunoassay kit (DiaSorin Ltd, Workingham, UK). The within assay coefficient of variation of the method was 4.4%.

Statistical analysis

The study was powered at 80% in order to detect a 30% difference in OUCC (the primary outcome variable) between pre- and post-treatment, with α -error set at 0.05 (2-tailed). The standard deviation for OUCC from previous data [9] was $1.5 \text{ nmol mmol}^{-1}$. Analysis of variance (2-way) was used to compare the effects of pre- and post-treatment, in addition to comparing responses between COPD and COPDE groups. The Statgraphics® statistical software package (STSC Software Publishing Group, Rockville, USA) was used for the analyses.

Results

Twenty patients were enrolled and all completed the study protocol. There were 10 patients in the COPD group (nine male and one female, mean $\pm$ SEM age: 55 ± 4 years with smoking history of 34 ± 8 pack years), and 10 patients in the COPDE group (four male and six female, mean age: 59 ± 2 years with smoking history of 35 ± 6 pack years). Data for DL_{CO} and lung function are shown in Table 1. ICS treatment for the COPD vs the COPDE groups comprised of BDP: 680 ± 85 ($n = 5$) vs 1000 ± 237 ($n = 4$) μg daily and FP: 700 ± 87 ($n = 5$) vs 917 ± 65 ($n = 6$) μg daily. Some patients received addi-

tional therapy with salmeterol (COPD vs COPDE $n = 4$ vs $n = 6$), formoterol ($n = 1$ vs $n = 0$), theophylline ($n = 2$ vs $n = 1$), ipratropium ($n = 1$ vs $n = 2$) and oxitropium ($n = 0$ vs $n = 1$).

The OUCC data are shown in Figure 1. OUCC values (nmol mmol^{-1}) did not differ significantly between the COPD and COPDE groups during the pre-FP dose period ($P = 0.67$): 7.86 ± 1.03 vs 7.13 ± 1.34 (95% CI on the difference $-2.83, 4.30$), or during the post-FP period ($P = 0.78$): 4.64 ± 0.97 vs 4.27 ± 0.82 (95% CI on the difference $-2.30, 3.04$). There were significant differences in the suppression of OUCC between the pre- and post-FP periods within both the COPD group ($P = 0.03$): 7.86 ± 1.03 vs 4.64 ± 0.97 (95% CI on the difference $0.47, 5.98$), and the COPDE group ($P = 0.006$): 7.13 ± 1.34 vs 4.27 ± 0.82 (95% CI on the difference $1.03, 4.69$). There was no significant differ-

Figure 1

Individual data (mean $\pm$ SEM) for OUCC. The lines join values for each patient from the pre- and post-FP dosing periods

	COPD	COPDE	P	95% CI
DL_{CO} (% predicted)	83 ± 5	49 ± 3	0.0001	22, 45
FEV_1 (% predicted)	51 ± 3	43 ± 4	0.12	-2, 19
FEF_{25-75} (% predicted)	29 ± 2	22 ± 4	0.13	-2, 16
FVC (% predicted)	67 ± 4	65 ± 5	0.75	-11, 15
FEV_1 reversibility (%)	8.7 ± 1.6	8.6 ± 1.9	0.97	-5.1, 5.3

Table 1

Mean $\pm$ SEM DL_{CO} and lung function with P value and 95% CI on the difference between the COPD and COPDE groups

Figure 2

Individual data (mean $\pm$ SEM) for serum osteocalcin concentrations. The lines join values for each patient from the pre- and post-FP dosing periods

ence ($P = 0.81$) for pre- minus post-FP OUCC between the COPD and COPDE groups: 3.22 ± 1.22 vs 2.86 ± 0.81 (95% CI on the difference $-2.71, 3.44$).

Serum osteocalcin

The serum osteocalcin concentration data are shown in Figure 2. Serum osteocalcin concentrations (nmol l^{-1}) did not differ significantly between the COPD and COPDE groups during the pre-FP dose period ($P = 0.72$): 7.24 ± 0.35 vs 6.92 ± 0.76 (95% CI on the difference $-1.46, 2.08$) or during the post-FP period ($P = 0.54$): 6.34 ± 0.48 vs 5.72 ± 0.84 (95% CI on the difference $-1.42, 2.66$). There were significant differences in the suppression of serum osteocalcin between the pre- vs post-FP periods within both the COPD group ($P = 0.04$): 7.24 ± 0.35 vs 6.34 ± 0.48 (95% CI on the difference $0.01, 1.78$), and the COPDE group ($P = 0.03$): 6.92 ± 0.76 vs 5.72 ± 0.84 (95% CI on the difference $0.12, 2.29$). There was no significant difference ($P = 0.63$) for pre- minus post-FP serum osteocalcin concentrations between the COPD vs COPDE groups: 0.89 ± 0.39 vs 1.20 ± 0.48 (95% CI on the difference $-1.61, 0.99$).

FEV₁

FEV₁ (% predicted) was not significantly different between the pre-FP vs post-FP dosing period for either the COPD group ($P = 0.31$): 47 ± 4 vs 52 ± 3 (95% CI on the difference $-15, 5$) or the COPDE group

($P = 0.79$): 38 ± 3 vs 37 ± 3 (95% CI on the difference $-9, 11$).

Discussion

Our results showed that the degree of cortisol or osteocalcin suppression was similar when comparing severe COPD patients with or without a significant component of emphysema. This would suggest that emphysema *per se* does not confer any protection from the systemic adverse effects of FP. We tried as far as possible to match our patients for airway calibre. Thus there was no significant difference in FEV₁ % predicted between the groups, despite a significantly lower DL_{CO} in the patients with emphysema. However, it was evident that even in the group without a major component of emphysema, there was a slight reduction in DL_{CO}, indicating that there may have been a small element of alveolar destruction.

These findings were unexpected, as decreased lung absorption of FP in the COPDE group compared with the COPD group would be anticipated. This is because decreased DL_{CO} in the former group would be associated with a loss of available alveolar surface area. It is possible that absorption of FP from the lungs occurs more proximally in the bronchioles rather than in the alveoli or alveolar ducts. This hypothesis would be in keeping with the observation of decreased absorption of FP in asthmatic patients with impaired airway calibre but who have normal DL_{CO} [6, 10, 11]. As such, alveolar loss would result in very little influence on the overall lung absorption of FP. This might be expected as the mass median aerodynamic diameter of FP from a spacer would be approximately $2 \mu\text{m}$ [12], which is too large to reach the alveoli, the latter requiring particles of less than $1 \mu\text{m}$ in diameter. An alternative explanation may be that the total surface area of the alveoli is of such magnitude that even when half of them are lost, there is no significant influence on the lung absorption of FP.

We decided to measure the fractional moiety of OUCC because of its greater sensitivity to corticosteroids compared with an integrated blood or urine 24 h cortisol profile [13, 14]. To ensure that patients were receiving the optimal lung dose of FP, we primed each spacer device and educated each patient as to the proper use of the device, namely taking single puffs without delay [15]. Moreover, as the systemic effects of FP arise exclusively from lung absorption, doubling the respirable fraction by utilizing a spacer device with a pressurized metered dose inhaler would result in a doubling of the systemic bioavailability [16]. We used a higher dose of FP than during routine ICS therapy to ensure that a

detectable systemic signal in patients with severely impaired airway calibre was observed.

In conclusion, the systemic bioactivity of high dose inhaled FP does not appear to be influenced by alveolar absorption in patients with severe COPD who have emphysema. The clinical implication is that severe COPD patients who are receiving high dose FP are equally susceptible to its systemic adverse effects irrespective of whether emphysema is present.

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