Effects of fluticasone propionate on methacholine dose-response curves in nonsmoking atopic asthmatics


ABSTRACT: Methacholine is frequently used to determine bronchial hyperresponsiveness (BHR) and to generate dose-response curves. These curves are characterized by a threshold (provocative concentration of methacholine producing a 20% fall in forced expiratory volume in one second (PC20) = sensitivity), slope (reactivity) and maximal response (plateau). We investigated the efficacy of 12 weeks of treatment with 1,000 µg fluticasone propionate in a double-blind, placebo-controlled study in 33 atopic asthmatics.

The outcome measures used were the influence on BHR and the different indices of the methacholine dose-response (MDR) curve. After 2 weeks run-in, baseline lung function data were obtained and a MDR curve was measured with doubling concentrations of the methacholine from 0.03 to 256 mg·mL⁻¹. MDR curves were repeated after 6 and 12 weeks. A recently developed, sigmoid cumulative Gaussian distribution function was fitted to the data. Although sensitivity was obtained by linear interpolation of two successive log₂ concentrations, reactivity, plateau and the effective concentration at 50% of the plateau value (EC50) were obtained as best fit parameters.

In the fluticasone group, significant changes occurred after 6 weeks with respect to means of PC20 (an increase of 3.4 doubling doses), plateau value fall in forced expiratory volume in one second (FEV₁) (from 58% at randomization to 41% at 6 weeks) and baseline FEV₁ (from 3.46 to 3.75 L) in contrast to the placebo group. Stabilization occurred after 12 weeks. Changes for reactivity were less marked, whereas changes in log₂ EC50 were not significantly different between the groups.

We conclude that fluticasone is very effective in decreasing the maximal airway narrowing response and in increasing PC20. However, it is likely that part of this increase is related to the decrease of the plateau of maximal response.


Bronchial hyperreactivity (BHR) is a hallmark of asthma. Nonspecific bronchoconstrictor stimuli, such as histamine or methacholine, are widely-used to demonstrate this BHR and to generate dose-response curves in asthmatics. These curves are sigmoid in shape, with a distinct threshold, linear slope in the midpart, and maximum response [1]. The provocative concentration producing a fall of 20% in the forced expiratory volume in one second (PC20) is called the sensitivity, which is lowered in asthmatics and is associated with a leftward shift of the dose-response curve [2].

The slope in the mid-part is defined as reactivity. Initially it was felt that slope measurements could provide relevant information [3] but as yet the clinical relevance of the reactivity is unclear. Asthmatics show an increased reactivity [1, 4, 5] as compared with normals. Also, a significant correlation has been found between reactivity and log₂ PC20 in these patients [4, 6].

Plateau values reflect maximal airway narrowing. Asthmatics not only show a leftward shift of the dose-response curve but also higher or even unmeasurable plateau levels as compared to normals [1].

MORENO et al. [7] postulated that any augmentation of airway narrowing stimuli ("prejuncional" mechanisms) can result in a leftward shift of the curve, while any increase in response of the effector organ ("postjuncional" mechanisms) [5, 7] theoretically results in an increase in the maximal plateau level. In practice, PC20 has been used to diagnose BHR and less attention has been paid to the overall shape of the dose-response curve and the plateau value. Previous investigations [1, 4, 5] have focused on the importance of measuring parameters of the entire log-dose-response curve, i.e. the sensitivity, reactivity and plateau value. Recognition and distinction of these components of hyperresponsiveness may have implications for the diagnosis and therapy of asthma. Although PC20 is generally used as an index for the shift of the curve along the concentration axis, the fit of the sigmoid function also enables calculation of the effective concentration at half of the plateau.
response (EC50). This index is commonly used in pharmacology [8], and is less dependent on the absolute value of the plateau response.

Anti-inflammatory therapy with inhaled corticosteroids (ICS) both shifts the dose-response curve to the right, i.e. decreases sensitivity [9], and reduces the maximum response [10], presumably by preventing the fixed element of airway obstruction caused by inflammation.

A new topically active glucocorticoid, fluticasone propionate (FP), has been shown to be more clinically effective than other ICS and to have fewer systemic side-effects in equi-effective doses at the upper end of the dose range [11, 12]. The aim of the present study was to investigate the efficacy of FP, 1,000 µg·day⁻¹, on BHR and its in vivo influence on the different characteristics of the methacholine dose-response curve in atopic asthmatics.

Methods

Subjects

Thirty three nonsmoking atopic asthmatics (23 males and 10 females; median age 26 yrs; range 18–56 yrs) were selected if they met the following criteria during the run-in period: PC20 histamine ≤8 mg·mL⁻¹ and ≥9% reversibility in forced expiratory volume in one second (FEV1), relative to baseline, following inhalation of 1,000 µg terbutaline. Atopy was defined by at least one positive skin-prick test to a panel of 16 common aeroallergens in the presence of positive and negative controls.

In the month preceding the run-in period, patients were allowed to take only inhaled short-acting beta₂-agonists, on an as needed basis. All other medication was stopped. Patients with a history suggesting respiratory infection or exacerbation of asthma in the month prior to the study were excluded.

All subjects gave written informed consent to the study, which was approved by the local Ethics Committee.

Study design

The study was of a randomized, double-blind, placebo-controlled design, which is schematically presented in figure 1. After a run-in period of 2 weeks, there was a 12 week treatment period, and then a follow-up period of 2 weeks. During the 2 week run-in period, patients discontinued use of their usual inhaled bronchodilator, which was replaced with salbutamol 400 µg or placebo, both given twice daily as dry powder via the Diskhaler. Patients continued salbutamol inhaler, each day and night. Additionally, they noted their coughing, sputum production and use of the study medication and symptoms. Patients also recorded their coughing, sputum production and use of the study medication and symptoms. Patients also noted an overall 24 h symptom score concerning dyspnoea.

Following the run-in period, the patients were randomized to treatment with either inhaled FP 500 µg or placebo, both given twice daily as dry powder via the Diskhaler. Patients continued salbutamol 400 µg p.r.n. but could take up to eight doses as needed for symptomatic relief.

After 6 weeks and 12 weeks of treatment, patients attended the clinic on two separate days (within three successive days): on one occasion maximal reversibility was tested, while on the other a methacholine dose-response curve (see below) was performed. Two weeks after the end of the treatment period a follow-up visit was scheduled.

Lung function testing

Where possible all measurements were made at the same time of day at each visit, and patients were asked not to use their bronchodilator or the study medication for 8 h before attending the clinic.

Inclusion measurements. FEV1 was derived from a maximal expiratory flow-volume curve, using a pneumotachometer (Jaeger, Würzburg, Germany). Reversibility
was tested 20 min after four separate inhalations of 250 µg of terbutaline sulphate from a metered-dose inhaler, administered through a 750 mL spacer device.

A histamine provocation test was performed by means of a 2 min tidal breathing method [13] using a noseclip.

**Study measurements.** Maximal reversibility was tested by administering cumulative doses of terbutaline starting with a single puff of 250 µg, while measuring FEV1 and forced vital capacity (FVC) after 15 min. Measurements were stopped after a maximum of four puffs at a time were given, or at any time when the difference between two consecutive measurements was less than 5%.

Methacholine was administered according to a standardized tidal breathing method [2]. Dose-response curves were obtained after inhalation of doubling concentrations of acetyl-β-methylcholine-bromide (0.03–256 mg·mL⁻¹ in normal saline). 1 mg·mL⁻¹ is equivalent to 0.82 mg·mL⁻¹ of methacholine chloride solution; therefore, a fixed conversion constant of 0.29 should be subtracted from the log₂ dose values for comparison with methacholine chloride data. Methacholine and histamine was chosen as the bronchoconstrictor stimulus because it produces less systemic side-effects when given in high doses [14]. Solutions of methacholine were stored at 4°C and administered at room temperature. The aerosols were generated by a De Vilbiss 646 nebulizer (output 0.13 ml·min⁻¹) and inhaled by tidal breathing for 2 min.

The response to methacholine was measured as change in FEV1 expressed as percentage of initial value and related to log₂ dose. A test was interrupted if the FEV₁ fell by more than 60%, or if unpleasant side-effects or dyspnoea compelled the patient to stop.

A recently developed and validated sigmoid cumulative Gaussian distribution (CGD) function was fitted to the data [4]. Although the sensitivity (log₂ PC₂₀) was obtained by linear interpolation of two successive log₂ concentration values [13], the plateau and the reactivity (defined as the slope at the 50% point of the CGD function) and the effective concentration at this point (EC₅₀) were obtained as best fit parameters. Hence, reactivity denotes the percentage change from baseline with doubling dose (dd) at the steepest point of the CGD function. Details of the fit procedure and validation of the CGD fit are according to AERTS et al. [4].

**Statistical analysis**

The paired t-test was used to analyse changes in FEV₁, reversibility and indices of bronchial hyperresponsiveness with respect to baseline. The unpaired t-test was used for comparisons between groups. The patient recorded diary data were averaged over all days; the Mann-Whitney test was used for comparison between the groups. Group means and standard error of the mean (±SEM) at the various time-points were calculated.

**Results**

Sixteen patients were randomized into the FP group and 17 patients into the placebo group. Baseline values were comparable in both groups on entry to the study except that a larger mean log₂ EC₅₀ methacholine was found in the FP group (p=0.05). Thirty one of the 33 subjects completed the study (table 1). One patient receiving placebo and one receiving FP were withdrawn after experiencing a pulmonary exacerbation. Data of these two patients have not been included in the analysis. In one patient, a reliable PC₂₀ methacholine could be obtained during all methacholine dose-response measurements, but no reliable reactivity or plateau values were measured. All parameters (PC₂₀ methacholine, reactivity, EC₅₀ and plateau value) were obtained in 90 out of 93 curves. Although in all cases only the fitted plateau value was used for the analysis (as mentioned above), in 61 out of 91 measurements an experimental plateau could also be obtained. In the remaining curves, the flattening made it possible to estimate the plateau value with reasonable accuracy.

Mean values for reactivity (%/dd) and plateau (% fall in FEV₁ from baseline) before, during and after treatment are shown in figure 2. Examples of dose-response curves to methacholine in the FP and placebo group are shown before and after 12 weeks of treatment in figure 3. During placebo treatment, mean log₂ PC₂₀ methacholine hardly changed, from 0.04 (SEM 0.78) at baseline to 0.34 (0.69) after 6 weeks and to 0.26 (0.46) after 12 weeks. During treatment with FP, however, mean log₂ PC₂₀ methacholine increased from 0.31 (SEM 0.59) to 3.73 (SEM 0.69) after 6 weeks and to 3.77 (SEM 0.72) after 12 weeks. After 6 weeks, the mean difference in change from baseline between the FP and the placebo group was 3.12 (SEM=0.76) (p<0.0005; 95% confidence interval (95% CI) 1.37–4.67). After 12 weeks, this was 3.25 (SEM 0.75) (p<0.0005; 95% CI 1.71–4.78).

During placebo treatment, the mean plateau value hardly changed, as can be seen in figure 2. During treatment with FP, however, the mean plateau value decreased from 58% (SEM 5%) to 41% (SEM 5%) after 6 weeks and to 36% (SEM 4%) after 12 weeks. After 6 weeks the mean difference in change from baseline between the FP and placebo groups were shown before and after 12 weeks of treatment in figure 3. During placebo treatment, the mean log₂ PC₂₀ methacholine hardly changed, from 0.04 (SEM 0.78) at baseline to 0.34 (0.69) after 6 weeks and to 0.26 (0.46) after 12 weeks. During treatment with FP, however, mean log₂ PC₂₀ methacholine increased from 0.31 (SEM 0.59) to 3.73 (SEM 0.69) after 6 weeks and to 3.77 (SEM 0.72) after 12 weeks. After 6 weeks, the mean difference in change from baseline between the FP and the placebo group was 3.12 (SEM=0.76) (p<0.0005; 95% confidence interval (95% CI) 1.37–4.67). After 12 weeks, this was 3.25 (SEM 0.75) (p<0.0005; 95% CI 1.71–4.78).

While achieving treatment effects, the mean PC₂₀ of methacholine showed a significant (95% CI 1.37–6.78) increase of 3.12 (SEM=0.76) (p<0.0005; 95% confidence interval (95% CI) 1.37–4.67). After 12 weeks, this was 3.25 (SEM 0.75) (p<0.0005; 95% CI 1.71–4.78).

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<table>
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All values are expressed as mean, and so in parenthesis. *: change in FEV₁, expressed as percentage baseline, after 1,000 µg terbutaline; ‡: plateau value, expressed as percentage fall in FEV₁. M: male; F: female; FP: fluticasone propionate; FEV₁: forced expiratory volume in one second; % pred: percentage of predicted value; PC₂₀: provocative concentration causing a 20% fall in FEV₁; H: histamine; M: methacholine; EC₅₀: effective concentration at half the plateau response; dd: doubling dose.
the placebo group was -19.3 (SEM 4.68) (p<0.0005; 95% CI -28.9 to -9.72). After 12 weeks this difference was -18.8 (SEM=5.67) (p =0.003; 95% CI -30.4 to -7.15). In neither of the treatment groups did mean reacti-
vity change substantially (fig. 2). However, there were
significant differences when the results of the treatment
groups were compared. After 6 weeks, the mean dif-
fERENCE in change from baseline between the FP and the
placebo group was -4.05 (SEM=1.60) (p=0.017; 95% CI
-7.32–-0.78). After 12 weeks, this was -3.69 ( SEM=1.87)
(p=0.058; 95% CI -7.52–0.13).

Log₂ EC50 changes with respect to baseline were not
significantly different between the groups. The mean
values were 0.0 (SEM 0.5), 0.8 (SEM 0.5), 0.2 (SEM 0.4)
mg·mL⁻¹ for the placebo group and 1.3 (SEM 0.4), 2.9
(SEM 0.4), 2.4 (SEM 0.3) mg·mL⁻¹ for the FP group at
baseline, 6 and 12 weeks, respectively. No significant
correlation was found between Log₂ EC50 and plateau
estimates.

Baseline values for FEV1 as absolute values hardly
changed during placebo treatment. FEV1 decreased
from 3.27 (SEM 0.24) L at baseline to 3.02 (SEM 0.24) L
after 6 weeks and to 3.07 (SEM 0.24) L after 12 weeks.
In the FP group FEV1 increased significantly from 3.46
(SEM 0.25) L at baseline to 3.75 (SEM 0.24) L after 6
weeks and to 3.73 (SEM 0.22) L after 12 weeks. After 6
weeks, the mean difference in change from baseline
between the FP and the placebo group was 0.54 (SEM 0.17)
(p=0.003; 95% CI 0.19–0.88) after 6 weeks, and 0.47
(SEM 0.16) (p=0.007; 95% CI 0.14–0.81) after 12 weeks.

Because of the skewed distribution of the data, max-
imal reversibility was analysed after log transformation.
After 6 weeks, maximum reversibility in the FP group
was 68% lower in comparison to the placebo group
(95% CI 37–84%; p=0.002). After 12 weeks this was
54% (95% CI 11–76%; p= 0.022).

Compared with placebo, FP significantly improved indi-
vidual night-time symptom score (sleeping disturbances)

Fig. 2. – a) Plateau value (percentage fall in FEV1 from baseline; and b) reactivity (%/dd) before, during and after treatment with placebo
(— ■ —) and fluticasone propionate (— – —). Values are presented as mean±SEM. FEV1: forced expiratory volume in one second; dd: dou-
bling dose.

Fig. 3. – Examples of dose-response curves to methacholine before (○) and 12 weeks after treatment (●) with: a) placebo; and b) fluticas-
one propionate. FEV1: forced expiratory volume in one second.
at end-point (p=0.01), whereas individual daytime symptom score (interfering with normal daily activities) almost reached significance (p=0.06). The overall 24 h symptom score also significantly improved in the FP treated group compared with placebo (p=0.01).

Discussion

The aim of the present study was to investigate the efficacy of a new inhaled corticosteroid, fluticasone propionate (FP), on BHR and its in vivo influence on the different characteristics of the methacholine dose-response curve in atopic asthmatics.

The results of the study show that FP is very effective in decreasing the maximal degree of airway narrowing after 6 weeks of treatment, and that this effect is sustained after 12 weeks. An improvement in FEV1 was accompanied by an increase in PC20 methacholine and a decrease in plateau value in the FP group but not in the placebo group. Although logEC50 increased more in the FP group than in the placebo group, the difference between these changes was not significant. Reactivity improved only slightly in the first 6 weeks of treatment with FP.

For the interpretation of the entire dose-response curve a recently developed and validated sigmoid function (cumulative Gaussian distribution) was fitted to the data [4]. Although the sensitivity (logPC20) was obtained by linear interpolation of two successive log2 concentration values, the reactivity defined as the slope at the 50% point of the CGD function (%/dd), EC50 and the plateau value were obtained as additional fit parameters. The model fit was used for two reasons: firstly, because it enabled smoothing of the curve, thereby minimizing fluctuations due to variation in patient co-operation or other causes; and secondly, because it facilitated extrapolation of the whole curve, where it was impossible to obtain direct estimates of plateau values, because of, for example, severe dyspnoea of the patient or feelings of general discomfort, which occasionally forced an interruption of the measurements [4]. In the present investigation, however, prolonged administration of methacholine was possible beyond the fitted plateau value in 67% of the cases, which further contributed to the reliability of reactivity and plateau estimates.

In contrast to other studies [9, 15–17] the improvement in PC20 methacholine in the present study is high (approximately 3.5 doubling doses after 6 and 12 weeks). This may be due to differences between the patients studied (atopic asthmatics [15] versus nonatopic asthmatics [9]), or to a difference in study medication prescribed [9, 15–17], or dosage used [9, 15–17]. Also, the difference in provocative concentration used [18] makes comparison difficult, although we know that in asthma PC20 is similar for histamine and methacholine [18, 19].

The greater increase in PC20 methacholine found in the present study may be due to the relatively high dose and/or high efficacy of FP prescribed. The normal daily dose of inhaled steroids in mild-to-moderate asthma varies somewhere between 800–1,200 µg. One recent investigation demonstrated that 200 µg FP was as effective as 400 µg beclomethasone dipropionate with respect to peak expiratory flow (PEF) rate, symptom scores, percentage of symptom-free days and nights, use of rescue β₂-agonist medication and clinical lung function [20]. This was also shown by others [11, 21]. Taking these results into account, the daily dose of 1,000 µg FP used in the present study may be considered to be relatively high; this could, in part, explain the large improvement in PC20 methacholine. True comparisons with the above-mentioned studies remain difficult, however, because none of them investigated the differences in effect on PC20 between FP and the other inhaled steroids.

Another reason for careful interpretation of the study results is the interaction between changes in plateau estimates (a postfunctional index [5]) and PC20 (sensitivity, presumed to be a prefunctional index). EC50, as a pharmacologically well-based index for the horizontal shift of sigmoid curves, independent of the plateau value, was found to change similarly in both groups. This means that part of the PC20 changes may be due to changes in plateau values, which in turn makes comparisons between different studies difficult.

It is possible that, since PC20 methacholine was not measured sooner than after 6 weeks of treatment, the effect measured may have occurred earlier than this time. After 12 weeks of treatment, no further improvement was found. This is in keeping with the findings of others [16, 22]. Kerstiens et al. [22] demonstrated, in patients with obstructive lung diseases (chronic obstructive pulmonary disease and asthma), that the largest improvement in PC20 histamine occurred after 6 months of treatment. Continuation of the therapy in their study resulted in only a slight, but not significant, further increase. Haaijtena et al. [17] also showed, in patients with newly detected asthma, that the marked decrease in bronchial responsiveness was already apparent after 6 weeks of treatment; although this decrease continued over the 2 yrs of the study, the trend over time was not significant.

FP also influenced the plateau value of the methacholine dose-response curve, whereas no change was observed during placebo treatment. FP induced a significant decrease in percentage fall in FEV1 after 6 weeks. A further, although not significant, decrease was found after 12 weeks. This finding may be of clinical importance. A maximal response that is increased to a severe or even unmeasurable degree of airway narrowing is potentially dangerous. The major reason why asthmatics get into trouble is not primarily the increased sensitivity of their airways to bronchoconstrictor stimuli, but the excessive degree of airway narrowing [23, 24]. Successful treatment of their asthma, therefore, should be directed towards preventing or at least diminishing this excessive response. Like other steroids, FP may result in diminished airway wall thickness by its effect on inflammatory mediators, decreasing mucosal swelling or plasma exudation [5]. Since we have shown FP to be very effective in diminishing the plateau value, it may, in our opinion, be considered a useful addition to the already existing arsenal of ICS.

Reactivity has been defined in some studies as the slope of the line fitted to the data upward from the threshold (PC20) [6, 25, 26]. In our opinion, such an approach becomes inaccurate because of the curvilinear shape reached at higher doses. Therefore, reactivity is better defined as the steepest slope of the log dose-response curve (50% point of the CGD function), thus
enabling comparison of reactivity estimates between different investigations. In the present study, FP also influenced reactivity. Although small changes were found after placebo as well as after FP treatment, only the change caused by FP from baseline to 6 weeks reached significance in comparison with placebo. After 6 weeks, a stabilization of reactivity seemed to occur. The change in reactivity during the first 6 weeks of FP treatment may be because, in the presence of an increasing stimulus, airway obstruction develops less progressively after treatment with FP than without treatment. Although reactivity is certainly coupled to pharmacodynamic properties, its interpretation is as yet unclear [6, 26, 27]. Further investigations will be needed in this respect to fully understand the clinical implications of the present findings.

Like other ICS [16, 22], treatment with FP increased FEV1 and decreased maximal reversibility, as can be expected when baseline values increase. Improvements in asthma symptom scores were not as consistent as the expected when baseline values increase. Improvements in FEV1 and decreased maximal reversibility, as can be seen.

In conclusion, fluticasone propionate proved to be very effective in decreasing the maximal response of airway narrowing in atopic asthmatic patients. The changes in provocative concentration of methacholine causing a 20% fall in forced expiratory volume in one second could suggest that an effect is exerted on sensitivity. However, the lack of significance in changes in the effective concentration at half of the plateau response makes this doubtful. Further studies are, therefore, warranted in this aspect.

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