Dose–response for adrenal suppression with hydrofluoroalkane formulations of fluticasone propionate and beclomethasone dipropionate

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Aims With the recent introduction of hydrofluoroalkane (HFA) inhalers it is important to know the relative systemic safety profiles of inhaled corticosteroids. We therefore decided to compare systemic bioavailability of HFA-beclomethasone dipropionate (BDP) *vs* HFA-fluticasone propionate (FP).

Methods Sixteen healthy volunteers were randomised in placebo-controlled single blind cross-over fashion to receive 3 weeks with HFA-FP or HFA-BDP, given as 1 week cumulative doubling doses (nominal ex-valve) of 500, 1000 and 2000 μg day^{-1}, with a 1 week placebo run-in and wash-out. Overnight (22.00 h to 08.00 h) and early morning (08.00 h) urinary cortisol/creatinine excretion and 08.00 h serum cortisol were measured after each placebo and dosing period. All data were log-transformed to normalize their distribution.

Results Urine and serum cortisol were suppressed by 2000 μg FP and BDP *vs* placebo and by 1000 μg BDP *vs* placebo for urinary cortisol/creatinine ($P<0.05$). Overnight urinary cortisol/creatinine ratio (the primary endpoint) was suppressed more by 1000 μg BDP *vs* 1000 μg FP ($P<0.05$), amounting to a geometric mean fold difference (95% CI) of 1.64 (1.04–2.56). There were also more individual low values less than 3 nmol $mmol^{-1}$ with BDP than FP at 1000 μg: $n=8/16$ *vs* $n=2/16$ ($P<0.05$).

Conclusions There was dose-related suppression of corrected urinary cortisol/creatinine with the HFA formulations of BDP and FP. Suppression of overnight urinary cortisol/creatinine ratio was significantly greater with HFA-BDP than HFA-FP at 1000 μg. This suggests that the greater glucocorticoid potency of HFA-FP may be offset by the greater lung bioavailability of HFA-BDP

Keywords: adrenal suppression, beclomethasone, dipropionate, fluticasone propionate, hydrofluoroalkane inhalers

Introduction

With the impending implementation of the Montreal Protocol and the introduction of chlorofluorocarbon (CFC) free inhalers confusion exists regarding equivalent doses of inhaled corticosteroids, and there are no clear guidelines as yet on this transition. For example, considering CFC formulations, fluticasone propionate (FP) exerts approximately two-fold greater systemic bioavailability (as adrenal suppression) compared with beclomethasone dipropionate (BDP) [1], and so one might extrapolate that the same relationship applies to their hydrofluoroalkane (HFA) formulations. However, the situation may be more complicated as CFC-FP has twice the systemic bioavailability of HFA-FP [2], whilst CFC-BDP has half the bioavailability of HFA-BDP [3]. We therefore decided to compare adrenal suppression between HFA-BDP (Beclazone, 250 μg per actuation, Norton Healthcare, Ireland) pressurized metered dose inhaler and HFA-FP (Flutide Forte, 250 μg per actuation, Glaxo-Wellcome, Germany) within their recommended nominal (ex-valve) dose range up to 2000 μg day^{-1}.

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Methods

Patients

Sixteen healthy volunteers, mean age 24.8 (s.e. 1.4) years were recruited from the adult population of Dundee. They were randomised in placebo-controlled single-blind crossover fashion to receive 3 weeks treatment with HFA-FP or HFA-BDP, given as 1 week cumulative doubling doses (nominal ex-valve) of 500, 1000 and 2000 μg day^{-1}, with a 1 week placebo run-in and wash-out. Inhaler technique was reinforced at each visit, and patients were instructed to mouth rinse after each administration. The Tayside Committee on Medical Research Ethics gave ethical approval for the study, and all patients gave written informed consent.

Cortisol assays

Overnight (22.00 h to 08.00 h) and early morning (08.00 h) urinary cortisol/creatinine excretion was measured after each placebo and dosing period. Subjects also had blood for 08.00 h serum cortisol taken after lying supine for 30 min. A full description of the methods for fractionated urine collection and plasma and urine cortisol/creatinine assay is given elsewhere [4]. There was no cross reactivity with either FP or BDP.

Statistical analysis

The study was designed with 80% power to detect a 20% difference in overnight urinary cortisol/creatinine ratio (the primary endpoint) between treatments with the alpha error set at 0.05 (2-tailed). All data were log-transformed to normalize their distribution, followed by multifactorial analysis of variance (with subject, sequence and treatment as factors) and Bonferroni's multiple-range testing set at 95% confidence limits (two-tailed). The χ^2 test compared individual low values for overnight urinary cortisol/creatinine excretion for each formulation.

Results

There were no significant differences between placebo values prior to HFA-FP and HFA-BDP for overnight and early morning urinary cortisol/creatinine excretion, and 08.00 h serum cortisol. There was significant ($P<0.05$) suppression of overnight and early morning urinary cortisol/creatinine with 1000 μg day^{-1} of HFA-BDP and 2000 μg day^{-1} of both HFA-BDP and HFA-FP as compared with placebo (Table 1). This amounted to a geometric mean fold difference (95% CI) of 2.31 (1.41–3.76) for 2000 μg FP *vs* placebo, 2.65 (1.63–4.33) for 2000 μg BDP *vs* placebo, and 1.74 (1.11–2.73) for 1000 μg BDP *vs* placebo. At the 1000 μg dose for overnight urinary cortisol/creatinine there was a 1.64-fold (95% CI 1.04–2.56) greater mean suppression with HFA-BDP than HFA-FP as well as more individual low values (Figure 1) less than 3 nmol mmol^{-1} (8/16 *vs* 2/16 patients, $P<0.05$). 08.00 h serum cortisol showed significant suppression with both drugs at 2000 μg day^{-1}, amounting to a 1.84-fold (95% CI 1.08–3.14) difference for FP, and a 1.90-fold (1.11–3.25) difference for FP.

Discussion

We have shown that there was dose-related adrenal suppression with HFA formulations of FP and BDP, whilst

Table 1 Geometric means (s.e. mean) are shown for overnight urinary cortisol/creatinine ratio (ONUC/C ratio), early morning urinary cortisol/creatinine ratio (EMUC/C ratio) and 08.00 h serum cortisol. Asterisk indicates significant ($P<0.05$) difference from placebo; cross indicates significant difference between HFA-BDP and HFA-FP at 1000 μg.

	ONUC/C ratio (nmol mmol^{-1})	*EMUC/C ratio (nmol mmol^{-1})*	*08.00 h serum cortisol (nmol l^{-1})*
Pooled placebo	6.13 (0.80)	23.67 (3.66)	437.3 (27.5)
HFA-FP			
500 μg	5.94 (0.77)	21.06 (3.52)	407.7 (15.3)
1000 μg	5.76 (0.72)	15.23 (2.24)	398.5 (19.8)
2000 μg	2.66 (0.37)⋆	8.52 (1.95)⋆	239.7 (36.0)⋆
HFA-BDP			
500 μg	5.39 (0.70)	19.67 (3.28)	423.2 (15.8)
1000 μg	3.52 (0.44)⋆†	12.19 (1.80)⋆	387.2 (19.3)
2000 μg	2.31 (0.28)⋆	6.62 (1.54)⋆	231.9 (34.8)⋆

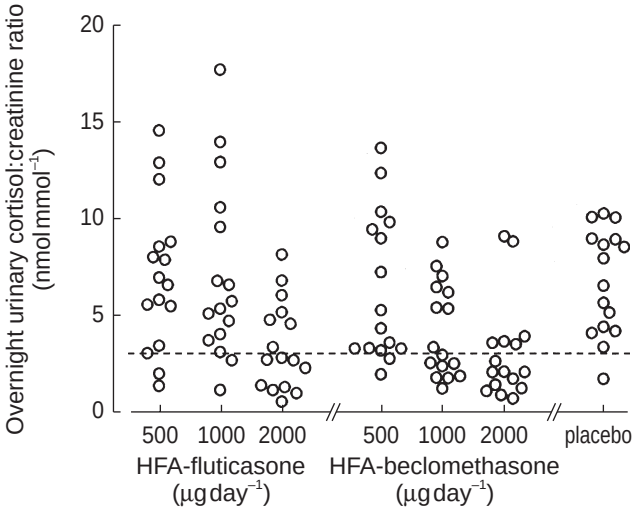

Figure 1 Individual data for overnight urinary cortisol/creatinine ratio for each dose (500 μg, 1000 μg and 2000 μg) of HFA-beclomethasone and pooled placebo. Data points below the 3 nmol mmol^{-1} cut off line represent clinically significant cortisol supression.

the latter exhibited greater suppression at 1000 μg day^{-1}. This can be explained due to their relative systemic bioavailabilities and potencies as follows: a) HFA-FP has half the systemic bioavailability of CFC-FP [2]; b) CFC-FP has twice the systemic potency of CFC-BDP [1]; c) CFC-BDP has half the systemic bioavailability of HFA-BDP [3]. Thus, it may not be possible to directly extrapolate the relative systemic effects from CFC to HFA inhaled corticosteroid formulations.

We elected to measure fractionated moieties of overnight and early morning urinary cortisol/creatinine excretion as this has been shown to be as sensitive as full 24 h urine collection or an integrated 24 h serum cortisol profile [4, 5]. For outpatient studies the fractionated collections were easier to perform and compliance is better than the full 24 h urine collection. On inspecting the scatter plot for overnight urinary cortisol/creatinine it is evident that there is considerable interindividual variability in response to exogenous glucocorticoid administration, except there was more suppression at the high dose of both formulations. It was not surprising to find significant suppression with 08.00 h serum cortisol only at the highest dose of HFA-BDP and FP, as this is known to be less sensitive than measuring effects on fractionated urinary cortisol [4, 5].

We used doses of both formulations which are recommended for use in asthma up to 2000 μg daily. Given that the systemic bioavailability of the Norton HFA-BDP is twice that of CFC-BDP [3] it seems curious that patients are recommended to switch on a microgram equivalent basis. Indeed with another HFA-BDP formulation (Qvar, 3 M Healthcare) the recommendation is for a switch from CFC-BDP on a 0.5 μg equivalent basis, with a maximum dose of 800 μg day^{-1} based on good dose–response studies [6].

What are the potential clinical implications of our results? Both HFA-BDP and HFA-FP showed dose-related adrenal suppression, although we cannot evaluate the therapeutic ratio as we do not know their relative therapeutic efficacy. However assuming HFA-FP will exhibit at least the same degree of degree of antiasthmatic potency as HFA-BDP, then we could hypothesize that at least at high doses HFA-FP would appear to have a superior therapeutic ratio. Proper dose–response studies in asthmatic patients are required to investigate this hypothesis.

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