

# Effect of intranasal azelastine and beclomethasone dipropionate on nasal symptoms, nasal cytology, and bronchial responsiveness to methacholine in allergic rhinitis in response to grass pollens

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**Background:** We compared the effect of nasal azelastine (0.56 mg/day), nasal beclomethasone dipropionate (BDP, 200 µg/day) and matched placebo on seasonal symptoms, nasal cytology, and the increase in bronchial responsiveness occurring during pollen season in a group of subjects with history of allergic rhinitis to grass pollens only.

**Methods:** The study was completed by nine subjects in the azelastine group, 13 subjects in the BDP group, and 13 subjects in the placebo group. Treatments were randomly administered for 6 weeks. Each subject recorded daily nasal, eye and chest symptoms and additional treatment requirement for the entire pollen season. Each subject performed nasal lavage 4 weeks into the pollen season. Bronchial responsiveness to methacholine was measured before and 4 weeks into the pollen season. Response was expressed as provocative dose causing a 20% fall in forced expiratory volume in 1 second in micromoles.

**Results:** Azelastine-treated subjects had significantly fewer nasal symptoms during week 4 ( $p < 0.05$ ), and BDP-treated subjects had fewer nasal symptoms during week 4 ( $p < 0.05$ ) and week 5 ( $p < 0.05$ ) compared with subjects given placebo. Both treatments significantly reduced the need for additional medications. BDP, but not azelastine, treatment significantly reduced the percent of eosinophils recovered in nasal lavage ( $p < 0.05$ ). Neither azelastine nor BDP protected against the increase in bronchial responsiveness to methacholine occurring during the pollen season.

**Conclusion:** We demonstrated that both azelastine and BDP are effective treatments for nasal symptoms of seasonal allergic rhinitis after 4 weeks of therapy. However, we were not able to demonstrate an antiinflammatory activity of nasally administered azelastine. Nasal therapy with azelastine and BDP did not block the increase in bronchial responsiveness to methacholine caused by seasonal allergen exposure. (*J ALLERGY CLIN IMMUNOL* 1995;95:515-23.)

**Key words:** Seasonal rhinitis, azelastine, beclomethasone dipropionate, nasal lavage, bronchial responsiveness

Seasonal allergic rhinitis is a common disease characterized by nasal itch, sneezing, nasal obstruction, and rhinorrhea. Nasal symptoms, as well

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## Abbreviations used

|                    |                                                         |
|--------------------|---------------------------------------------------------|
| BDP:               | Beclomethasone dipropionate                             |
| FEV <sub>1</sub> : | Forced expiratory volume in 1 second                    |
| PD <sub>20</sub> : | Provocative dose causing a 20% fall in FEV <sub>1</sub> |

as eye and chest symptoms, are the consequence of allergic inflammation and mediator release taking place during pollen season.<sup>1-3</sup> Allergic inflammation is due to an influx of inflammatory cells, such as eosinophils and mast cells, to the inflammatory

site.<sup>2,3</sup> Seasonal allergic rhinitis is often associated with seasonal asthma, and bronchial hyperresponsiveness is often measurable in subjects with a clinical history of seasonal allergic rhinitis.<sup>4,5</sup> In these subjects the degree of bronchial responsiveness has been shown to increase during natural exposure to seasonal pollens,<sup>6</sup> probably as a consequence of allergic inflammation within the bronchial airways.

Topical treatment of seasonal allergic rhinitis in response to pollens includes locally administered antihistamines, corticosteroids, disodium cromoglycate, and nedocromil sodium. Azelastine is a new H<sub>1</sub>-receptor antagonist,<sup>7</sup> which has been demonstrated to inhibit immunologic release of histamine from basophils of allergic subjects<sup>8</sup> and from human lung mast cells,<sup>9</sup> neutrophil and eosinophil superoxide generation,<sup>10</sup> release of leukotrienes C<sub>4</sub> and D<sub>4</sub> from passively sensitized guinea pig<sup>11</sup> and human lungs,<sup>9</sup> eosinophil chemotaxis in sensitized dog trachea challenged with antigen,<sup>12</sup> and macrophage chemotaxis.<sup>13</sup> Orally administered azelastine reduces early nasal response to allergen<sup>14</sup> and significantly attenuates nasal symptoms in subjects with seasonal allergic rhinitis.<sup>15</sup> More recently, azelastine as an aqueous nasal spray solution has become available for topical treatment of rhinitis.<sup>7, 16</sup>

In the last few years topical nasal corticosteroids have been established as the first-line treatment for allergic rhinitis.<sup>17</sup> Among topical corticosteroids, beclomethasone dipropionate (BDP) has been shown to significantly reduce nasal symptoms,<sup>18</sup> to decrease the influx of inflammatory cells,<sup>19, 20</sup> and to attenuate the increase in bronchial responsiveness that occurs during natural exposure to seasonal pollens.<sup>21</sup>

This study was therefore undertaken to compare the effect of topical nasal azelastine and BDP on nasal symptoms, on changes in nasal cytology, and on the increase in bronchial responsiveness to methacholine occurring during pollen season in subjects with allergic rhinitis.

## METHODS

### Population

Forty-five adults participated in the study. All subjects had a history of rhinitis and conjunctivitis during grass pollen season for at least 3 consecutive years. Skin prick tests with a standard battery of 10 common aeroallergens were performed in each subject. Subjects showing a positive skin prick test response only to grass pollen extracts were selected. Skin test response to grass pollen extracts (Lab. Farmaceutico Lofarma, Milan, Italy), assessed as the wheal diameter, had to be equal to or

greater than skin test response to histamine (10 mg/ml).<sup>22</sup> None of the subjects reported a history of persistent coughing or wheezing during natural pollen exposure (seasonal asthma). None of them had ever been treated with allergy immunotherapy. Presence of deviated nasal septum, nasal polyps, and sinusitis was excluded by means of roentgenograms. All subjects gave informed consent to participate in the study.

### Study design

We used a randomized, double-blind, placebo-controlled, parallel-group study design. Subjects were instructed to self-administer twice daily (at awakening and at bedtime) either azelastine, 1 spray (0.14 mg) in each nostril, or BDP, 1 spray (50 µg) in each nostril or matched placebo. Doses were those recommended by manufacturers. The study period lasted 6 weeks: treatment started the last week of April 1993 and continued until the first week of June 1993. During the study period, nasal (itch, rhinorrhea, sneezing, and stuffiness), chest (cough and wheezing), and eye (congestion and itching) symptoms were recorded each evening. Each symptom was scored as 0, none; 1, mild (on few occasions); 2, moderate (rather frequent, i.e., more than 2 and less than 5 times a day); 3, severe (persistent, i.e., more than 5 times a day). Symptom diaries were monitored at the clinic every week. Nasal lavage was accomplished in each subject 4 weeks into the pollen season. Bronchial responsiveness to methacholine was measured before and 4 weeks into the pollen season. Assessments of nasal lavage and bronchial responsiveness during the pollen season were done on the same day between 8:00 and 10:00 AM. Rescue medication included cetirizine (oral tablet, 10 mg), cromolyn (eye drops) and salbutamol (metered-dose inhaler, 100 µg/puff).

### Nasal lavage

Each nostril was lavaged with 5 ml of saline solution, warmed to 37°C. After 4 minutes, lavage fluid was recovered and pooled in a plastic tube. Returned fluid was filtered and then centrifuged at 1500 rpm for 10 minutes. The cell pellet was resuspended, and total cell count was determined with a Neubauer hemocytometer. A 0.5 ml aliquot of the original fluid was placed in a Cytospin centrifuge (Shandon, Inc., Pittsburgh, Pa.) at 700 rpm for 5 minutes. Differential cell count of neutrophils, eosinophils, monocytes, and epithelial cells was performed on the cytospin slide after staining with Diff-Quick (Baxter Healthcare Corp., Scientific Div., McGaw Park, Ill.). Differential count was performed on 300 cells with a light microscope (Diaplan; Leitz, Hamburg, Germany) at a magnification of ×1000. All counts were done by one observer in blinded fashion.

### Bronchial responsiveness

Bronchial responsiveness to methacholine was assessed according to a standard procedure.<sup>23</sup> Bronchial

medications, if any, were withheld for at least 12 hours before the challenge. After three reproducible measurements of forced expiratory volume in 1 second ( $FEV_1$ ) were performed, doubling increasing concentrations of methacholine from 0.1 mg/ml were inhaled at 5-minute intervals. Solutions were delivered by a De Vilbiss 646 nebulizer (De Vilbiss Medizinische GmbH, Langen, Germany) attached to a dosimeter (model MB3; Mefar, Brescia, Italy). Inhalations were discontinued when  $FEV_1$  fell by 20% from measurements taken after saline challenge or when 23  $\mu$ mol of methacholine was administered. Bronchial responsiveness was expressed as the provocative dose producing a 20% fall in  $FEV_1$  ( $PD_{20}$ ) and expressed in micromoles.

### Pollen count

Grass pollens were collected daily during the spring of 1993 by a pollen trap, and counts are expressed as number of grains per cubic meter.

### Statistical analysis

Mean daily symptom scores for nasal symptoms (maximal value = 12), eye symptoms (maximal value = 3), and chest symptoms (maximal value = 6), as well as medication requirements, were average for each subject and for each week of the study. Cell count for each cell type was expressed as percentage of total cells. Differences among treatment groups were examined by analysis of variance and post-hoc comparisons (Newman Keuls test). Changes in baseline  $FEV_1$  before and during the pollen season were assessed by analysis of variance. Differences between methacholine  $PD_{20}$  values measured before and during pollen season in each treatment group were examined by Wilcoxon signed-ranks test. All methacholine  $PD_{20}$  values were logarithmically transformed before analysis. For statistical purposes, a  $PD_{20}$  value equal to 23  $\mu$ mol was assigned to subjects in whom  $FEV_1$  did not fall by 20%. A  $p$  value of less than 0.05 was considered statistically significant.

### RESULTS

The study was completed by 36 of 45 enrolled subjects. Their characteristics are reported in Table I. Five subjects receiving azelastine treatment did not complete the study (two because of pregnancy, one because asthma developed, and two because of changes in residence). Two subjects receiving BDP treatment did not complete the study (one because asthma developed and the other because of an unrelated disease). Two subjects receiving placebo withdrew from the study (one because of uncontrolled rhinitis and the other because asthma developed). Inhaled or oral steroids were required to control symptoms in the three subjects in whom seasonal asthma developed. Therefore they were not included in the final analysis.

The number of nasal symptoms in the azelastine-treated group was significantly lower than that in the placebo group only during week 4 ( $p < 0.05$ ) (Fig. 1). Subjects assigned to BDP treatment had significantly fewer nasal symptoms during week 4 ( $p < 0.05$ ) and week 5 ( $p < 0.05$ ) of the grass pollen season compared with subjects receiving placebo (Fig. 1). Differences between the two active treatments were not significant at any time interval. Eye and chest symptoms in the azelastine and BDP groups were similar and not different from those recorded in the placebo group. Because few subjects used cromolyn and salbutamol, the analysis for additional treatment was limited to cetirizine tablets. The use of cetirizine tablets was significantly lower in both groups receiving the active treatments as compared with the placebo group (Fig. 2).

Nasal lavage was successfully accomplished in all but one azelastine-treated subject. All slides had more than 300 cells. Mean total number of cells recovered in the nasal lavage of the azelastine group ( $1.1 \times 10^5$ ) was similar to that of the BDP group ( $1.2 \times 10^5$ ) and both values were not significantly different from that of the placebo group ( $1.5 \times 10^5$ ). Number of eosinophils ranged between 10.6% and 75.6% in the azelastine group, between 0% and 67.3% in the BDP group, and between 4.3% and 65.6% in the placebo group. Azelastine treatment did not reduce the percentage of eosinophils or neutrophils compared with placebo (47.8% vs 34.5% and 11.8% vs 21.9%, respectively) (Fig. 3). Subjects treated with BDP had significantly fewer eosinophils (14.2% vs 34.5%;  $p < 0.05$ ) but not neutrophils (20.1% vs 21.9%) compared with placebo-treated subjects (Fig. 3). In addition, BDP treatment was significantly better than azelastine in reducing eosinophil recruitment in nasal lavage ( $p < 0.05$ ).

Bronchial responsiveness to methacholine outside grass pollen season, expressed as  $PD_{20}$  value, was measurable in 21 of 36 subjects. The methacholine  $PD_{20}$  value was greater than 23  $\mu$ mol in three of 10 subjects receiving azelastine treatment, in five of 13 subjects receiving BDP treatment, and in seven of 13 subjects receiving placebo treatment. Baseline  $FEV_1$  values, measured outside the pollen season, were similar in the three groups and did not change significantly during the pollen season (Table II). In the three groups, methacholine  $PD_{20}$  values outside the pollen season were not significantly different (Table II). During the pollen season, methacholine  $PD_{20}$  significantly decreased in all treatment groups (Table II, Fig. 4). The ratio of change in  $PD_{20}$  values (before and

TABLE I. Subjects' characteristics

| Subject No.      | Sex | Age (yr)   | Height (cm)  | Smoking habit | Predicted FEV <sub>1</sub> |
|------------------|-----|------------|--------------|---------------|----------------------------|
| Azelastine group |     |            |              |               |                            |
| 1                | M   | 49         | 166          | Ex            | 3.22                       |
| 2                | M   | 20         | 164          | N             | 3.98                       |
| 3                | M   | 30         | 170          | N             | 3.95                       |
| 4                | M   | 17         | 175          | N             | 3.98                       |
| 5                | M   | 26         | 173          | N             | 4.22                       |
| 6                | M   | 19         | 170          | N             | 4.26                       |
| 7                | F   | 34         | 170          | N             | 3.28                       |
| 8                | F   | 19         | 173          | N             | 3.75                       |
| 9                | M   | 28         | 178          | N             | 4.35                       |
| 10               | F   | 19         | 169          | N             | 3.62                       |
| Mean $\pm$ SD    |     | 26 $\pm$ 9 | 171 $\pm$ 4  |               | 3.91 $\pm$ 0.39            |
| BDP group        |     |            |              |               |                            |
| 1                | M   | 28         | 179          | Y             | 4.39                       |
| 2                | M   | 18         | 185          | N             | 4.94                       |
| 3                | F   | 33         | 161          | Y             | 2.93                       |
| 4                | F   | 29         | 172          | N             | 3.46                       |
| 5                | M   | 16         | 180          | N             | 3.84                       |
| 6                | M   | 23         | 171          | N             | 4.22                       |
| 7                | M   | 18         | 170          | N             | 4.29                       |
| 8                | F   | 19         | 158          | N             | 3.18                       |
| 9                | M   | 29         | 178          | N             | 4.32                       |
| 10               | F   | 21         | 166          | N             | 3.42                       |
| 11               | F   | 45         | 159          | N             | 2.55                       |
| 12               | M   | 34         | 166          | N             | 3.66                       |
| 13               | M   | 20         | 171          | N             | 4.28                       |
| Mean $\pm$ SD    |     | 26 $\pm$ 8 | 170 $\pm$ 8  |               | 3.81 $\pm$ 0.65            |
| Placebo group    |     |            |              |               |                            |
| 1                | M   | 19         | 186          | N             | 4.87                       |
| 2                | M   | 13         | 155          | N             | 3.25                       |
| 3                | F   | 28         | 157          | Y             | 3.04                       |
| 4                | M   | 33         | 185          | Y             | 4.46                       |
| 5                | F   | 23         | 160          | N             | 3.20                       |
| 6                | F   | 25         | 152          | N             | 2.61                       |
| 7                | M   | 17         | 170          | N             | 3.44                       |
| 8                | F   | 22         | 169          | N             | 3.56                       |
| 9                | F   | 30         | 170          | N             | 3.29                       |
| 10               | F   | 28         | 159          | Y             | 3.09                       |
| 11               | M   | 35         | 177          | Ex            | 4.12                       |
| 12               | F   | 23         | 158          | N             | 3.36                       |
| 13               | M   | 29         | 177          | Ex            | 4.19                       |
| Mean $\pm$ SD    |     | 25 $\pm$ 6 | 167 $\pm$ 11 |               | 3.58 $\pm$ 0.62            |

N, Nonsmoker; Y, yes (current smoker); Ex, ex-smoker.

during pollen season) ranged between 0.49 and 5.97 in the azelastine group, between 0.71 and 17.7 in the BDP group, and between 0.65 and 12 in the placebo group. These differences were not significant.

## DISCUSSION

The results of this study demonstrate that the regular use of topical azelastine, aqueous nasal

spray, is effective in reducing symptoms of seasonal allergic rhinitis after 4 weeks of therapy and confirm that topical BDP is, overall, more effective than antihistamines.<sup>24</sup> An antiinflammatory activity, as demonstrated by the decrease of eosinophils in nasal lavage, is evident for BDP treatment but not for azelastine treatment. Neither azelastine nor BDP significantly attenuates the increase in bronchial responsiveness to

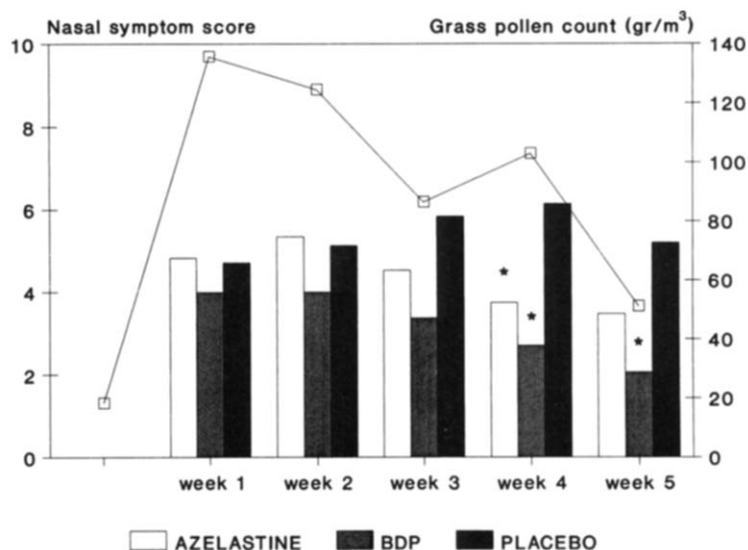


**FIG. 1.** Mean weekly symptom scores for each treatment group and mean weekly grass pollen counts during 5 weeks of study. Line represents mean weekly pollen count. \* $p < 0.05$  compared with placebo group.  $gr/m^3$ , Grains per cubic meter.

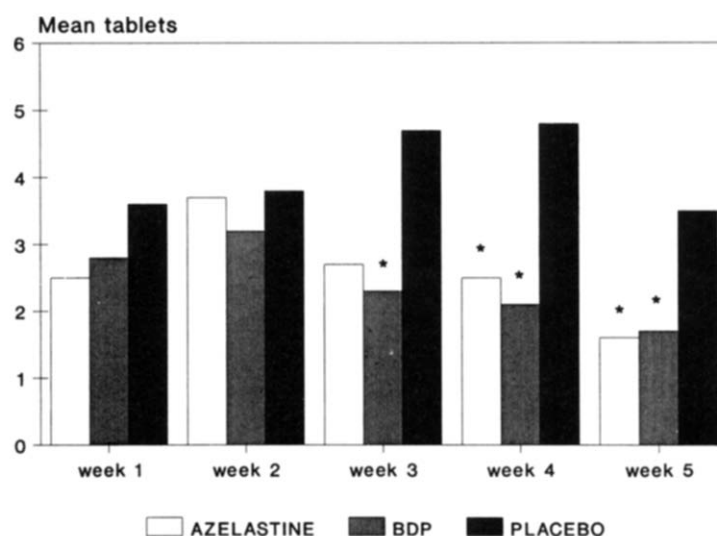


**FIG. 2.** Mean weekly antihistamine tablets for each treatment group during 5 weeks of study. \* $p < 0.05$  compared with placebo group.

methacholine occurring during natural pollen exposure.

Oral azelastine has been shown to significantly reduce nasal symptoms in seasonal<sup>15</sup> and perennial allergic rhinitis.<sup>17</sup> The effect is dose-dependent, and the maximal efficacy is found at a daily dose of 4 to 8 mg. However, at the highest dosage, side effects are also significant.<sup>7</sup> It is likely that topical treatment with azelastine is better tolerated than oral treatment.<sup>25</sup> We did not record any side effects in the azelastine-treated subjects. Intranasal BDP is known to provide optimal relief of nasal symp-

toms of allergic rhinitis,<sup>18</sup> which occurs after few weeks of treatment.<sup>24</sup> The beneficial results of therapy are better than those of oral antihistamines.<sup>24</sup> In addition, it has been demonstrated that nasal BDP in subjects with seasonal rhinitis and mild asthma decreases not only nasal but also bronchial asthmatic symptoms.<sup>26-28</sup> Although we started nasal treatments 1 week before the pollen season, a significant therapeutic effect was evident only after some weeks. Moreover, it seems that their therapeutic effect was more evident when the grass pollen count started to decrease. We did not

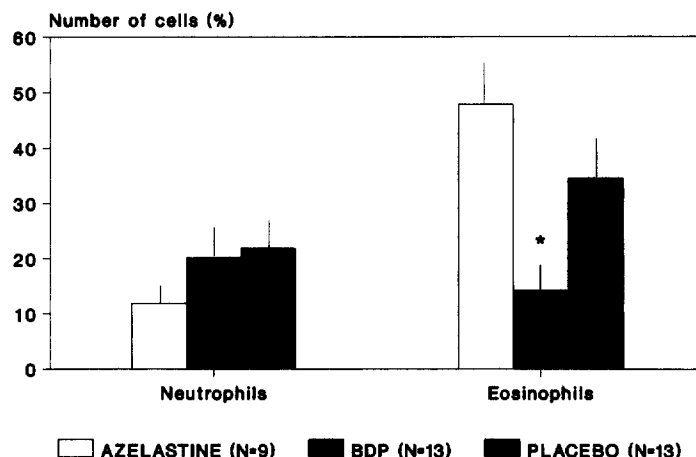


FIG. 3. Mean number of neutrophils and eosinophils in nasal lavage obtained during the grass pollen season in each treatment group. \* $p < 0.05$  compared with placebo group.

find any clear evidence of control of cough and wheezing by either active treatment. However, these symptoms were present in only few subjects. There are at least two reasons that could explain this difference. We administered half of the daily dose of BDP to our subjects with allergic rhinitis compared with that previously applied.<sup>24</sup> Moreover, we selected subjects with allergic rhinitis without any history of respiratory symptoms, whereas subjects with mild seasonal asthma were enrolled in previously reported studies.<sup>26-28</sup>

Although azelastine has been reported to have antiinflammatory activity,<sup>7</sup> we were unable to demonstrate any modulating effect on the recruitment of inflammatory cells in nasal lavage during pollen exposure, whereas we confirmed that topical BDP significantly reduces eosinophil influx.<sup>20, 29</sup> The effect of topical azelastine on nasal cytology of patients with seasonal allergic rhinitis has not previously been evaluated. When subjects with seasonal allergic rhinitis are exposed to pollens, the increase in eosinophil number correlates closely with pollen counts and nasal symptoms,<sup>2</sup> chemotactic factors for eosinophils are released,<sup>30</sup> and eosinophils have an increased propensity to release their granules.<sup>31</sup> Therefore eosinophil recruitment and activation are regarded as good clinical indexes of local allergic inflammation. However, antihistamines such as terfenadine and cetirizine, which are also able to prevent seasonal nasal symptoms, do not affect the influx of eosinophils after nasal allergen stimulation.<sup>32</sup> Yet, azelastine may affect eosinophil function because in vitro experiments demonstrate that it is able to reduce the generation of superoxide radicals from purified circulating eosinophils.<sup>10</sup> Alternatively,

azelastine may block mast cell histamine release or antagonize its effects. An inhibitory effect on histamine release from sensitized human lung fragments has been reported.<sup>9</sup> However, drug concentrations were much higher than those expected to be achieved in the nasal mucosa after an oral dose of 8 mg (serum concentration approximately 4 ng/ml)<sup>33</sup> or even after a nasal dose of 0.14 mg (serum concentration approximately 0.4 ng/ml).<sup>25</sup> Moreover, oral azelastine, given at a therapeutic dosage, failed to significantly prevent histamine release after both bronchial<sup>34</sup> and nasal allergen challenges,<sup>14</sup> whereas it blocked the early asthmatic response and the immediate nasal obstruction. Therefore it is likely that azelastine mainly acts by antagonizing the effects of released histamine at the level of sensory nerve endings and blood vessels. Besides, azelastine also exhibited an inhibitory effect on leukotriene production both in vitro<sup>14</sup> and in vivo,<sup>35, 36</sup> which may be relevant to its therapeutic activity.

After treatment with either topical azelastine or BDP, there was no statistically significant protective effect on seasonal increase in bronchial responsiveness to methacholine. Oral azelastine, 4 mg twice daily, given for 2 weeks also failed to inhibit the seasonal increase in bronchial responsiveness,<sup>16</sup> whereas a small but significant reduction of the increase in bronchial amount of responsiveness has been found after 6-week treatment with nasal BDP in subjects with seasonal rhinitis and asthma.<sup>21</sup> It is likely that this lack of activity is due to an incomplete control of nasal obstruction, which therefore allowed a greater deposition of aeroallergens within the lower airways. In addition, other factors may explain the discrepant results

**TABLE II.** Individual values of baseline FEV<sub>1</sub> and methacholine PD<sub>20</sub> measured outside and during the grass pollen season in each treatment group

| Subject No.      | Outside season            |                           | During season             |                           |
|------------------|---------------------------|---------------------------|---------------------------|---------------------------|
|                  | FEV <sub>1</sub> (% pred) | PD <sub>20</sub> M (μmol) | FEV <sub>1</sub> (% pred) | PD <sub>20</sub> M (μmol) |
| Azelastine group |                           |                           |                           |                           |
| 1                | 92.2                      | 0.32                      | 94.7                      | 0.60                      |
| 2                | 108.5                     | 10.44                     | 108.0                     | 2.80                      |
| 3                | 110.6                     | 4.18                      | 110.6                     | 0.70                      |
| 4                | 100.0                     | 18.65                     | 102.5                     | 9.14                      |
| 5                | 110.7                     | 1.50                      | 107.8                     | 0.57                      |
| 6                | 94.6                      | 23.00                     | 92.3                      | 4.56                      |
| 7                | 103.9                     | 19.49                     | 101.8                     | 5.02                      |
| 8                | 102.9                     | 17.48                     | 99.5                      | 3.95                      |
| 9                | 105.0                     | 23.00                     | 103.9                     | 8.39                      |
| 10               | 94.2                      | 23.00                     | 90.3                      | 23.00                     |
| Mean ± SD        | 102.3 ± 6.8               |                           | 101.2 ± 6.9               |                           |
| BDP group        |                           |                           |                           |                           |
| 1                | 87.9                      | 16.24                     | 84.1                      | 23.00                     |
| 2                | 90.5                      | 10.62                     | 82.6                      | 0.60                      |
| 3                | 128.3                     | 2.19                      | 128.3                     | 2.19                      |
| 4                | 98.6                      | 14.02                     | 96.5                      | 1.30                      |
| 5                | 138.8                     | 23.00                     | 137.0                     | 23.00                     |
| 6                | 113.0                     | 8.17                      | 113.0                     | 5.52                      |
| 7                | 101.4                     | 23.00                     | 79.5                      | 4.62                      |
| 8                | 89.6                      | 14.54                     | 87.1                      | 2.03                      |
| 9                | 87.0                      | 4.20                      | 87.0                      | 0.89                      |
| 10               | 98.5                      | 23.00                     | 98.8                      | 23.00                     |
| 11               | 83.9                      | 3.58                      | 83.9                      | 2.06                      |
| 12               | 112.8                     | 23.00                     | 111.5                     | 23.00                     |
| 13               | 110.3                     | 23.00                     | 106.3                     | 4.42                      |
| Mean ± SD        | 103.1 ± 16.8              |                           | 99.7 ± 18.5               |                           |
| Placebo group    |                           |                           |                           |                           |
| 1                | 113.1                     | 14.42                     | 84.1                      | 4.53                      |
| 2                | 89.8                      | 14.04                     | 82.6                      | 1.17                      |
| 3                | 118.8                     | 17.12                     | 128.3                     | 4.66                      |
| 4                | 118.4                     | 23.00                     | 96.5                      | 23.00                     |
| 5                | 95.9                      | 23.00                     | 137.0                     | 23.00                     |
| 6                | 96.9                      | 14.91                     | 113.0                     | 23.00                     |
| 7                | 120.1                     | 23.00                     | 79.5                      | 2.32                      |
| 8                | 110.4                     | 10.47                     | 87.1                      | 4.14                      |
| 9                | 109.1                     | 23.00                     | 87.0                      | 18.40                     |
| 10               | 104.9                     | 1.60                      | 98.8                      | 1.03                      |
| 11               | 94.2                      | 23.00                     | 83.9                      | 5.16                      |
| 12               | 92.9                      | 23.00                     | 111.5                     | 23.00                     |
| 13               | 126.7                     | 23.00                     | 106.3                     | 16.89                     |
| Mean ± SD        | 107.0 ± 12.1              |                           | 105.3 ± 12.7              |                           |

obtained with BDP treatment. We selected subjects with strict allergic rhinitis showing a very low degree of bronchial responsiveness to methacholine outside the pollen season, whereas Corren et al.<sup>21</sup> studied the effect of nasal BDP in subjects with a history of seasonal asthma, showing a degree of responsiveness to methacholine approxi-

mately 10 times lower, when measured outside the pollen season. Moreover, peak pollen count during our study period was three times higher than that reported by Corren et al.,<sup>21</sup> and we measured bronchial responsiveness when the pollen count was approximately 10 times higher. Finally, we cannot exclude that a type 2 statistical error might

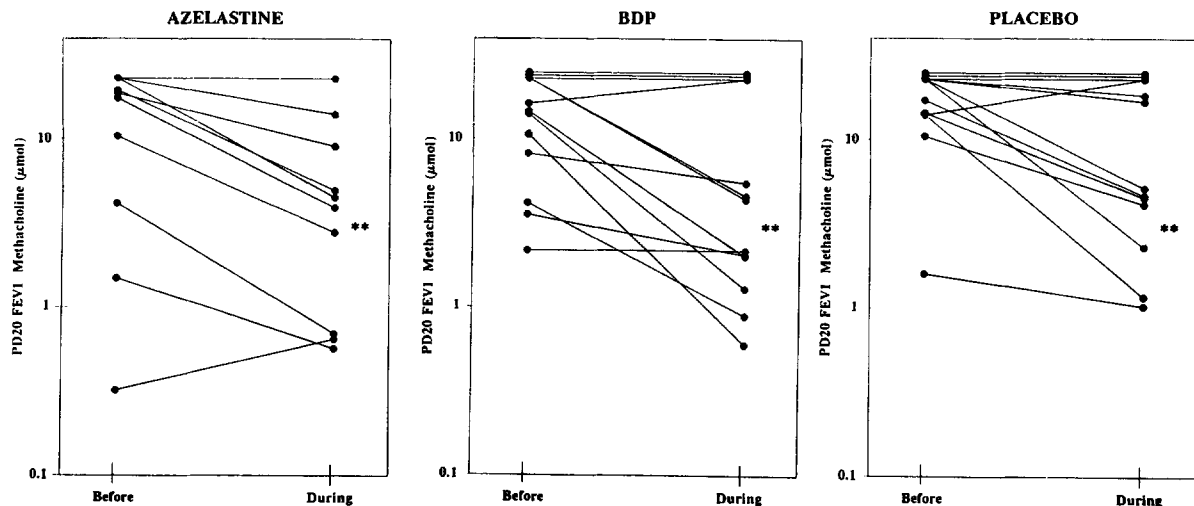


FIG. 4. Individual values of methacholine PD<sub>20</sub>, expressed as micromoles, at baseline and during the grass pollen season in each treatment group. \*\* $p < 0.015$  compared with baseline.

also have occurred, because the sample groups were small.

In conclusion, our study provides further evidence that topical azelastine and BDP are effective treatments for seasonal allergic rhinitis. BDP, but not azelastine, likely achieves its efficacy by controlling allergic nasal inflammation. In addition, our results do not clearly support an effect of nasal treatment in the reduction of the increase in bronchial responsiveness occurring during pollen season in subjects with allergic rhinitis.

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## Neuropsychiatric effects of medications for allergic diseases

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### Abbreviations used

CNS: Central nervous system  
OTC: Over-the-counter  
PPA: Phenylpropanolamine

Adverse reactions to drugs and the perceptions associated with them influence prescribing patterns and undermine compliance. This concern gains significance in the treatment of chronic dis-