

Respiratory pathophysiologic responses

Protective effect of inhaled budesonide against unlimited airway narrowing to methacholine in atopic patients with asthma

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Background: Patients with asthma who have moderate to severe airway hyperresponsiveness often demonstrate progressive, unlimited airway narrowing in response to inhaled bronchoconstrictor stimuli, which is likely to be due to inflammatory changes within the airway wall. It is unknown whether regular therapy with inhaled steroids can limit this excessive response.

Objective: We investigated the effect of inhaled budesonide on the development of a plateau on the dose-response curve to methacholine in patients with asthma who did not show such a plateau before the study.

Methods: Thirty-one atopic patients with asthma (age, 19 to 31 years; FEV₁ > 70% of predicted value; PC₂₀ < 8 mg/ml) with documented absence of a maximal-response plateau to methacholine on two occasions during the run-in period, participated in a double-blind, placebo-controlled, parallel study. Standardized methacholine challenges were performed at -1, 0, 4, 8, and 12 weeks of treatment with inhaled budesonide, 800 µg two times a day, or corresponding placebo, and after a 2-week washout period. Airway response was measured by FEV₁ (percent fall from baseline). A maximal-response plateau was considered if three or more consecutive data points fell within a 5% response range.

Results: Thirty patients completed the study. There was a steady increase in the number of budesonide-treated patients exhibiting a maximal-response plateau on the dose-response curve from zero of 15 patients at run-in to nine of 14 patients at week 12, as compared with four of 16 patients in the placebo group ($p = 0.03$, chi square test). This was accompanied by a significant improvement in PC₂₀ in the budesonide group as compared with the placebo group ($p < 0.01$ at week 12), whereas the changes in FEV₁ were not significantly different between the groups ($p = 0.77$ at week 12).

Conclusion: Regular treatment with the inhaled corticosteroid budesonide limits maximal airway narrowing in response to methacholine by introducing a plateau on the dose-response curve in patients with asthma, who were initially characterized by the absence of a plateau. This indicates that inhaled steroids are likely to reduce the hazard of unlimited airway narrowing in asthma. (*J Allergy Clin Immunol* 1997; 99:330-7.)

Key words: Asthma, airway hyperresponsiveness, glucocorticosteroids, budesonide, methacholine, excessive airway narrowing, maximal-response plateau

Asthma is a chronic inflammatory disease of the airways that is characterized by episodic wheezing, dyspnea, chest tightness, and coughing, which is often associated with atopy and airway hyperresponsiveness to various bronchoconstrictor stimuli.¹ One of the major functional abnormalities in asthma is the capacity for acute airway narrowing, in some cases leading to life-threatening events.² The potential severity of acute airway narrowing in the individual patient is likely to be reflected by the maximal response to inhaled bronchoconstrictor challenges in the laboratory.^{3,4} In patients with relatively severe asthma, a maximal response is often not measurable, as demonstrated by the absence of a plateau on the dose-response curve.³ Such an unlimited response is often referred to as excessive airway narrowing, which can be regarded as a more troublesome and hazardous feature than increased sensitivity to bronchoconstrictors per se.⁵ Indeed, it has been demonstrated that the maximal degree of airway narrowing (e.g., in response to methacholine) is associated with the severity of asthma symptoms.⁶

Hypersensitivity and unlimited airway narrowing in response to bronchoconstrictor stimuli are unlikely to be determined by the same mechanisms. Hypersensitivity may be explained by abnormalities in epithelial function, autonomic neural control, or increased numbers or activity of inflammatory cells.⁷ On the other hand, an elevated maximal response may result from an increase in the amount or contractility of airway smooth muscle,⁸ decreased airway elasticity,⁹ loss of parenchymal elastic recoil pressure,^{10,11} decrease in interdependence between airway wall and parenchyma,^{12,13} or an increase in mucosal or adventitial thickness caused by plasma exudation in the airways.^{14,15} These mechanisms enhance the severity of airway narrowing during smooth muscle contraction, eventually leading to regional airway closure.^{4,12} On the basis of this complex pathophysiology, it may not be surprising that therapeutic intervention can have distinct effects on the sensitivity and maximal response to bronchoconstrictor stimuli in asthma.

Bronchodilators, such as β_2 -agonists, acutely reduce the sensitivity to bronchoconstrictors¹⁶ but do not protect against unlimited airway narrowing in patients with

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Abbreviation used

MFEV₁: Level of maximal response in FEV₁ to inhaled methacholine

relatively severe asthma.¹⁷ However, it can be postulated that inhaled corticosteroids are effective against an unlimited response because of their antiinflammatory effects, which lead to a reduction in airway wall swelling.^{12, 18} Indeed, inhaled budesonide has been shown to reduce the level of the maximal response to methacholine after 4 weeks of treatment in patients with mild asthma who already showed a plateau.¹⁹ Even though this observation indirectly confirms the role of inflammatory mechanisms in determining maximal airway narrowing, it can be argued that the clinical relevance of lowering an existing plateau in mild asthma is questionable. Hence, to examine the potential benefits of inhaled steroids on unlimited airway narrowing, their effects on the shape of the bronchoconstrictor dose-response curve must be investigated in patients with more severe airway hyperresponsiveness.

In this study we have tested the hypothesis that inhaled corticosteroids can reverse the capacity of unlimited airway narrowing in patients with asthma, thereby reducing the possibility of life-threatening obstruction. To that end, we investigated whether 12 weeks of therapy with inhaled budesonide would introduce a maximal-response plateau to methacholine in patients with asthma who initially did not show a plateau on their dose-response curves.

METHODS

Subjects

Thirty-nine patients with asthma were enrolled in the run-in portion of the study. Most of the patients were treated for asthma by their family physician and were recruited by local advertisement. Of these patients, eight individuals were not randomized because they did not meet the inclusion criterion of having an absence of a maximal-response plateau to methacholine on a second occasion (five patients), because their asthma deteriorated (two patients), or because they experienced nausea during placebo treatment (one patient). Thirty-one patients (mean age, 22.8 years; range, 19 to 31 years) participated in the blinded study (Table I). They were all nonsmokers or ex-smokers (for at least 12 months, <5 pack-years), except for subject 28, who admitted to having smoked not more than one cigarette a day.

The patients had a history of episodic dyspnea and wheezing and were atopic, as reflected by a positive skin prick test response (≥ 3 mm wheal) to one or more airborne allergens (Vivo-diagnost, ALK, Benelux). Without a bronchodilator, the baseline FEV₁ had to be more than 70% of the predicted value.²⁰ The patients displayed moderate to severe airway hyperresponsiveness to methacholine; the geometric mean provocative concentration of methacholine to cause a 20% decrease in FEV₁ (PC₂₀) was 0.45 mg/ml at enrollment into the study.²¹ Patients had to demonstrate the absence of a maximal-response plateau on the dose-response curve to methacholine²² at enrollment and at the end of the run-in

period. None of the patients had used inhaled or oral corticosteroids, theophylline, antihistamines, sodium cromoglycate, or nedocromil sodium in the 12 weeks before the study. All patients were stable while using an inhaled short-acting bronchodilator alone on an as-needed basis, which was withheld for at least 8 hours before each measurement. There was no history of upper respiratory tract infection or relevant exposure to allergens during the 2 weeks before the experiments in any of the subjects. The study was approved by the Ethics Committee of the Leiden University Hospital, and all participants gave witnessed, informed consent.

Study design

The study had a double-blind, placebo-controlled, parallel design. It was divided into a run-in period (1 week of single-blind treatment with placebo), a treatment period (12 weeks of double-blind treatment with placebo or budesonide), and a washout period (2 weeks of single-blind treatment with placebo). The subjects were randomly allocated into two treatment groups to receive either budesonide (2 puffs of 400 μ g each, twice a day; total dosage, 1600 μ g per day) or placebo (2 puffs of 500 μ g of micronized lactose each, twice a day,) inhaled by the use of a dry powder inhaler (Turbohaler; Astra).²³ Complete dose-response curves to methacholine were obtained in the run-in period (weeks -1 and 0); after 4, 8, and 12 weeks of treatment; and after 1 and 2 weeks of washout (weeks 13 and 14). The measurements were made at the same time of day, with a 3-hour window in each subject. During the treatment period, the methacholine tests were performed 12 ± 3 hours after the last dose of the test medication was given.

Inhalation challenge

Methacholine inhalation challenges were performed according to a standardized method.²¹ In this way, complete dose-response curves were obtained by inhaling doubling concentrations (0.04 to 624 mg/ml) of methacholine (acetyl- β -methacholine bromide; Janssen Pharmaceuticals, Belgium) in phosphate-buffered saline. Methacholine bromide had been chosen because of the unavailability of methacholine chloride for human use. Both methacholine salts are equipotent, on a molar base, in inducing bronchoconstriction in human beings (PC₂₀ methacholine bromide = $1.2 \times$ PC₂₀ methacholine chloride).²⁴ Methacholine solutions were stored and nebulized at room temperature. The aerosols were generated by a DeVilbiss 646 nebulizer (DeVilbiss Co., Somerset, Pa.) operated by oxygen (output, 130 mg/minute), which was connected to an inspiratory and expiratory valve box and inhaled by tidal breathing through the mouth with the nose clipped during 2 minutes at 5-minute intervals.

Response measurements

The airway response to methacholine was measured by spirometry, with a dry rolling-seal spirometer (Morgan Spiroflow, Rainham/Gillingham, U.K.) and an on-line computer. The response to methacholine was measured by FEV₁ 45 seconds after completion of each inhalation.²² The tests were discontinued if FEV₁ dropped more than 60% from baseline, if FEV₁ reached a value less than 35% of predicted, when 624 mg/ml methacholine had been administered, if the subject felt too much discomfort, or when a plateau on the dose-response curve was reached. Inhaled short-acting β_2 -agonists were administered after completion of each challenge.

TABLE I. Characteristics of randomized patients at enrollment (week 0)

Subject no	Sex	Age (yr)	FEV ₁ (% predicted)	PC ₂₀ (mg/m)	Slope* (% fall/ln mg/ml)
Budesonide-treated group					
1†	F	22	99.5	0.32	12.4
2†	F	20	78.5	0.21	19.4
3	F	22	95.2	0.17	33.2
4	M	23	90.8	0.06	16.3
5†	F	23	78.3	0.23	9.4
6	F	23	78.3	0.25	29.5
7†	M	21	90.8	0.29	12.9
8	F	20	91.3	0.39	29.6
9†	M	24	92.3	0.40	15.9
10†	F	21	93.7	0.55	17.5
11†	M	20	97.0	0.98	25.4
12	F	24	93.0	0.39	26.7
13†	M	31	81.6	1.27	16.4
14†	M	21	89.3	0.49	17.8
15‡	M	23	90.7	0.39	13.4
Mean		22.3	89.4	0.34§	19.7
SD		2.6	6.9	1.04	7.3
Placebo-treated group					
16	F	24	72.8	0.05	17.1
17	M	31	76.7	0.30	14.4
18	M	26	103.1	0.31	19.0
19	F	23	80.4	0.27	24.4
20	F	20	87.8	0.36	21.1
21	F	22	90.5	0.33	11.8
22	F	21	78.9	0.27	27.2
23†	M	22	90.7	0.63	10.8
24	M	21	87.9	0.25	12.5
25	M	19	74.5	0.62	35.3
26	M	25	117.1	0.80	17.1
27	F	22	91.6	1.78	11.5
28	M	30	74.4	0.22	11.0
29†	F	24	102.6	1.58	13.9
30†	F	24	79.1	3.06	13.4
31†	M	20	111.0	7.82	17.9
Mean		23.2	88.7	0.54§	17.4
SD		3.3	13.6	1.75	6.8

*Slope of dose-response curve to methacholine.

†Subjects who subsequently had a maximal-response plateau at the end of the treatment period (week 12).

‡Subject who was withdrawn 2 days after randomization (erroneous inclusion).

§Geometric mean.

||Doubling doses.

Analysis

Responses to methacholine were expressed as percentage decrease in FEV₁ from baseline values and plotted against the ²log nebulized noncumulative methacholine concentration in milligrams per milliliter.^{21,22} The dose-response curves were characterized by their position, slope, and maximal response. The position was expressed as PC₂₀, which was calculated by log-linear interpolation between the two adjacent data points,²¹ and was statistically analyzed logarithmically. The slope of the sigmoid-shaped dose-response curve was calculated by linear regression analysis of the data points used for calculation of the PC₂₀ plus all consecutive data points up to the first data point on the plateau.¹⁷ A maximal response plateau was considered if three or more data points of the highest doses fell within a 5% response range. The level of the maximal FEV₁ response

(MFEV₁) was calculated by averaging the consecutive data points on the plateau.²²

The differences in the presence of a maximal-response plateau between the treatment groups were tested by chi square analysis (without Yates' correction). The changes in ²logPC₂₀, and slope from week 0 within the groups and the differences between the groups were analyzed by using one-way analysis of variance. Values were expressed as means ± SD. A *p* value of less than 0.05, two-tailed, was considered statistically significant.

The sample size of the study was estimated as follows. On the basis of a predicted increase in PC₂₀ of two doubling doses in the active treatment group,^{19,25} it was assumed that the dose-response curve would reach a position in which plateaus are usually observed (8 mg/ml > PC₂₀ > 0.25 mg/ml)^{19,22} in 66% of the patients treated with budesonide, whereas only 7% of the

TABLE II. Methacholine dose-response parameters during run-in, treatment, and washout periods

Parameters tested	Run-in	Treatment			Washout	
	Wk 0	Wk 4	Wk 8	Wk 12	Wk 13	Wk 14
Budesonide treatment (<i>n</i> = 14)						
FEV ₁ (% predicted)*	88.5 (9.2)	90.8 (9.5)	94.0 (7.2)	91.8 (10.0)	89.7 (10.0)	88.7 (10.2)
PC ₂₀ (mg/ml)†	0.28 (0.85)	0.44 (1.13)	0.57 (1.17)	0.73‡ (1.54)	0.38 (1.24)	0.39 (1.18)
Slope (% fall/ln mg/ml)*	17.5 (5.9)	15.3 (5.8)	16.2 (6.5)	16.0 (7.5)	16.2 (7.8)	18.3 (7.3)
Placebo treatment (<i>n</i> = 16)§						
FEV ₁ (% predicted)*	88.8 (13.4)	90.5 (12.3)	87.0 (15.1)	92.4 (13.7)	88.8 (14.2)	89.8 (13.0)
PC ₂₀ (mg/ml)†	0.46 (2.04)	0.50 (1.89)	0.45 (1.97)	0.45 (1.71)	0.51 (1.93)	0.47 (1.55)
Slope (% fall/ln mg/ml)*	14.6 (2.9)	13.1 (2.6)	13.2 (4.0)	13.1 (3.0)	12.5 (3.4)	13.8 (4.2)

*Results are expressed as mean (±SD) values.

†Results are expressed as geometric mean (±SD in doubling doses).

‡Change from week 0 significantly different between budesonide and placebo.

§*n* = 14 after week 12.

placebo-treated patients would develop a plateau by chance. Thereby, a statistical power of 0.8 ($\beta = 0.2$), when $\alpha = 0.05$, is reached with 15 patients in each group, by using the chi square analysis of the presence or absence of plateau.

All analyses were performed with the Statistical Package of the Social Sciences (SPSS-PC+).

RESULTS

None of the subjects experienced clinically relevant side effects. One patient in the budesonide group (subject 15) was withdrawn 2 days after randomization when erroneous inclusion (plateau on dose-response curve at week 0) was discovered. Two patients in the placebo group (subjects 16 and 28) were withdrawn at week 12 because of an exacerbation of asthma, which required additional treatment with antiinflammatory agents. In the analysis these two subjects were included up to the visit before the one at which they were withdrawn (i.e., up to week 8). The average use of as-needed bronchodilators was 0.45 puffs per day in the entire group of subjects during the run-in period. The mean treatment compliance was 95%, as estimated by self-reported doses in diaries.

Lung function

The placebo and budesonide groups were not different with respect to baseline FEV₁ ($p = 0.93$), PC₂₀ ($p = 0.15$), and slope ($p = 0.10$) of the methacholine dose-response curve as measured in the run-in period (week 0) (Table I). There were no differences between the groups in changes in FEV₁ during the course of the study ($p = 0.77$ at week 12) (Table II).

Plateau

The position and shape of the average methacholine dose-response curves in the two groups at week 0 and

week 12 are displayed in Fig. 1. None of the subjects reached a maximal-response plateau to methacholine at the two visits during the run-in period, as required. During the treatment period, the number of patients demonstrating a maximal-response plateau in the budesonide group steadily increased during treatment from zero of 15 patients to nine of 14 patients at 12 weeks. This proportion was significantly greater than the four of 16 patients in the placebo group ($p = 0.03$ at week 12) (Table II, Fig. 2). After the 2-week washout period, this difference between groups was no longer significant.

In those subjects who reached a plateau at week 12, the levels (mean ± SD) of MFEV₁ were 43.8 ± 9.7 and 48.2 ± 5.6 in the budesonide ($n = 9$) and placebo ($n = 4$) groups, respectively.

PC₂₀ and slope

During budesonide treatment, there was an increase in PC₂₀ ($+1.37 \pm 1.7$ doubling doses) as compared with the run-in period, whereas during placebo treatment there was a decrease in PC₂₀ (-0.15 ± 1.3 doubling doses) (Table II, Fig. 3). These changes in PC₂₀ were significantly different between the two groups ($p < 0.01$ at week 12). Two weeks after discontinuation of budesonide treatment, the PC₂₀ returned to a level not significantly different from that of the run-in period ($p = 0.50$) (Fig. 3).

The slope of the dose-response curve decreased slightly in both the budesonide and placebo groups (Table II). The changes in slope were not significantly different between the groups ($p = 0.93$).

DISCUSSION

This study has shown that regular treatment with the inhaled corticosteroid budesonide introduces a plateau on the bronchoconstrictor dose-response curve in pa-

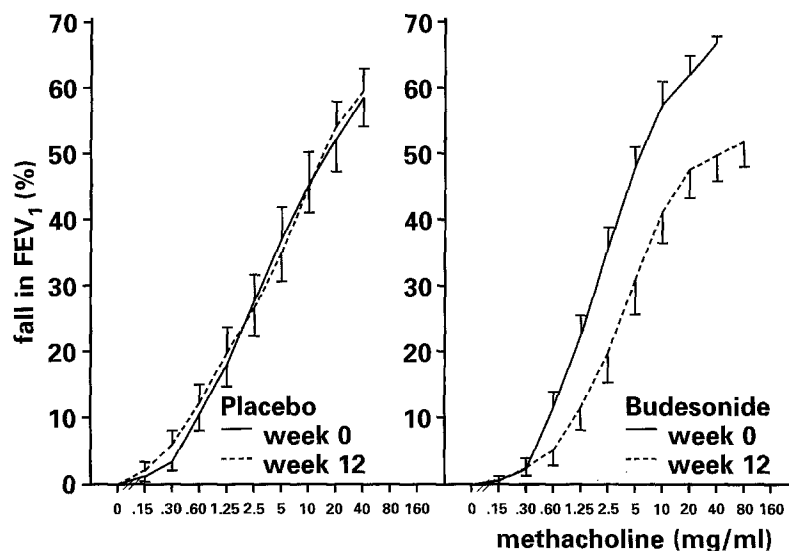


FIG. 1. Average dose-response curves to inhaled methacholine in the placebo-treated group (*left*) and in the budesonide-treated group (*right*) at week 0 (entry, *continuous lines*) and week 12 (end of treatment period, *dotted lines*). Data points have been included if more than 50% of patients inhaled the plotted methacholine dose.

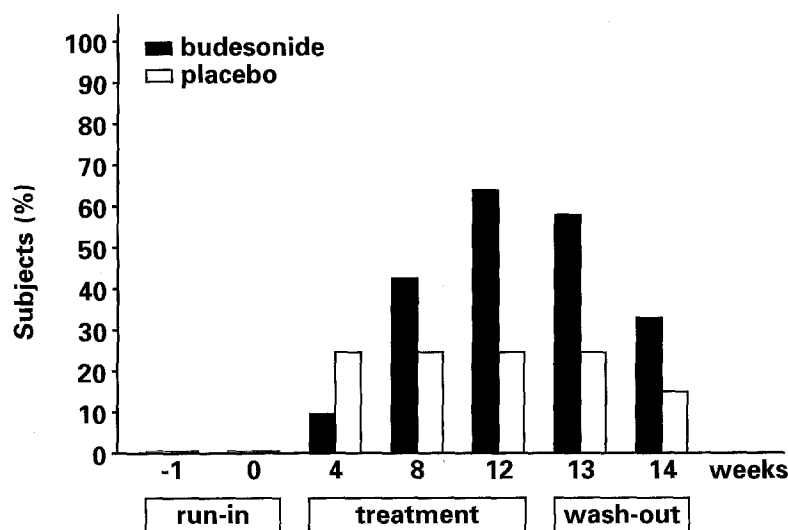


FIG. 2. Percentage of patients exhibiting a maximal-response plateau on the dose-response curve of FEV₁ to inhaled methacholine in placebo and budesonide groups during run-in, treatment, and washout periods.

tients with asthma who initially exhibited unlimited obstruction. This suggests that steroids may reverse the potential for development of hazardous degrees of airway narrowing in patients with relatively severe asthma.

To our knowledge, this is the first study on the effects of inhaled steroids on the shape of the dose-response curve to inhaled methacholine in patients with asthma without a maximal-response plateau. Our results extend those obtained in a previous study, showing a reduction of the methacholine plateau level from a 42% to a 34% fall in FEV₁ after 4 weeks of budesonide treatment in patients with mild asthma who already exhibited a

plateau at entry into the study.¹⁹ The potential development of plateaus by inhaled steroids in asthmatic patients with more severe hyperresponsiveness has only been addressed in one uncontrolled study by Rodwell et al.,²⁶ in which unlimited airway narrowing in response to hypertonic saline solution remained unchanged after 6 to 12 weeks of treatment with beclomethasone dipropionate (600 to 1500 µg daily). However, the differences in design, bronchoconstrictor stimulus, dose, and duration of treatment between that study and ours preclude a proper comparison.

We believe that these findings were obtained with