A comparison of the systemic bioactivity of inhaled budesonide and fluticasone propionate in normal subjects

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1 The aim of this study was to compare the systemic bioactivity of low and high doses of inhaled budesonide and fluticasone propionate given by respective dry powder inhaler devices.

2 A randomised, single blind cross-over design was used in nine healthy subjects who were given 800 μg day⁻¹ of budesonide Turbohaler (B800) for 1 week, followed by 1 week of 1600 μg day⁻¹ (B1600), or fluticasone Diskhaler 750 μg day⁻¹ (F750) for 1 week followed by 1 week of 1500 μg day⁻¹ (F1500). There was a 1 week washout between treatments with fluticasone or budesonide. A twice daily dosing regime was used and mouth-rinsing was employed to reduce gut bioavailability as well as to obviate local adverse effects.

3 Parameters of hypothalamic-pituitary adrenal (HPA) axis activity and bone metabolism were measured at baseline (B₀/F₀), at the end of each week of treatment and after the 1 week washout (F₀ or B₀).

4 Both fluticasone and budesonide significantly (P < 0.05) attenuated the post tetra-cosactrin serum cortisol at low and high doses whilst early morning cortisol was unchanged. No dose-response effect was observed with either drug, and there was no significant difference between treatment with fluticasone or budesonide.

5 Neither budesonide nor fluticasone produced significant suppression of plasma osteocalcin, although the higher doses of both drugs significantly reduced fasting urinary calcium levels.

6 Thus, whilst fluticasone and budesonide exhibited equivalent systemic bioactivity, when appropriate corrections are made for differences in lung deposition between the Turbohaler and Diskhaler, the systemic glucocorticoid activity of fluticasone may be greater than that of budesonide on a microgram equivalent basis.

7 The finding of significant HPA-axis suppression with low doses of fluticasone and budesonide despite the use of mouth rinsing would suggest that absorption across the lung-vascular bed is the major determinant of systemic adverse effects.

Keywords budesonide fluticasone propionate corticosteroid systemic bioavailability asthma

Introduction

The use of high dose inhaled corticosteroids, is now well-established in the management of chronic asthma [1]. Their increasing use has lead to concern over the potential systemic adverse effects, and in this respect uncertainty remains regarding the extent and clinical relevance of these effects [2]. The risk-benefit ratio of inhaled corticosteroids is determined by their relative potencies for topical (airway) and systemic glucocorticoid activity. Using the Mackenzie skin vasoconstrictor assay it has been shown that budesonide and fluticasone propionate exhibit equivalent topical anti-inflammatory potency [3], both being

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approximately two-fold more potent than beclometasone dipropionate [4, 5]. There are however, doubts as to how this method relates to airway or systemic glucocorticoid activity. The systemic effects of inhaled steroids may arise from the absorption of the drug from the oropharynx, from the gut after swallowing, as well as from the lung vascular-bed. In terms of oral bioavailability budesonide and fluticasone undergo extensive first-pass hepatic metabolism after absorption from the gut. The oral systemic bioavailability of budesonide has been calculated as being 11% [6] and that for fluticasone as 1% [7]. In view of this extensive first-pass hepatic metabolism, absorption across the lung vascular-bed assumes relatively more importance in determining the propensity for systemic effects because there is no pulmonary first-pass metabolism of either budesonide or fluticasone. The latter will in turn be influenced by factors affecting lung deposition of the drug including the degree of peripheral airway narrowing and the type of delivery device. The relative importance of absorption from the lung can be increased further by reducing gastrointestinal absorption with mouth-rinsing after dosing [8].

We have therefore, for the first time compared the systemic bioactivity of low and high doses of budesonide and fluticasone, given by respective dry powder inhaler devices. Normal volunteers were used to avoid possible confounding effects of previous exposure to oral or inhaled corticosteroids, as well as to obviate the effects of abnormal airway geometry on peripheral lung deposition and hence systemic absorption with different inhaler delivery devices. It was also decided to employ mouth-rinsing in order to reduce oral bioavailability as far as possible, and also to minimise local adverse effects.

**Methods**

**Subjects**

Nine (four females) healthy, non-smoking subjects, mean (s.e. mean) age 21 (0.35) years, completed the study. None of the subjects was on regular medication and all had a normal physical examination, an FEV1 greater than 90% of predicted, and normal serum electrolytes, calcium, phosphate and alkaline phosphatase. The study was approved by the local Ethics Committee and subjects gave written informed consent.

**Protocol**

A single (investigator) blind, randomised, crossover design was used. After baseline measurements (B0 or F0) subjects received budesonide 800 μg day⁻¹ (B800) [Pulmicort Turbohaler, 400 μg per actuation, Astra Pharmaceuticals, Kings Langley, Herts] for 1 week increasing to 1600 μg day⁻¹ (B1600) for a further week; or fluticasone propionate 750 μg day⁻¹ (F750) [Flixotide Diskhaler, 250 μg per actuation, Allen and Hanburys, Uxbridge, Middlesex) increasing to 1500 μg day⁻¹ (F1500). The treatment order was budesonide given first in five subjects, with fluticasone being given first in four subjects. Subjects were given full instruction in the correct use of each device and both drugs were administered in twice daily divided doses. Mouth-rinsing was employed after each dose to minimise absorption from the oropharynx and gastrointestinal tract after swallowing, as well as to obviate local adverse effects. There was a 1 week washout period between active treatments with either fluticasone or budesonide. Measurements were made at entry into the study (B0 or F0), at the end of each week of treatment with budesonide (B800, B1600) or fluticasone (F750, F1500) and at the end of the 1 week washout (F0 or B0).

**Measurements**

Subjects attended the laboratory after an overnight fast. A cannula was inserted into an antecubital fossa vein to allow blood sampling, and subjects then rested supine for a period of 30 min. After the rest period blood samples were taken (between 08.00 h and 09.00 h) for measurement of plasma alkaline phosphatase, plasma osteocalcin, serum calcium, phosphate and early morning cortisol. Subjects then received 250 μg of tetracosactrin (Synacthen, Ciba Laboratories, Horsham, Sussex) given intravenously. Thirty minutes later a further blood sample was taken for measurement of serum cortisol after tetracosactrin stimulation. A fasting urine sample was also obtained on the study day for estimation of fasting calcium excretion.

At each visit subjects were examined for the presence of oral candidiasis and questioned regarding the occurrence of dysphonia or sore throat.

**Assays**

Serum cortisol was measured using a commercial radio-immunoassay (r.i.a.) kit (Incstar, Wokingham, Berkshire). The coefficients of variability (c.v.) for analytical imprecision within and between assays were 9.4% and 6.6% respectively. The normal reference range for morning cortisol is 193–690 nmol 1⁻¹. Plasma osteocalcin was assayed using r.i.a. (Incstar) with an intra-assay C.V. of 4.37%, and a normal reference range of 1.8–6.6 ng ml⁻¹. Plasma alkaline phosphatase, serum and urinary calcium and serum phosphate, were analysed using automated spectrophotometry (Cobas Bio, Hoffman La Roche, USA). The normal reference range for alkaline phosphatase is 98–279 iu l⁻¹, and the intra-assay and interassay C.V. were 0.3% and 2.84% respectively. Serum calcium had a reference range of 2.02–2.60 mmol l⁻¹ and intra-assay and interassay c.v. of 1.22% and 1.03% respectively. The reference range for serum phosphate is 0.87–1.45 mmol l⁻¹ with inter- and intra-assay c.v. of 0.9% and 2.4%. The assay for fasting urinary calcium had intra- and interassay C.V. of 1.20% and 1.22% respectively.
**Statistical analysis**

Data was analysed using a ‘Statgraphics’ software package (STSC Software Group, Rockville, Maryland, USA).

The power of the study was based on the ability to detect a mean difference of 60 nmol l⁻¹ in the serum cortisol post tetracosactrin with 80% power (i.e. β error of 0.20), with an alpha error of 0.05 (two-tailed). The primary comparison was between treatments: i.e. B₈₀₀ vs B₁₆₀₀ vs F₇₅₀ vs F₁₅₀₀. A secondary comparison was also made within each treatment (i.e. B₀ vs B₈₀₀ vs B₁₆₀₀ or F₀ vs F₇₅₀ vs F₁₅₀₀), and between the two baselines (B₀ and F₀). Comparisons were made by multifactorial analysis of variance (MANOVA) using subjects, treatments, doses, and periods as within factors. Where the overall MANOVA was significant, Duncan’s multiple-range testing with 95% confidence limits was used to define where these differences were significant. In such instances the 95% confidence interval for the difference between the means was also calculated. A probability level of \( P < 0.05 \) (two-tailed) was considered to be significant for all tests.

**Results**

Both drugs were well-tolerated with no clinical evidence of dysphonia or oral candidiasis during each 2 week study period, at either low or high dosage when used in conjunction with mouth-rinsing.

**Baseline values (Table 1)**

There were no significant differences between baseline values for parameters of hypothalamic-pituitary-adrenal (HPA) axis activity. Baseline values for plasma alkaline phosphatase and serum phosphate were significantly \( (P < 0.05) \) lower prior to treatment with budesonide compared with fluticasone with values being as follows (as means and 95% CI for the difference): 130.7 iu l⁻¹ vs 142.8 iu l⁻¹ (3.8–20.5 iu l⁻¹) for alkaline phosphatase, and 1.06 mmol l⁻¹ vs 1.20 mmol l⁻¹ (0.03–0.24 mmol l⁻¹) for phosphate. Other parameters of bone metabolism were not significantly different at the two baseline visits.

**HPA-axis function**

Neither fluticasone nor budesonide had any significant effect on morning serum cortisol compared with baseline (B₀, F₀), (Table 1), with no significant differences in levels between the two drugs (Figure 1a), whilst the lower doses of both drugs significantly \( (P < 0.05) \) attenuated the post-tetracosactrin cortisol level (Table 1). There was no significant difference between the low and high doses of each treatment or between the two drugs (Figure 1b).

**Bone metabolism**

There were no significant changes in plasma osteocalcin during low or high doses of either drug compared with baseline (Table 1) or when comparing between the two treatments (Table 1 and Figure 1c). Plasma alkaline phosphatase significantly \( (P < 0.05) \) increased during treatment with budesonide (B₈₀₀ and B₁₆₀₀) in comparison with B₀ (Table 1) whilst there was no change in alkaline phosphatase during low or high dose fluticasone treatment. When comparing between treatments, however, there were no significant differences between the two drugs (Figure 1d). Serum calcium was not significantly affected by either treatment (Table 1). Fasting urinary calcium excretion was significantly \( (P < 0.05) \) lower following B₁₆₀₀, F₇₅₀ and F₁₅₀₀ compared with B₀ and F₀ respectively (Table 1). There were no significant differences in fasting urinary calcium between the two treatments. Serum phosphate was increased significantly \( (P < 0.05) \) compared with baseline values dur-

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Biochemical parameters of HPA-axis activity and bone metabolism</th>
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<tr>
<td></td>
<td>B₀</td>
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<tr>
<td>AM cortisol (nmol l⁻¹)</td>
<td>393.5</td>
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<tr>
<td>Post-tetracosactrin cortisol (nmol l⁻¹)</td>
<td>691.0</td>
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<tr>
<td>Plasma osteocalcin (ng ml⁻¹)</td>
<td>4.33</td>
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<tr>
<td>Plasma alkaline phosphatase (iu l⁻¹)</td>
<td>130.7</td>
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<tr>
<td>Serum calcium (mmol l⁻¹)</td>
<td>2.15</td>
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<tr>
<td>Serum phosphate (mmol l⁻¹)</td>
<td>1.06</td>
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<tr>
<td>Fasting urinary calcium (mmol l⁻¹)</td>
<td>2.93</td>
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Values are given as means (and 95% CI for the difference from baseline). 
*indicates a statistically significant \( (P < 0.05) \) difference from baseline (B₀ or F₀) when comparing effects of budesonide 800 μg, 1600 μg day⁻¹ or fluticasone 750 μg day⁻¹, 1500 μg day⁻¹.
Discussion

The results of this study show that both fluticasone and budesonide were comparable in terms of their effects on HPA-axis activity with significant suppression of the tetracosactrin response occurring at low doses of either drug (i.e., F₇₅₀ and B₈₀₀). Furthermore, no dose-response effect was observed for either drug. Although the sample size was relatively small, the fact that a significant within-treatment effect on both post-tetracosactrin cortisol response and fasting urinary calcium was found, would perhaps suggest it is unlikely that clinically relevant differences between treatments were missed because of type 2 error.

With regard to parameters of bone metabolism, no significant differences were found between treatments and there was no evidence of significant suppression of biochemical parameters of bone formation as assessed by osteocalcin, and alkaline phosphatase. The rise in alkaline phosphatase during treatment with budesonide but not fluticasone was most likely to have been due to the lower B₀ compared with F₀. Indeed, values for B₈₀₀ and B₁₆₀₀ showed no significant change compared with the F₀ value for alkaline phosphatase.

A similar, but non-significant trend in alkaline phosphatase has, however been noted previously [9, 10] using similar doses of inhaled budesonide. It is important to appreciate that whilst the rise in alkaline phosphatase was statistically significant, the levels
remained within the normal range in all cases. Furthermore, if budesonide was suppressing bone formation, alkaline phosphatase, a marker of osteoblast function would be expected to fall as has been shown in subjects taking oral prednisolone [9]. It is possible that an increase in alkaline phosphatase could represent an effect of budesonide on the liver isoenzyme. Budesonide also produced a significant rise in serum phosphate, within the normal range, compared with the value at B0. Again B0 was significantly lower than F0 for this parameter, although a previous study reported by Toogood and co-workers show that budesonide produced a rise in serum phosphate by increasing the tubular resorption of phosphate [11]. The significant fall in fasting urinary calcium with high dose treatment is consistent with the findings of Toogood et al. where night-time hypocalcuria occurred along with an increase in the maximum tubular resorption of calcium [11].

The pattern of HPA axis suppression seen in this study, namely attenuation of the post tetracosactrin cortisol is in agreement with a previous study by Brown et al. [12] where the post tetracosactrin serum cortisol appeared to be more sensitive and specific than early morning cortisol in terms of detecting suppression, in asthmatic patients taking high dose inhaled steroids. In this respect Brown and co-workers found that 24 h urinary free cortisol and the short tetracosactrin test had equivalent sensitivity at detecting adrenal suppression [12]. We did not perform repeated hourly plasma cortisol sampling over the duration of each study day, because the response to tetracosactrin would have invalidated any subsequent cortisol measurements. We believe that the measurement of the tetracosactrin cortisol response more closely mimics the physiological stress response than the use of unstimulated plasma cortisol or urinary free cortisol. Furthermore, in our own experience, we have previously found the measurement of 24 h urinary free cortisol excretion to be less reliable than the short tetracosactrin response. Osteocalcin appears to be the most sensitive parameter of bone metabolism being significantly suppressed when alkaline phosphatase, urinary hydroxyproline and calcium excretion are unaltered [9, 13, 14]. Interestingly, we found that fasting urinary calcium, and not osteocalcin was significantly altered by high-dose inhaled steroid.

In this study, where gut absorption was minimised as far as possible by mouth rinsing, we were still able to show a significant attenuation of serum cortisol response to tetracosactrin thus emphasising the importance of absorption from the lung vascular-bed in determining systemic bioactivity. This is supported by the findings of two previous studies. Firstly, Selroos et al. showed that mouth rinsing reduced the systemic bioavailability of inhaled budesonide delivered by Turbhaler by approximately 15%, as assessed by suppression of early morning cortisol [8]. In a pharmacokinetic study with the budesonide Turbhaler, using the charcoal-block technique, it was shown that the oral bioavailability of inhaled budesonide was in the order of 20% [15]. The importance of lung bioavailability for fluticasone is also supported by data from Bain et al. [16], who using r.i.a. demonstrated significant circulating plasma levels of fluticasone following 1000 μg from a metered dose inhaler, with a profile consistent with lung rather than gut absorption.

Data from two different radiolabelled deposition studies have shown the Turbohaler to produce 27% lung deposition and the Diskhaler 12% deposition [17, 18]. Thus, when correcting for differences in lung deposition between the two devices, it would appear that fluticasone may exhibit greater systemic bioactivity that budesonide on a microgram equivalent basis. This hypothesis is supported by a single-dosing study of 250 μg, 500 μg and 1000 μg doses of fluticasone propionate Diskhaler compared with a single 800 μg dose of budesonide Turbohaler, both taken with mouth rinsing in normal volunteers [19]. Fluticasone propionate produced dose-related suppression of the area under the plasma cortisol versus time curve for 0 to 20 h (AUC0–20). The percentage suppression from placebo was 8% for fluticasone 250 μg, 18% for fluticasone 500 μg and 29% for fluticasone 1000 μg; in comparison with 16% for budesonide 800 μg. A further evaluation after seven doses of fluticasone 1000 μg twice daily resulted in a 66% suppression of cortisol AUC0–20. Clearly, studies comparing equivalent doses of the two drugs administered by the same device, such as a metered-dose inhaler or spacer, are therefore required in order to further investigate this issue.

Larger multicentre studies in asthmatics have compared high doses of fluticasone propionate and beclomethasone dipropionate given by metered-dose inhaler, and have yielded conflicting results regarding relative systemic bioactivity. No differences were found between fluticasone propionate and beclomethasone dipropionate both given at a dose of 1500 μg day⁻¹, in terms of morning plasma cortisol, tetracosactrin response and urinary free cortisol [20]. In contrast, Bakke et al. reported a fall in plasma cortisol from 360 nmol l⁻¹ to 226 nmol l⁻¹ and in ACTH from 34 ng l⁻¹ to 22 ng l⁻¹ with fluticasone propionate 2000 μg day⁻¹, whereas no suppression was detected with beclomethasone dipropionate 1600 μg day⁻¹ [21]. Barnes and colleagues showed a 1.3 fold greater dose-ratio for plasma cortisol suppression with beclomethasone dipropionate, despite a two-fold difference in dose between fluticasone propionate 1000 μg day⁻¹ and beclomethasone dipropionate 2000 μg day⁻¹ [22]. Thus, if as has been suggested, that fluticasone propionate has greater airway glucocorticoid potency then beclomethasone dipropionate or budesonide, it is perhaps not surprising to find that it also has greater systemic glucocorticoid potency, on a microgram equivalent basis.

Although this study, using normal subjects can be seen to represent an in vivo bioassay for the systemic effects of inhaled corticosteroids, it clearly has limitations which need to be addressed. The biochemical indices of bone turnover used are at best only surrogate parameters of bone turnover, and it is therefore necessary to design prospective studies in asthmatics, monitoring bone density itself. However, the difficulties of performing prospective studies in asthmatics in terms of confounding effects of exposure to pre-
vious inhaled and oral corticosteroids are well-recognised [2]. Furthermore, the altered geometry of asthmatic airways may affect the pulmonary deposition of drugs, an effect that may vary with the type of inhaler device used, in turn making extrapolation from studies in normal subjects difficult.

References

2 Lipworth BJ. Clinical pharmacology of inhaled corticosteroids in bronchial asthma. Pharmac Ther 1993; 58: 173–209.

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