SHORT PAPER

Plasma concentrations of fluticasone propionate and budesonide following inhalation from dry powder inhalers by healthy and asthmatic subjects

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Thorax 2003;**58**:258–260

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Revised version received 21 September 2002
Accepted for publication 26 October 2002

Background: All currently available inhaled corticosteroids reach the systemic circulation and have the potential to produce adverse effects with long term use. This risk is often assessed by measuring the effect of different inhaled corticosteroids on the hypothalamic-pituitary-adrenal (HPA) axis in healthy subjects. Absorption of fluticasone propionate and its effects on the HPA axis are greater in healthy subjects than in subjects with moderately severe asthma, but we have failed to show any difference in morning budesonide plasma levels or systemic effects between healthy and asthmatic subjects following inhalation of budesonide. To provide more information on the absorption of fluticasone propionate and budesonide, we have compared the plasma levels of both drugs over 8 hours in healthy and asthmatic subjects.

Methods: The area under the plasma concentration-time curves (AUC) and the maximum concentration (Cmax) of fluticasone propionate and budesonide after a single inhaled dose of each drug were compared in 12 healthy control subjects and 12 subjects with moderately severe asthma.

Results: Peak plasma levels of budesonide occurred much earlier and were approximately 20-fold higher than those of fluticasone propionate in both healthy and asthmatic subjects. The AUC and Cmax for fluticasone propionate were lower by 307 (95% CI 62 to 522) pg/ml/h or 43% (p=0.02) and 52 (95% CI −11 to 115) pg/ml or 39% (p=0.1) in subjects with asthma compared with healthy control subjects. In contrast, the AUC and Cmax for budesonide were almost identical between the two groups (mean differences 826 (95% CI −1493 to 3143) pg/ml/h (p=0.5) and 157 (95% CI −1026 to 1339) pg/ml (p=0.8).

Conclusions: Following inhalation, healthy subjects have higher plasma levels of fluticasone propionate than subjects with asthma whereas budesonide plasma levels are similar in the two groups of subjects. Comparing the systemic effects of budesonide and fluticasone propionate in healthy subjects is unlikely to be relevant to subjects with asthma.

The long term use of higher doses of inhaled corticosteroids has been associated with a number of adverse effects including a reduction in bone mineral density.[1] The propensity to cause adverse effects with long term use is likely to differ between inhaled corticosteroids since there are marked differences in their pharmacokinetic properties. In a recent study the bioavailability of fluticasone propionate was greater in healthy subjects than in subjects with asthma,[2] and we have shown that fluticasone propionate has a greater effect on the hypothalamic-pituitary-adrenal (HPA) axis in healthy subjects than in subjects with asthma. However, we found no difference in morning budesonide plasma levels or the systemic effects of budesonide between healthy and asthmatic subjects.[3]

Studies comparing the systemic activity of inhaled corticosteroids have been performed in healthy and asthmatic subjects. If the pharmacokinetics of some, but not all, inhaled steroids are influenced by the nature of the subjects being studied, results from studies in healthy subjects may not be relevant to subjects with asthma. To provide more detailed information about the absorption of fluticasone propionate and budesonide in healthy and asthmatic subjects, we have compared the plasma levels of the two drugs following inhalation of a single dose from their respective dry powder inhalers.

METHODS

Subjects

Twelve subjects with moderately severe asthma were matched by age and sex to 12 healthy control subjects. Subjects with asthma had to be taking a high dose of an inhaled corticosteroid (beclomethasone dipropionate or budesonide 1000–2000 µg/day or fluticasone propionate 500–1000 µg/day) and have a forced expiratory volume in 1 second (FEV_1) less than 75% predicted with an increase of more than 12% after 200 µg inhaled salbutamol. All subjects had to be non-smokers and have a past smoking history of less than 10 pack years. Subjects using oral or topical steroids were excluded. All subjects gave written informed consent to the study, which was approved by Nottingham City Hospital ethics committee.

Protocol

Subjects with asthma were changed to an equivalent dose of beclomethasone dipropionate 5 days before the first of the two study visits, which were at the same time of day and at least 3 days apart. At each visit a venous cannula was inserted and asthmatic subjects had their FEV_1 measured. Fluticasone propionate 1000 µg or budesonide 1200 µg were then inhaled via the Accuhaler (GlaxoWellcome, Uxbridge, UK) and the Turbuhaler (Astra-Zeneca, Lund, Sweden), respectively. Venous blood samples were taken over the next 8 hours, centrifuged at 1500 rpm for 10 minutes at 4°C, and plasma samples were frozen at −70°C. Corticosteroid drug assays were performed blind to the nature of the subjects by liquid chromatography tandem mass spectrometry at the Department of International Bioanalysis, GlaxoWellcome Research, Ware, UK. The lower limits of detection for the assays were between 10 and 30 pg/ml for fluticasone propionate and 50 and 100 pg/ml for budesonide.

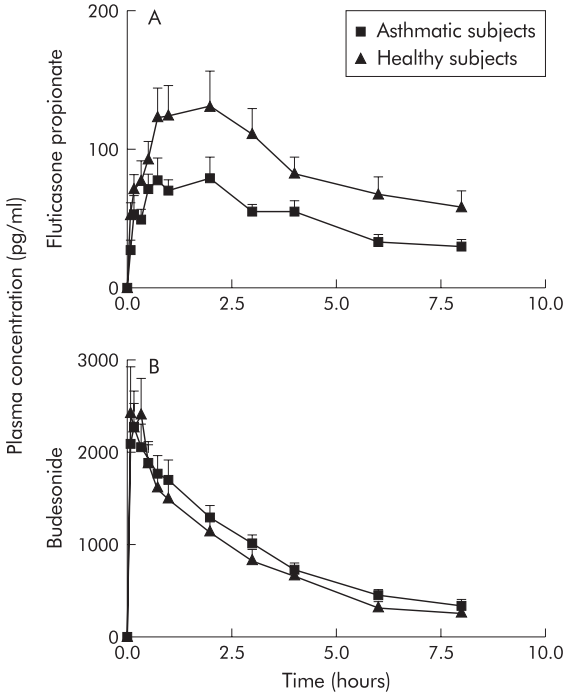

Figure 1 Mean (SE) plasma concentrations of (A) fluticasone propionate and (B) budesonide in healthy subjects and subjects with moderately severe asthma.

The study size was based on the primary outcome variable—the area under the plasma drug concentration curve. No data were available for budesonide but 12 subjects in each group provided 80% power to detect a difference between groups of approximately 1 SD or 800 pg/ml/h.[2]

Statistical analysis

Area under the curve was determined by the trapezoid method and data from healthy and asthmatic subjects were compared by the two tailed Student's *t* test, using GraphPad PRISM (Graphpad Software Inc, CA, USA).

RESULTS

All 24 asthmatic and healthy subjects (mean age 56 and 57 years, respectively; eight men in each group) completed the study. Mean FEV_1 in the subjects with asthma (1.5 l, 49% predicted) was similar on the two study days (mean difference 0.19 l, p=0.7). Data were excluded for one visit from two asthmatic subjects. One subject who usually takes fluticasone propionate had fluticasone propionate in his baseline plasma sample and one subject had no detectable budesonide in any sample. None of the steroid plasma values were below the lower limit of quantification of the assays but 16 of the 132 budesonide plasma values were above the limit of quantification of the assay (2000 pg/ml) but were included in the analysis.

Budesonide was absorbed much faster than fluticasone propionate with maximum plasma concentration (Cmax) occurring at 5–10 minutes and 1–2 hours, respectively (fig 1). The mean budesonide Cmax and area under the budesonide concentration-time curve were approximately 20 times higher than those for fluticasone propionate (table 1).

For fluticasone propionate Cmax and the AUC were lower by 39% and 43%, respectively, in subjects with asthma compared with healthy control subjects (fig 1, table 1). In contrast, following inhalation of budesonide Cmax and AUC were almost identical in healthy control and asthmatic subjects (fig 1, table 1).

DISCUSSION

This study has shown a number of interesting differences in the pharmacokinetics of budesonide and fluticasone propionate following the inhalation of single doses of drug from their respective dry powder inhalers: (1) plasma concentrations of fluticasone propionate peak later than those of budesonide; (2) plasma levels of fluticasone propionate are lower than those of budesonide; (3) healthy subjects have higher fluticasone propionate plasma levels than subjects with moderately severe asthma, whereas budesonide plasma levels are similar in healthy and asthmatic subjects.

The first two findings can be explained by differences in the lipophilicity of the two drugs. When compared with budesonide, fluticasone propionate is considerably more lipophilic leading to a much slower rate of dissolution in bronchial fluid and greater retention in pulmonary tissue.[4] As the systemic bioavailability of both drugs is largely due to drug absorbed from the pulmonary tract, these differences probably explain the difference in time taken to reach peak plasma concentration. Once absorbed, the lipophilic nature of fluticasone propionate probably explains why its plasma levels are some 20-fold lower than those of budesonide. However, in our previous study there was little difference in systemic activity when the same doses of fluticasone propionate and budesonide were compared,[3] which suggests that systemic activity is related to other variables such as drug potency and the concentration of drug at the steroid receptor rather than steroid plasma levels.

Higher plasma levels of fluticasone propionate in healthy subjects compared with subjects with asthma confirms the previous findings of Brutsche *et al*[2] and explains the greater systemic activity seen following inhalation of fluticasone propionate in healthy subjects than in subjects with asthma in our previous study.[3] Similar budesonide plasma levels in healthy and asthmatic subjects in this study is consistent with the lack of any difference in morning budesonide plasma levels in our last study, and explains why we found no difference in systemic activity following the inhalation of budesonide in healthy and asthmatic subjects.[3]

In both our studies we used dry powder inhalers to reduce variability in inhaler technique. Poor functioning of the Accuhaler compared with the Turbuhaler in patients with airflow obstruction and limited inspiratory flow is therefore a possible explanation for our findings. Against this, however, are data showing more variable performance with the Turbuhaler than

Table 1 Mean peak plasma concentration (Cmax) and area under the plasma concentration time curve (AUC) for fluticasone propionate and budesonide in healthy subjects and subjects with moderately severe asthma

	Fluticasone propionate			Budesonide		
	Healthy subjects	Asthmatic subjects	Difference (95% CI), p value	Healthy subjects	Asthmatic subjects	Difference (95% CI), p value
Cmax (pg/ml)	130	78	52 (–11 to 115), p=0.1	2432	2276	157 (–1026 to 1339), p=0.8
AUC (pg/ml/h)	712	404	307 (62 to 552), p=0.02	6467	7293	–826 (–3143 to 1493), p=0.5

the Accuhaler at low inspiratory flow,[5] and the almost identical results obtained by Brutsche *et al* following inhalation of fluticasone propionate from a metered dose inhaler.[2]

Differences in the pattern of distribution of inhaled drugs between subjects with and without asthma combined with differences in the rate of absorption of fluticasone propionate and budesonide may provide an alternative explanation for our findings. Radiolabelled studies have shown a more central deposition pattern following inhalation in subjects with airflow obstruction than in healthy subjects.[6] The reduced systemic absorption of fluticasone propionate in subjects with asthma compared with healthy subjects may therefore result from increased deposition of fluticasone propionate in the proximal airways leading to clearance of the drug by mucociliary mechanisms. Budesonide may not be affected in the same way either because airflow obstruction does not affect the peripheral to central deposition ratio when budesonide is delivered by Turbuhaler or because the rapid absorption of budesonide across the bronchial mucosa reduces the amount of drug cleared by mucociliary mechanisms.

Thus, we have shown that the relative systemic activity of single doses of fluticasone propionate and budesonide will vary depending on the nature of the subjects being studied. Our results explain why studies performed on healthy subjects have concluded that the systemic activity of fluticasone propionate exceeds that of budesonide[7 8] whereas studies performed on subjects with asthma have concluded that the systemic activity of fluticasone propionate is less than or equal to that of budesonide.[9 10]

Taken together, our two studies suggest that the relative systemic activity of fluticasone propionate and budesonide in healthy subjects is not relevant to subjects with asthma and that studies comparing the systemic activity of these two drugs should be performed in subjects with asthma.

ACKNOWLEDGEMENTS

We thank S Pacey (Senior Pharmacist) for supplying the inhalers and randomisation schedule and GlaxoWellcome for funding the study and performing the fluticasone propionate and budesonide assays.

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Supported by a grant from GlaxoWellcome, UK.

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