Relative lung delivery of fluticasone propionate via large volume spacer or nebuliser in healthy volunteers

Abstract Objectives: High-dose nebulised fluticasone propionate (FP) has been advocated for use in patients with severe persistent asthma. As there is complete first-pass inactivation of FP for the swallowed fraction, systemic absorption is due solely to its lung bioavailability. We wished to compare the relative lung delivery of FP, using adrenal suppression as a surrogate for the respirable dose, when administered via large volume spacer (FP-spacer) or nebuliser (FP-neb) in healthy adults.

Methods: Fourteen healthy subjects, mean (SEM) age 29.4 ± 2.6 years, were studied in a placebo-controlled, randomised study with three-way crossover design. Single nominal 2-mg doses of the following were given at 1700 hours in randomised sequence:

a. FP-spacer: fluticasone pressurised metered dose inhaler (as Flixotide 250 µg ex-valve per actuation), eight puffs via a primed Volumatic 750-ml spacer
b. FP-neb: (as Flixotide Nebule 2 mg/2 ml) via Pari LC Plus nebuliser
c. Placebo nebuliser

Following each dose, measurements were made of corrected 0800-hours urinary cortisol/creatinine ratio (the primary outcome variable) and 0800-hours plasma cortisol.

Results: Significant (P < 0.05) suppression of both endpoints occurred only with FP-spacer, FP-neb being statistically no different from placebo. Geometric mean fold differences between FP-spacer and placebo were 9.8-fold [95% confidence interval (CI) 3.4, 28.8] for urinary cortisol/creatinine and 4.1-fold (95% CI 2.2, 7.5) for plasma cortisol. Comparing FP-spacer with FP-neb, these differences were 6.8-fold (95% CI 2.3, 20.0) for urinary cortisol/creatinine and 3.3-fold (95% CI 1.8, 6.0) for plasma cortisol.

Conclusion: For a 2-mg labelled nominal dose of fluticasone, the spacer produced about a sevenfold higher relative lung dose than the nebuliser. This suggests that a very little of the labelled nebulised dose is respirable. Other factors such as patient preference, cost and compliance will determine the inhaler device that is chosen.

Keywords Asthma · Cortisol · Corticosteroids

Introduction

All inhaled corticosteroids may be associated with dose-related systemic adverse effects, being absorbed into the systemic circulation via the gastrointestinal tract after swallowing (oral bioavailability) or via the lung (lung bioavailability). Fluticasone propionate (FP) exhibits negligible oral bioavailability since buccal absorption is insignificant, and any swallowed drug is subject to almost complete (99%) first-pass hepatic inactivation [1]. Inhaled FP, however, is well absorbed from the lung without first-pass inactivation, entering directly into the systemic circulation as the active unchanged moiety. Thus, the systemic effects of FP are due solely to absorption from its respirable dose and can be assessed by measuring sensitive and reproducible markers of adrenocortical activity including early morning urinary cortisol (corrected for urinary creatinine) and early morning plasma cortisol. The early morning sample coincides with the peak diurnal levels of cortisol secretion from the adrenal gland.

FP may be prescribed in nebulised form (Flixotide Nebules, Allen & Hanburys, Uxbridge, UK) for adults with severe persistent asthma, in a dose range of 0.5–2 mg twice daily. There is, however, only limited evidence supporting nebulised delivery of FP in this patient group [2]. Furthermore, no controlled studies...
exist comparing delivery of FP via spacer or nebuliser in patients with severe asthma. Increasing FP dose may paradoxically be associated with a less favourable therapeutic ratio, with increasing systemic effects despite no further significant improvement in clinical and inflammatory markers [3]. As high labelled doses of FP are administered via the nebulised route, it is therefore important to question what effect delivery via a nebuliser has on its lung deposition (and hence risk of systemic effect) compared with a spacer device.

**Methods**

**Subjects**

Fourteen healthy non-smoking volunteers (eight females) were recruited into the study, mean (±SEM) age 29.4 ± 2.6 years. Approval for the study was obtained from the Tayside Medical ethics committee, and all patients gave written informed consent.

**Study design**

The study had a placebo-controlled, randomised three-way crossover design. Subjects attended an initial screening, during which they were instructed in the correct use of:

a. A pressurised metered dose inhaler (pMDI) and primed 750-ml volume plastic spacer (Volumatic, Allen & Hanburys)
b. A breath-enhanced jet nebuliser with valve system and adult’s mouthpiece (Pari LC Plus, PARI Medical Limited., Surrey UK)

Optimal technique was also reinforced at three subsequent laboratory visits, each separated by at least a 1-week washout period. All treatments were administered under supervision at the same time of day (1700 hours), without mouth rinsing or gargling. All subjects took all treatment protocols (a–c) in randomly selected order:

a. FP-pMDI (as Flixotide, Allen & Hanburys, 250 μg ex-valve per actuation), eight consecutive puffs (total dose ex-valve 2 mg, total dose ex-actuator 1.76 mg), administered using the spacer
b. FP (as Flixotide Nebule, 2 mg/2 ml, Allen & Hanburys), total labelled dose 2 mg, via the nebuliser
c. Placebo nebuliser

Primed spacer and pMDI were used under optimal conditions, with five deep breaths per actuation, repeated consecutively for a total of eight actuations. Each nebuliser was driven by compressed air (BOC Medical Gases, Surrey, UK) at a flow rate of 6 l/min, with a total “fill” volume of 4 ml fluid, and subjects wore nose clips. Subjects receiving FP received a dose of 2 mg (as Flixotide Nebule, 2 mg/2 ml) diluted with 2 ml sodium chloride injection BP (Baxter Healthcare Ltd., Norfolk, UK). Patients receiving nebulised placebo received 4 ml sodium chloride injection BP. Each subject used the same spacer and nebuliser throughout the study, all nebulisers previously having been calibrated to ensure similar output.

**Measurements**

After completion of the inhalation sequence, the subjects went home and were instructed to void their first waking urine sample the following morning and encouraged to drink fluids thereafter. Returning to the laboratory that morning, at 0730 hours, they were asked to lie supine for 30 min before an 0800-hours plasma cortisol sample was taken. Following this, subjects voided a second sample of urine, just after 0800 hours, which was retained for analysis. The volume of this sample was recorded, and aliquots were taken for urinary cortisol and creatinine concentration. All assays were performed in duplicate in a blinded fashion by a separate technician as previously described [4].

**Data analysis**

The study was powered with a sample size of 14 with at least 80% power to detect a 20% difference in 0800-hours urinary cortisol/creatinine excretion, the primary outcome variable. All data were logarithmically transformed to normalise their distribution. Comparisons were made using an analysis of variance with subject, treatment and period as factors. This was followed by Bonferroni multiple-range testing set at 95% confidence interval in order to obviate multiple pair-wise comparisons. Hence all comparisons are reported as being significant ($P < 0.05$, two-tailed) or not.

**Results**

Compared with placebo, significant ($P < 0.05$) suppression of 0800-hours urinary cortisol (both corrected/uncorrected for urinary creatinine) and 0800-hours plasma cortisol occurred when fluticasone propionate was administered using the spacer but not the nebuliser (Table 1 and Fig. 1). For the primary endpoint of 0800-hours corrected urinary cortisol/creatinine, there was about a sevenfold difference between the two devices. Results for 0800-hours corrected urinary cortisol/creatinine were also analysed with respect to gender (Table 2, Fig. 2). Similar results were seen between sexes, administration of FP via spacer being significantly ($P < 0.05$) different to administration via nebuliser and placebo.

Individual data for plasma cortisol levels are shown (Fig. 3) to illustrate dispersion and outliers. The number of abnormal low values for plasma cortisol below 150 nmol/l was 9 subjects of 14 for FP-spacer and 0 of 28 for either placebo or FP-neb treatment ($P < 0.001$, Chi squared test).

**Discussion**

We have demonstrated that relative lung delivery from a single 2-mg labelled dose of FP is significantly greater

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**Table 1** Geometric mean fold differences [95% confidence interval (CI) for fold difference] between treatments are shown below. *FP* fluticasone propionate, *PL* placebo, *neb* nebuliser

<table>
<thead>
<tr>
<th></th>
<th>FP-spacer vs PL</th>
<th>FP-spacer vs FP-neb</th>
<th>FP-neb vs PL</th>
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<tbody>
<tr>
<td>0800-hours Urinary cortisol (nmol/l)</td>
<td>7.7 (2.9, 20.5)*</td>
<td>7.4 (2.8, 19.5)*</td>
<td>1.1 (0.4, 2.8)</td>
</tr>
<tr>
<td>0800-hours Urinary cortisol/creatinine (nmol/mmol)</td>
<td>9.8 (3.4, 28.8)*</td>
<td>6.8 (2.3, 20.0)*</td>
<td>1.4 (0.5, 4.2)</td>
</tr>
<tr>
<td>0800-hours Plasma cortisol (nmol/l)</td>
<td>4.1 (2.2, 7.5)*</td>
<td>3.3 (1.8, 6.0)*</td>
<td>1.2 (0.7, 2.3)</td>
</tr>
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</table>

* $P < 0.05$

*Primary outcome variable*