Sensitivity and Validity of Three Bronchial Provocation Tests To Demonstrate the Effect of Inhaled Corticosteroids in Asthma*

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Study objectives: To compare the sensitivity and validity of mannitol, histamine, and cold air challenges to demonstrate the effect of inhaled corticosteroids (ICS) in asthma.

Design: A prospective study.

Participants: Seventeen patients with recently diagnosed, steroid-naive asthma who fulfilled the diagnostic criteria of Finnish Social Insurance Institution and were hyperresponsive to both mannitol and histamine.

Interventions: The following procedures were carried out at baseline and after 3 months and 6 months of treatment with inhaled budesonide, 800 μg/d: symptom assessment with a questionnaire, ambulatory peak expiratory flow (PEF) measurements twice daily for 2 weeks, and bronchial challenges with mannitol, histamine, and cold air.

Results: Budesonide decreased the sum symptom score, daily use of bronchodilating drugs, and diurnal PEF variation, but did not change FEV₁ percentage of predicted significantly. In addition, budesonide significantly decreased mannitol (p = 0.005) and histamine (p = 0.002) response dose ratios. The magnitude of the budesonide-induced change in responsiveness to these two challenges did not differ significantly. The effect of budesonide on cold air responsiveness did not reach statistical significance (p = 0.064). Change in mannitol responsiveness correlated significantly with the changes in sum symptom score and in FEV₁. Change in cold air responsiveness correlated with the changes in sum symptom score and in diurnal PEF variation. Change in histamine responsiveness correlated only with change in FEV₁.

Conclusions: Mannitol challenge is both a sensitive and valid test to demonstrate the effects of ICS in asthma. Histamine challenge is equally sensitive for this purpose, but its validity may be lower than that of mannitol challenge. Cold air challenge seems to be a valid test to demonstrate the effects of ICS, but its sensitivity may be lower than that of mannitol and histamine challenges.

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Key words: asthma; asthma treatment; bronchial hyperresponsiveness; bronchial provocation; cold air; histamine; mannitol

Abbreviations: AHR = airway hyperresponsiveness; CI = confidence interval; ICS = inhaled corticosteroids; PD₁₅ = provocative dose causing a 15% fall in FEV₁; PEF = peak expiratory flow; RDR = response dose ratio

Asthma is now considered as a disease characterized by airway inflammation and airway hyperresponsiveness (AHR).¹ Current guidelines advocate treatment with inhaled corticosteroids (ICS), with adjustment of treatment to the minimal level consistent with an alleviation of symptoms and optimization of spirometric parameters²; however, there is growing evidence to support that this approach may be oversimplistic. It has been shown that although symptoms, physiology, airway inflammation, and remodeling are interrelated in asthma, the changes are not temporally concordant. If the goal of the treat-

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ment is maximal benefit in remodeling, more prolonged and higher doses of ICS treatment may be necessary than suggested by the present guidelines. It has been shown that a treatment strategy aimed at reducing AHR in conjunction with optimizing symptoms and lung function by ICS leads to a greater reduction in the thickness of the subepithelial reticular layer, compared with a treatment strategy aimed at optimizing symptoms and lung function only. These findings suggest a role for serial measurements of AHR in the long-term management of asthma.

The tests to demonstrate AHR fall into two categories: those that act directly on smooth muscle, and those that cause the airways to narrow indirectly by a release of endogenous mediators. Some studies have suggested that indirect tests may be more sensitive in demonstrating the effect of ICS on bronchial responsiveness than direct tests; bronchial responsiveness decreased more to indirect than to direct tests during treatment with ICS. However, other studies have failed to show this kind of difference in sensitivity between direct and indirect tests. Mannitol challenge is a novel indirect test, and inhaled budesonide has been shown to reduce the responsiveness to it in asthmatic patients; however, there are no previous studies comparing mannitol with other bronchial provocation tests with this respect, and this was one reason to carry out the present study.

In addition to sensitivity, validity is another property that is obligatory if a bronchial provocation test will be used to monitor the effect of ICS treatment in asthma. Validity means that the test actually measures the phenomenon it is supposed to measure. If a bronchial provocation test would be used to monitor the effect of ICS treatment in asthma, a physician probably supposes that a decrease in responsiveness to the test during treatment means that patient’s asthma is healing; however, without knowledge about the validity of the test, the physician actually cannot be sure whether the decrease in responsiveness actually represents the healing process of asthma, or merely a presence of ICS treatment. To the best of our knowledge, there are no previous studies comparing the validity of different types of bronchial provocation tests in monitoring the effect of ICS in asthma, and this was the second aim of the present study. We therefore investigated the association of the changes in responsiveness to the provocation tests with changes in other indexes of asthma severity, namely symptom frequency, spirometric indexes, and diurnal peak expiratory flow (PEF) variation.

Materials and Methods

Subjects

The patients were selected from patients who participated in a study comparing mannitol, histamine, and cold air challenges in the diagnostics of asthma (unpublished data; October 2001). For that study, we recruited all consecutive patients for whom a new diagnosis of asthma was given in our outpatient clinic during a period of 18 months. A patient was recruited to the present study if he/she was found hyperresponsive to both mannitol (provocative dose causing a 15% fall in FEV1 (PD15) ≤ 635 mg) and histamine challenges (PD15 ≤ 1 mg). The diagnosis of asthma was based in patient history and clinical examination, in addition to objective evidence of reversible airway obstruction, according to the Finnish Social Insurance Institute criteria. At least one of the following criteria had to be fulfilled: (1) at least 15% fall in FEV1 after exercise challenge; (2) at least 15% improvement in FEV1 after inhaled bronchodilating drug in spirometry; (3) at least 20% spontaneous PEF variation in ambulatory peak flow monitoring on at least 2 days; and (4) at least 15% improvement in PEF after inhaled bronchodilating drug in ambulatory peak flow monitoring on at least 2 days. The exclusion criteria were previous usage of ICS or oral corticosteroids, febrile respiratory tract infection within 4 weeks, and FEV1 < 50% of predicted, and diffusion capacity of the lung < 80% of predicted. The last exclusion criterion was included due to the fact that smokers were also included, and we wanted to rule out patients with emphysema. Nineteen patients fulfilled these criteria; however, 1 patient discontinued the treatment with budesonide within 1 month due to hoarseness, and another patient discontinued the study without naming the reason for it. The remaining 17 patients form the population of the present study, and their basic characteristics are given in Table 1. The patients refrained from taking short-acting β2-agonists for 6 h before the challenges. No asthma medications other than inhaled budesonide and short-acting β2-agonists were used. The institutional ethics committee approved this study, and all subjects gave their informed written consent for participation in the study.

Protocol

The patients were examined at three time points: before treatment, and after 3 months and 6 months of treatment with inhaled budesonide (Pulmicort Turbuhaler, 400 μg per dose; AstraZeneca; Södertälje, Sweden), one dose bid. Before treatment, spirometry (Model M9449; Medikro; Kuopio, Finland) was carried out before and 15 min after 0.4 mg of inhaled salbutamol according to the American Thoracic Society guidelines. Diffusion capacity of the lung was measured by the single-breath method (2200 Pulmonary Function Laboratory; SensorMedics; Aachen, Germany). Skin-prick tests were carried out against common aeroallergens. At each of these three time points the subjects completed a symptom questionnaire. This was followed by mannitol, cold air, and histamine challenges in random order, within 2 weeks, with at least 2 nights between the challenges. The challenges were performed at approximately the same time of a day, by the same research nurse. During these 2 weeks, the patients recorded their PEF values in the morning and in the evening. The compliance for treatment was asked and the inhalation technique was checked during each visit.

Questionnaire

In a self-administered questionnaire, the frequency of dyspnea, cough, wheezing, and sputum production during the last month

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Distribution of asthma severity according to Global Initiative for Asthma classification (Table 1).2

**Table 1—Basic Characteristics of the 17 Patients**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>51 (43–58)</td>
</tr>
<tr>
<td>Male/female gender, No.</td>
<td>12/5</td>
</tr>
<tr>
<td>Atopic subjects, No.</td>
<td>7</td>
</tr>
<tr>
<td>Current smokers, No.</td>
<td>3</td>
</tr>
<tr>
<td>Duration of asthmatic symptoms before start of treatment, mo†</td>
<td>24 (3.5–396)</td>
</tr>
<tr>
<td>Distribution of asthma severity according to Global Initiative for Asthma classification</td>
<td>Mild persistent asthma, 2 patients Moderate persistent asthma, 15 patients</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, % of predicted‡</td>
<td>77 (68–85)</td>
</tr>
<tr>
<td>Improvement in FEV&lt;sub&gt;1&lt;/sub&gt; after 0.4 mg of salbutamol, %</td>
<td>6.8 (3.4–10.2)</td>
</tr>
<tr>
<td>Diffusion capacity of the lung, % of predicted‡</td>
<td>107 (98–116)</td>
</tr>
</tbody>
</table>

*Data are presented as mean (95% CI) unless otherwise indicated.

†Expressed as median (minimum–maximum) values.

‡Predicted values are from Viljanen et al.18,19

was asked. The alternatives for each symptoms were less than once per month (giving one point in the sum symptom score), one to five times per month (two points), approximately once per week (three points), several times per week (four points), and daily (five points). The sum symptom score was calculated as the sum of points for the four symptoms asked. The triggers (22 alternatives) of the symptoms as well as nocturnal symptoms were asked. The daily use of bronchodilating drugs during the last month was defined, as well as the smoking habits. On the basis of symptom frequency and lung function information before treatment, the asthma severity was determined using the Global Initiative for Asthma classification (Table 1).5

**Ambulatory PEF Monitoring**

Patients recorded three PEF values in the morning and in the evening for 2 weeks (Mini Wright; Clement Clarke International; Harlow, UK), and the best of three recordings was always used in the analysis. The variation for each day was calculated by dividing the difference between the evening and the morning PEF values by the mean of these values, and expressed in percentages.21 The mean of these values for 14 days was calculated. A technically satisfactory ambulatory recording at all three time points was obtained from only 13 subjects.

**Mannitol Challenge**

Spray-dried mannitol powder, packed in gelatin capsules containing 5 mg, 10 mg, 20 mg, and 40 mg, was inhaled in doubling doses up to 160 mg, which was then repeated three times using an Inhalator (Boehringer Ingelheim; Ingelheim, Germany). The test continued until the FEV<sub>1</sub> had fallen 15%, or the maximal cumulative dose of 635 mg had been administered. PD<sub>15</sub> was calculated by linear interpolation of the relationship between the percentage decrease in FEV<sub>1</sub> and the cumulative dose of mannitol required to provoke this decrease. The response dose ratio (RDR) value was calculated as the percentage fall in FEV<sub>1</sub> after the last dose, divided by the cumulative dose, in milligrams. The cut-off value for a positive response was defined as PD<sub>15</sub> ≥ 635 mg according to Anderson et al.22

**Histamine Challenge**

Histamine was administered using a dosimetric nebulizer (Spira Electro 2; Respiratory Care Center; Hämeenlinna, Finland). The nebulization time was 0.4 s, set to start 100 mL after the beginning of inspiration. The peak inspiratory flow did not exceed 0.5 L/s, and the nebulization pressure was two bars. These settings give a calibrated output of 6.5 μL per inhalation. Histamine diphosphate was inhaled from the dose of 25 μg on with fourfold increments until the FEV<sub>1</sub> had fallen 15%, or until the maximal dose of 1.6 mg had been administered.23 The PD<sub>15</sub> and RDR values were calculated as above, but using noncumulative doses. The cut-off value for a positive response was defined as PD<sub>15</sub> ≤ 1.0 mg. This cut-off value was chosen because PD<sub>15</sub> was not below it in any of the healthy subjects in the original study by Sovijarvi et al.21 describing this histamine challenge method.

**Cold Air Challenge**

Patients breathed frigid air (range, – 14.6 to – 10.2°C) for 4 min at the minute ventilation level, which was calculated as prechallenge FEV<sub>1</sub> × 25. In order to maintain eucapnia, the inflow of carbon dioxide was calculated as target minute ventilation × 0.05. Spirometry was performed in triplicate before the challenge and in duplicate at 3 min, 5 min, and 10 min after the end of the challenge. The greater of the two FEV<sub>1</sub> values at each time point was used for the analysis. The response was calculated as prechallenge FEV<sub>1</sub> minus the lowest value for FEV<sub>1</sub> measured postchallenge, divided by the prechallenge FEV<sub>1</sub> and expressed as percentages. A cut-off value for a positive response was defined as a ≥ 9% fall in FEV<sub>1</sub> according to Koskela et al.24

**Statistical Analysis**

The results are expressed as means and 95% confidence intervals (CIs); however, geometric means and 95% CIs were used for RDR and PD<sub>15</sub> values. These values were log-transformed before statistical analysis. In case a 15% fall in FEV<sub>1</sub> was not reached during mannitol or histamine challenges, a PD<sub>15</sub> value of 1,270 mg was given for mannitol challenge (double the maximal cumulative dose of mannitol, 635 mg) and 3.2 mg for histamine challenge (double the maximal noncumulative dose of histamine, 1.6 mg). The budesonide-induced change in mannitol and histamine PD<sub>15</sub> values are expressed as fold changes, with doubling of PD<sub>15</sub> indicating a value of two, etc. The change in RDR values are expressed as log RDR during treatment minus log RDR at baseline. PD<sub>15</sub> values are mainly used in descriptive results due to their familiarity to clinicians; however, RDR values were used for comparisons between the challenges and correlation analysis since these values could always be exactly calculated even when a 15% fall in FEV<sub>1</sub> could not be reached during the challenge. To be able to compare cold air challenge with...
mannitol and histamine challenges, a fixed-dose response was calculated for the latter two challenges. This was determined as the percentage fall in FEV₁ after the highest common dose of mannitol and histamine challenges used on all three occasions. Repeated-measures analysis of variance was used to assess the effect of treatment on various indexes. The Student paired t test and analysis of variance were used to compare changes in responsiveness between the challenges at each time point. Pearson correlation values were used to investigate the relationship between the changes in the responsiveness to the challenges and the changes in other indexes of asthma severity. All analyses were carried out using SPSS for Windows 9.0 (SPSS; Chicago, IL).

RESULTS

Inhaled budesonide decreased the sum symptom score, the frequency of each symptom, daily use of bronchodilating drugs (Fig 1), and diurnal PEF variation but did not change FEV₁ percentage of predicted significantly. Figure 2 shows the superior sensitivity of diurnal PEF variation over single measurements of FEV₁ in demonstrating the effect of budesonide in asthma. Table 2 describes the responsiveness of the patients to the bronchial challenges at various stages of the study. Fourteen of the 17 patients (82%) who were mannitol responsive initially became unresponsive at some stage of the study; these figures were 8 of 17 patients (47%) for histamine and 6 of 7 patients (86%) for cold air challenges. Budesonide significantly decreased mannitol (p = 0.005) and histamine (p = 0.002) RDR values (Fig 3). Budesonide-induced change in RDR values did not differ significantly between mannitol and budesonide challenges. In addition, budesonide significantly decreased the fixed-dose responses to mannitol (p = 0.035) and histamine (p = 0.009), but its effect on cold air responses did not reach statistical significance (p = 0.064; Fig 4).

After 3 months of treatment with budesonide, the correlations between changes in responsiveness to the provocation tests were weak (Table 3); after 6 months of treatment, the changes in responsiveness to all tests correlated significantly. The correlation was especially close between the changes in mannitol RDR and histamine RDR values at 6 months of treatment.

![Figure 1](http://journal.publications.chestnet.org/pdaccess.ashx?url=data/journals/chest/20384/ on 06/26/2017)
To explore the validity of the tests to demonstrate the healing process of asthma by inhaled budesonide, the correlation between changes in the responsiveness to the tests and the changes in other indexes of asthma severity was analyzed (Table 4). Change in mannitol responsiveness correlated significantly with the changes in sum symptom score and in FEV<sub>1</sub>. In addition, change in mannitol responsiveness tended to correlate with change in daily use of bronchodilating drugs. Change in cold air responsiveness correlated with the changes in sum symptom score and in diurnal PEF variation. Change in histamine responsiveness correlated with change in FEV<sub>1</sub>.

**Discussion**

This study shows that histamine and mannitol challenges are equally sensitive tests to demonstrate...
the effect of ICS on bronchial responsiveness. The decrease in bronchial responsiveness to these challenges was statistically significant and of similar magnitude after 3 months and 6 months of treatment with inhaled budesonide. Cold air challenge seems to be less sensitive than mannitol and histamine challenges since the change in responsiveness to it did not reach statistical significance. This study also shows that mannitol and cold air challenges are valid tests to demonstrate the healing of asthma by ICS since the change in responsiveness to them correlated significantly with the change in symptom severity, as well as with changes in lung function parameters. Histamine challenge seems to be less valid than the other two challenges, since the change in responsiveness to it did not correlate significantly with changes in asthmatic symptoms.

Our study could not confirm the findings that suggest that indirect challenges would be more sensitive than direct challenges to demonstrate the effect of ICS on bronchial responsiveness.\textsuperscript{5–10} Of the many types of indirect challenges, adenosine challenge is the one most consistently shown to be more sensitive than direct challenges in this respect.\textsuperscript{5–8} In addition, one study\textsuperscript{10} has showed bradykinin to be more sensitive than methacholine, and another study\textsuperscript{9} in children showed cold air to be more sensitive than methacholine. The studies\textsuperscript{11–14} that have not shown any difference between indirect and direct challenges in demonstrating the effects of ICS have included the following indirect stimuli: bradykinin, dry air hyperventilation, exercise, and hyperosmolar saline solution. Our study adds mannitol and cold air to that list. In fact, dry air hyperventilation was less sensitive than histamine challenge in one study,\textsuperscript{12} corresponding with our finding that cold air hyperventilation was less sensitive than histamine. In conclusion, these findings suggest that a special sensitivity to demonstrate ICS-induced changes in bronchial responsiveness is not a feature of all indirect challenges as a group, but is restricted to adenosine and possibly to some other challenges.

The poor sensitivity of cold air challenge to demonstrate ICS-induced changes in bronchial responsiveness is probably due to the mild responses to cold air at baseline. Only 7 of 17 patients who were both mannitol and histamine responsive demonstrated > 9% falls in FEV\textsubscript{1} after cold air challenge. This

![Figure 3](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/20384/)
finding is in accordance with our previous study\textsuperscript{24} pointing to a low sensitivity of cold air also in the diagnostic of adult asthma. As a consequence of small baseline responses, the ICS-induced changes in the cold air responses could also not be large; however, in a study by Nielsen and Bisgaard,\textsuperscript{9} cold air was more sensitive than methacholine to demonstrate the effect of budesonide in 2- to 5-year-old asthmatic children; they used very similar equipment and protocol to those in the present study. This finding is in agreement with our previous results that the responsiveness to cold air increases with younger age.\textsuperscript{24} In conclusion, cold air is probably a sensitive tool to demonstrate the effect of ICS in pediatric asthma, but not in adult asthma.

To the best of our knowledge, the present study is the first to compare the validity of different types of bronchial provocation tests in monitoring the effect of ICS in asthma. Validity in this study represents convergence validity, \textit{i.e.}, the relationship of the instrument to other instruments that measure the same thing.\textsuperscript{16} Our results suggest that the convergence validity of the indirect challenges, mannitol and cold air, to demonstrate the healing of asthma by ICS may be higher than that of histamine, a direct

### Table 3—Pearson Correlation Coefficients Between the Changes in the Responsiveness to the Challenges After Treatment With Inhaled Budesonide

<table>
<thead>
<tr>
<th>Changes</th>
<th>Histamine RDR</th>
<th>Histamine fall in FEV\textsubscript{1}</th>
<th>Cold Air Fall in FEV\textsubscript{1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannitol RDR</td>
<td>-0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mannitol fall in FEV\textsubscript{1}</td>
<td>0.36</td>
<td>0.59*</td>
<td></td>
</tr>
<tr>
<td>Histamine fall in FEV\textsubscript{1}</td>
<td></td>
<td>0.57*</td>
<td></td>
</tr>
<tr>
<td>Mannitol RDR</td>
<td>0.81†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mannitol fall in FEV\textsubscript{1}</td>
<td>0.50*</td>
<td>0.64†</td>
<td></td>
</tr>
<tr>
<td>Histamine fall in FEV\textsubscript{1}</td>
<td></td>
<td>0.60†</td>
<td></td>
</tr>
</tbody>
</table>

\*p ≤ 0.05.  
†p ≤ 0.01.  
‡p ≤ 0.001.
challenge. Change in responsiveness to these indirect challenges, but not to histamine, correlated significantly with the change in symptom severity. Leuppi et al.\textsuperscript{25} showed that in stable asthmatic patients with ICS treatment, hyperresponsiveness to mannitol predicts asthma exacerbation during ICS dose tapering better than does hyperresponsiveness to histamine challenge. This finding is in accordance with our finding that the validity of mannitol challenge to assess asthma severity during treatment with ICS may be better than that of histamine challenge. Validity of a bronchial provocation test is obligatory if a test will be used to monitor the effect of ICS on asthma in everyday clinical practice. Our results suggest that if responsiveness to mannitol or cold air decreases during a treatment with ICS, the patient’s asthma is probably actually improving. On the contrary, if the responsiveness to histamine decreases during treatment, a clinician cannot be sure whether this decrease represents healing of asthma, or merely a satisfactory compliance to therapy.

The very close correlation between changes in mannitol and histamine responsiveness after 6 months of treatment with inhaled budesonide suggests that in the long run, these two challenges probably measure similar components of the healing process of asthma. This finding is important since the studies\textsuperscript{3,4} showing an association between changes in AHR and changes in remodeling parameters have included only direct stimuli for the measurement of AHR. Therefore, a decrease in mannitol responsiveness by ICS probably also mean an improvement in remodeling parameters.

We would like to emphasize the large interindividual variation of the budesonide-induced change in responsiveness to the challenges. Some patients showed a rapid and large decrease; some showed no change at all. It was not uncommon that a patient became unresponsive at 3 months of treatment, but was again responsive at 6 months, probably reflecting the dynamic nature of asthma and the seasonal changes in the contents of aeroallergens. The majority of patients (82%) became unresponsive to the indirect challenge, mannitol, at some stage of the study. On the contrary, only 47% became unresponsive to the direct challenge, histamine, at some stage of the study. Thus, if mannitol will be used to monitor the effect of ICS in asthma, the long-term goal of treatment can be total unresponsiveness to them. However, if a direct challenge like histamine will be used to that purpose, a realistic goal of treatment in most cases would be a decrease in responsiveness, the magnitude of which may be difficult to define.

The present study can be criticized because it was not placebo controlled. The reason for this was that in Finland it is not considered ethically acceptable to delay antiasthma treatment with ICS in a patient with persistent asthma for as long as 6 months. The length of the study was considered important given the chronic nature of asthma. To our knowledge, our study is the longest comparison of bronchial provocation tests during treatment with ICS.\textsuperscript{5–14} The present study can also be criticized due to the lack of objective measurement of drug compliance; however, we asked the compliance during every visit and always encouraged the patients to take their medication regularly. We believe that if someone is motivated to visit our laboratory as many as 10 times during 6 months, he/she is probably also motivated to take the prescribed medication regularly.

In conclusion, mannitol challenge is both a sensitive and valid test to demonstrate the effects of ICS in asthma. If this challenge will be used to monitor the effect of ICS in asthma, the goal of treatment should be unresponsiveness. Histamine challenge seems also to be a sensitive test for this purpose, but its validity may be lower than that of mannitol challenge. Cold air challenge, in turn, seems to be a valid test to demonstrate the effects of ICS, but its sensitivity may be lower than that of mannitol and histamine challenges.

ACKNOWLEDGMENT: The authors thank Pirjo Vääntinen, RN, for her assistance.

### Table 4—Pearson Correlation Coefficients Between the Changes in Responsiveness to the Challenges and Changes in Symptom Frequency, Daily Doses of Bronchodilating Drugs, and Lung Function\textsuperscript{*}

<table>
<thead>
<tr>
<th>Changes</th>
<th>Mannitol RDR</th>
<th>Histamine RDR</th>
<th>FEV\textsubscript{1} Fall After Cold Air</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sum symptom score</td>
<td>0.44 (p = 0.01)</td>
<td>0.22 (p = 0.21)</td>
<td>0.52 (p = 0.002)</td>
</tr>
<tr>
<td>Daily doses of bronchodilating drugs</td>
<td>0.31 (p = 0.08)</td>
<td>0.05 (p = 0.76)</td>
<td>0.13 (p = 0.47)</td>
</tr>
<tr>
<td>Mean diurnal PEF variation</td>
<td>0.25 (p = 0.22)</td>
<td>0.27 (p = 0.18)</td>
<td>0.65 (p &lt; 0.001)</td>
</tr>
<tr>
<td>FEV\textsubscript{1} % of predicted</td>
<td>-0.40 (p = 0.02)</td>
<td>-0.37 (p = 0.03)</td>
<td>-0.26 (p = 0.14)</td>
</tr>
</tbody>
</table>

\textsuperscript{*}In each correlation analysis, 34 pair of values were used, representing 17 asthmatic patients studied at two time points after the start of treatment with inhaled budesonide; however, in the analysis of mean diurnal PEF variation, only 26 pair of values were used since acceptable ambulatory PEF recording was obtained at all time points from only 13 subjects.
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