

Reduction of budesonide after a year of increased use: A randomized controlled trial to evaluate whether improvements in airway responsiveness and clinical asthma are maintained

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We have demonstrated recently that 1 year of regular inhaled budesonide use can produce substantial improvements in airway responsiveness accompanied by significant improvements in clinical asthma severity. The present study was designed to evaluate whether these improvements are maintained when the dose of budesonide is reduced. At the end of the original study, 28 subjects with asthma, who had been in the active-treatment arm of the study were randomized either to continue taking the dose of budesonide taken in the original study or to have the dose reduced. Airway responsiveness to methacholine, bronchodilator requirements, symptoms, and spirometry were assessed after 6 weeks and 3 months. During the 3 months, no subject experienced an asthma exacerbation, and there was no evidence of change in airway responsiveness in subjects who had their steroids reduced (provocative concentration causing a 20% drop in FEV₁: initial, 2.03 mg/ml; final, 1.91 mg/ml), and this change was not different from change in subjects maintained with a higher dose (initial, 3.02 mg/ml; final, 3.12 mg/ml) ($p = 0.39$). Similarly, there was no evidence of any change in bronchodilator requirements ($p = 0.89$). However, after 3 months of reduced steroid use, there was a small decline in spirometry (FEV₁, percent predicted: initial, 84.4%; final, 81.5%), and this change was significantly different from change in subjects in whom steroids were not reduced (initial, 90.2%; final, 90.2%) ($p = 0.002$). At 3 months, symptoms (predominantly sputum production) were also beginning to redevelop in the reduced budesonide group ($p = 0.056$). The results suggest that, when inhaled steroids are reduced after prolonged treatment, improvements in airway responsiveness can be maintained for at least 3 months and that a deterioration in spirometry and symptoms may precede an increase in responsiveness. (J ALLERGY CLIN IMMUNOL 1991;87:483-9.)

There is now extensive evidence that the regular use of inhaled steroids can produce improvements in airway hyperresponsiveness in asthma.¹⁻⁵ Recently,

Abbreviation used

PC₂₀: Provocative concentration causing a 20% fall in FEV₁

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we examined the effects of prolonged treatment with budesonide on airway responsiveness and clinical asthma severity in both inhaled steroid-dependent⁶ and nonsteroid-dependent subjects with asthma.⁷ In both studies, the use of inhaled budesonide was associated with substantial improvements in methacholine airway responsiveness, with some patients returning to the normal range, and improvements in asthma symptoms, bronchodilator use, and number of asthma exacerbations.

TABLE I. Subjects' characteristics at baseline according to treatment group

Subject No.	Budesonide (µg/day)	PC ₂₀ (mg/ml)	FEV ₁ % pred	Asthma severity score	Bronchodilator use (puffs/day)	Allergen exposure score	URTI score	Atopic status
Reduced: nonsteroid dependent								
1	0	4.7	79.1	0	0	0	0	-
2	0	2.2	85.9	0	2.3	4	0	-
3	0	3.8	128.0	0	0	4	0	-
4	0	0.64	81.1	1	6.0	4	0	-
5	0	14.5	89.0	0	0	0	0	-
6	0	2.3	94.5	0	0	0	0	-
7	0	2.0	63.6	2	0	4	0	-
8	0	22.0	83.2	0	0	0	0	-
Reduced: steroid dependent								
9	200	0.32	114.7	0	0	0	0	+
10	200	20.0	67.5	1	1.0	0	0	+
11	200	2.2	81.3	0	4.0	0	0	-
12	400	0.58	70.0	1	0	0	0	+
13	400	0.28	70.8	1	8.1	0	0	-
14	400	0.23	72.7	0	4.3	0	0	++
Maintained: nonsteroid dependent								
15	400	1.1	86.8	0	0.9	0	0	+
16	400	64.0	91.9	0	0	4	1	+
17	400	1.4	73.5	0	6.0	1	0	++
18	400	64.0	92.2	0	0	0	0	-
19	400	21.0	83.0	0	0	0	0	+
20	400	1.1	103.5	0	1.0	0	0	-
Maintained: steroid dependent								
21	400	0.27	84.8	0	4.1	0	0	+
22	400	1.5	86.0	0	0.4	0	0	-
23	400	0.44	89.3	0	0	0	0	+
24	400	0.78	93.1	2	2.9	4	4	-
25	800	2.2	75.5	0	4.0	0	0	+
26	800	0.68	95.1	0	5.7	0	1	-
27	800	11.8	101.2	0	0	0	0	-
28	800	14.0	106.4	0	4.6	0	0	+

URTI, Upper respiratory tract infection.

Short-term crossover studies, in which active treatment has been administered for 4 weeks or less, suggest that airway responsiveness deteriorates within weeks of inhaled steroid reduction.²⁻⁴ If the inflammatory process is more fully resolved after longer treatment with inhaled steroid, the redevelopment of airway hyperresponsiveness and clinical asthma symptoms may be delayed or possibly prevented. The present study was designed to examine the effect of reducing the dose of inhaled budesonide in subjects with asthma who had been using an increased dose regularly for 1 year.

METHODS

Subjects

Twenty-eight participants of previous studies^{6,7} who had completed a year of regular increased budesonide use were

asked to participate in this "follow-up" study. Two subjects were not included; one subject declined because she wanted to conceive and the other subject was experiencing an exacerbation that required oral steroids. A year previously, all subjects had airway hyperresponsiveness to methacholine (PC₂₀, <8.0 mg/ml)⁸ and symptomatic asthma. Originally, 14 subjects had symptoms that were nontroublesome with bronchodilators alone. During the year, they had taken 400 µg of budesonide daily and demonstrated a fourfold mean improvement in airway responsiveness and a significant improvement in clinical asthma severity, with five subjects returning to the normal range of responsiveness accompanied by a complete resolution of symptoms. The others, 14 subjects had been considered inhaled steroid-dependent a year previously. They had taken twice their regular maintenance dose of inhaled budesonide for 1 year and demonstrated both a threefold mean improvement in airway responsiveness, with three subjects returning to the normal range and a significant improvement in clinical asthma se-

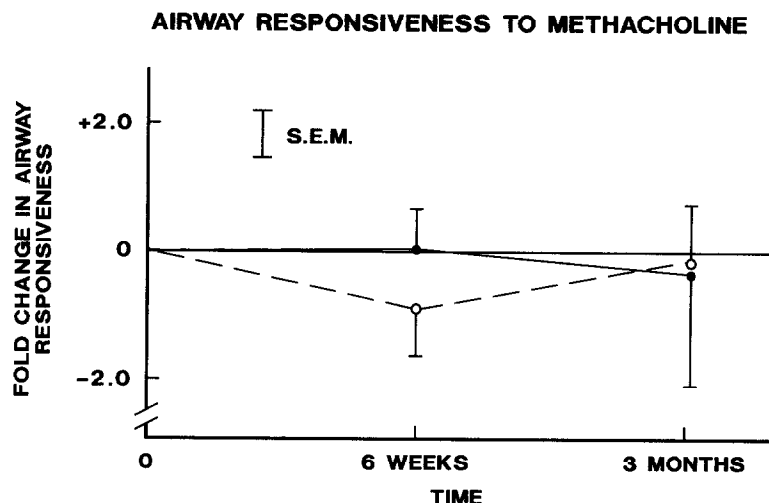


FIG. 1. Airway responsiveness to methacholine. At 3 months, the change from baseline between the two groups was not significant ($p = 0.44$); reduced budesonide (○); dose of budesonide maintained (●).

verity. All subjects signed an informed consent that had been approved by the St. Joseph's Hospital Ethics Committee.

Study design

The present study was a double-blind, randomized, comparison of two parallel treatment groups and was designed to follow immediately after completion of the previous studies.^{6,7} The 14 nonsteroid-dependent subjects who had been taking budesonide, 400 μg for 1 year, were randomized either to continue taking 400 μg daily or to change to placebo. The 14 subjects who had been taking twice their maintenance dose of budesonide were randomized either to continue this dose or return to the dose that had been considered their maintenance dose a year earlier (i.e., the dose was halved) (Table I).

Patients were randomized at their final clinic visit for the previous studies, and the final assessment for those studies became the initial assessment for this study. Further assessments were made at 6 weeks and 3 months.

The primary outcome measures were airway responsiveness to methacholine, measured with a standardized tidal-breathing protocol,⁹ clinical asthma severity, and spirometry. Compliance with taking the trial medication was also assessed at each clinic visit and was calculated from observed and expected canister weight loss. The dates of all known allergen exposures (to which the subject was sensitized) and symptoms of upper respiratory tract infections were also recorded and scored (4, current; 3, within the last week; 2, 2 to 3 weeks previously; 1, 3 to 4 weeks previously).

Clinical asthma severity was assessed in three ways: bronchodilator use, questionnaire, and number of asthma exacerbations. During the study, subjects were instructed to keep symptoms "nontroublesome" (not awakened at night by symptoms and no limitation of normal daily activities) with inhaled β -agonists only when they were needed. Each

subject used the same bronchodilator throughout the study, and the amount used was recorded in a diary for 1 week after each clinic visit. At each clinic visit, an asthma severity questionnaire was completed. There were six items: (1) awakened at night by symptoms, (2) awakened in the morning with symptoms, (3) limitation of normal daily activities, (4) sputum, (5) use of bronchodilator more than four times per day, and (6) FEV₁ prebronchodilator <70% predicted; 1 point was scored for each of the first five items that had been positive on 1 or more days during the previous week and 1 point was scored for reduced spirometry. Therefore the maximum asthma severity score was 6.

An asthma exacerbation was defined as requiring bronchodilator more than four times per day for 2 to 3 consecutive days or a rapid deterioration in symptoms.

Statistical analysis

Airway responsiveness to methacholine was expressed as the concentration of methacholine needed to provoke a fall in FEV₁ of 20% (PC₂₀). Data demonstrated instability of variance, and therefore, all PC₂₀ values were logarithmically transformed before analysis. During analysis, it was found that all the outcomes in the two reduction groups were very similar, and also, the outcomes in the two groups in whom steroids were not reduced were very similar. Therefore, for simplicity, the data have been combined and are presented as two groups, reduced and maintained. Changes during the 3 months in the two treatment groups were compared using unpaired t tests. Associations were evaluated using Pearson's correlation coefficient, and proportions were evaluated using Fisher's exact test. Results were considered significant at $p < 0.05$ (one-sided).

RESULTS

All twenty-eight subjects completed the study, and all subjects were assessed at 6 weeks and 3 months.

TABLE II. Change in outcomes (between baseline and 3 months)

Subject No.	PC ₂₀ (ln mg/ml)	FEV ₁ % pred	Asthma severity score	Bronchodilator (puffs/day)	Allergen exposure score	URTI score
Reduced: nonsteroid dependent						
1	1.37	-3.3	0	0	0	0
2	-0.71	-16.7	+1	-1.4	-4	+2
3	-1.77	-8.4	0	0	-2	0
4	0.54	-5.1	+2	-3.1	-1	0
5	-1.43	-0.8	0	0	0	0
6	1.35	6.2	0	0	0	0
7	-1.45	4.2	0	0.3	0	0
8	0.42	2.5	0	0	0	0
Reduced: steroid dependent						
9	0.66	-0.7	+1	0	0	0
10	0.07	5.0	-1	-1.0	-4	-1
11	-0.19	-3.3	0	0	-1	0
12	0.88	-6.0	0	0	0	+4
13	1.44	-11.6	+2	-0.8	0	0
14	-1.20	-2.7	+4	-0.3	0	0
Maintained: nonsteroid dependent						
15	-0.20	1.9	0	0	+1	0
16	0.00	2.0	0	0	0	0
17	-0.62	7.6	0	0	0	0
18	-0.51	-1.1	0	0	0	0
19	-1.03	-1.7	0	0	+4	0
20	0.06	-2.3	0	0	0	0
Maintained: steroid dependent						
21	0.25	-1.6	0	-0.7	0	0
22	-0.53	-5.6	0	-0.3	0	0
23	0.24	4.6	0	0	+4	+4
24	-0.83	-14.8	-1	3.4	-4	0
25	-0.54	5.4	+1	0	+4	0
26	0.97	-0.2	0	-1.7	0	-1
27	0.62	4.1	0	0	0	0
28	0.54	2.1	+1	-0.3	0	0

URTI, Upper respiratory tract infection.

Airway responsiveness to methacholine remained very stable in both treatment groups during the 3 months, and there was no evidence of any deterioration in subjects in whom steroids were reduced ($p = 0.44$) (Fig. 1) (Table II). The power to detect a twofold change in airway responsiveness was 98.3%. It is unlikely that this result was influenced by the magnitude of improvement during the previous year with additional budesonide, since the change was similar in the reduced (plus 3.49-fold) and the maintained groups (plus 4.97-fold) ($p = 0.46$). There was little evidence of any change in bronchodilator use during the 3 months of follow-up ($p = 0.89$) (Fig. 2), and no subject required additional inhaled steroid because of an asthma exacerbation.

At baseline, the FEV₁ percent predicted was slightly higher in the maintained group than in the reduced

group. At 6 weeks, there was little change in the FEV₁ percent predicted, but by 3 months, there had been a small decrease in subjects taking reduced steroids. This change from baseline was significantly different from the change observed in subjects in whom steroids were not reduced ($p = 0.002$) (Fig. 3). In the reduced group, five subjects experienced a decrease in FEV₁ of >0.2 L, and in the maintained group, a similar decrease occurred in two subjects.

At 6 weeks, the asthma severity scores for the subjects receiving reduced steroids were very similar to scores for the maintained group. By 3 months, there was an increase in asthma severity score from baseline in the reduced group compared to the maintained group ($p = 0.056$) (Fig. 4); the predominant symptom producing this increase in score was sputum production. The five subjects in the reduced group who

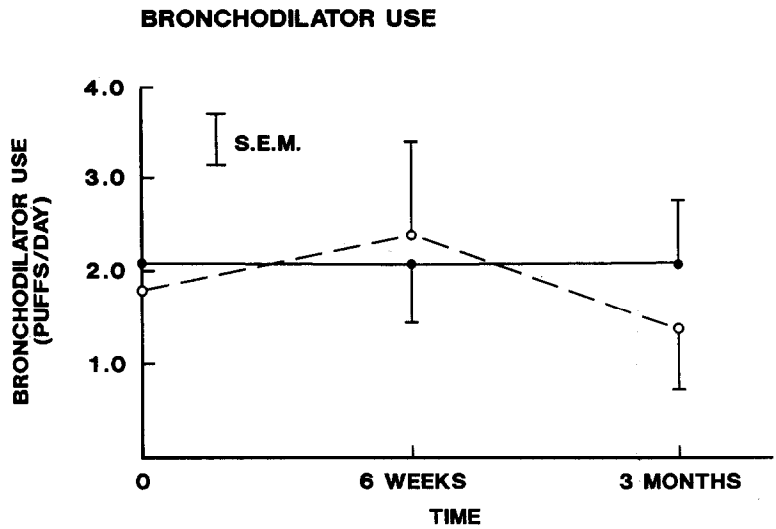


FIG. 2. There was no evidence of any increase in bronchodilator use in the reduced group ($p = 0.88$); reduced budesonide (○); dose of budesonide maintained (●).

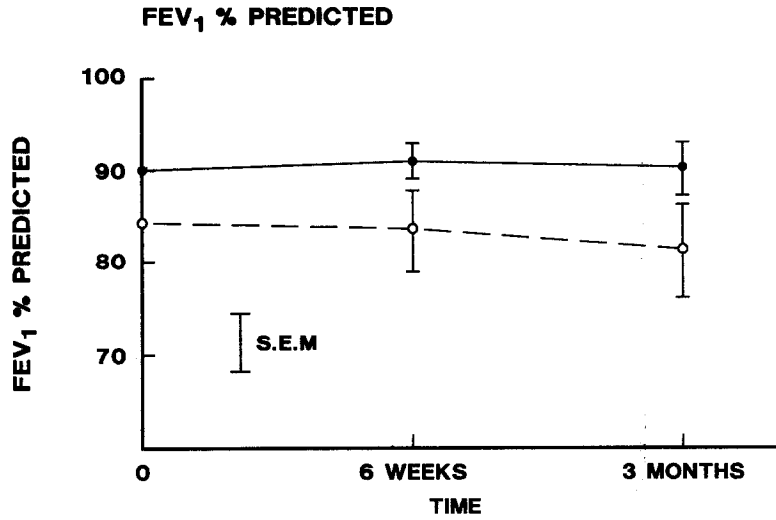


FIG. 3. By 3 months, the decrease in FEV₁ percent predicted from baseline in the reduced group (○) was greater than in the maintained group (●) ($p = 0.002$).

experienced a deterioration in symptoms also had a decrease in FEV₁.

Patients who demonstrated more than a twofold improvement in airway responsiveness receiving inhaled steroids were less likely to experience a deterioration in symptoms at 3 months ($p = 0.003$). There was also a trend toward an inverse relationship between improvement in responsiveness while subjects received inhaled steroids and decrease in FEV₁ after reduction ($r = 0.42$). Similarly, only one of the five subjects whose PC₂₀ was <2.0 mg/ml after a year of budesonide treatment did not develop symptoms ($p = 0.003$), and the final level of responsiveness

also tended to be inversely related to deterioration in FEV₁ ($r = 0.39$). There was no evidence of a relationship between pretreatment airway responsiveness and the development of symptoms ($r = 0.18$).

Compliance with taking the trial medications was very good in both the reduced group (mean, 103.1%; SD, 21.5) and the maintained group (mean, 99.3%; SD, 8.4).

DISCUSSION

The results of this study demonstrate that, when inhaled budesonide is withdrawn or reduced after a year of regular, increased use, improvements in air-

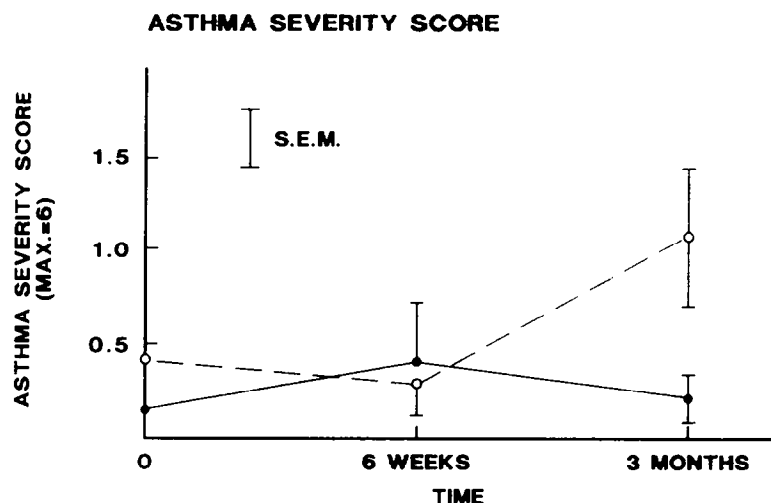


FIG. 4. By 3 months, there was a strong trend toward a greater deterioration in asthma severity score from baseline in the reduced budesonide group (○) than in the maintained group (●) ($p = 0.056$).

way responsiveness and the reduced need for bronchodilators may persist for at least 3 months. By 3 months, however, symptoms, predominantly sputum production, are tending to recur, and spirometry is beginning to deteriorate in some patients.

The finding that methacholine airway responsiveness did not deteriorate during a 3-month period contrasts with the results of shorter studies.^{2,4} It is possible that there is more complete resolution of the inflammatory process during a long period of treatment with more thorough repair of epithelial damage,¹⁰ possibly accompanied by a reduction in the number of mucosal mast cells.¹¹ Under these circumstances, a longer or more severe exposure to an inflammatory stimulus might be required to create new damage and result in an increase in airway responsiveness.

In those subjects who began to deteriorate, the first signs were an increase in sputum production and a reduction in FEV₁. It is possible that the initial inflammatory changes may occur at the mucosal level and include an increase in output from the mucous glands, some microvascular leakage,¹² and edema, and that these changes may occur before disintegration of the epithelial layer and hyperresponsiveness begin to develop.¹³

The cause of some subjects demonstrating a deterioration in symptoms and spirometry, when budesonide was reduced, while other subjects remained asymptomatic, remains unclear. Both allergen exposure and respiratory infections are associated with deterioration in clinical asthma. However, in this study, the sample size was too small to provide sufficient

statistical power to evaluate the effects of these inflammatory stimuli.

In this study, the best predictors of patients most likely to deteriorate, when budesonide was reduced, appear to be the magnitude of improvements in airway responsiveness while patients were receiving medication and the final level of responsiveness at the end of the year of treatment. Patients who demonstrated less than a twofold improvement in airway responsiveness and who remained in the moderate to severe range after a year receiving additional, regular budesonide were more likely to deteriorate when the medication was reduced. However, a possible explanation is that the initial dose of inhaled steroids was inadequate, resulting in residual inflammation, incomplete recovery, and increased susceptibility to renewed inflammation.

At the present time, the recommended objectives of the treatment of asthma are to achieve control or the best results, to maintain this status with the minimum of medication, and to prevent severe exacerbations by an early increase in anti-inflammatory treatment.¹⁴ The results of this and the initial studies^{6,7} suggest that increased doses of inhaled steroids may have to be prolonged to achieve optimal improvement and minimize or delay the risk of exacerbation after reduction of the medication. However, the optimum duration of increased use, which may also depend on the dose, still has to be established. Some subjects, after a year of increased steroid use, demonstrated no evidence of deterioration after 3 months of reduction. This finding raises the question of whether permanent

resolution of airway hyperresponsiveness and clinical asthma are possible, and this too will need to be addressed in future studies.

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