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The effect of beclomethasone dipropionate treatment on the nasal provocation test

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SUMMARY

A total of 50 patients with hay fever of perennial rhinitis were treated for 14 days with beclomethasone dipropionate nasal spray. Dosage was one puff (50 μg) in each nostril four times a day to a total daily dose of 400 μg.

Rhinomanometry was used to determine the efficacy of beclomethasone dipropionate in immediate type allergic responses provoked by a nasal challenge with either grass pollen or house dust/house mite allergen. Treatment with beclomethasone dipropionate nasal spray resulted in a significant increase in tolerance to both house dust/house mite allergen ($P = 0.01$) and grass pollen allergen ($P = 0.005$).

Passive anterior rhinomanometry would seem to offer an easy suitable technique for measuring nasal resistance during nasal provocation tests.

INTRODUCTION

Use of locally administered corticosteroids has been an accepted method of therapy in otolaryngology for many years. As early as 1952, cortisone depot preparations were being injected into the inferior turbinates to alleviate allergic rhinopathies (Wall and Shure, 1952; De Gandt, 1969).

This method was subsequently abandoned because of the resultant elevation of plasma cortisol levels (D'Hont, 1975). Later, dexamethasone phosphate nasal aerosol was used successfully in patients with hay fever (Normann et al., 1967). However, local use of dexamethasone also resulted in significant increase in plasma cortisol levels and suppression of urinary excretion of 17-ketosteroids (Normann et al., 1967).

Development of beclomethasone dipropionate represented a major therapeutic advance. This potent anti-inflammatory agent has been used successfully in the treatment of eczema (Raffle and Frain-Bell, 1967) and asthma (Brown et al., 1972; Clark, 1972) without any apparent systemic side effects, notably suppression of the hypothalamic-pituitary-adrenal (HPA) axis (Harris et al., 1973; Harris, 1980).

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Its exclusive local action at the bronchi level was shown clearly by Morrow-Brown and Storey (1973–1975) when patients with asthma being treated with beclomethasone dipropionate had flair-ups of nasal complaints.

The efficacy of nasal application of beclomethasone dipropionate in treating allergic rhinopathies and polyposis nasi was then demonstrated in many double-blind cross-over and non-cross-over studies (Hansen and Mygind, 1974; Mygind et al., 1975–1976; Lehdensuo and Haahtel, 1977; Morrow-Brown and Storey, 1974; Clement and Pauwels, 1980). One disadvantage in these types of studies was that the efficacy of the therapeutic agent was judged by means of a score system which reflected the subjective complaints of the patients. Moreover, the temperate climate of many western European countries makes it very difficult to assess efficacy of a therapeutic agent in seasonal allergic rhinitis satisfactorily. The variability of the pollen challenge depends upon variations in the weather (Blair and Butler, 1976).

Therefore, nasal provocations tests, which can be performed outside of the pollen season, offer a more reliable alternative than methods previously employed. Studies of this type have been reported by Vilsvik et al., 1975; Mygind et al., 1977 and Okuda and Senba, 1980. While the study by Okuda and Senba (1980) involved a substantial number of patients with perennial rhinitis, results were not determined objectively by rhinomanometry, but by anterior rhinoscopy. Moreover, it was multicentric in design and results were judge by more than one person. The objective of this present investigation was to assess the efficacy of beclomethasone dipropionate in immediate type allergic responses using rhinomanometry to determine results.

METHODS AND MATERIALS

Patient selection

The 50 patients selected for this trial (25 with perennial rhinitis and 25 with hay fever) had an allergic index ≥ 6 based on the point system outlined in Table 1. The average allergic index (maximum 10 points) was 7.9 for the grass pollen group and 7.4 for the perennial rhinopathy group.

Materials

The allergens used for skin testing and nasal provocation were supplied by the HAL Company*, and were available in three concentrations:

grass pollen - 1000 U/ml, 10,000 U/ml, 20,000 U/ml
house dust - 0.5%, 5%, 50%
house mites - 10 U/ml, 50 U/ml, 100 U/ml.

* HAL-Allergenen Laboratorium, Haarlem, The Netherlands.

Table 1.

All the subjects had to have an allergic index $\geqq 6$.
The criteria for this index were:
a. RIST $\geqq 150 = 1$ point;
RIST $< 150 = 0$ pounts.
b. Blood eosinophilia $\geqq 250 = 1$ point;
Blood eosinophilia $< 250 = 0$ points.
c. RAST $\geqq 3+ = 2$ points;
$2+ = 1$ point;
$< 2+ = 0$ points.
d. Positive history (sneezing, nasal blocage, watery nasal discharge) = 2 points.
e. Skin test $\geqq 3+ = 2$ points;
$2+ = 1$ point;
$< 2+ = 0$ points.
f. Strong positive nasal provocation test (at least a two times increase in one nasal cavity of the nasal pressure with a flow of 15 liters a minute): pressure increase factor $\geqq 2 =$ 2 points.
g. Moderate positive nasal provocation test (increase of nearly 2 times in only two subjects with perennial rhinopathy because of the high initial pressure): pressure increase factor nearly 2 = 1 point.

Introduction of the allergen aerosol and measurement of nasal patency was accomplished using a passive anterior rhinometer (Heyer Company) as described by Clement et al., 1981. As a measure of nasal patency the pressure gradient (flow of 15 l/min) was determined for both nasal cavities in each test subject.

Dosage and administration

Each patient was instructed to administer one puff (50 µg) of beclomethasone dipropionate* in each nostril four times a day for a total daily dose of 400 µg. Dosage was to continue for 14 days. Medications that could affect the course of the disease or outcome of treatment were to be discontinued three days before the first nasal provocation test.

Measurements and statistical methods

Nasal provocation tests were conducted in each patient just prior to the first dose of beclomethasone and again after completion of 14 days of therapy. Comparisons were then made in allergen concentrations needed to evoke a positive reaction. For each nasal cavity the initial pressure gradient at the beginning of the provocation (flow = 15 l/min), the pressure gradient increase and the pressure gradient increase factor after provocation were compared before and after treatment.

* Aldecin® Nasal Spray, N.V. Essex Belgium, S.A., Belgium.

Changes in allergen concentration, pre- and post-therapy were analyzed statistically using the McNemar test. Comparisons of initial pressure gradient at the beginning of the provocation test before and after treatment were analyzed via the Student t-test and confirmed using non-parametric analysis. The pressure gradient increase factors were compared and analyzed using a commercially available computer package (SPSS), the sign test and Wilcoxon matchpair signed ranks test.

RESULTS

A significant decrease in allergen concentration threshold to grass pollen ($P = 0.005$) and house dust/house dust mites ($P = 0.01$) was achieved after 14 days of therapy with beclomethasone dipropionate nasal spray (Table 2).

From the pressure gradient data it was impossible to get significant results because there existed an important overlap between the mean values before and after provocation. Therefore the notion of pressure gradient increase factor was introduced. The pressure increase factor is a number which indicates the ratio of the end pressure gradient after provocation over the initial pressure gradient (pressure gradient increase factor = end pressure gradient/initial pressure gradient). Treatment in patients with hay fever resulted in a significant decrease of the pressure gradient increase factor in the right nostril only ($P = 0.025$) (Table 3). In patients with perennial rhinitis, however, both nasal cavities showed a highly

Table 2. Maximal concentration of the allergen (= end concentration) needed for a positive nasal challenge.

A. Grass pollen

	end concentration				
			20.000 U		
number of patients	1000 U	10.000 U	with reaction	without reaction	total number of patients
before treatment	1	13	11	0	25
after treatment	0	4	19	2	25

B. House dust and house dust mites

	end concentration				
			50%		
number of patients	0.5%	5%	with reaction	without reaction	total number of patients
before treatment	0	4	21	0	25
after treatment	0	1	15	9	25

Table 3. Comparison of the pressure increase after provocation.

A. Grass pollen

	mean	standard deviation	probability p
left nasal cavity : before treatment	4.75	0.46	0.375
after treatment	4.48	0.85	
right nasal cavity: before treatment	5.80	1.50	0.025
after treatment	3.35	0.45	

B. House dust and house dust mites

	mean	standard deviation	probability p
left nasal cavity : before treament	3.76	0.46	0.000
after treatment	1.85	0.15	
right nasal cavity: before treatment	2.98	0.37	0.001
after treatment	1.80	0.15	

significant decrease in pressure gradient increase factor after challenge with house dust/house dust mites allergen ($P = 0.000$ and 0.001), (Table 3).
Because a pressure increase factor equal to two is generally considered clinically significant, the data were categorized using the break-point of two (Figure 1). The following four possibilities result after nasal provocation:

1. the left and right nasal cavities show an increase in pressure at least equal to two ($L \geqq 2$, $R \geqq 2$);
2. the left cavity shows an increase of at least two while the right shows an increase less than two ($L \geqq 2$, $R < 2$);
3. the left nasal cavity shows an increase less than two and the right an increase of at least two ($L < 2$, $R \geqq 2$);
4. the left and right cavities show an increase of less than two ($L <$, $R < 2$).

A significant change ($P = 0.025$) in the pressure increase factor was demonstrated in both groups of patients.
Comparisons of initial pressures at the beginning of the provocation test before treatment and after treatment showed no clear-cut decrease of the initial pressure after the completion of the trial period in either group.

DISCUSSION

Seemingly marked discrepancies in the effectiveness of beclomethasone between the minimal protection seen after a grass pollen challenge and the marked effectiveness of the drug in the treatment of hay fever have been reported by Mygind et al., 1977. In this study, beclomethasone offered slight protection against nasal challenge with minute amounts of allergen. Based on their observations the investigators hypothesized that the efficacy of beclomethasone dipro-

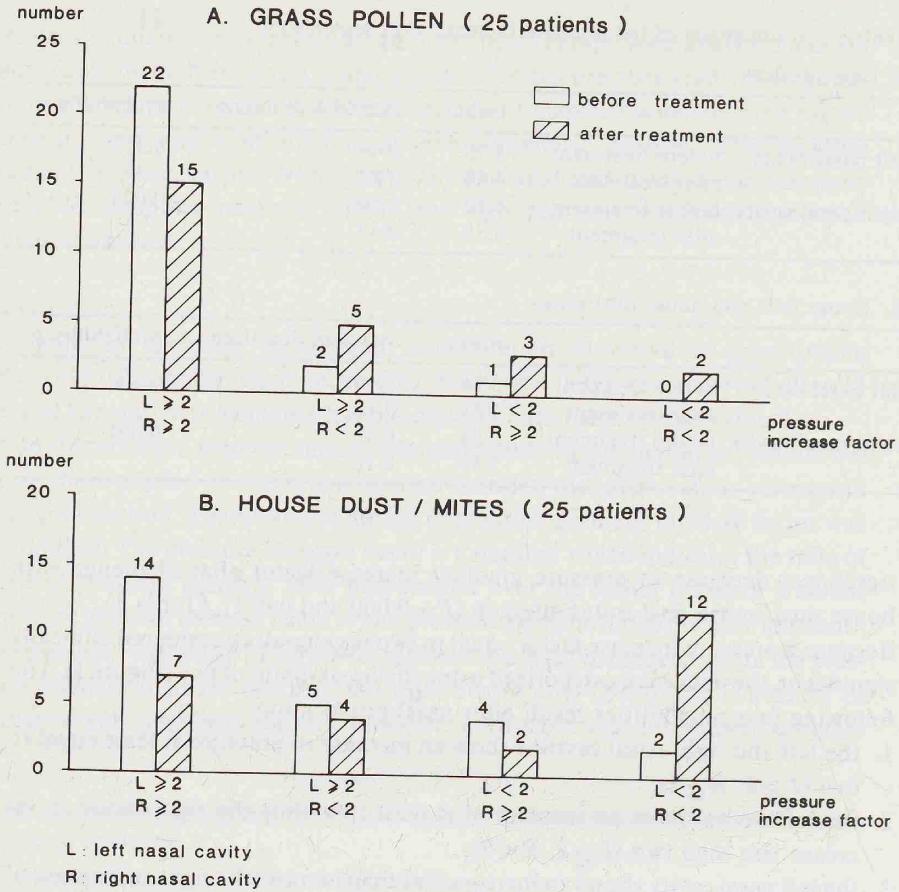

Figure 1. Influence of beclomethasone treatment on nasal provocation.
A pressure gradient increase equal to or greater than twice the initial value is considered as a positive provocation test.
A. grass pollen nasal provocation
B. house dust or mites nasal provocation.

pionate seen in patients with hay fever was due to an inhibition of the priming effect of Connell during natural exposure. A second hypothesis of the good clinical results seen in these patients may result from inclusion of the role of type III reactions as well as that of type I. A review of the literature shows that corticosteroids therapy controls type III reactions very well (Pepys, 1973).
Mygind et al., 1977 reported poor results in nasal provocation tests conducted in patients with hay fever treated with corticosteroids. In sharp contrast were the data presented by Vilsvik et al. (1975) and Okuda and Senba (1981) in patients with hay fever and perennial rhinitis, respectively. Perhaps a more detailed analy-

sis of the methods and materials used by the different investigators would clarify the discrepancies.

Mygind et al. (1977) used posterior rhinomanometry to measure nasal patency. It is a fact that posterior rhinomanometry yields only information on the patency of the whole nose. In order to interpret meaningfully results of a nasal challenge, the patency of each nasal cavity must be evaluated. Very often only one nasal cavity will react (Clement et al., 1981). Because the non-reactive opposite cavity may have good permeability, results of posterior rhinomanometry may only reflect in a poor way reactivity.

Recently, use of an oscillation method has been advocated for measurement of nasal resistance (Berdel et al., 1981). This method can be valid only when a linear relationship exists between impedance and resistance. With respect to the bronchi, this linear relationship holds true, but does not with respect to the nose (Clement et al., 1978; Clement and Daele, 1980). Therefore, this method would seem to be unreliable for measurement of nasal resistance. Although not the most accurate method, passive anterior rhinomanometry (Clement and Daele, 1980) would seem to offer the easiest and most suitable technique for measuring nasal resistance during nasal provocation tests.

Results of the present study indicate that various measurements in the nasal challenge test must be considered, including concentration of allergen needed to evoke a positive response and the pressure gradient (or pressure gradient increase factor) at the end of the test. Treatment with beclomethasone dipropionate nasal spray resulted in a significant increase tolerance to both house dust/house dust mite allergen ($P = 0.01$) and grass pollen allergen ($P = 0.005$).

CONCLUSION

Use of beclomethasone dipropionate nasal spray can significantly increase the threshold to a type I reaction to nasal challenge but cannot block the reaction completely. The causative allergen of hay fever may be more potent than that of perennial rhinitis in these patients. Consequently, the protection threshold achieved after therapy with beclomethasone dipropionate may be lower for grass pollen and thus might explain, in part, the better efficacy seen in the house dust/house mite group.

RÉSUMÉ

On a appliqué le béclométhasone dipropionate pendant 15 jours à un groupe de patients, souffrant de rhume de foins ou qui étaient allergiques à la poussière domestique et au dermatophagoides pteronyssinus.

Dosage: une pulvérisation (50 µg) dans chaque narine, 4 fois par jour, ce qui donne une dose totale de 400 µg par jour.

L'efficience du béclométhasone dipropionate est déterminée à l'aide de la rhino-

manométrie; ceci après provocation nasale chez des patients allergiques qui présentent une réaction du type I, aux allergènes; ici le pollen graminé, la poussière domestique et le dermatophagoide domestique. Un traitement au béclométhasone dipropionate (en forme de spray nasal) augmentait considérablement la tolérance aussi bien au pollen ($P = 0.005$) qu'à la poussière domestique et au dermatophagoides (($P = 0.01$).

La rhinomanométrie passive antérieure semble être une technique facile et appropriée pour mesurer la résistance nasale pendant la provocation nasale.

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