

Long-term effects of budesonide on airway responsiveness and clinical asthma severity in inhaled steroid-dependent asthmatics

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ABSTRACT: Budesonide 400 µg daily, in nonsteroid-dependent asthma, can produce improvements in airway responsiveness and clinical asthma severity, with some patients returning to normal responsiveness and becoming asymptomatic. This study examined whether similar improvements occur when asthmatics, who are dependent upon inhaled steroids, take either a regular maintenance dose of inhaled steroid or twice that amount for a year. Thirty two asthmatics were each stabilized on the minimum amount of inhaled steroid that would keep symptoms non-troublesome. In a double-blind, randomized manner, half were assigned to remain on a maintenance dose (MD) and the rest received twice that dose (MD×2) for one year. Before and monthly throughout the study, airway responsiveness to methacholine was measured and clinical asthma severity assessed by questionnaire, inhaled bronchodilator use and number of asthma exacerbations. There was a significant improvement in airway responsiveness and clinical asthma severity in both treatment groups. Those on MD×2 showed the greatest improvement but the difference between the two groups did not reach significance. This study provides strong evidence that prolonged use of inhaled steroids is associated with improvement in airway responsiveness and clinical asthma severity in inhaled steroid-dependent asthma with a suggestion that the improvements are dose related.

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Airway hyperresponsiveness in asthma develops as part of a complex inflammatory process [1] and is related directly to both clinical asthma severity [2] and the severity of inflammation [3]. Randomized, controlled trials have produced strong evidence that inhaled corticosteroids can give rise to large improvements in airway hyperresponsiveness in nonsteroid-dependent asthmatics [4-6] and that, with prolonged treatment, some patients can return to the normal range of responsiveness with total resolution of their asthma symptoms [7, 8].

A three week study of regular inhaled steroids in more severe asthmatics [5] and two uncontrolled observations over a year in steroid dependent patients [9, 10] have suggested that similar improvements in responsiveness may occur in more severe asthmatics, but there have been no long-term, randomized, controlled studies in these patients. Similarly, there have been no controlled evaluations of the clinical changes associated with alterations in airway responsiveness in these more severe asthmatics.

The purpose of this study was to determine whether

a year of regular inhaled steroid, in inhaled steroid-dependent asthmatics, can produce improvements in airway responsiveness, possibly with full resolution, and to evaluate the clinical relevance of such improvements. It was not possible to carry out a conventional placebo-controlled trial because the patients could not be withdrawn from inhaled steroid. In nonsteroid-dependent asthmatics, improvements in responsiveness are dose related [11] and, since a similar pattern might be expected in more severe asthmatics, the study question was addressed using a two dose design. The subjects were randomized either to remain on a regular maintenance dose of inhaled steroid or to receive twice that dose for one year.

Methods

Subjects

Thirty two adult asthmatics were selected from patients attending the Firestone Regional Chest and Allergy Clinic at St. Joseph's Hospital and the McMaster

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University Medical Centre in Hamilton. All were required to have airway hyperresponsiveness to methacholine (provocative concentration producing a 20% fall in forced expiratory volume in one second (PC_{20}) <8.0 mg·ml⁻¹) [2] and asthma symptoms that required regular treatment with both inhaled steroids and bronchodilators.

In each patient the minimum dose of inhaled steroids, that would keep asthma symptoms non-troublesome, was established in a standardized manner. Each potential subject took beclomethasone dipropionate 400 µg daily until symptoms were non-troublesome. Non-troublesome was defined as: not awakened at night by symptoms, no sputum, no limitation of normal daily activities, forced expiratory volume in one second (FEV_1) $>70\%$ predicted pre-bronchodilator, or $>80\%$ post-bronchodilator, and inhaled bronchodilators needed no more than 2 puffs, 4 times per day. If these criteria were not achieved, the patient was excluded. If the criteria were met, the dose was reduced by 100 µg per week until symptoms began to deteriorate. The minimum maintenance dose was considered to be 100 µg above the dose at which symptoms first started to deteriorate. At the beginning of this study, budesonide was still an investigational drug in Canada and only subjects who met the entry criteria and were randomized were allowed to use it. Therefore, minimum maintenance inhaled steroid doses were established using beclomethasone dipropionate which has been shown to have similar topical potency to budesonide [12].

Subjects were required to be stable on their maintenance dose of beclomethasone dipropionate for at least 4 wks before randomization and they were also required not to have needed or taken prednisone or cromoglycate within two months of enrolment. Women were not included if pregnant or nursing and those of child-bearing potential had to agree to use a reliable contraceptive method throughout the study. All subjects signed an informed consent that had been approved by the St. Joseph's Hospital Research Committee.

Study design

In this double-blind, parallel group comparison, patients were randomized either to take a maintenance dose (MD) of budesonide or twice that dose (MD×2) for one year. After establishing minimum maintenance requirements (beclomethasone dipropionate 100, 200, 300 or 400 µg daily), patients were stratified into "lower dose" (beclomethasone dipropionate 100 and 200 µg daily) or "higher dose" (beclomethasone dipropionate 300 and 400 µg daily). Those in the lower dose strata were randomized to take either budesonide 200 µg (MD) or budesonide 400 µg (MD×2) daily for one year and those in the higher dose strata were randomized to take either budesonide 400 µg (MD) or budesonide 800 µg (MD×2) daily for one year.

At the beginning of the study, airway responsiveness to methacholine was measured using a standardized tidal

breathing technique [13]. Spirometry was measured, clinical asthma severity and asthma history were documented by questionnaire, and atopic status was estimated by skin prick tests with 16 common allergen extracts.

Monthly throughout the study, subjects attended the clinic for assessment of the two primary outcome measures which were airway responsiveness to methacholine and clinical asthma severity. At each clinic visit, compliance with taking the trial medication was calculated from the observed and expected canister weight loss. The dates of all known allergen exposures and symptoms of upper respiratory tract infections were also recorded and scored: 4=current; 3=within the last week; 2=2-3 wks ago; 1=3-4 wks ago.

The monthly assessment of clinical asthma severity was determined from the following clinical features: symptoms, medication use and airway calibre and also from the number of asthma exacerbations requiring additional treatment. During the study, subjects were instructed to keep symptoms non-troublesome (defined above) using inhaled bronchodilators only as needed. Each subject used the same bronchodilator throughout the study and the amount used was recorded in a diary for one week after each monthly clinic visit. At each monthly clinic visit, spirometry was measured and an asthma severity questionnaire was completed [8, 14]. This instrument contains six dichotomous questions that are each considered to be clinical indicators of poor asthma control [15]. Symptoms: 1) awakened at night by symptoms; 2) awakened in the morning with symptoms; 3) limitation of normal daily activities; 4) sputum. Medication use: 5) bronchodilator more than 4 times per day. Airway calibre: 6) FEV_1 prebronchodilator $<70\%$ predicted.

One point was scored for each of the first five items that had been positive on one or more days during the previous week and one point scored for reduced spirometry at the clinic visit. Therefore, the maximum monthly asthma severity questionnaire score was 6.

An asthma exacerbation was defined as requiring bronchodilator more than four times per day for two to three consecutive days or a rapid deterioration in symptoms. If a subject developed an exacerbation, the trial medication was continued and the subject given additional budesonide in a non-blind manner, 200 µg twice daily. If, after a week, symptoms had resolved, they took the additional budesonide 200 µg once daily for one further week. If symptoms persisted, further weekly courses of 200 µg twice daily were given until resolution. If symptoms deteriorated or showed no improvement after two days of additional budesonide, prednisone was given in a dose of 30 mg daily for five days and then reduced by 5 mg daily to zero. No primary outcome measurements were made for 4 wks after additional steroids. For respiratory infections with purulent sputum, antibiotics were given. Doses and dates of all additional medications were recorded.

Subjects were instructed to use only the medication that we gave them for their asthma and not to receive

immunotherapy. They were asked to avoid major environmental changes.

Statistical analysis

Airway responsiveness to methacholine was expressed as the concentration of methacholine that would provoke a 20% fall in FEV₁ (PC₂₀). All PC₂₀ data were logarithmically transformed before analysis to improve the stability of the variance. The effect of budesonide on the primary outcome measures was assessed using repeated measures analysis of variance with and without within-subject covariate adjustment for FEV₁, allergen exposure and upper respiratory tract infections. Factors examined were treatment, time and treatment × time interaction. The mean for each three monthly period was calculated (1–3, 4–6, 7–9, 10–12) to ensure that all cells in the repeated measures analysis of variance (ANOVA) were filled and that no data were omitted from the analysis. Medication data were analysed using Wilcoxon rank sum test. All subjects who were randomized were included in the analysis. Treatment differences were considered significant at $p < 0.05$. The alternative hypothesis was that the MD×2 group would show greater improvement than the MD group and therefore one-sided tests were used.

Results

Thirty one of the 32 subjects who were randomized, completed the study. One subject, on twice his maintenance dose of budesonide, was withdrawn at three months after apparently becoming sensitized to the trial aerosol. There should have been a total of 407 monthly assessments but 34 were omitted. Twelve assessments in the MD group and 15 in the MD×2 group were not made because additional steroids had been taken during the previous 4 wks; one in the MD group and 2 in the MD×2 group were not made because the subjects had

current respiratory infections; three assessments in the MD group were omitted for other health reasons and one on MD was missed due to failure to attend the clinic.

At enrolment, airway hyperresponsiveness was slightly more severe in the MD×2 group (mean PC₂₀: 0.307 mg·ml⁻¹) than in the MD group (mean PC₂₀: 0.677 mg·ml⁻¹). However, because there was a wide range of responsiveness in both groups (table 1), this difference was not significant. During the year, there was a significant improvement in airway responsiveness in both groups ($p = 0.007$) (fig. 1). Although the mean improvement in the MD×2 group tended to be larger (approximately threefold) than the mean improvement in the MD group (approximately twofold), neither the treatment effect between the two groups ($p = 0.19$) nor the treatment/time interaction ($p = 0.89$) were significant. Even at the end of the study, the difference between the two treatment groups did not quite reach conventional significance ($p = 0.11$) (95% confidence interval (CI) -1.2 fold to +3.5 fold). FEV₁, but not allergen exposure or respiratory infection, was a significant covariate but adjusting for the covariates did not alter the significance level of the treatment effect or the treatment/time interaction. For both groups as a whole, the largest improvements in responsiveness occurred during the first six months (fig. 1) but within individual subjects stable plateaux (<twofold change in PC₂₀) were rare. In both treatment groups there was a very wide range of change in responsiveness over the year (fig. 2). In the MD×2 group, 13 subjects showed an improvement, with three returning to the normal range of responsiveness [2]. In the MD group, ten improved, with two returning to the normal range. Changes in airway responsiveness over the year were not related to the duration of inhaled steroid use before enrolment ($r = 0.15$), duration of asthma ($r = -0.30$), atopy ($r = -0.04$) or airway responsiveness at enrolment ($r = -0.34$). In the MD group, change in airway responsiveness showed no evidence of being related to whether subjects were on their true maintenance dose (200 or 400 µg) or slightly more than their true maintenance dose (100 or 300 µg) ($r = -0.14$).

Table 1. – Subject characteristics at enrolment

Characteristic	MD	MD×2
n	16	16
Gender male/female	6/10	7/9
Age yrs (SD)	42 (14.4)	41 (10.1)
Atopic status*	7	6
FEV ₁ % pred (SD)**	86 (13.7)	83 (13.8)
PC ₂₀ mg·ml ⁻¹ Mean	0.677	0.302
Range	0.064–6.6	0.023–2.3
Duration of inhaled steroid use yrs Mean	4.9	6.1
Range	<1–13	<1–13

*: number of subjects with a 2 mm or larger wheal response to one or more skin prick tests with 16 common allergens; **: CRAPO *et al.* [16]; MD: maintenance dose; MD×2: twice maintenance dose; FEV₁: forced expiratory volume in one second; PC₂₀: provocative concentration producing a 20% fall in FEV₁.

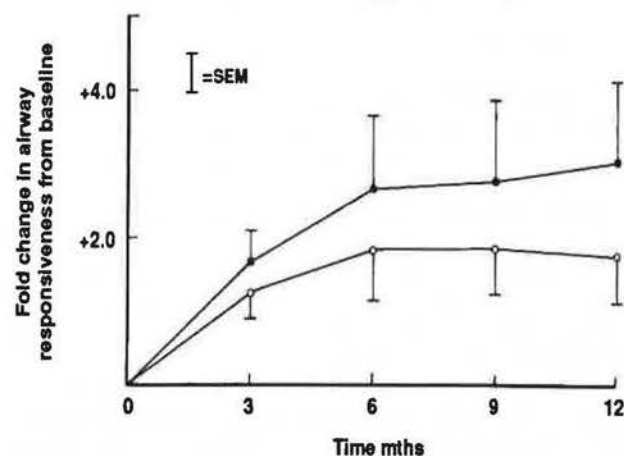


Fig. 1. – Airway responsiveness to methacholine expressed as a fold change from baseline. O: maintenance dose; ●: twice maintenance dose. Error bars represent within-subject variance over time.

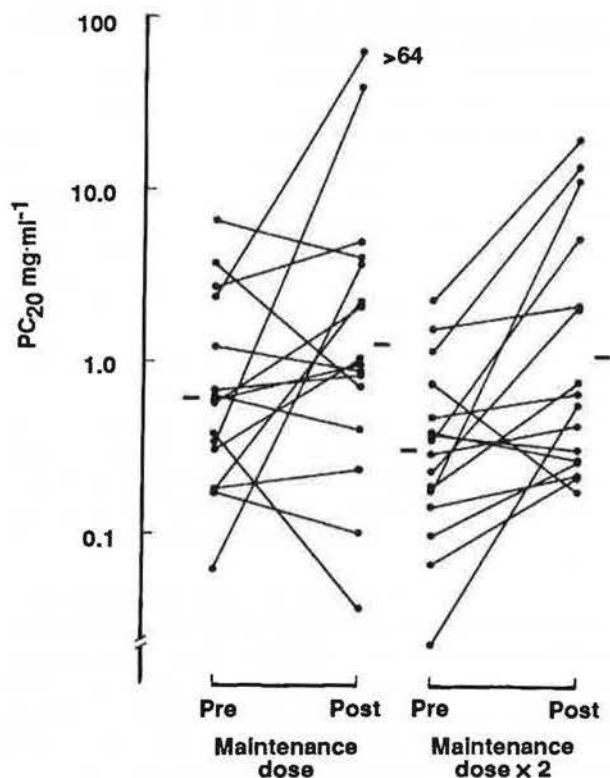


Fig. 2. - Airway responsiveness to methacholine (PC_{20}) immediately before starting and on the last day of medication. Number of subjects showing >twofold improvement in PC_{20} : maintenance dose = 6; twice maintenance dose = 9. PC_{20} : provocative concentration producing a 20% fall in forced expiratory volume in one second.

At enrolment, the overall asthma severity score was slightly higher in the MDx2 group (1.75) than in the MD group (0.94) but this difference was not conventionally significant ($p=0.06$). During the year of treatment, this score tended to improve in both groups but the change did not quite reach significance ($p=0.06$), nor did the difference between the two groups both in terms of the treatment effect ($p=0.25$) and the treatment/time interaction ($p=0.19$) (fig. 3). However, the symptom component of this instrument (questions 1-4) showed a significant improvement over the year ($p=0.011$) but with no evidence of any difference between the two groups ($p=0.47$) (fig. 3).

Bronchodilator use in the two groups was very similar initially (MD=5.29 puffs·day⁻¹; MDx2=5.34 puffs·day⁻¹). There was a significant reduction in the need for bronchodilators over the year in both groups ($p<0.001$) (fig. 3). Although there was a trend towards a greater reduction in the MD group, the difference between the two groups, both for a treatment effect ($p=0.42$) and a treatment/time interaction ($p=0.48$), was not significant.

The initial FEV₁ in the two groups was similar (MD=2.78 l; MDx2=2.66 l). Over the year both groups showed a small but significant improvement ($p<0.001$) (fig. 3). As with the other outcome measures, there was no evidence of any difference between the two groups in terms of either a treatment effect ($p=0.49$) or a treatment/time interaction ($p=0.48$).

Exacerbations of asthma requiring additional inhaled steroids tended to be less in the MDx2 group both in terms of the number of subjects experiencing exacerbations and the number of courses required. In the MDx2 group, four subjects required a total of

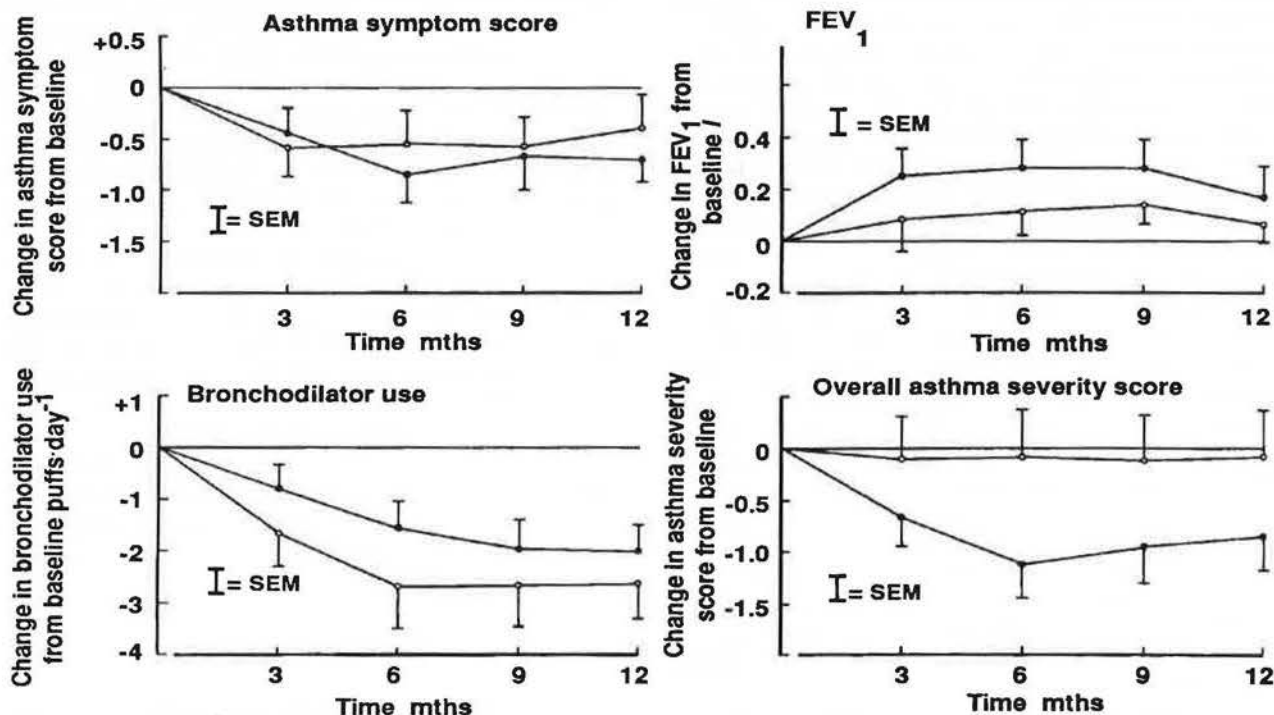


Fig. 3. - Asthma symptom score, daily bronchodilator use, FEV₁ % predicted and overall asthma severity score, expressed as a change from baseline. O: maintenance dose; ●: twice maintenance dose. Error bars represent within-subject variance over time. FEV₁: forced expiratory volume in one second.

11 wks of additional budesonide and none required any prednisone. In the MD group, seven subjects required a total of 13 wks of additional budesonide and 2 subjects required 3 courses of prednisone.

Compliance with using the trial medication was very good (MD:98.8±10.7; MD×2: 98.5±11.8). No subject required treatment for candidiasis but hoarseness, dysphonia, cough or throat irritation were reported on one or more occasions by five subjects in the MD group and by six subjects in the MD×2 group. Other possible side-effects were mild and transient and were equally distributed between the two groups.

Discussion

The results of this study have shown that coincident with regular budesonide use, either as a maintenance dose or twice that amount, for one year, inhaled steroid-dependent asthmatics showed an improvement in both airway responsiveness to methacholine and clinical asthma severity (asthma symptoms, bronchodilator use and FEV₁). Patients in the higher dose group tended to show larger improvements in responsiveness and overall clinical asthma severity and fewer asthma exacerbations requiring additional treatment, but the differences between the two groups did not reach conventional significance.

The variance and sample size provided sufficient power (94%) to detect a twofold difference in responsiveness between the two treatment groups, a difference that is generally considered to be clinically significant and larger than the natural fluctuations which occur in asthmatics who are not on inhaled or oral steroids [8, 9]. However, the maximum observed difference between the two groups was just less than twofold (1.72 fold) and not conventionally significant. The 95% confidence interval for the true difference in airway responsiveness between the two groups was -1.2 to +3.5 fold. This trend towards a dose effect is further supported by the observation in a short-term study in nonsteroid-dependent asthmatics, that improvement in responsiveness is dose-related [11]. The clinical relevance of the difference between the two groups can be explored by examining the clinical outcomes. Although not statistically significant, the pattern of improvement in the overall clinical asthma score was similar to that of airway responsiveness. The clinical asthma score was mainly subjective and reflected changes perceptible to the patient. Therefore, if the trend observed was in fact a true difference between the two groups, this suggests that the difference may be clinically important. Similarly, there tended to be fewer asthma exacerbations in the MD×2 group. However, a similar pattern was not observed for bronchodilator use. Therefore, the clinical importance of any difference in airway responsiveness between the two doses remains equivocal.

Two findings in this study require further discussion. Firstly, both groups showed improvement in airway responsiveness and asthma severity and secondly, there

was a wide variability in the improvement in airway responsiveness in both groups.

A number of factors may have contributed to the improvement in the maintenance dose group. Firstly, budesonide may have a higher topical potency than beclomethasone dipropionate which was used to establish the minimum maintenance dose. Secondly, those with a minimum maintenance dose of 100 and 300 µg received 200 and 400 µg, respectively, if randomized to the low dose group but analysis provided no evidence of this being important. Thirdly, some spontaneous variations in asthma severity might be expected. Some patients would be destined to show spontaneous improvement, others to remain stable or to deteriorate. Exacerbations were treated with more intensive steroid therapy which would have prevented deterioration in responsiveness. Thus, because of those manifesting spontaneous improvement, the mean airway responsiveness of the group could be expected to improve.

The reason for the heterogeneous treatment effect remains obscure because none of the obvious possible predictors showed a correlation with improvement. However, there are four possible mechanisms which may have contributed to the wide variation of changes in airway responsiveness during the year. Firstly, there may have been large spontaneous fluctuations in airway responsiveness during the year or instability at baseline but these, both in the light of previous studies [5, 8, 9] and the stability of within-subject variation over time (fig. 1), seem unlikely. Secondly, at enrolment the potential for improvement varied greatly between subjects. Some patients may have been optimally treated with inhaled steroids prior to the study and have already reached a plateau of improvement within the hyperresponsive range [8]. That is, even after aggressive treatment, there was residual, inhaled steroid resistant, hyperresponsiveness. Whereas, other subjects may have been treated previously with an insufficient dose or for insufficient time to have reached a plateau and, therefore, have had variable potential for improvement. Thirdly, there may have been imprecision in estimating the maintenance dose with the result that some subjects in the maintenance group were overtreated and some in the twice maintenance group would have shown an improvement if they had received a higher dose. Fourthly, for reasons as yet unclear, the effect of budesonide on airway responsiveness varies greatly between patients.

The relative contribution of these mechanisms is speculative. However, the results for the population as a whole are consistent with previous findings that regular use of inhaled steroid can improve airway responsiveness and clinical asthma severity [8].

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References

1. O'Byrne PM. – Airway inflammation and airway responsiveness. *Chest*, 1986, 90, 575–577.
2. Juniper EF, Frith PA, Hargreave FE. – Airway responsiveness to histamine and methacholine: relationship to minimum treatment to control symptoms of asthma. *Thorax*, 1981, 36, 575–579.
3. Kirby JG, Hargreave FE, Gleich GJ, O'Byrne PM. – Bronchoalveolar cell profiles of asthmatic and nonasthmatic subjects. *Am Rev Respir Dis*, 1987, 136, 379–383.
4. Kraan J, Koeter GH, Mark ThW, Sluiter HJ, DeVries K. – Changes in bronchial hyperreactivity induced by 4 weeks of treatment with antiasthmatic drugs in patients with allergic asthma: a comparison between budesonide and terbutaline. *J Allergy Clin Immunol*, 1985, 76, 628–636.
5. Jenkins CR, Woolcock AJ. – Effect of prednisone and beclomethasone dipropionate on airway responsiveness in asthma: a comparative study. *Thorax*, 1988, 43, 378–384.
6. Ryan G, Latimer KM, Juniper EF, Roberts RS, Hargreave FE. – Effect of beclomethasone dipropionate on bronchial responsiveness to histamine in controlled nonsteroid-dependent asthma. *J Allergy Clin Immunol*, 1985, 75, 25–30.
7. Kerrebijn KF, Van Essen-Zandervliet EE, Neijens HJ. – Effect of long-term treatment with inhaled corticosteroids and beta-agonists on the bronchial responsiveness in children with asthma. *J Allergy Clin Immunol*, 1987, 79, 653–659.
8. Juniper EF, Kline PA, Vanzielegem MA, Ramsdale EH, O'Byrne PM, Hargreave FE. – Effect of long-term treatment with inhaled corticosteroids on airway hyperresponsiveness and clinical asthma in nonsteroid-dependent asthmatics. *Am Rev Respir Dis*, 1990, 142, 832–836.
9. Juniper EF, Frith PA, Hargreave FE. – Long-term stability of airway responsiveness to histamine. *Thorax*, 1982, 37, 288–291.
10. Woolcock AJ, Yan K, Salome CM. – Effect of therapy on bronchial hyperresponsiveness in the long-term management of asthma. *Clin Allergy*, 1988, 18, 165–176.
11. Kraan J, Koeter GH, Van der Mark ThW, Boorsma M, Kukler J, Sluiter HJ, DeVries K. – Dosage and time effects of inhaled budesonide on bronchial hyperreactivity. *Am Rev Respir Dis*, 1988, 137, 44–48.
12. Boe J, Rosenhall L, Alton M, *et al.* – Comparison of dose-response effects of inhaled beclomethasone dipropionate and budesonide in the management of asthma. *Allergy*, 1989, 44, 349–355.
13. Juniper EF, Frith PA, Dunnett C, Cockcroft DW, Hargreave FE. – Reproducibility and comparison of responses to inhaled histamine and methacholine. *Thorax*, 1978, 33, 705–710.
14. Juniper EF, Kline PA, Vanzielegem MA, Hargreave FE. – 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. *J Allergy Clin Immunol*, in press.
15. Hargreave FE, Dolovich J, Newhouse MT. – The assessment and treatment of asthma: a conference report. *J Allergy Clin Immunol*, 1990, 85, 1098–1111.
16. Crapo RO, Morris AH, Gardner RM. – Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am Rev Respir Dis*, 1981, 123, 659–664.

Effets au long cours du budesonide sur la réactivité des voies aériennes et sur la sévérité de l'asthme clinique chez les asthmatiques dépendant des stéroïdes par inhalation. E.F. Juniper, P.A. Kline, M.A. Vanzielegem, E.H. Ramsdale, P.M. O'Byrne, F. Hargreave.

RÉSUMÉ: L'administration quotidienne de 400 µ de budesonide, chez des asthmatiques non stéroïdo-dépendants, peut entraîner des améliorations de la réactivité des voies aériennes et de la sévérité de l'asthme clinique, certains patients revenant même à une réactivité normale et devenant asymptomatiques. Cette étude a examiné si des améliorations similaires surviennent lorsque des asthmatiques, dépendant de stéroïdes en inhalation, prennent, soit une dose d'entretien régulière de stéroïdes inhalés, ou deux fois cette quantité pendant une année. Trente-deux asthmatiques furent stabilisés à la quantité minimale de stéroïdes inhalés qui maintenaient leurs symptômes supportables. La moitié d'entre eux ont été assignés de façon randomisée en double aveugle, soit au maintien de la même dose d'entretien, soit au doublement de cette dose pendant un an. La réactivité des voies aériennes à la methacholine a été mesurée avant et chaque mois pendant l'étude, tandis que la sévérité de l'asthme clinique était appréciée par un questionnaire en même temps que l'utilisation des bronchodilatateurs par inhalation et le nombre d'exacerbations de l'asthme. L'on a noté une amélioration significative de la réactivité des voies aériennes et de la sévérité de l'asthme clinique dans les deux groupes de traitement. Les sujets soumis à la double dose ont eu l'amélioration la plus marquée, mais la différence entre les deux groupes n'atteignait pas la signification statistique. Cette étude apporte des arguments puissants en faveur du fait que l'utilisation prolongée de stéroïdes par inhalation s'accompagne d'une amélioration de la réactivité des voies aériennes et de la sévérité de l'asthme clinique, chez des sujets dont l'asthme est dépendant des stéroïdes par inhalation. Elle suggère que ces améliorations sont liées à la dose utilisée.

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