

Effect of inhaled fluticasone propionate on airway responsiveness in treatment-naive individuals - a lesser benefit in females

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ABSTRACT: A randomized double-blind placebo-controlled parallel group study with inhaled fluticasone propionate over 6 weeks, designed to quantify the beneficial effect on airway responsiveness, and so assess whether short pulses of intermittent prophylactic treatment might serve as an alternative means of managing mild asthma, is reported.

The 20–50-yr-old participants, who were recruited from an epidemiological study of the general population, had never knowingly received any regular treatment for asthma. Fluticasone propionate at the maximum recommended dose level (2,000 µg daily) and placebo were administered *via* metered-dose inhalers, and airway responsiveness was quantified conventionally by the provocative dose of methacholine causing a 20% fall in forced expiratory volume in one second (FEV₁) (PD₂₀) at 2-week intervals during the treatment phase and at various intervals subsequently.

Compared with placebo fluticasone propionate was associated with a highly significant decrease in airway responsiveness (1.9 doublings of the geometric mean PD₂₀), which was maximal at the end of the 6-week treatment period. No persisting benefit was detectable at the next measurement 2 weeks later, or thereafter. Multiple linear regression analysis showed that the magnitude of the fluticasone propionate effect was significantly greater in males than in females (3.2 *versus* 1.2 doublings respectively of the geometric mean PD₂₀), but was uninfluenced by current smoking, age or FEV₁.

In conclusion, in the absence of any possibility of tachyphylaxis, inhaled fluticasone propionate at this dose causes a steadily increasing improvement in airway responsiveness over a 6-week period, which is modified by sex but lost almost immediately on treatment cessation. Short pulses of intermittent prophylactic treatment would not, therefore, be useful as a means of managing mild asthma.

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In an epidemiological study of a normal population of males and females many subjects were identified in whom airway responsiveness could be quantified but who had never knowingly received corticosteroid treatment, whether for asthma or other diseases, nor knowingly received any regular medication for asthma for >3 months [1]. The majority were not recognized to have (or to have had) asthma. Volunteers from among them were sought to evaluate the effect on airway responsiveness of inhaled fluticasone propionate, a potent topical steroid thought to have an enhanced benefit-risk ratio because of a high level of "first pass" hepatic metabolism and low oral bioavailability [2].

The aim of this study was to quantify the effect of 6 weeks treatment at the maximum recommended dose by its peak and duration over the following 20 weeks. It was wondered whether short "pulses" of intermittent prophylactic treatment might offer an alternative means of

management of mild asthma (or a means of preventing 'subclinical asthma' from becoming symptomatic) if the initial effect was sufficiently strong and sufficiently prolonged. The secondary aims were to assess the possible influence of sex and smoking on any treatment effect, since female sex and smoking are both associated with heightened disease severity [3–6].

Methods

Airway responsiveness

Airway responsiveness was measured using methacholine inhalation tests with optimal precision, and quantified conventionally by the provocative dose of methacholine causing a 20% fall in forced expiratory volume in one second (FEV₁) (PD₂₀) [7]. A failure to produce a 20% fall in FEV₁ after the final dose following a doubling cumulative dose protocol (range 3,125–6,400 µg) constitutes a negative test. With the test system used, PD₂₀ of <200 µg are generally associated with other clear evidence of

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active asthma, whereas PD₂₀ of >1,000 µg are generally not associated with asthmatic symptoms. PD₂₀ in the range 200–1,000 µg represent a "grey" zone in which some subjects have mild symptomatic asthma and others do not. PD₂₀ are generally repeatable within one doubling dose under ideal conditions or 1.6 doubling doses. Thus the coefficient of repeatability is of the order of 2–3.

Subjects

It was attempted to recruit 15 subjects into each of four subgroups determined by sex and smoking status, with the expectation that 10 would complete the study in each category. Calculations from stored data from repeated methacholine tests in other subjects suggested that this would provide 80% power at a 5% significance level for detecting a clinically meaningful difference in fluticasone propionate benefit between females and males (2.8-fold difference in geometric mean PD₂₀, two tailed), or between nonsmokers and smokers (2.5-fold difference, one tailed). Volunteers were chosen to have PD₂₀ of <1,600 µg from two baseline methacholine tests conducted within 2 weeks but separated by 48 h.

Participants were also chosen to be aged 20–50 yrs. Only those in one of two smoking categories over the preceding 2 yrs were accepted: "nonsmokers" who had not smoked, and "smokers" who had smoked at least five cigarettes daily. None were taking β-blocking or antimuscarinic drugs, and none were using aspirin or other nonsteroidal anti-inflammatory agents other than at a constant dose. None had had any respiratory tract infection requiring antibiotics within the preceding 4 weeks, an uncontrolled systemic disease or a history of alcohol abuse. All were able to use a metered-dose inhaler (MDI) adequately and all gave written informed consent to participate. The investigation was approved by the local Ethics Committee and conducted according to the Declaration of Helsinki.

Study medication

Placebo or fluticasone propionate at the maximum dose recommended for regular use (2,000 µg daily) was administered each morning for six weeks *via* seemingly identical pressurized MDIs at seemingly identical doses.

Protocol

The study was carried out in a randomized double-blind placebo-controlled parallel group fashion, stratified by sex and smoking habit. Fully compliant participants visited the research laboratory on eight occasions (study visits V0–7). The initial recruitment visit (V0) during the pretreatment phase of the study was used to obtain baseline data concerning: demography; smoking; clinical examination; weight; height; spirometry; methacholine responsiveness; and expired carbon monoxide concentration. A placebo MDI was then prescribed for all participants in order to familiarize them with its use. At the second pretreatment phase visit (V1) and at all subsequent visits during the treatment phase (V2–4) and follow-up phase (V5–7), spirometry and the methacholine test were repeated.

The pretreatment phase was completed with 1–2 weeks for each individual participant. Randomization for treatment with placebo or fluticasone propionate was carried out at V1 for subjects who met the inclusion criteria and were willing to proceed with the investigation. Treatment was commenced immediately following V1, and was given for 6 weeks exactly. The effects were evaluated during the treatment phase after 2, 4 and 6 weeks of treatment (V2, 3 and 4). Further evaluations were made during the follow-up phase 8, 12 and 26 weeks after V1 (V5, 6 and 7). These were 2, 6 and 20 weeks after completion of the treatment phase.

Statistical analysis

SAS 6.0 (SAS Institute, Cary, NC, USA) was used for statistical analyses. Because the methacholine was administered using a doubling cumulative dose protocol, all PD₂₀ were log-transformed in order to obtain a normal distribution. Categorical variables were compared using the Chi-squared test and continuous variables were compared using Student's t-test. Changes in PD₂₀ from baseline (geometric mean of V0 and V1; VBPD₂₀) were compared using a paired t-test. A Bonferroni correction was used with these Chi-squared tests and t-tests to allow for multiple testing ($\alpha=0.01$). Multiple linear regression analysis was used to model the effect of treatment on lnPD₂₀ at visits V2–7 while controlling for the effects of sex, smoking, age, FEV₁ and VBPD₂₀. Possible interactions between treatment and sex, smoking, age and FEV₁ were tested at each visit to establish whether the treatment effect depended on these variables.

Results

Subjects

A total of 52 subjects completed the pretreatment phase of the study satisfactorily and reattended for at least one (but non necessarily all) of the treatment phase visits. All but 13 attended all eight visits. The distribution by treatment group, sex and smoking category is given in table 1, with demographic data and mean baseline FEV₁ and lnPD₂₀. There were no important aberrations in distribution between the treatment and sex/smoking groupings, although females were necessarily shorter than males and had lower FEV₁, and smokers had lower FEV₁ than nonsmokers. There were no significant differences in PD₂₀ between the treatment groups or sexes at baseline.

Expired levels of carbon monoxide

The one missing value (in a nonsmoker) was replaced by the nonsmoking mean. A level of ~9 parts per million (ppm) has been suggested as the diagnostic threshold for separating nonsmokers from smokers [8]. Only one of the 27 nonsmokers yielded a higher value (13 ppm) and only one of the 25 smokers a lesser value (7 ppm). The mean \pm SD levels for the nonsmokers and smokers were clearly and significantly different at 4.8 ± 2.1 ppm and 19.5 ± 7.7 ppm respectively ($p<0.0001$).

Table 1. – Distribution of smoking category and demographic and baseline data by sex and treatment

	Placebo	Fluticasone propionate	Total
Subjects	26	26	52
Females	15	16	31
Nonsmokers	6	7	13
Smokers	9	9	18
Age yrs	35±7	33±10	34±8
Height m	1.67±0.04	1.64±0.06	1.66±0.05
BMI kg·m ⁻²	24.6±5.8	23.7±3.0	24.1±4.5
VBFEV ₁ % pred	101.7±13.8	100.9±11.4	101.3±12.4
VBlnPD ₂₀ µg	5.63±1.31	5.68±0.83	5.65±1.07
Males	11	10	21
Nonsmokers	7	7	14
Smokers	4	3	7
Age yrs	34±8	28±7	31±8
Height m	1.79±0.06	1.82±0.07	1.8±0.07
BMI kg·m ⁻²	25.0±1.2	22.5±3.2	23.9±2.6
VBFEV ₁ % pred	96.5±13.3	106.0±13.9	101.1±14.1
VBlnPD ₂₀ µg	5.26±1.40	5.41±1.10	5.33±1.23

Data are presented as n or mean±SD. BMI: body mass index; VB: mean at baseline (V0 and V1) (forced expiratory volume in one second (FEV₁); arithmetic mean; provocative dose of methacholine causing a 20% fall in FEV₁ (PD₂₀): geometric mean).

Baseline forced expiratory volume in one second and provocative dose of methacholine causing a 20% fall in forced expiratory volume in one second

The arithmetic mean (SD) baseline (V0 and V1) FEV₁ (VBFEV₁) was 3.61±0.89 L, which was 101% of the predicted value, and the VBPD₂₀ was 251 µg. The corresponding values for the two treatment groups and the sex subgroups are given with SD in table 1.

Change in forced expiratory volume in one second

The numbers of participants at each of the V2–7 differed (table 2), and so the mean FEV₁ are not directly comparable. No significant changes occurred at any of the V2–7 in either the placebo or the fluticasone propionate group from the respective baseline values.

Table 2. – Geometric provocative dose of methacholine causing a 20% fall in forced expiratory volume in one second (PD₂₀) at each study visit compared with the respective baselines (VB) by treatment group

	V2	V3	V4	V5	V6	V7
Subjects n	52	47	48	46	45	43
Placebo						
Subjects n	26	24	25	25	25	23
VB µg	238	230	240	240	240	215
V2–7 µg	262	269	294	290	368	351
p-value	NS	NS	NS	NS	0.01	0.0003
Fluticasone						
Subjects n	26	23	23	21	20	20
VB µg	264	245	236	266	262	272
V2–7 µg	481	569	1111	378	472	419
p-value	0.003	0.002	0.0001	NS	0.03*	0.04*

*: NS with Bonferroni correction. V2–4: treatment phase; V5–7: follow-up phase.

Change in provocative dose of methacholine causing a 20% fall in forced expiratory volume in one second

For five participants (all in the fluticasone propionate group), negative results were obtained from methacholine tests at the end of the treatment phase (V4). For these, a PD₂₀ of 6,401 µg was assigned, which is likely to have underestimated the true increase in PD₂₀ in the subjects concerned. Table 2 shows the changes in geometric mean PD₂₀ from the respective baselines at each of V2–7. There were no changes in the placebo group during the treatment phase, but, in the fluticasone propionate group, the PD₂₀ increased steadily with increasing significance. The difference in geometric mean PD₂₀ between the placebo and fluticasone propionate groups was not significant at V2 (262 versus 481 µg), was borderline significant at V3 with the Bonferroni correction (269 versus 569 µg, p<0.05) and was very significant at V4 (294 versus 1,111 µg, p<0.003). The differences during the follow-up phase (V5, 6 and 7) were not significant, indicating that the effect of fluticasone propionate did not persist even to the first PD₂₀ measurement 2 weeks after treatment was discontinued. In parallel, no significant change was noted at V5 from baseline in either the placebo or the fluticasone propionate group. There were, however, mild but significant (or borderline significant) changes from baseline in both groups at V6 and 7 (*i.e.* 12 and 26 weeks after V1), indicating a secular effect over the time-course of the study. This amounted to less than one doubling of the geometric mean PD₂₀.

Peak change and duration of effect

Data from the 52, 47 and 48 subjects who attended at V2, 3 and 4 respectively showed a steadily increasing benefit from fluticasone propionate, but not placebo, throughout the 6-week period of treatment (fig. 1). There was no persisting benefit once treatment was discontinued, and so maximum benefit was observed at V4. A fundamentally similar pattern was noted among the 39 subjects who attended all of V0–7.

Multiple linear regression models

Initial models showed no effect of smoking, age or FEV₁ on PD₂₀ at V2–7 after allowing for the VBPD₂₀ (*i.e.* these variables were not associated independently with change in PD₂₀). Nor were there any interactions between these variables and treatment (*i.e.* they did not modify the effect of fluticasone propionate). They were consequently removed from the later and definitive models. When controlling for sex and VBPD₂₀ (which did exert significant influence), the effect of fluticasone propionate was marginally nonsignificant at V2 (p<0.06) but very significant at V3 (p<0.005) and 4 (p<0.001). The effect was maximal at V4, but it was nonsignificant at all subsequent post-treatment visits, V5–7.

The VBPD₂₀ was, as expected, a significant predictor of PD₂₀ at all subsequent visits (p<0.0001). The model also demonstrated a significant treatment/sex interaction, indicating that fluticasone propionate exerted a greater effect in males than in females, although sex alone exerted no

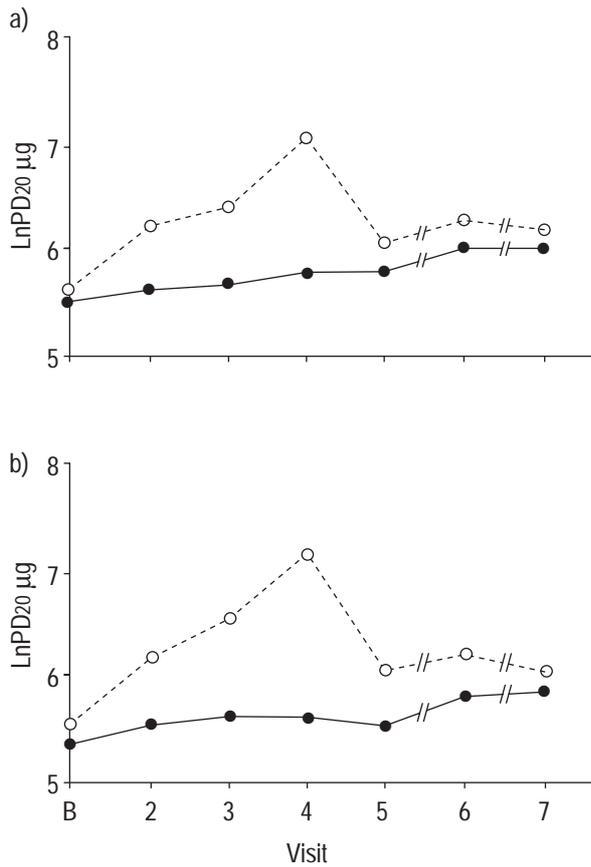


Fig. 1. – Geometric mean provocative dose of methacholine causing a 20% fall in forced expiratory volume in one second (PD₂₀) at each visit (V) for: a) all participants; and b) the 39 participants attending all study visits (○: fluticasone propionate 2,000 µg daily; ●: placebo). Vs took place (with number of participants (a) in parentheses) at: baseline (B), 0 weeks (n=52); V2, 2 weeks (n=52); V3, 4 weeks (n=47); V4, 6 weeks (n=48); V5, 8 weeks (n=46); V6, 12 weeks (n=45); V7, 26 weeks (n=43).

influence. Thus at V4, there were 1.2 doublings in geometric mean PD₂₀ from baseline in females, which could be attributed to fluticasone propionate and an additional 2.0 doublings in males ($p < 0.04$). This is equivalent to a 2.3 fold increase in the VBPD₂₀ in females and an overall 9.0 fold increase in males. In order to estimate the net effect of fluticasone propionate in the study population as a whole, a final analysis ignored the effect of the treatment/sex interaction, and assessed only the effects of treatment and the VBPD₂₀ on PD₂₀ at V4. Fluticasone propionate was associated with 1.9 doublings (3.8 fold increase) of PD₂₀ from baseline ($p < 0.0002$).

Three of the participants, all randomized to the fluticasone propionate group (two male, one female, all non-smokers), showed particularly marked improvements in airway responsiveness, with increases in PD₂₀ from baseline to V4 exceeding 20 fold (4.3 doublings). No obvious technical problems were detected, and their serial PD₂₀ were consistent with a genuine response to fluticasone propionate treatment. Furthermore, changes in PD₂₀ over similarly wide ranges and similarly short periods have been noted in individuals with emergent occupational asthma in and away from the workplace, and in conducting specific inhalation provocation tests [9–11]; SAS "diag-

nostics" testing did not identify an statistical outliers. Nevertheless, the influence of these participants was assessed by excluding their data and rerunning the analyses. The effect of fluticasone propionate continued to be significant (0.9 doublings in geometric mean PD₂₀ in females, $p < 0.04$), and a significant treatment/sex interaction favouring males was still evident (an additional 1.4 doublings in males, $p < 0.04$). There were thus significant increases of 1.8 and 5.0 fold overall in the females and males respectively in this reduced population.

In addition, the analyses were rerun using the dose/response slope (DRS) method of quantifying airway responsiveness [12], lest there had been an important loss of precision because a PD₂₀ of 6,401 µg had been assigned to methacholine tests which gave a negative result after the pretreatment phase of the study. The DRS values were skewed, and so their logarithms were used in the further analyses. These produced, reassuringly, identical outcomes to the PD₂₀ analyses. All significant associations between airway responsiveness and fluticasone propionate were confirmed at the same levels of significance, including the treatment/sex interaction, and no new associations were found.

Discussion

The study confirmed that inhaled fluticasone propionate, at 2,000 µg daily, has a beneficial effect on airway responsiveness, but this was no longer evident at the first measurement point 2 weeks after completing the 6-week period of treatment. Consequently no support was found for the notion that intermittent pulsed therapy might be of value as an alternative means of managing mild asthma, or of preventing the emergence of symptoms in subjects with "subclinical" levels of airway responsiveness. This is unfortunate. The recent trend to use inhaled steroids progressively earlier in the management of asthma could have been strengthened if the advantages were achievable with the lesser risks and costs associated with intermittent rather than continuous use.

The geometric mean PD₂₀ increased sequentially and very significantly over 6 weeks as a consequence of fluticasone propionate treatment by 1.9 doublings (3.8-fold) if the sex interaction term is ignored. This takes account of the nonsignificant changes in the placebo group. The use of "fold" increment is not, however, strictly appropriate to PD₂₀ since this is essentially a logarithmic term, but the convention is convenient to clinicians. "Doublings" provides a more acceptable measure of logarithmic change, and is a commonly used alternative term.

The outcome observed may be compared with that of the one other study of similar design, that of OLIVIERI *et al.* [13]. They observed an equivalent improvement in airway responsiveness of ~2.6 fold after 6 weeks' fluticasone propionate treatment [13]. Their study focused on the serial examination of constituents of bronchoalveolar lavage fluid in a necessarily smaller number of participants (n=17), and this possibly explains their failure to note an improvement of significant degree earlier in the 6-week period. The lesser mean response was probably a consequence of the lesser daily dose of fluticasone propionate (500 µg), and this suggests that the beneficial response in airway responsiveness to fluticasone propionate is, not surprisingly, dose-dependent.

The participants in the present study were selected, perhaps uniquely, to have never previously received corticosteroid treatment nor any other regular treatment for asthma, and so the response observed was not limited in any way by tachyphylaxis. Although the improvement in airway responsiveness at V4 represents the maximum effect of fluticasone propionate treatment during the investigation, there was an important trend of increasing benefit throughout the 6-week treatment period. It is possible, therefore, that further benefit would have occurred had the treatment period been more prolonged.

It is also possible that the censoring effect, by which PD₂₀ were restricted to 6,401 µg in five fluticasone propionate treated subjects who gave negative results to the methacholine test at V4, may have led to an underestimation of the true magnitude of the fluticasone propionate effect. However, this underestimation is not likely to have been of major degree since only five of the 23 fluticasone propionate group participants were affected in this way, and by chance they had lower VBPD₂₀ (geometric mean 173 µg) than the other 18 (257 µg). They consequently contributed more, not less, than average to the overall increase in geometric mean PD₂₀ in the fluticasone propionate group. Furthermore, the DRS analyses of the methacholine tests, which provided a measure of airway responsiveness even when the cumulative decrement in FEV₁ failed to reach 20%, gave essentially identical outcomes to those using PD₂₀.

The selection procedure produced a study population with a normal mean baseline level of ventilatory function, and so the failure to observe an increase in FEV₁ in the fluticasone propionate group as a consequence of treatment, despite the previous naivety to such treatment, is not unexpected. This usefully confirms that the changes observed in PD₂₀ were fundamentally a consequence of true improvements in airway responsiveness, and not merely a consequence of improvements in ventilatory function.

The sex difference in the response to fluticasone propionate provides an outcome of particular interest. The authors are not aware of any previous reports of sex acting as an effect modifier for corticosteroid therapy in asthma, although preliminary and unpublished results from the European Study of Chronic Obstructive Pulmonary Disease (EUROSCOP) study assessing the effect of inhaled corticosteroids on the progression of chronic obstructive pulmonary disease (COPD) [14] did suggest a sex difference benefiting males. Subsequent analyses have suggested that this was a consequence of confounding, and that an adverse effect of continuing smoking was the true explanation for the apparent sex difference (R. Pauwels, personal communication). A degree of confounding was also feared in the present study (the effect of fluticasone propionate appeared particularly strong in males who were nonsmokers), but, if sex was excluded from the regression analyses, no effect of smoking was detected, nor was there a treatment/smoking interaction. The same outcome was observed from the DRS analyses, and so the results indicate that the effect of fluticasone propionate was modified by sex rather than smoking in the young adult population selected to have PD₂₀ of <1,600 µg (rather than COPD). Thus males appear to be more responsiveness than females, but it may be convenient to consider that a relative failure to respond to inhaled fluticasone propionate is more prevalent in females.

Such effect modification is biologically plausible because a number of recent reports suggest that females affected by asthma (and treated accordingly with inhaled corticosteroids) have more severe disease than males. Not only does a male dominance in asthma prevalence in childhood give way to a mild female dominance in adult life but also adult female asthmatics report greater impairment in quality of life, have a disproportionate number of hospital admissions and accrue greater management costs [15–20]. It has been argued that these differences could be a consequence primarily of subjective differences in perception between the sexes [21, 22], and such differences have been demonstrated by the authors [23], but this does not explain all of the sex effect since there are also reported differences of a more objective nature. For example, LIN and REHMAN [24] noted that of asthmatic subjects with severe exacerbations necessitating intensive care, females required longer periods of intubation than males. TOUGH *et al.* [25] noted in males but not females that there was a marked seasonal pattern to asthma mortality, which suggested that summer environmental factors were strong determinants of asthma death in males. During the winter season, when these factors were less influential and male mortality was low, the unchanged (*i.e.* perennial) level of female mortality was disproportionately high. ROBERTS *et al.* [26] noted a mortality of 2.25 per 100,000 in 1989 in females compared with 1.38 in males. Mortality data concerning asthma are, however, a further notorious source of inaccuracy [27]. If, nevertheless, there is an important sex anomaly concerning the clinical severity of asthma, the present findings may help to explain it.

It is concluded that, in the absence of any possibility of tachyphylaxis, inhaled fluticasone propionate at 2,000 µg daily caused a steadily increasing improvement in airway responsiveness over a 6-week period, which was enhanced by male sex but lost almost immediately on treatment cessation. Short pulses of intermittent prophylactic treatment would not, therefore, be useful as a means of managing mild asthma.

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