Early report

Comparison of pharmacokinetics and systemic effects of inhaled fluticasone propionate in patients with asthma and healthy volunteers: a randomised crossover study

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Summary

Background Inhaled corticosteroids are currently the cornerstone of asthma treatment. Some studies of high-dose fluticasone propionate in patients with no or mild asthma have, however, suggested substantial systemic absorption. We investigated the pharmacokinetics of fluticasone propionate in patients with asthma receiving appropriate doses for severity.

Methods We did a double-blind, randomised, crossover study in 11 patients with asthma and 13 matched healthy controls (age 20–65 years; asthma patients forced expiratory volume in 1 s <75% and stable on high-dose inhaled corticosteroids). Patients received one 1000 µg intravenous dose or 1000 µg daily for 7 days inhaled (via spacer device) fluticasone propionate. In the 12 h after dosing, we monitored plasma fluticasone propionate and cortisol concentrations by mass spectrometry and competitive immunoassay with use of direct chemiluminescence. Analysis was by intention to treat.

Findings After inhalation, geometric mean values were significantly lower in the asthma group than in controls (1082 [95% CI 850–1451] vs 2815 pg mL⁻¹ 1 h⁻¹ [2262–3949], −62% difference [45–72]; p<0.001), maximum concentrations (117 [91–159] vs 383 pg/mL [302–546], −68% [−50 to −81]; p<0.001), and systemic bioavailability (10·1 [7·9–14·0] vs 21·4% [15·4–32·2], −54% [−27 to −70]; p<0.001). Intravenous-dose clearance, volume of distribution at steady state, plasma half-life, and mean residence time, were similar in the two groups. Less suppression of plasma cortisol concentrations was seen in the asthma group than in controls 4–12 h after inhalation fluticasone propionate.

Interpretation Systemic availability of fluticasone propionate is substantially less in patients with moderate to severe asthma than in healthy controls. Inhaled corticosteroids that are absorbed through the lungs need to be assessed in asthma than in healthy controls. Inhaled corticosteroids that is substantially less in patients with moderate to severe asthma than in healthy controls. Inhaled corticosteroids, because of topical application, have a substantially better therapeutic index than oral steroids. Further improvements have been seen because of reduced oral bioavailability for newer inhaled corticosteroids. About 20% of the total inhaled dose from most metered-dose inhalers is deposited in the lungs and 80% stays in the oropharynx and is swallowed. Molecules with a high hepatic first-pass metabolism and low oral bioavailability, such as fluticasone propionate, therefore, have lower systemic exposure than other inhaled corticosteroids.

For fluticasone propionate, any systemic activity results from absorption of the drug deposited in the lungs and its oral bioavailability is negligible. Fluticasone propionate has a high therapeutic index and efficacy. The drug has been used successfully for several years for all severities of asthma and has proved to be well tolerated. No clinically important systemic effects are reported for the normal therapeutic dose range. By contrast, pharmacokinetic studies have suggested hypothalamic-pituitary-adrenal suppression with higher doses. However, those studies involved normal volunteers or patients who had mild asthma and were receiving inappropriately high doses, well in excess of those needed to control their disease. In patients with moderate or severe asthma requiring higher doses of inhaled corticosteroids, factors such as airflow obstruction and ventilation-perfusion mismatch could alter drug deposition in the lung and change systemic absorption.

To clarify the safety of higher doses of fluticasone propionate in asthma, we studied the pharmacokinetics and pharmacodynamics of the drug in patients with moderately severe asthma compared with normal controls in a randomised double-blind, double-dummy, crossover design (figure 1).

Methods

Study population

We recruited individuals from outpatient clinics at the North West Lung Centre, who had physician-diagnosed asthma, gave written informed consent, and were aged between 20 years and 65 years. The inclusion criteria included forced expiratory volume in 1 s (FEV₁) lower than 75% at screening, previous bronchodilator use, and a stable condition on high-dose inhaled corticosteroids (beclometasone dipropionate [BDP] 2000 µg/day or budesonide 1600 µg/day). For each patient, we selected
healthy volunteers (generally staff and relatives of staff at the North West Lung Centre), matched for sex, age, and body-mass index. All participants were non-smokers (>6 months). Exclusion criteria were: clinically important disease, systemic disease other than asthma, or both, pregnancy or lactation in women, suspected hypersensitivity to inhaled corticosteroids, treatment with oral or parenteral corticosteroids in the past 6 weeks, or inhaled fluticasone propionate in the past 2 months.

**Study design**

Participants were trained in an optimum inhalation technique before entering a 1-week run-in period. They were randomly assigned 1000 μg fluticasone propionate (500 μg twice daily), or a therapeutically equivalent dose of 2000 μg of BDP daily (1000 μg twice daily), inhaled at 0800 h and 2000 h from metered-dose inhalers with use of spacer devices (Volumatic, Glaxo Wellcome, UK; figure 1).

We assessed adherence by weighing the aerosol canisters before and after each treatment period. On the day before the pharmacokinetic sampling, participants were telephoned at 2000 h to remind them to take the last canisters before and after each treatment period. On the study day all participants attended the study-day visit at 0700 h after fasting overnight and abstaining from alcohol for 24 h. We measured baseline spirometry and blood pressure. FEV₁, FVC, and residual volume (% predicted) were measured with a VMAX22 spirometer (Sensor Medics BV), according to ATS methods of administration were identical for intravenous treatment and placebo or inhaled treatment and BDP. The infusion was administered over 10 min with the aid of a syringe driver. Inhalation treatment was taken in a sitting position. During the first hour after dosing, participants remained in bed. We took venous blood samples at baseline and 10 min, 20 min, 30 min, and 45 min, and at hours 1, 2, 3, 4, 6, 8, 10, and 12 after dosing to measure plasma concentrations of fluticasone propionate and cortisol. For the next week, participants crossed over to the other run-in treatment, after which they returned for a second pharmacokinetic-sampling day.

All static and dynamic pulmonary-function tests were measured with a VMAX22 spirometer (Sensor Medics BV, Bilthoven, Netherlands) and a body box (Autobox 6200 DL, Sensor Medics BV), according to ATS recommendations. Carbon-monoxide transfer factor was assessed with Transfer Test (Morgan Ltd, Chatham, Kent, UK).

In addition to establishing plasma cortisol profiles on sampling days, we measured plasma cortisol concentrations at 0800 h and 24 h urinary cortisol concentrations at the screening visit and on the two sampling days (ie, at a steady state for fluticasone propionate 500 μg and BDP 1000 μg).

All blood samples were drawn into heparinised tubes. They were immediately placed on ice and centrifuged within 30 min at 1500 rpm for 10 min at 4°C. Plasma and urine samples were immediately frozen at −70°C until assay. Masked analysis of plasma and urine samples was done at the Department of International Bioanalysis, Glaxo Wellcome Research and Development, Ware, UK. Fluticasone propionate was isolated from plasma by solid-phase extraction liquid chromatography—tandem mass spectrometry (LC-MS-MS) that uses thermally and spectrometry (LC-MS-MS) that uses thermally and
pneumatically assisted electrospray ionisation.19 The assay has a lower limit of detection of 20 pg/mL, with between-assay and within-assay coefficients of variance at less than 6%. Plasma and urinary cortisol concentrations were measured by a competitive immunoassay with use of direct chemiluminescence (Product 672303 and ACS:180SE, Chiron Diagnostics, Harefield, Middlesex, UK). For this assay, the lower limit of detection is 6 nmol/L and the coefficient of variance is less than 3%.

We did the study according to the 1995 Declaration of Helsinki, and the design was approved by the local ethics committee.

Statistical analysis
We calculated sample size based on the main outcome variable, the area under the curve for plasma fluticasone propionate concentrations. According to previous studies, we assumed a within-participant variability of 10%. To detect a significant difference of 15% with a statistical power of 90%, we would need to enrol ten participants in each group.

We analysed data by intention to treat. Pharmacokinetic data were analysed by a conventional non-compartmental approach with WinNonLin Pro software (version 1.5).20 Systemic availability was calculated, with reference to the nominal dose, as the area under the plasma concentration time curve after inhalation divided by the area under the curve after intravenous administration. Plasma clearance and apparent volume of distribution at steady-state were calculated by conventional equations. We analysed 24 h urinary cortisol concentrations as a cortisol-to-creatinine ratio and as total free cortisol excretion. Pharmacokinetic and cortisol data were log-normalised for group comparisons and are presented as geometric means with 95% CI. The lung-function variables followed a normal distribution and are presented as arithmetic mean (SD).

We compared the results for asthma and control groups by two-tailed Student’s t test. One-way and multiple ANOVA was applied to identify significant differences between the three different cortisol time points—screening, and sampling days 1 and 2—and the plasma cortisol profiles on the kinetic sampling days . Non-parametric data were compared by Mann-Whitney U and 2×2 χ² tests. We used bivariate correlations with Pearson’s correlation coefficient for the systemic availability and the area under the curve for fluticasone propionate after inhalation against FEV₁, carbon monoxide transfer, and body-mass index. We set significance at 0·05. Statistical analyses were performed with SPSS software (version 7.5).

Results
Of 18 patients with asthma and 16 healthy volunteers screened, 11 and 13, respectively, entered the study (figure 1). One patient with asthma did not fulfil the lung-function entry criteria on the first sampling day and did not continue. One control attended the sampling day for inhaled fluticasone propionate, but refused to attend for the intravenous study day. One patient had an extravasation at the intravenous site and the data were omitted from analysis. Ten patients with asthma and 11 controls completed the study, and had full data available for analysis. Baseline characteristics were similar in the two groups (table 1). All treatments were well tolerated and no serious adverse events occurred at any time during the study.

The pharmacokinetics of fluticasone propionate differed significantly between the asthma and control groups, seen in plasma area-under-curve values for inhaled fluticasone propionate (1082 [850–1451] vs 2815 pg mL⁻¹ h⁻¹ [2262–3949], mean difference 0·38 [95% CI 0·28–0·55]; p<0·001; figure 2), systemic availability (10·1 [7·9–14·0] vs 21·4% [15·4–32·2], 0·46 [0·30–0·73]; p=0·001), and maximum fluticasone propionate concentration (117 [91–159] vs 383 [302–546] pg/mL, 0·31 [0·19–0·50]; p<0·001).

All intravenous pharmacokinetic parameters were similar in the two groups (clearance, time at which maximum fluticasone propionate concentration was reached, area under curve, volume of distribution at steady state, fluticasone propionate plasma half-life, and mean residence time, table 2).

Table 2: Inhaled and intravenous pharmacokinetic parameters
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Long-term studies on potential systemic effects of inhaled corticosteroids have been generally reassuring.\textsuperscript{22} Short-term effects on bone metabolism, especially on osteocalcin concentrations, are seen with these drugs,\textsuperscript{23,24} but cross-sectional studies on bone density suggest no effect or only small changes. Such studies are, however, confounded by the use of rescue steroids.\textsuperscript{25} A longitudinal study on bone density in patients with moderate or severe asthma taking 1000 µg fluticasone propionate daily for 2 years showed no adverse effect, assessed by computed tomography, on trabecular bone density, which remained almost twice that of patients taking maintenance oral steroids.\textsuperscript{26}

All inhaled corticosteroids, if given in high enough doses, lead to hypothalamic-pituitary-adrenal suppression. No thresholds have yet been proposed to define high risk and low risk of excessive metabolic effects. We saw less hypothalamic-pituitary-adrenal suppression in the asthma group than in the control group, which parallels reduced systemic bioavailability. These findings underscore pharmacokinetic differences between patients with asthma and healthy controls, and the related impact on the hypothalamic-pituitary-adrenal axis. Baseline urinary cortisol excretion among controls was significantly higher than in the asthma group, which suggests some suppression of the hypothalamic-pituitary-adrenal axis after the high doses of fluticasone, budesonide, and beclomethasone administered in the run-in period.

Our results agree with other comparisons of the systemic effects of fluticasone propionate and other inhaled corticosteroids, which have been done at different doses in healthy individuals and patients with mild asthma. In a meta-analysis, the systemic effects of fluticasone propionate and budesonide were compared, and results differed between patients with asthma and healthy people.\textsuperscript{21} At roughly equal doses, in healthy volunteers, fluticasone propionate increases suppression of cortisol concentrations more than budesonide (budesonide/fluticasone propionate suppression ratio 3.3 for the residual cortisol concentration at the end of treatment). In patients with asthma, however, fluticasone propionate and budesonide have an equal effect on the hypothalamic-pituitary-adrenal axis (budesonide/fluticasone propionate suppression ratio 1.0) for equivalent doses.

The recent information on factors that influence the systemic bioavailability of inhaled corticosteroids, especially for drugs with minimum oral bioavailability, such as fluticasone propionate, in which drug delivery, and pulmonary deposition, have key roles. Almost all fluticasone propionate present in the systemic circulation has been absorbed in an unchanged active form via the lungs.\textsuperscript{20} Once present in the bloodstream, this drug remains potent, with a high binding affinity to the corticosteroid receptor. Until now, despite the characteristic differences in the airways in asthma, the assumption had been made that drug deposition, pulmonary drug absorption, and systemic effects measured in healthy individuals can predict the outcomes in people with asthma. Asthma is, however, characterised by reversible and non-homogeneous airflow obstruction, leading to ventilation-perfusion mismatch. Several studies, some by use of three-dimensional imaging techniques,\textsuperscript{20} have shown that the uniformity of deposition in the lungs is greater in healthy individuals than in patients with airway disease. It is suggested that the narrowing of airways in asthma results in less penetration of the drug particles and, consequently more central-airway deposition.\textsuperscript{20} Drug particles, which deposit on the airways, are more prone to clearance by mucociliary action than those that deposit in alveoli, which will be totally absorbed. Therefore, for a drug with a relatively slow dissolution rate in the lung, such as fluticasone propionate,\textsuperscript{20} there is more potential for drug depositing in the airways of patients to be removed from the lung by mucociliary clearance and swallowed, thereby not giving rise to a similar degree of systemic exposure to that seen in healthy volunteers. For other drugs, the magnitude of the effect might be less and deserves further investigation.

The positive correlation between the carbon monoxide transfer coefficient and the systemic bioavailability we saw suggests that ventilation-perfusion mismatch is important. This phenomenon was seen in the absence of pathologically low transfer factors in either group. Given the potential differences in the pattern of deposition, the role of carbon monoxide might be confounded by differences in mucociliary clearance between patients with asthma and normal individuals.

Relevant pharmacokinetic and pharmacodynamic data on inhaled corticosteroids with minimum oral bioavailability can be derived only when appropriate doses are given for severity of asthma. Studies are needed to define the factors that influence pulmonary absorption of inhaled corticosteroids in patients with lung disease. In severe asthma, even higher inhaled doses might be given safely, and with more safety than oral corticosteroids. Patients with asthma should be managed on the minimum dose of inhaled corticosteroids to control their disease and this should be regularly reviewed. Combination therapy, such as with a long-acting β-agonist, might be appropriate in some patients rather than increasing the dose of inhaled corticosteroids.

**Contributors**

Martin Brutsche was involved in study concept, design, execution, analysis, and in writing the paper. Ingrid Carlen Brutsche, Mohamed Munnaver, Stephen Langley, and Catherine Masterson were involved in study design and execution. Peter Daley-Yates and Ronan Brown were involved in study concept design and analysis. Adrian Custovic was involved in study design and analysis and writing the paper. Ashley Woodcock was the principal investigator and was involved in study concept and design, analysis, and writing of the paper.

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