

Predictive Value of the Response to Inhaled Adenosine 5'-Monophosphate for Reducing the Dose of Inhaled Corticosteroids in Asthma

L Prieto,^{1,2} A Ferrer,¹ J Domenech,¹ V López,¹ J Marin²

¹Sección de Alergología, Hospital Universitario Dr. Peset, Valencia, Spain

²Universidad de Valencia, Valencia, Spain

■ Abstract

Background: Guidelines recommend stepping down inhaled corticosteroids (ICS) in patients with well-controlled asthma. However, no information is available on the index that should be used to predict the outcome of reducing the ICS dose.

Objective: The aim of this study was to investigate the degree of airway responsiveness to adenosine 5' monophosphate (AMP) as an index for deciding whether to reduce ICS dose.

Patients and Methods: The study population comprised 70 patients with asthma that was well controlled with ICS. Patients were treated for a 2-week baseline period with their usual dose of ICS. For the following 12 weeks, patients were treated with ICS at half their previous dose. Bronchial challenge with AMP was performed at the end of the baseline period and after 2 weeks of treatment with a reduced dose of ICS. Concentration-response curves were used to show the provocative concentration of AMP causing a 20% fall (PC₂₀) in forced expiratory volume in 1 second (FEV₁).

Results: A decrease in the PC₂₀ of AMP of at least 1 doubling concentration 2 weeks after reducing the ICS dose was a significant predictor of the failure of dose reduction ($P=0.0011$). In contrast, increased responsiveness to inhaled AMP at baseline did not predict the failure of dose reduction.

Conclusions: Our results suggest that, in patients whose asthma is well controlled with ICS, measurement of the modification in the response to AMP 2 weeks after the dose of ICS was halved is a suitable method for assessing the risk of asthma exacerbation following a reduction in ICS dose.

Key words: Inhaled corticosteroids. Adenosine 5'-monophosphate. Airway responsiveness. Asthma.

■ Resumen

Antecedentes: En los pacientes asmáticos bien controlados, las guías recomiendan reducir las dosis de esteroides inhalados. No obstante, no existe ningún tipo de información acerca de qué determinaciones pudieran utilizarse para predecir el éxito o fracaso de esta estrategia terapéutica.

Objetivo: Investigar la utilidad de la determinación de la respuesta bronquial a AMP para predecir la evolución del asma tras reducir la dosis de esteroides inhalados.

Pacientes y métodos: Se estudiaron 70 pacientes asmáticos bien controlados con esteroides inhalados. Durante las primeras 2 semanas, los pacientes fueron tratados con sus dosis habituales de esteroides inhalados, para a continuación y durante las 12 semanas siguientes recibir tratamiento con la mitad de la dosis de estos fármacos indicada basalmente. Se realizaron estudios de la respuesta bronquial a AMP, tanto basalmente como al cabo de dos semanas de reducir la dosis de esteroides inhalados. Las curvas concentración-respuesta se caracterizaron mediante la concentración de agonista que inducía una caída del FEV₁ del 20% (PC₂₀).

Resultados: La identificación de una reducción de la PC₂₀ AMP de al menos una concentración doble, 2 semanas después de reducir la dosis de esteroides inhalados, podía predecir el riesgo de exacerbación del asma como consecuencia de la disminución de la dosis de la medicación controladora ($P=0.0011$). Por el contrario, la determinación de la respuesta basal a AMP no tenía capacidad predictiva significativa.

Conclusiones: Los resultados del estudio sugieren que, en pacientes asmáticos bien controlados con esteroides inhalados, la identificación de las modificaciones de la respuesta a AMP al cabo de 2 semanas de reducir la dosis de esteroides inhalados a la mitad permite evaluar el riesgo de futuras exacerbaciones de la enfermedad.

Palabras clave: Esteroides inhalados. Adenosina 5'-monofosfato. Hiperrespuesta bronquial. Asma.

Introduction

Treatment with inhaled corticosteroids (ICS) is the basis for effective long-term control of asthma [1], because it reduces asthma symptoms, bronchodilator use, and airway hyperresponsiveness. When asthma has been controlled for 3 to 6 months, asthma management guidelines [1,2] recommend stepping down the dose of ICS to minimize the risk of adverse effects. However, the index that should be used to predict the success or failure of reducing ICS dose has yet to be defined.

Airway hyperresponsiveness is usually considered an abnormal response of the lower respiratory tract to a number of nonsensitizing bronchoconstrictive stimuli [3]. In the laboratory, airway hyperresponsiveness is most commonly assessed using direct bronchoconstrictor stimuli, such as methacholine or histamine, although it can also be assessed using indirect bronchoconstrictor stimuli such as adenosine 5'-monophosphate (AMP). AMP-induced bronchoconstriction mainly occurs indirectly via stimulation of A₂-purinoceptors on mast cells, which facilitate the release of proinflammatory mediators (histamine and leukotrienes) and subsequent smooth-muscle contraction [4,5]. The provocative concentration of AMP required to produce a 20% fall (PC₂₀) in forced expiratory volume in 1 second (FEV₁) is thought to be more closely correlated with the extent of airway inflammation and response to corticosteroids than the PC₂₀ of methacholine [6,7]. These findings appear to support the concept that airway responsiveness to AMP might prove useful in tailored adjustment of the dose of ICS.

In a previous investigation [8], we showed that, in asthmatic patients whose disease was already stabilized and well controlled with ICS, baseline combined measurements of both AMP responsiveness and exhaled nitric oxide levels can be used to predict the success or failure of reducing the ICS dose. However, we also found that a decrease in the PC₂₀ of AMP of at least 1 doubling concentration 2 weeks after the reduction in ICS dose was a factor of borderline significance for predicting loss of asthma control when the ICS dose was reduced. Therefore, in this study, we assessed whether determination of airway responsiveness to inhaled AMP at baseline or identification of changes in the response to this bronchoconstrictor agent 2 weeks after reducing the ICS dose could be used as an index to assess reducing ICS dose in asthmatic patients.

Patients and Methods

Patients

The study population comprised nonsmoking patients aged 18 to 60 years with a previous history of asthma and treatment with an ICS for at least 6 months. Patients with stable asthma requiring medium to high doses of ICS (beclomethasone 500-1000 µg/d or equivalent twice-daily regimen) to maintain asthma control were also recruited. In the 3 months before the study, patients had asthma symptoms no more than twice a week and did not wake at night because of asthma. Their dose of ICS remained unchanged during the previous 6 months, and FEV₁ at baseline had to be more than 80% of predicted. The study protocol was approved by the local ethics committee, and written informed consent was obtained from all the participants.

Study Design

This prospective study was performed in a single-blind manner at a single center. The study lasted 14 weeks and consisted of a 2-week run-in period (baseline), during which patients continued to take their habitual dose of ICS, and a dose reduction period (12 weeks), during which the patients' current ICS dose was halved. At the screening visit, patients completed a questionnaire about their asthma history, and spirometry was performed. Additionally, patients completed a diary card to record peak flow, asthma symptoms, and salbutamol use. During the run-in period, all patients were treated with their habitual dose of ICS in order to demonstrate stability of disease. They also recorded nighttime asthma symptoms daily using a score from 0 (no symptoms) to 3 (symptoms so severe that the patient was unable to sleep), daytime symptoms from 0 (no symptoms) to 3 (symptoms so severe that the patient could not perform normal daily activities), use of salbutamol, and morning and evening peak expiratory flow (PEF) values (best of 3) using a Mini Wright peak flow meter (Clement Clarke International). A prerequisite for study enrolment was a stable clinical condition during the run-in period defined as no more than 4 doses of albuterol as needed, ≤4 days with PEF variability ≥20%, and mean daytime and nighttime symptom scores <1.

For the next 12 weeks, eligible patients were treated with ICS at half their previous dose using their habitual inhalation device. Patients completed a diary twice daily by recording PEF, daytime and nighttime symptoms, and use of rescue salbutamol. Bronchial challenge with AMP was performed at the end of the baseline period and after 2 weeks of treatment with a reduced dose of ICS; spirometry was performed at the screening visit, at the end of the baseline period, and after 2, 8, and 12 weeks of treatment with a reduced dose of ICS. Patients were asked not to take salbutamol for at least 6 hours, ICS for at least 12 hours, and antihistamines for at least 72 hours before each visit. The physician responsible for the follow-up visits and for identifying the asthma exacerbation was unaware of the results of the AMP challenge test.

The primary outcome was identification of an asthma exacerbation, which was based on at least 1 of the following criteria: (1) a decrease in morning PEF of >20% on at least 2 consecutive days, as compared with the mean of the second 7 days of the run-in period; (2) awakening on 3 nights or more per week; (3) bronchodilator use 1 to 2 times daily for at least 4 consecutive days; or (4) use of systemic corticosteroids for asthma. Patients who experienced an exacerbation went to the laboratory as soon as possible within the following 24 hours to undergo the investigations used in the study. Secondary outcomes specified in the protocol included measures of pulmonary function (morning and evening peak expiratory flow rate and FEV₁) and measures of asthma symptoms and salbutamol use from the patients' diary cards.

Lung Function

Lung function was measured using a calibrated pneumotachograph (Jaeger MasterScope; Erich Jaeger GmbH) according to standardized guidelines [9]. The reference values were those of the European Community for Coal and Steel [10].

AMP Challenge

Airway responsiveness to AMP was assessed using a standardized dosimetric method, as described in detail elsewhere [11]. Immediately before administration, AMP (Sigma Chemical Co) was dissolved in 0.9% saline solution to produce a doubling concentration range of 0.39 mg/mL to 400 mg/mL. Each solution was administered from a jet nebulizer attached to a breath-activated dosimeter (model MB3; Mefar) for 1 second with a pause of 6 seconds. Normal saline solution was inhaled initially, followed by 5 breaths of doubling concentrations of AMP at 2 to 3-minute intervals. Single measurements of FEV₁ were taken 60 to 90 seconds after the inhalation of each concentration, unless the forced expiratory maneuver was judged to be technically unsatisfactory. The test was interrupted when a fall in FEV₁ of at least 20% from the postsaline value was recorded or the maximum concentration had been given. The PC₂₀ was calculated using an algebraic formula [12].

Statistical Analysis

If patients withdrew because of an asthma exacerbation, we analyzed their data by intention to treat (last observation carried forward). Data were analyzed with a standard statistical software package (InStat for Windows version 3.0, GraphPad Software). All PC₂₀ values were log-transformed before analysis and presented as geometric means with 95% confidence intervals (CI). All other numerical variables are reported as arithmetic means with a 95% CI. Changes in PC₂₀ were expressed in terms of doubling concentrations of methacholine calculated as $\Delta \log PC_{20} / \log 2$.

Possible predictors for failure of ICS reduction were determined using the log-rank test. A χ^2 analysis and Kaplan-Meier survival curves were used to demonstrate differences in the probability of failure of ICS reduction between patients with increased responsiveness to AMP and those with normal responsiveness to AMP. The cut-off points evaluated were 200 mg/mL and 400 mg/mL at baseline and increase in 1 doubling concentration over the baseline value 2 weeks after the dose of ICS was halved.

The variables recorded in the diaries were expressed as mean values, and the means for the run-in period were used as the reference value. For FEV₁ and PC₂₀, the values measured at the end of the run-in period were used as the reference. Comparisons of treatment effects with a reduced dose of ICS on FEV₁ and variables recorded in the diaries were made using 2-factor repeated-measures analysis of variance to analyze the effect of the 2 independent variables group and time on the variables described previously. A *P* value of .05 (2-sided) was considered the limit of significance.

Results

The demographic data for the 70 patients who were included in the analysis are given in Table 1. An asthma exacerbation was recorded in 19 patients when the dose of ICS

Table 1. Patient Characteristics at Baseline^a

Number of patients	70
Age, y	34 (31-36)
Male/female, No.	18/52
Duration of asthma, y	16.7 (14.9-18.5)
Skin test positive, No.	51
Duration of ICS use, mo	29.0 (22.7-35.2)
ICS dose, μ g/d (beclomethasone equivalent) ^b	546 (494-598)
FEV ₁ , % predicted	98.3 (95.0-101.6)
FEV ₁ /FVC, %	80.4 (78.9-82.9)
PC ₂₀ \leq 400 mg/mL, No	35
PC ₂₀ \leq 200 mg/mL, No	31

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; PC₂₀, provocative concentration of adenosine 5' monophosphate causing a 20% fall in FEV₁.

^a Data are presented as mean (95% confidence interval) unless otherwise indicated.

^b Beclomethasone dipropionate equivalent dose of ICS was calculated on the basis of fluticasone propionate being twice as potent as beclomethasone dipropionate and budesonide equipotent, so that the equivalent fluticasone propionate dose was multiplied 2-fold.

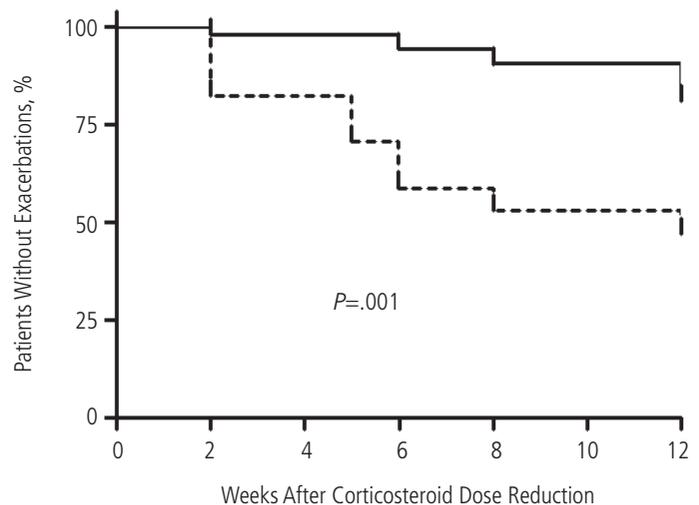


Figure 1. Kaplan-Meier survival curve based on the change in PC₂₀ from the run-in period to the visit performed 2 weeks after the reduction of ICS dose at a cut point of 1 doubling concentration. The dashed line represents the group with a positive result, and the continuous line represents the group with a negative result.

was halved; no exacerbations were recorded in the remaining 51 patients.

Predictive Power Using Modifications in the PC₂₀ of AMP 2 Weeks After Reducing the Dose of ICS

Changes in PC₂₀ values of at least 1 doubling concentration 2 weeks after the reduction in ICS dose were recorded in 17 patients (positive group); the remaining 53 patients had changes $<$ 1 doubling concentration (negative group). An

asthma exacerbation over the 12 weeks of treatment with a reduced dose of ICS was detected in 9 of 17 patients (53%) in the positive group and in only 10 of 53 patients (19%) in the negative group ($P=.011$). A change in the PC₂₀ of AMP of at least 1 doubling concentration 2 weeks after the reduction in ICS dose increased the relative risk of exacerbation by 2.8 (95%CI, 1.4-5.7). Figure 1 shows the Kaplan-Meier plot for time to first asthma exacerbation using the modifications in the PC₂₀ of AMP values 2 weeks after the dose of ICS was halved. A decrease in the PC₂₀ of AMP (cut point, 1 doubling concentration) was a significant predictor of failure of dose reduction ($P=.0011$).

In the positive group, a significant reduction in FEV₁ was observed at week 2, but not at weeks 8 and 12 (Table 2). In the negative group, changes from baseline were significant at week 12, but not at weeks 2 and 8. The difference between the 2 groups was significant at weeks 2 (mean, 0.15 L; 95%CI, 0.05-0.25; $P=.005$) and 8 (mean, 0.10 L; 95%CI, 0.02-0.19; $P=.02$), but not at week 12 (mean, -0.01 L; 95%CI, -0.12 to 0.11; $P=.96$).

In the positive group, a significant reduction in evening PEF values was recorded at all time points (Figure 2). In the negative group, these changes did not reach significance at any time point. The difference between the 2 groups was significant at weeks 2 (mean, 21 L/min; 95%CI, 6-36; $P=.007$) and 8 (mean, 19 L/min; 95%CI, 4-34; $P=.02$), but not at week 12 (mean, 19 L/min; 95%CI, -3 to 41; $P=.10$). In both groups, changes in morning PEF were not significant (Table 2). However, the change in morning PEF from baseline was consistently larger in the positive group, the mean difference in the change between the groups being 22 L/min (95%CI, 7-38; $P=.005$) at week 2, 22 L/min (95%CI, 5-39; $P=.01$) at week 8, and 24 L/min (95%CI, 1-47; $P=.04$) at week 12.

In the negative group, changes in symptom scores (Table 3) did not reach significance, whereas changes in rescue salbutamol increased significantly at week 12 compared with baseline. By contrast, patients in the positive

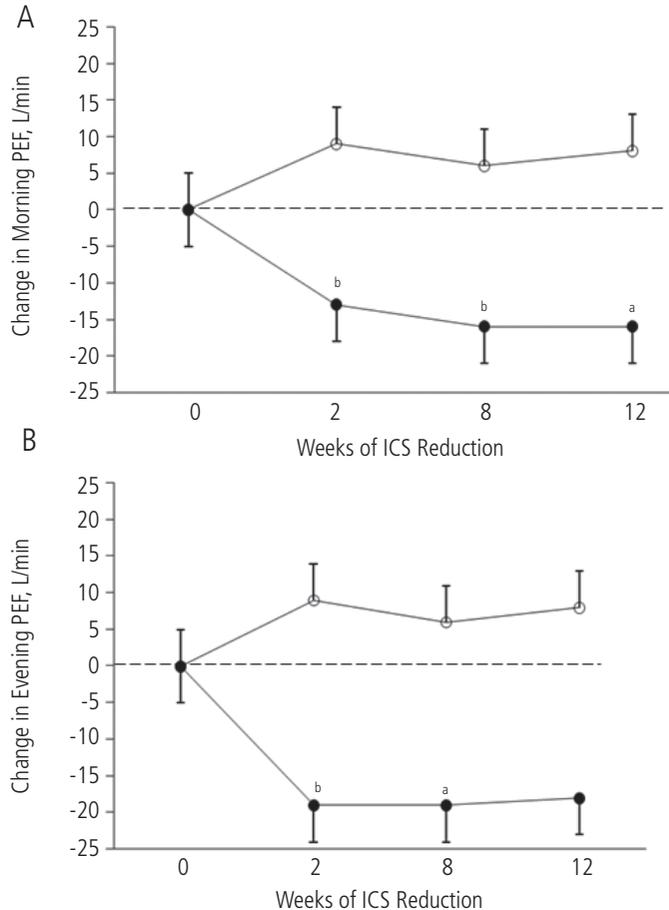


Figure 2. Mean change from baseline in the morning (A) and evening (B) peak expiratory flow (PEF). Filled circles represent the group with a decrease in PC₂₀ \geq 1 doubling concentration; open circles represent the group with a decrease in PC₂₀ <1 doubling concentration. Error bars represent SEM. P values indicate significant differences between the groups.

^a $P < .05$.

^b $P < .01$.

Table 2. Changes in Peak Expiratory Flow (PEF) and Forced Expiratory Volume in 1 Second (FEV₁)^a

	Baseline	Week 2	Week 8	Week 12
Positive group^b				
FEV ₁ , L	3.47 (2.94-4.00)	3.32 (2.77-3.88)	3.37 (2.84-3.90)	3.39 (2.84-3.95)
P Value		<.05	NS	NS
Morning PEF, L/min	449 (388-509)	436 (381-491)	433 (379-487)	433 (383-484)
P Value		NS	NS	NS
Evening PEF, L/min	456 (396-515)	437 (382-492)	437 (382-492)	438 (383-492)
P Value		<.05	<.05	<.05
Negative group^c				
FEV ₁ , L	3.18 (2.97-3.38)	3.18 (2.97-3.39)	3.17 (2.98-3.37)	3.10 (2.89-3.30)
P Value		NS	NS	<.01
Morning PEF, L/min	424 (396-453)	433 (400-466)	430 (398-463)	432 (398-467)
P Value		NS	NS	NS
Evening PEF, L/min	430 (400-461)	433 (401-466)	431 (399-462)	431 (398-464)
P Value		NS	NS	NS

Abbreviations: NS, nonsignificant; PC₂₀, provocative concentration of AMP required to produce a 20% fall in FEV₁.

^aP values indicate statistical significance compared to baseline within the group.

^bPositive group: patients with a decrease in PC₂₀ \geq 1 doubling concentration.

^cNegative group: patients with a decrease in PC₂₀ <1 doubling concentration.

Table 3. Changes in Clinical Signs^a

	Baseline	Week 2	Week 8	Week 12
Positive Group^b				
Daytime symptom score	0.02 (0.00-0.06)	0.14 (0.00-0.30)	0.26 (0.11-0.42)	0.33 (0.18-0.48)
<i>P</i> Value		NS	<0.01	<0.01
Nighttime symptom score	0.03 (0.00-0.05)	0.13 (0.00-0.26)	0.23 (0.11-0.35)	0.25 (0.13-0.36)
<i>P</i> Value		NS	<0.001	<0.001
Salbutamol use	0.03 (0.00-0.07)	0.25 (0.00-0.49)	0.44 (0.20-0.67)	0.55 (0.33-0.78)
<i>P</i> Value		NS	<0.001	<0.001
Negative group^c				
Daytime symptom score	0.06 (0.03-0.09)	0.07 (0.04-0.10)	0.08 (0.04-0.12)	0.09 (0.05-0.14)
<i>P</i> Value		NS	NS	NS
Nighttime symptom score	0.03 (0.01-0.06)	0.03 (0.01-0.05)	0.04 (0.02-0.05)	0.04 (0.02-0.06)
<i>P</i> Value		NS	NS	NS
Salbutamol use	0.05 (0.02-0.07)	0.11 (0.04-0.17)	0.12 (0.06-0.17)	0.16 (0.09-0.22)
<i>P</i> Value		NS	NS	<0.01

Abbreviations: NS, nonsignificant; PC₂₀, provocative concentration of adenosine 5' monophosphate required to produce a 20% fall in forced expiratory volume in 1 second.

^a*P* values indicate statistical significance compared to baseline within the group.

^bPositive group: patients with a decrease in PC₂₀ ≥1 doubling concentration

^cNegative group: patients with a decrease in PC₂₀ <1 doubling concentration.

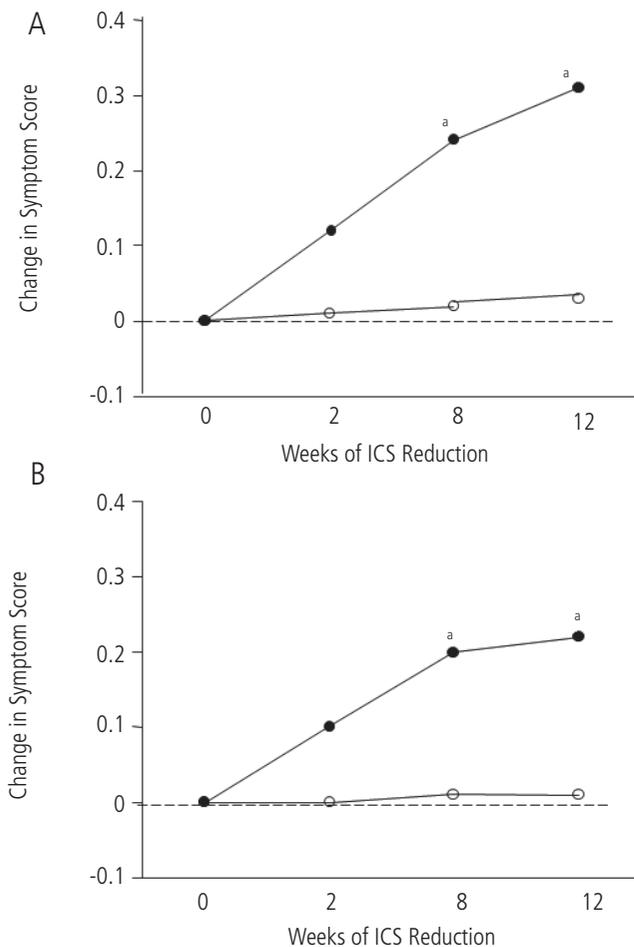


Figure 3. Mean change from baseline in daytime (A) and nighttime (B) symptom scores in patients with a decrease in PC₂₀ ≥1 doubling concentration (filled circles) and patients with a decrease in PC₂₀ <1 doubling concentration (open circles). *P* values indicate significant differences between the groups. ICS indicates inhaled corticosteroid.

^a*P*<.01.

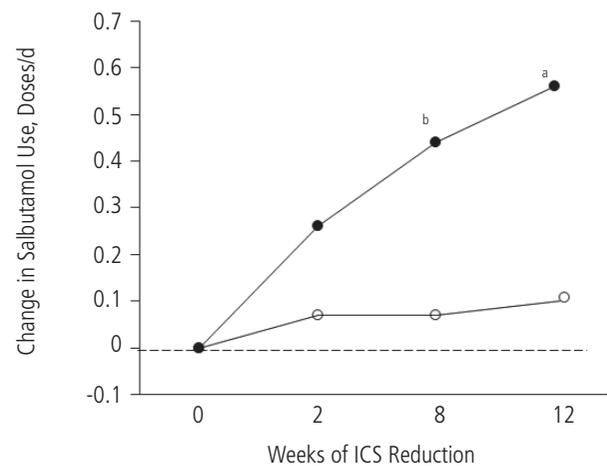


Figure 4. Mean change from baseline in salbutamol inhaler use in patients with a decrease of PC₂₀ ≥1 doubling concentration (filled circles) and patients with a decrease of PC₂₀ <1 doubling concentration (open circles). *P* values indicate significant differences between the groups. ICS indicates inhaled corticosteroid.

^a*P*=.001.

^b*P*<.01.

group reported increments in the severity of symptoms and salbutamol use at weeks 8 and 12 (Figures 3 and 4). Differences between the groups for both daytime and nighttime symptoms were significant at weeks 8 and 12, but not at week 2. At week 8, the mean difference (95%CI) in the change between the groups was 0.22 (0.06-0.37, *P*=.008) for daytime symptoms, 0.20 (0.08-0.33, *P*=.004) for nighttime symptoms, and 0.34 (0.10-0.58, *P*=.008) for salbutamol use. At week 12, the mean difference (95%CI) in the change between the groups was 0.27 (0.11-0.43, *P*=.002) for daytime symptoms, 0.22 (0.10-0.34, *P*=.002) for nighttime symptoms, and 0.41 (0.19-0.64, *P*=.001) for salbutamol use (Figures 3 and 4).

Predictive Power of Airway Responsiveness to AMP at Baseline

Increased responsiveness to inhaled AMP at baseline (cut points for PC₂₀ of 200 mg/mL or 400 mg/mL) was not a predictor of failure of reducing ICS (Figure 5). An asthma exacerbation occurred in 10 of 30 patients (33%) with a PC₂₀ value ≤200 mg/mL at baseline, compared with 9 of 40 patients (23%) with a PC₂₀ value >200 mg/mL ($P=.42$). In addition, an asthma exacerbation was identified in 12 of 35 (34%) patients with a PC₂₀ of AMP at baseline ≤400 mg/mL and in 7 of 35 (20%) with a PC₂₀ of AMP >400 mg/mL ($P=.28$).

Discussion

The results of the present study demonstrate that in asthma patients whose disease is stabilized and well controlled with ICS, measurement of the change in AMP responsiveness 2 weeks after reducing the dose of ICS can be used to predict the success or failure of the reduction. The identification of a decrease in the PC₂₀ of AMP of at least 1 doubling concentration 2 weeks after the dose of ICS was halved is associated with a greater risk of asthma exacerbation over a 3-month period. Therefore, this change in the response to AMP is a clear predictor of failure of reducing the dose of ICS. By contrast, the presence of increased responsiveness to AMP at baseline is not a useful predictor.

International guidelines [1,2] agree that the ICS dose should be reduced to reach the minimum effective dose in patients with well-controlled asthma. However, this recommendation is largely based on clinical experience, and few studies have examined the options and most favorable conditions for stepping down treatment. In 19 of the 70 patients (27%) in the current study, an exacerbation was detected after reduction of ICS; therefore, it is evident that in a significant proportion of patients with well-controlled asthma and a moderately high ICS dose, the dose of the drug can be reduced without clinical deterioration. These data are consistent with those reported in previous investigations [8,13-16]. Consequently, for patients whose asthma is well controlled with a moderately high dose of ICS, a reduction in dose may be considered.

Although the strategy for stepping down therapy is evident [17,18] in patients receiving high-dose ICS, strategies for stepping down therapy in patients with well-controlled asthma receiving conventional doses of ICS have not been well defined. Everyday clinical practice is also severely hindered by the lack of readily available reliable markers that can be used to optimize ICS therapy in patients with asthma. Our study indicates that a decrease in PC₂₀ of at least 1 doubling concentration 2 weeks after the dose of ICS was halved is associated with an increased risk of asthma exacerbation over the following weeks of treatment with a reduced dose of ICS. Moreover, a 50% reduction in ICS dose was possible

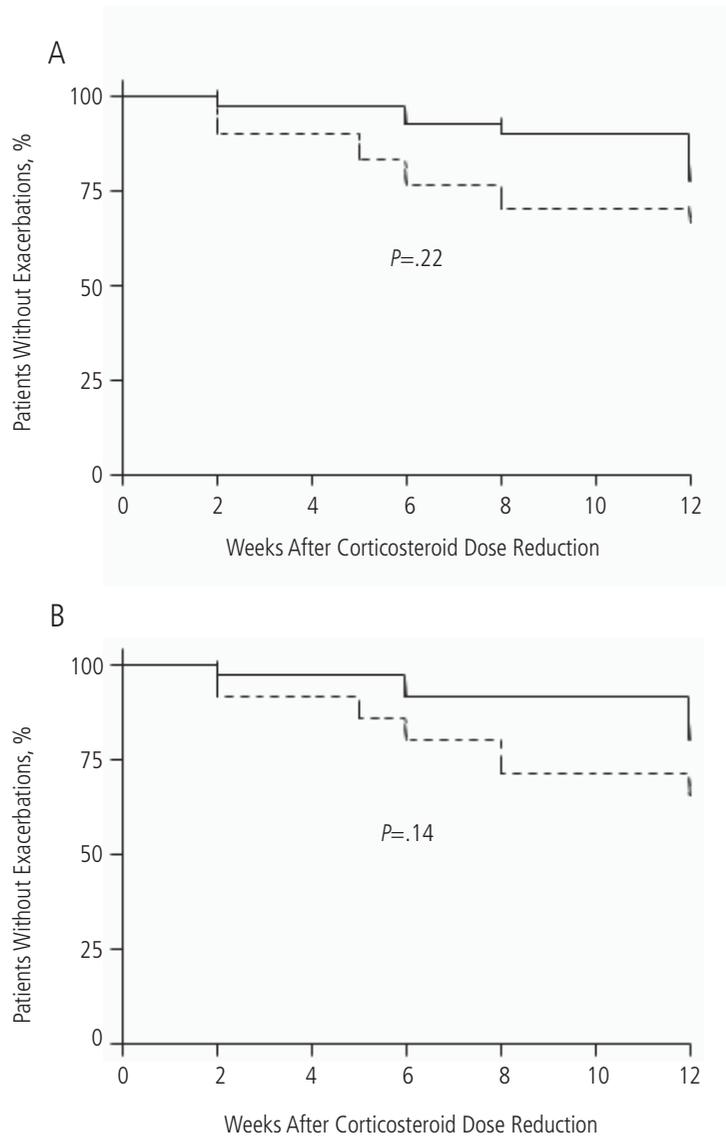


Figure 5. Kaplan-Meier survival curve based on the baseline determination of AMP PC₂₀ at a cut point of 200 mg/mL (A) and 400 mg/mL (B). The dashed line represents the group with a positive result, and the continuous line represents the group with a negative result.

in patients with a decrease in PC₂₀ of <1 doubling concentration without evidence of a significant deterioration in the parameters of asthma control (symptoms, use of rescue salbutamol, and pulmonary function). On the contrary, in the group with a decrease in PC₂₀ of ≥1 doubling concentration, reducing the ICS dose was associated with a decrease in evening PEF and with an increase in symptoms and bronchodilator use. These results confirm and extend our previous observations [8], where we showed that, when asthma is well controlled with ICS, the presence of both AMP-induced bronchoconstriction and fraction of exhaled nitric oxide (FE_{NO}) levels of ≥15 ppb is a clear predictor of failed ICS reduction. In our previous study [8], we also hypothesized that a decrease in the PC₂₀ of AMP of at least 1 doubling concentration 2 weeks after the dose

of ICS was halved might be a predictor of the failure of ICS reduction. However, the difference in the risk of exacerbation following ICS dose reduction between patients with a decrease in PC₂₀ of ≥ 1 doubling concentration and those with a decrease of < 1 doubling concentration did not reach statistical significance ($P=0.06$). The present study was performed on a larger number of patients, and the results demonstrate conclusively that a decrease in the PC₂₀ of AMP of ≥ 1 doubling concentration is associated with an increased risk of exacerbation over a 3-month period. Furthermore, the results of the present study confirm our previous observations [8] that a single baseline assessment of the PC₂₀ of AMP is not useful for predicting the progress of asthma after reduction of the ICS dose.

Therefore, we have 2 different strategies to predict the response to reducing ICS dose in patients with well-controlled asthma: determination of AMP responsiveness plus FE_{NO} values at baseline and measurement of the response to AMP at baseline and after 2 weeks of treatment with a reduced dose of ICS. The more convenient strategy should be determined in prospective studies designed to compare the sensitivity and specificity of each method for predicting the stability of asthma after ICS dose reduction.

Our study is subject to a series of limitations. First, the design was chosen to closely emulate normal clinical practice when the dose of ICS is reduced (single-blind approach and use of different ICS products and doses). One might argue that some patients could report more severe clinical manifestations because they were informed that the ICS dose was reduced. However, this effect would be independent of the response to inhaled AMP and, therefore, would not have biased the study results. Furthermore, although our study was not double-blind, exacerbations were identified without knowledge of the results of the AMP challenge; therefore, any bias from not blinding probably had no marked effect on our results. Second, the ICS dose was reduced by 50% only if strict criteria for stable asthma were met. The reason for selecting patients with stable asthma was that this group would most likely be considered for a reduction in their ICS dose. Our findings are therefore pertinent to the population for which step-down is recommended. It is possible, however, that inclusion in a trial leads to improved adherence to treatment. If one assumes this to have been the case in our study, then a degree of caution should be adopted when extrapolating our results to the clinical setting. Third, as our study was limited to patients receiving 500 μ g to 1000 μ g of inhaled beclomethasone dipropionate or daily equivalent, we should be cautious when extrapolating our findings to patients who receive higher or lower doses of ICS. Finally, although the current study suggests that step-down can be commenced after a long period of established control with ICS in most patients, it was of relatively short duration (12 weeks after step-down). Over a longer period of follow-up, slow but steady deterioration could be observed. Prospective evaluations of the level of asthma control over a longer period of follow-up are required.

Our results show that the absence of bronchoconstriction in response to AMP at baseline is not a reliable index when assessing the opportunity for reducing the dose of ICS in asthmatic patients whose disease is well controlled with ICS. Although no studies have investigated the utility of

determining responsiveness to AMP as a marker of the safety of reducing the dose of ICS, our results are supported by those reported by Leuppi et al [19]. The authors demonstrated that airway hyperresponsiveness to mannitol (an indirect bronchoconstrictor) was not a significant predictor of the failure of step-down.

The present results have clinical implications. ICS have been associated with a number of dose-related side effects including bruising, cataract formation, glaucoma, reduced bone density, and adrenal suppression [20,21]. Therefore, titration of the dose of ICS to the lowest possible level is recommended to minimize the risk of adverse effects [22]. The results of the present study suggest that, in stable asthmatic patients receiving ICS treatment, a decrease in the PC₂₀ of AMP of ≥ 1 doubling concentration 2 weeks after the dose of ICS was halved can predict the risk of asthma exacerbation following ICS dose reduction.

In summary, in asthmatic patients whose disease is well controlled with ICS, we found that measurement of the modification of the PC₂₀ of AMP after 2 weeks of treatment with a reduced dose of ICS is an efficient method for assessing the risk of asthma exacerbation following step-down. This approach facilitates implementation of the recommendations of guidelines [1,2], which recognize the need to control asthma with the lowest adequate doses of ICS.

Acknowledgments

The authors thank the patients for their cooperation and Rocio Rojas for her technical assistance. They also thank the pharmaceutical company Bial-Aristegui (Bilbao, Spain) for their help and collaboration during the study.

Funding

The authors declare that no funding was received for this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. National Asthma Education and Prevention Program Expert Panel Report 3. Guidelines for the diagnosis and management of asthma. Full report-2007. National Heart, Lung and Blood Institute. NIH Publication No. 07-4051.
2. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, Gibson P, Ohta K, O'Byrne PO, Pedersen SE, Pizzichini E, Sullivan SD, Wenzel SE, Zar HJ. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J*. 2008;31:143-78.
3. Woolcock AJ. What is bronchial hyperresponsiveness from the clinical standpoint? In: Page CP, Gardiner PJ, editors. *Airway hyperresponsiveness: is it really important for asthma?* Oxford: Blackwell Scientific Publications; 1993. p. 1-9.
4. Polosa R, Ng WH, Crimi N, Vancheri C, Holgate ST, Church

- MK, Mistretta A. Release of mast-cell-derived mediators after endobronchial adenosine challenge in asthma. *Am J Respir Crit Care Med.* 1995;151:624-9.
5. Van Schoor J, Joos GF, Kips TC, Drajesk JF, Carpentier PJ, Pauwels RA. The effect of ABT-761, a novel 5-lipoxygenase inhibitor, on exercise-and adenosine-induced bronchoconstriction in asthmatic subjects. *Am J Respir Crit Care Med.* 1997;155:875-80.
 6. Van den Berge M, Meijer RJ, Kerstjens HA, de Reus DM, Koeter GH, Kauffman HF, Postma DS. PC20 adenosine 5'-monophosphate is more closely associated with airway inflammation in asthma than PC20 methacholine. *Am J Respir Crit Care Med.* 2001;163:1546-50.
 7. Van den Berge M, Kerstjens HAM, Meijer RJ, De Reus DM, Koeter GH, Kauffman HF, Postma DS. Corticosteroid-induced improvement in the PC20 of adenosine monophosphate is more closely associated with reduction in airway inflammation than improvement in the PC20 of methacholine. *Am J Respir Crit Care Med.* 2001;164:1127-32.
 8. Prieto L, Bruno L, Gutiérrez V, Uixera S, Pérez-Francés C, Lanuza A, Ferrer A. Airway responsiveness to adenosine 5'-monophosphate and exhaled nitric oxide measurements. Predictive value as markers for reducing the dose of inhaled corticosteroids in asthmatic subjects. *Chest.* 2003;124:1325-33.
 9. American Thoracic Society. Standardization of spirometry, 1987 update. *Am Rev Respir Dis.* 1987;136:1285-98.
 10. Quanjer PH. Standardized lung function testing. *Bull Eur Physiopathol Respir.* 1983;19(Suppl):1-93.
 11. Prieto L, Gutiérrez V, Torres V, Uixera S, Marin J. Effect of salmeterol on seasonal changes in airway responsiveness and exhaled nitric oxide in pollen-sensitive asthmatic subjects. *Chest.* 2002;122:798-805.
 12. Cockcroft DW, Murdock KY, Mink IT. Determination of histamine PC20: comparison of linear and logarithmic interpolation. *Chest.* 1983;84:505-6.
 13. Juniper EF, Kline PA, Vanzielegghem 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.* 1991;87:483-9.
 14. Haahtela T, Järvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K, Nikander K, Persson T, Selroos O, Sovijarvi A, Stenius-Aarniala B, Svahn T, Tammivaara P, Laitinen LA. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med.* 1994;331:700-5.
 15. Prieto L, Gutiérrez V, Morales C. Maximal response plateau to methacholine as a reliable index for reducing inhaled budesonide in moderate asthma. *Eur Respir J.* 1999;13:1236-44.
 16. Hawkins G, McMahon AD, Twaddle S, Wood SF, Ford I, Thomson NC. Stepping down inhaled corticosteroids in asthma: randomised controlled trial. *Br Med J.* 2003;326:1115-20.
 17. Fowler SJ, Currie GP, Lipworth BJ. Step-down therapy with low-dose fluticasone-salmeterol combination or medium-dose hydrofluoroalkane 134a-beclomethasone alone. *J Allergy Clin Immunol.* 2002;109:929-35.
 18. Foresi A, Mastropasqua B, Chetta A, D'Ippolito R, Testi R, Olivieri D, Pelucchi A. Step-down compared to fixed-dose treatment with inhaled fluticasone propionate in asthma. *Chest.* 2005;127:117-24.
 19. Leuppi JD, Salome CM, Jenkins CR, Anderson SD, Xuan W, Marks GB, Koskela H, Brannan JD, Freed R, Andersson M, Chan HK, Woolcock AJ. Predictive markers of asthma exacerbation during stepwise dose reduction of inhaled corticosteroids. *Am J Respir Crit Care Med.* 2001;163:406-12.
 20. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy. *Arch Intern Med.* 1999;159:941-55.
 21. Wong CA, Walsh LJ, Smith CJP, Wisniewski AF, Lewis SA, Hubbard R, Cawte S, Green DJ, Pringle M, Tattersfield AE. Inhaled corticosteroid use and bone-mineral density in patients with asthma. *Lancet.* 2000;355:1399-1403.

■ *Manuscript received November 5, 2012; accepted for publication January 3, 2013.*

■ **Luis Prieto**

Departamento de Medicina
Facultad de Medicina y Odontología
Avda Blasco Ibáñez, 15
46010 Valencia, Spain
E-mail: jesus.l.prieto@uv.es