ASTHMA

Perception of airway narrowing during reduction of inhaled corticosteroids and asthma exacerbation

C M Salome, J D Leuppi, R Freed, G B Marks

Thorax 2003;**58**:1042–1047

See end of article for authors' affiliations

Correspondence to: Dr C Salome, Woolcock Institute of Medical Research, Box M77, Missenden Road Post Office, NSW 2050, Australia; cms@woolcock.org.au

Received 30 October 2002
Accepted 21 July 2003

Background: The perception of airway narrowing is reduced in subjects with severe asthma and may be related to the severity of airway inflammation. A study was undertaken to determine if the perception of airway narrowing changes during the reduction of inhaled corticosteroid (ICS) dose or during an asthma exacerbation.

Methods: Forty two asthmatic subjects with well controlled asthma had their daily ICS dose halved every 2 months until they were weaned off ICS or they developed an exacerbation. Perception was measured at baseline and at monthly intervals during bronchial challenge with mannitol as the slope and intercept of the regression of the Borg score and percentage fall in forced expiratory volume in 1 second (FEV_1), and as the Borg score at 20% fall in FEV_1 ($PS_{20}FEV_1$). Sputum was collected for measurement of inflammatory cell numbers.

Results: In 33 subjects who successfully halved their ICS dose without exacerbation there were significant reductions in slope ($p=0.01$), intercept ($p=0.01$), and $PS_{20}FEV_1$ ($p=0.003$). Sputum eosinophils and airway hyperresponsiveness increased significantly but, in 14 subjects from whom sputum was obtained, changes in eosinophils were not correlated with changes in perception. Change in airway hyperresponsiveness correlated with change in $PS_{20}FEV_1$ ($r=-0.40$, $p=0.025$). In 27 subjects who developed an exacerbation, slope decreased ($p=0.02$) and intercept increased ($p=0.01$) compared with the visit before the exacerbation. Changes in intercept correlated with changes in resting FEV_1 ($r=-0.57$, $p=0.002$).

Conclusions: Perception of airway narrowing decreases during ICS dose reduction and decreases further during a mild asthma exacerbation. These changes are related to concurrent changes in airway hyperresponsiveness and resting lung function. The effect of changes in airway inflammation on perception is unclear.

The perception of airway narrowing is likely to be an important determinant of the perception of symptoms of asthma. We have shown previously[1] that increasing the dose of inhaled steroids and bringing asthma under good control was associated with an increase in the perception of airway narrowing induced by challenge with histamine. This finding suggests that the perception of induced airway narrowing is determined, at least in part, by factors associated with the degree of asthma control, such as the severity of airway inflammation or airway hyperresponsiveness (AHR). There have been no previous studies to determine if interventions, such as the withdrawal of inhaled steroids, that cause an increase in airway inflammation or the loss of asthma control are associated with changes in the perception of induced airway narrowing.

Previous studies have shown that perception is reduced in subjects with severe asthma[2 3] and in subjects with recurrent exacerbations.[3] Subjects with poor perception may be at increased risk of exacerbations or severe asthma if they fail to detect the onset of an exacerbation in time to institute preventative treatment. Alternatively, perception may be directly altered by the factors associated with the asthma exacerbation. Poor perception in subjects with recurrent exacerbations was associated with increased sputum eosinophils,[3] suggesting that increasing airway inflammation may reduce perception directly. The perception of breathlessness is also reduced during airway narrowing that is slow in onset[4] and by recent past experience of breathlessness.[5 6] Since exacerbations of asthma can be gradual in onset, perception may be reduced by sensory adaptation to slowly developing airway obstruction or to gradually increasing symptoms in the period leading up to the exacerbation.

The aim of this study was to explore further the relation between the perception of induced airway narrowing and markers of both asthma control and airway inflammation by determining the effect on perception of reducing treatment with inhaled corticosteroids (ICS).

METHODS

Subjects

Fifty asthmatic subjects were recruited from an asthma outpatient clinic to participate in a study of the predictors of response to progressive reduction in ICS dose.[7] Subjects had physician diagnosed asthma with a history of wheezing and chest tightness. In the 4 weeks before the study subjects had asthma symptoms no more than twice a week, did not wake at night because of asthma, and had no respiratory tract infection. There had been no changes in their dose of ICS in the previous 4 weeks and no major changes in dose (>1000 μg daily) in the previous 3 months. Exclusion criteria were current smoking and the use of oral steroids within the previous 6 months.

Study design

Subjects underwent bronchial challenge with mannitol at 4-weekly intervals. The perception of airway narrowing was measured during the mannitol challenge. Exhaled nitric oxide (NO) and spirometric parameters were measured before the challenge tests and an attempt was made to collect sputum during or after the mannitol challenge. Short

acting β agonists were withheld for 6 hours, long acting β agonists for 24 hours, and antihistamines for 3 days before the challenge. No ICS were taken on the day of the study. Throughout the study subjects recorded asthma symptoms, β agonist use, and peak expiratory flow (PEF) twice daily before taking asthma medication.

Following 4 weeks baseline monitoring, subjects had their daily dose of ICS halved every 8 weeks until they suffered an asthma exacerbation or they were successfully weaned off ICS without an exacerbation for 8 weeks. The ICS treatment was stopped after a dose of 200 µg budesonide or beclomethasone, or 125 µg fluticasone was reached after successive reductions in steroid dose. An exacerbation was defined as a reduction in PEF by more than 3 standard deviations from the mean value obtained during the run in period[8] or a sudden rapid decline in peak flow or deterioration in symptoms.[9] Subjects contacted the investigating physician if all three of the PEF measurements made on any occasion fell below their ''trigger point'' and then attended the laboratory as soon as possible for measurement of lung function, exhaled NO, airway responsiveness to mannitol, and for collection of sputum. The physician responsible for the steroid reduction and for identifying the asthma exacerbation was unaware of the results of the mannitol challenge test and sputum analyses.

Asthma score

Overall asthma control was assessed using an asthma score[10] based on asthma symptoms, β_2 agonist use, and PEF variation in which each of the three components contributed a maximum of four points, giving the asthma score a possible range of 0–12. Daily PEF measurements were recorded twice daily throughout the study using hand held electronic diary card spirometers (Micro Medical DiaryCard, Rochester, Kent, UK). Subjects were asked to use the electronic diary card before medication, immediately upon waking, and in the evening to record symptoms and medication use and to perform three spirometric manoeuvres.

Lung function measurements

Spirometric tests were performed using a MicroLoop II Spirometer (Micro Medical Ltd, Kent, UK). Forced expiratory manoeuvres were repeated until two readings of forced expiratory volume in 1 second (FEV_1) within 100 ml were obtained, the largest of which was used in the analyses. Values for FEV_1 and forced vital capacity (FVC) were recorded as a percentage of the predicted values of Knudson *et al*.[11]

Mannitol challenge

A bronchial challenge test with a dry powder of mannitol was administered to all subjects using the protocol of Anderson *et al*.[12] In brief, a nose clip was applied and subjects then inhaled doses consisting of 0 (using an empty capsule as a control), 5, 10, 20, 40, 80, 160, 160 and 160 mg mannitol via a Halermatic (Rhône-Poulenc Rorer, Collegeville, PA, USA). The 80 mg and 160 mg doses were given in multiple doses of 40 mg capsules. At least two FEV_1 manoeuvres were performed 60 seconds after each dose and the highest FEV_1 was used in the calculation. The fall in FEV_1 during the challenge was calculated as a percentage of the value measured after the empty capsule. If the subject had a fall in FEV_1 of more than 10% in response to a single dose, the same dose was repeated. The challenge ceased when the FEV_1 fell by 15% or more or a cumulative dose of 635 mg had been administered. Salbutamol aerosol was administered to aid recovery when necessary. The dose response ratio (DRR) was calculated for all subjects as the percentage fall in FEV_1 at the last dose, divided by the total dose administered. The provoking dose of mannitol causing a 15% fall in FEV_1 (PD_{15}) was estimated by linear interpolation. Airway hyperresponsiveness to mannitol was defined as $PD_{15} \leqslant 635$ mg or DRR $\geqslant 0.023\%$ fall in FEV_1/mg.

Perception of breathlessness

The intensity of breathlessness was measured 1 minute after the inhalation of mannitol, immediately before the lung function measurement. Subjects were asked to rate ''the severity of any sensation of uncomfortable breathing which you are experiencing at this moment'' using a modified Borg scale.[13] The scale ranged from 0 to 10 and was marked with descriptive terms including ''just noticeable'' at 0.5, ''moderately uncomfortable'' at 5, ''severely uncomfortable'' at 7, to ''maximal discomfort'' at 10.

Regression analysis, using the method of least squares, was used to determine the slope and intercept of the relationship between Borg score (dependent variable) and the change in FEV_1 (independent variable) for individual subjects.[14–16] The individual Borg/FEV_1 slope and intercept values were used to calculate Borg scores at 20% fall in FEV_1 ($PS_{20}FEV_1$). Pearson correlation coefficients for the relationship between Borg score and change in FEV_1 were also calculated for each subject. Subjects with correlation coefficients <0.71, indicating that less than 50% of the variation in Borg score was attributable to change in FEV_1, were excluded from the analysis.

Exhaled nitric oxide (NO) measurement

Mixed exhaled NO was measured using an offline technique where the expired gas was collected into a reservoir for later analysis.[17 18] The measurement was performed with the subject standing, without wearing a noseclip. The patient took a deep breath and exhaled over 5–15 seconds to residual volume into an NO impermeable polyethylene bag (Scholle Industries Pty Ltd, Elizabeth West, Australia). The exhaled flow, measured by a rotameter (Dwyer Flowmeter Model VFASS-25, AMBIT Instruments Pty Ltd, Parramatta, Australia), was 10 l/min at a mouth pressure >20 cm H_2O. The exhaled gas from a single breath was analysed within an hour of collection using a chemiluminescence analyser (Thermo Environmental Instruments Model 42C) which has a lower limit of detection of 1 ppb.

Sputum inflammatory cells

Sputum collection was carried out in conjunction with the mannitol challenge. If subjects had to cough during the mannitol challenge, we asked them to spit whatever they produced into a sterile container. At the end of the mannitol challenge, subjects were asked to cough and expectorate and we collected whatever was produced. Subjects rinsed their mouths with water before coughing at each collection point to remove any particles and reduce salivary contamination. All specimens were retained for later examination under the microscope, even if there were no obvious sputum plugs.

Sputum was processed as described by Pizzichini *et al*.[19] Briefly, sputum plugs were selected and added to four times their volume of diluted dithiothriotol (0.1%) (Sputolysin Reagent, Calbiochem, USA). The samples were placed in a shaking water bath (37℃) for 30 minutes and then filtered through 50 µm nylon gauze. The slides were assessed for quality before they were counted, and slides with $>20\%$ squamous cells were rejected. A total cell count was performed and cytocentrifuge slides were prepared (Shandon Cytospin II, Sewickery, PA, USA). The inflammatory cells were expressed as a percentage of the total inflammatory cell count (400 cells) on slides fixed with methanol and stained with May-Grunwald Giemsa.

Data analysis

Values for Borg/FEV_1 slope, DRR, exhaled NO, neutrophil and eosinophil counts were log transformed before analysis. Summary statistics are reported as mean or geometric mean and 95% confidence intervals of the mean. Comparisons of values for the perception measurements at baseline with those after a successful ICS dose reduction, and at the visit immediately before an exacerbation with those during the exacerbation were made by paired *t* test. The magnitude of change in the variables over these time periods was calculated by subtracting the later measurement from the earlier measurement so that a positive value indicates a lower value at the later time point. Pearson's correlation coefficients were calculated to determine the association between the perception indices and the inflammatory cell numbers. Multiple linear regression using a stepwise backward elimination method was used to determine the contribution of multiple factors to the Borg/FEV_1 slope.

RESULTS

Table 1 shows the details of the 42 subjects whose data are included in the analysis. From the 50 recruited, four were excluded because they had a fall in FEV_1 of less than 5% and their correlation coefficients for the relation between Borg score and FEV_1 % fall were less than 0.71, implying that the stimulus of airway narrowing was too small to generate a response in terms of Borg score. A further four subjects were excluded because no data were collected during the exacerbation which developed following their first ICS dose reduction. Of the remaining 42 subjects, 33 successfully underwent at least one ICS dose reduction. Data were collected during an exacerbation from nine subjects following the first dose reduction and from another 18 subjects following subsequent dose reductions.

ICS reduction

In 33 subjects ICS doses were successfully halved without any exacerbation involving changes in PEF or symptoms in the following 8 weeks. Table 2 shows data obtained at baseline and 8 weeks after the steroid dose reduction. Perception changed significantly, with decreases in Borg/FEV_1 slope (mean difference (95% CI) 0.05 (0.02 to 0.08) Borg units/% fall FEV_1), intercept (0.33 (0.07 to 0.59) Borg units), and $PS_{20}FEV_1$ (1.27 (0.54 to 2.00) Borg units). The changes are illustrated in fig 1 which shows mean stimulus response curves constructed from the slope and intercept coefficients for each subject at baseline and 8 weeks. There were no significant changes in FEV_1, Borg score at rest, exhaled NO, or asthma score but airway responsiveness to mannitol increased. Change in AHR correlated significantly with change in $PS_{20}FEV_1$ ($r = -0.40$, $p = 0.025$), but weaker correlations with change in slope ($r = -0.32$, $p = 0.08$) and change in intercept ($r = -0.28$, $p = 0.13$) were not significant.

Sputum was collected both at baseline and after 8 weeks from 14 subjects. Sputum eosinophils increased following steroid reduction but there were no significant changes in other inflammatory cells (table 2). The change in sputum eosinophils was not significantly related to changes in $PS_{20}FEV_1$ ($r = 0.13$, $p = 0.67$), slope ($r = 0.08$, $p = 0.78$), or intercept ($r = 0.12$, $p = 0.69$). Multiple regression analyses were undertaken to determine if changes in perception were associated with changes in the inflammatory cell profile. Change in intercept had a significant negative association with changes in sputum inflammatory cells, with significant contributions to the model from the changes in the percentages of neutrophils, eosinophils, and macrophages (R^2 for the regression $= 0.52$, $p = 0.03$). Changes in slope and $PS_{20}FEV_1$ were not significantly associated with changes in the percentages of any of the inflammatory cells.

Table 1 Details of the 42 subjects included in the analyses, measured at the baseline visit before the first ICS dose reduction. Sputum inflammatory cells were measured in 24 subjects

	Mean (95% CI)
M:F (n)	23:19
Age (years)	43.4 (38.9 to 48.0)
Duration of asthma (years)	26.1 (21.5 to 30.8)
Ex-smokers (n)	12
Atopic (% of group)	95%
Exhaled NO (ppb)*	17.5 (14.9 to 20.6)
FEV_1 (% predicted)	85.5 (79.7 to 91.3)
No with +ve mannitol challenge	22
No taking LABA	7
ICS dose (μg/day, BDP equivalent)	975 (803 to 1147)
Perception	
Slope (Borg/FEV_1 % fall)*	0.26 (0.20 to 0.32)
Intercept (Borg units)	1.04 (0.7 to 1.38)
$PS_{20}FEV_1$ (Borg units)	6.16 (4.8 to 7.51)
Correlation coefficient (Borg score × FEV_1 % fall)	0.84 (0.79 to 0.89)
Sputum inflammatory cells (% total inflammatory cells)	
N	24
Eosinophils (%)*	2.7 (1.51 to 4.8)
Neutrophils (%)*	15.1 (10.5 to 21.7)
Macrophages (%)	66.4 (57.9 to 75.0)
Lymphocytes (%)	2.0 (0.34 to 3.73)

Values are means or *geometric means and 95% confidence intervals of the mean, unless otherwise indicated.
ICS = inhaled corticosteroids; FEV_1 = forced expiratory volume in 1 second; $PS_{20}FEV_1$ = Borg score at 20% fall in FEV_1.

Asthma exacerbation

In 27 subjects, steroid reduction continued until an exacerbation occurred, defined as a fall in PEF values ⩾3 standard deviations from the mean of their pre-steroid withdrawal run in values. Table 3 shows data obtained at the visit immediately before the exacerbation visit at a time when the subjects were clinically well and during the exacerbation. There was a significant decrease in Borg/FEV_1 slope (mean difference (95% CI) 0.05 (0.01 to 0.09) Borg units/% fall FEV_1) and an increase in intercept (0.95 (0.27 to 1.63) Borg units) but no significant change in $PS_{20}FEV_1$ (0.06 (−0.68 to 0.80) Borg units). Figure 2 shows stimulus-response curves generated from the individual slope and intercept data. During the exacerbation there were significant changes compared with the visit before the exacerbation in resting FEV_1, resting Borg score, asthma score, and AHR. Sputum collected at the prior visit and during the exacerbation in 13 of these subjects showed no significant changes in sputum inflammatory cell counts. The change in intercept was significantly correlated with the change in baseline FEV_1 % predicted ($r = -0.57$, $p = 0.002$; fig 3). No significant predictors of change in Borg/FEV_1 slope or $PS_{20}FEV_1$ during the exacerbation were found.

DISCUSSION

This study has shown that reducing the daily dose of ICS in asthmatic subjects was associated with a decrease in the intensity of the sensation of airway narrowing induced by mannitol challenge, shown by decreases in Borg/FEV_1 slope, intercept, and $PS_{20}FEV_1$. Reduction in the ICS dose was also associated with an increase in sputum eosinophilia and AHR to mannitol. The change in $PS_{20}FEV_1$ was correlated with change in AHR. Exacerbations of asthma following ICS dose reduction caused a further decrease in Borg/FEV_1 slope and an increase in intercept, but had no effect on $PS_{20}FEV_1$. The change in intercept was significantly correlated with the change in baseline FEV_1. The effects of ICS dose reduction on

Table 2 Changes in perception, lung function, and airway responsiveness to mannitol in 33 subjects at baseline and 8 weeks after the reduction of their daily steroid dose by half. These subjects remained clinically well during the 8 weeks following the reduction in steroid dose. Sputum inflammatory cells were measured in14 subjects with sputum collected at both visits

	Baseline	8 weeks after reduction	p value
Slope (Borg/FEV_1 % fall)*	0.20 (0.15 to 0.26)	0.14 (0.10 to 0.20)	0.013
Intercept (Borg units)	1.05 (0.67 to 1.43)	0.69 (0.42 to 0.96)	0.010
$PS_{20}FEV_1$ (Borg units)	6.16 (4.7 to 7.6)	4.77 (3.7 to 5.9)	0.003
Correlation coefficient	0.84 (0.77 to 0.90)	0.86 (0.80 to 0.92)	0.76
FEV_1 (% predicted)	85.6 (78.5 to 92.6)	84.7 (77.7 to 91.7)	0.33
Resting Borg score	0.48 (0.28 to 0.67)	0.40 (0.23 to 0.56)	0.33
Asthma score	3.00 (2.47 to 3.53)	3.29 (2.65 to 3.93)	0.11
FEV_1 max fall (%)	14.6 (12.5 to 16.5)	16.3 (14.4 to 18.3)	0.06
*DRR mannitol (% fall FEV_1/mg)	0.036 (0.024 to 0.055)	0.060 (0.039 to 0.094)	0.004
ICS dose (μg/day, BDP equivalent)	1019 (813 to 1225)	506 (403 to 609)	<0.0001
Exhaled NO (ppb)*	18.7 (15.5 to 22.5)	21.5 (15.7 to 28.2)	0.50
Sputum inflammatory cells (% total inflammatory cells):			
N	14	14	
Eosinophils (%)*	2.20 (1.02 to 4.78)	19.6 (13.4 to 28.0)	0.002
Neutrophils (%)*	16.6 (10.0 to 27.5)	9.8 (5.8 to 16.4)	0.17
Macrophages (%)	58.3 (44.8 to 76.0)	58.9 (49.1 to 70.7)	0.93
Lymphocytes (%)	2.5 (−0.33 to 5.4)	1.48 (0.43 to 2.52)	0.39

Values are means or *geometric means and 95% confidence intervals of the mean.
ICS = inhaled corticosteroids; FEV_1 = forced expiratory volume in 1 second; DRR = dose response ratio; $PS_{20}FEV_1$ = Borg score at 20% fall in FEV_1.

the clinical and inflammatory markers in this study have been reported elsewhere.[7] We have shown previously that, when asthma control remains unchanged, the perception indices are repeatable and there are no systematic changes over time that would suggest that the changes in perception could be attributable to a learning effect.[1]

The perception of airway narrowing could be affected by a number of factors including airway responsiveness, airway inflammation, or airway calibre which were altered during the ICS dose reduction and asthma exacerbation. When the ICS dose was reduced there was an increase in AHR and, in the subjects from whom sputum was obtained, in sputum eosinophilia. These changes occurred before there were any significant changes in the asthma score or spirometric function and before the subjects reported any exacerbation. This suggests that the decrease in perception that occurred during the ICS dose reduction is unlikely to be due to recent subjective experience of asthma symptoms or adaptation to airway obstruction. During the exacerbation that followed ICS dose reduction, perception decreased and AHR increased, but there were no significant changes in inflammatory cell numbers compared with the visit immediately before the exacerbation. Previous studies of ICS withdrawal[9 20] have shown that both AHR and sputum eosinophil numbers are increased during the subsequent exacerbation, but it is not clear whether these changes precede the exacerbation or are concurrent with it. In the present study, progressive changes in AHR and airway inflammation preceded the exacerbation but, by the time the exacerbation occurred, AHR to mannitol had increased by more than two doubling doses from the baseline values. In those subjects from whom sputum was obtained, at the exacerbation eosinophils had increased fourfold from baseline but neutrophils had not changed, suggesting that the exacerbations were probably not due to infections.

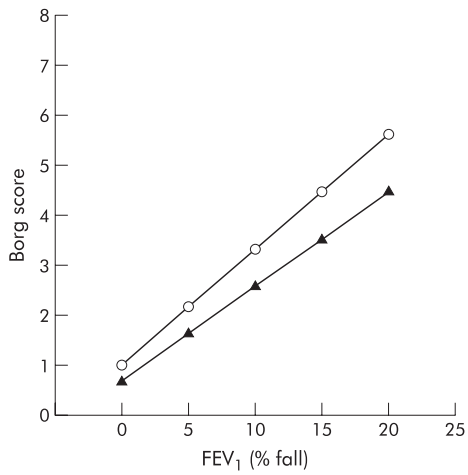

Figure 1 Stimulus response curves, derived from the slope and intercept values, at baseline (open circles) and 8 weeks after the dose of inhaled steroid was halved (triangles) in 33 asthmatic subjects.

Corticosteroids have a wide range of effects, apart from their anti-inflammatory effects, and could conceivably have had a direct effect on perception. However, this seems an unlikely explanation for the observed changes in perception. There was no association between the daily dose of ICS at the start of the study and any of the perception variables, and the magnitude of change in ICS dose was not a significant predictor of change in perception. This is consistent with our previous findings,[1] suggesting that there is no direct effect of ICS on the perception of airway narrowing that is independent of their anti-inflammatory effect. These findings imply that changes in perception are more likely to be due to changes in the underlying asthma severity or, possibly, the level of airway inflammation.

Change in AHR had a significant negative correlation with change in $PS_{20}FEV_1$ and a negative correlation with change in slope that approached significance ($p = 0.08$), indicating that greater increases in AHR were associated with greater decreases in perception. These findings are consistent with previous findings that greater airway responsiveness is associated with reduced perception in asthmatic subjects.[16 21 22] They are also consistent with those of our previous study[1] in which we found that decreases in AHR, which

Table 3 Effects of asthma exacerbation on perception, lung function, and exhaled NO in 27 subjects and on sputum inflammatory cells in 13 subjects from whom sputum was collected both at the visit before the exacerbation when they were clinically well and during the exacerbation

	Visit before exacerbation	Exacerbation	p value
Slope (Borg/FEV_1 % fall)*	0.19 (0.16 to 0.23)	0.13 (0.10 to 0.18)	0.021
Intercept (Borg units)	0.48 (0.02 to 0.94)	1.43 (0.82 to 2.04)	0.010
$PS_{20}FEV_1$ (Borg units)	4.78 (4.0 to 5.6)	4.84 (4.1 to 5.5)	0.89
Correlation coefficient	0.85 (0.80 to 0.90)	0.79 (0.71 to 0.87)	0.12
FEV_1 (% predicted)	85.3 (78.3 to 92.4)	80.9 (73.5 to 88.2)	0.040
Resting Borg score	0.49 (0.23 to 0.76)	1.18 (0.74 to 1.62)	0.009
Asthma score	3.54 (2.96 to 4.12)	6.70 (6.28 to 7.11)	<0.0001
FEV_1 max fall (%)	18.1 (15.9 to 20.3)	18.1 (15.9 to 20.3)	0.99
DRR mannitol (% fall FEV_1/mg)*	0.093 (0.065 to 0.134)	0.130 (0.086 to 0.198)	0.006
ICS dose (μg/day, BDP equivalent)	620 (458 to 782)	352 (253 to 451)	<0.0001
Exhaled NO (ppb)*	17.1 (11.7 to 24.8)	23.4 (18.0 to 31.3)	0.009
Sputum inflammatory cells (% total inflammatory cells)			
N	13	13	
Eosinophils (%)*	17.7 (9.9 to 31.4)	18.6 (9.3 to 37.2)	0.80
Neutrophils (%)*	9.43 (5.6 to 15.9)	5.9 (2.3 to 15.2)	0.92
Macrophages (%)	61.3 (49.7 to 72.9)	49.4 (38.6 to 60.1)	0.66
Lymphocytes (%)	0.78 (0.22 to 1.35)	0.39 (0.11 to 0.66)	0.21

Values are means or *geometric means and 95% confidence intervals of the mean.
ICS = inhaled corticosteroids; FEV_1 = forced expiratory volume in 1 second; DRR = dose response ratio; $PS_{20}FEV_1$ = Borg score at 20% fall in FEV_1.

occurred with the introduction of high dose ICS, were associated with an increase in perception.

The effect of changes in airway inflammation on the perception of induced airway narrowing has received little study. Previous cross sectional studies have shown that blunted perception is associated with high levels of eosinophils in biopsy specimens[23] and in induced sputum.[3] In the present study there were relatively few subjects with sputum available for analysis, probably because we used dry powder mannitol as the challenge agent rather than a wet aerosol. However, subjects who were able to produce sputum did not differ significantly in any clinical or lung function characteristic from those who could not. The methods for processing the sputum were standard and the quality of the slides obtained was good. The percentage of eosinophils in sputum increased significantly during ICS reduction, but the changes in eosinophils were not correlated with changes in any of the perception variables. There were no significant changes in the percentages of any of the other inflammatory cells, either following ICS dose reduction or during the exacerbation. Although the multiple regression analyses showed that changes in the inflammatory cell profiles might have contributed to the changes in perception as measured by the intercept variable, the nature of the associations suggests that they may not be specific to any particular inflammatory cell. However, these models are based on data from a relatively small number of subjects and the lack of specificity in this study may be due to the small sample size and the weakness of the association. Exhaled NO levels were

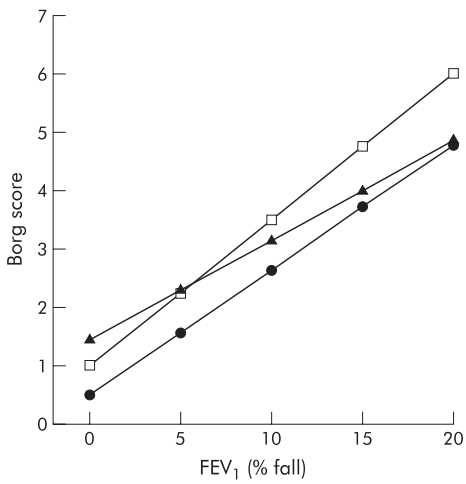

Figure 2 Mean stimulus-response curves derived from the slope and intercept values for 27 subjects measured at baseline (open squares), at the visit before an exacerbation (circles), and during the exacerbation (triangles).Differences between the baseline curve and the previous visit curve are similar to those shown in fig 1 during ICS dose reduction.

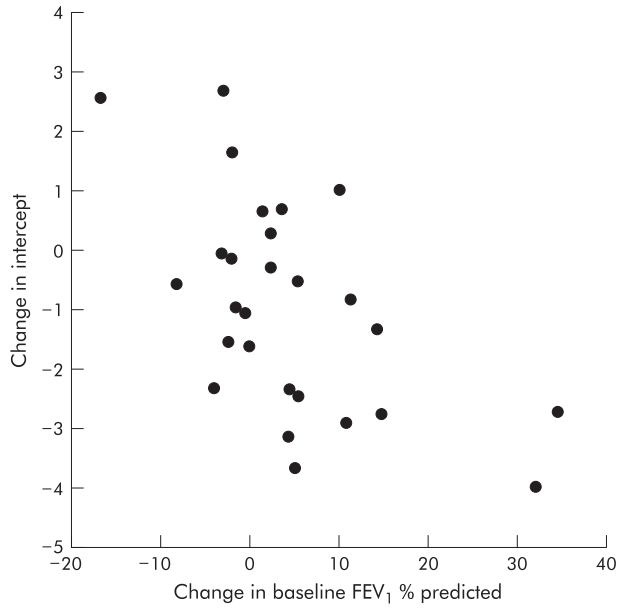

Figure 3 Relationship between the change in baseline FEV_1 as percentage predicted and the change in intercept between the exacerbation visit and the visit before the exacerbation in 27 subjects ($r = -0.57$, $p = 0.0018$). A positive value indicates that the value for intercept or FEV_1 (% predicted) was lower during the exacerbation than at the previous visit.

measured in all subjects but were not significantly associated with any measures of perception during either ICS dose reduction or exacerbation.

The decrease in resting FEV_1 during exacerbation was a strong predictor of the increase in intercept. The intercept represents the severity of breathlessness at zero fall in FEV_1 and is, as expected, closely related to the resting Borg score ($r = 0.8$, $p<0.0001$). During ICS dose reduction the intercept value decreased slightly, although the subjects remained clinically well with no change in lung function, symptom score, or in resting Borg score. Although there is a well described linear relationship between Borg score and % fall in FEV_1 during challenge,[15 24] this reduction in the intercept, in the absence of any change in resting Borg score, may reflect a small deviation from the linear relationship. However, there were no significant changes in the mean correlation coefficients between Borg score and % fall in FEV_1 during either ICS reduction or exacerbation.

Both the Borg/FEV_1 slope[15 24] and $PS_{20}FEV_1$[25] have been used in previous studies as indicators of the perception of acute changes in airway calibre during bronchial challenge tests. It is clear from the findings of this and previous studies[1 26] that these variables do not respond in the same way to changes in asthma status, particularly when there are concurrent changes in intercept. It has been suggested[26] that the slope reflects ''sensitivity'' to changes in FEV_1 while $PS_{20}FEV_1$ is an indicator of the ''absolute perceptual magnitude'' of the stimulus. These studies suggest that these different components of perception behave independently and may be affected by different physiological factors. Further studies will be required to determine which, if any, of these variables has any clinical usefulness in the management of patients with asthma.

In summary, this study has shown that a reduction of ICS dose causes a reduction in the perception of induced airway narrowing before any exacerbation of asthma occurs. Because the changes in perception preceded any changes in lung function or symptoms, it is unlikely that they are the result of an adaptation to slowly developing obstruction or recent experience of symptoms. The changes in perception coincided with increasing AHR during both ICS reduction and exacerbation, but it is unclear whether there is a causal association between these changes. This finding has implications for the management of asthma since it suggests that patients' perceptions of their airway status may be compromised during the down titration of the ICS dose, at a time when they are particularly vulnerable. It is likely that changes in airway inflammation and AHR precede the development of symptoms and changes in lung function associated with an asthma exacerbation. This study has shown that these changes are associated with a decrease in perception, and it is possible that decreased perception could contribute to a delay in the reporting of symptoms.

ACKNOWLEDGEMENTS

The study was supported by the National Health and Medical Research Council Australia, the Australian ARDS Association, and a grant in aid from Rhone-Poulenc Rorer, Australia. Jörg Leuppi was funded by the Swiss National Science Foundation; Novartis Foundation, Switzerland; ''Freiwillige Akademische Gesellschaft'', Basel, Switzerland; and the Swiss Respiratory Society.

The authors are grateful to Dr John Brannan for help with the mannitol challenges, to Drs Hak Kim Chan and Nora Chew for preparation of the mannitol powders, and to Dr Sandra Anderson for her advice on the protocol.

Authors' affiliations

C M Salome, J D Leuppi, G B Marks, Woolcock Institute of Medical Research (formerly known as Institute of Respiratory Medicine), University of Sydney, NSW 2006, Australia
R Freed, Department of Respiratory Medicine, Royal Prince Alfred Hospital, Camperdown 2050, Australia

REFERENCES

1 **Salome CM**, Reddel HK, Ware SI, *et al*. Effect of budesonide on the perception of induced airway aarrowing in subjects with asthma. *Am J Respir Crit Care Med* 2002;**165**:15–21.
2 **Chetta A**, Gerra G, Foresi A, *et al*. Personality profiles and breathlessness perception in outpatients with different gradings of asthma. *Am J Respir Crit Care Med* 1998;**157**:116–22.
3 **In't Veen JCCM**, Smits HH, Ravensberg AJJ, *et al*. Impaired perception of dyspnea in patients with severe asthma. Relation to sputum eosinophils. *Am J Respir Crit Care Med* 1998;**158**:1134–41.
4 **Turcotte H**, Boulet L-P. Perception of breathlessness during early and late asthmatic reponses. *Am Rev Respir Dis* 1993;**148**:514–8.
5 **Wilson RC**, Jones PW. Influence of prior ventilatory experience on the estimation of breathlessness during exercise. *Clin Sci* 1990;**78**:149–53.
6 **Wilson RC**, Oldfield WLG, Jones PW. Effect of residence at altitude on the perception of breathlessness on return to sea level in normal subjects. *Clin Sci* 1993;**84**:159–67.
7 **Leuppi JD**, Salome CM, Jenkins CR, *et al*. Predictive markers of asthma exacerbation during stepwise dose-reduction of inhaled corticosteroids. *Am J Respir Crit Care Med* 2001;**163**:406–12.
8 **Gibson PG**, Wlodarczyk J, Hensley MJ, *et al*. Using quality-control analysis of peak expiratory flow recordings to guide therapy for asthma. *Ann Intern Med* 1995;**123**:488–92.
9 **In't Veen JCCM**, Smits HH, Hiemstra PS, *et al*. Lung function and sputum characteristics of patients with severe asthma during an induced exacerbation by double-blind steroid withdrawal. *Am J Respir Crit Care Med* 1999;**160**:93–9.
10 **Reddel HK**, Jenkins CR, Marks GB, *et al*. Optimal asthma control, starting with high doses of inhaled budesonide. *Eur Respir J* 2000;**16**:226–35.
11 **Knudson RJ**, Lebowitz MD, Holberg CJ, *et al*. Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Respir Dis* 1983;**127**:725–34.
12 **Anderson SD**, Brannan J, Spring J, *et al*. A new method for bronchial-provocation testing in asthmatic subjects using a dry powder of mannitol. *Am J Respir Crit Care Med* 1997;**156**:758–65.
13 **Simon PM**, Schwartzstein RM, Weiss JW, *et al*. Distinguishable types of dyspnea in patients with shortness of breath. *Am Rev Respir Dis* 1990;**142**:1009–14.
14 **Bijl-Hofland ID**, Cloosterman SGM, Folgering HTM, *et al*. Measuring breathlessness during histamine challenge: a simple standardized procedure in asthmatic patients. *Eur Respir J* 1999;**13**:955–60.
15 **James AL**, Carroll N, De Klerk N, *et al*. Increased perception of airway narrowing in patients with mild asthma. *Respirology* 1998;**3**:241–5.
16 **Marks GBM**, Yates DH, Sist M, *et al*. Respiratory sensation during bronchial challenge testing with methacholine, sodium metabisulphite, and adenosine monophosphate. *Thorax* 1996;**51**:793–8.
17 **Massaro AF**, Gaston B, Kita D, *et al*. Expired nitric oxide levels during treatment of acute asthma. *Am J Respir Crit Care Med* 1995;**152**:800–3.
18 **Salome CM**, Roberts AM, Brown NJ, *et al*. Exhaled nitric oxide measurements in a population sample of young adults. *Am J Respir Crit Care Med* 1999;**159**:911–6.
19 **Pizzichini E**, Pizzichini MMM, Efthimiadis A, *et al*. Indices of airway inflammation in induced sputum: reproducibility and validity of cell and fluid-phase measurements. *Am J Respir Crit Care Med* 1996;**154**:308–17.
20 **Gibson PG**, Wong BJO, Hepperle MJE, *et al*. A research method to induce and examine a mild exacerbation of asthma by withdrawal of inhaled corticosteroid. *Clin Exp Allergy* 1992;**22**:525–32.
21 **Burdon JGW**, Juniper EF, Killian KJ, *et al*. The perception of breathlessness in asthma. *Am Rev Respir Dis* 1982;**126**:825–8.
22 **Bijl-Hofland ID**, Cloosterman SG, Folgering HT, *et al*. Relation of the perception of airway obstruction to the severity of asthma. *Thorax* 1999;**54**:15–9.
23 **Roisman GL**, Peiffer C, Lacronique JG, *et al*. Perception of bronchial obstruction in asthmatic patients. Relationship with bronchial eosinophilic inflammation and epithelial damage and effect of corticosteroid treatment. *J Clin Invest* 1995;**96**:12–21.
24 **Bijl-Hofland ID**, Folgering HTM, van den Hoogen H, *et al*. Perception of bronchoconstriction in asthma patients measured during histamine challenge test. *Eur Respir J* 1999;**14**:1049–54.
25 **Boulet L-P**, Leblanc P, Turcotte H. Perception scoring of induced bronchoconstriction as an index of awareness of asthma symptoms. *Chest* 1994;**105**:1430–3.
26 **Bijl-Hofland ID**, Cloosterman SGM, Folgering HTM, *et al*. Inhaled corticosteroids, combined with long-acting β_2-agonists, improve the perception of bronchoconstriction in asthma. *Am J Respir Crit Care Med* 2001;**164**:764–9.