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EXPERIENCES OF TREATING
ALLERGIC RHINITIS WITH INTRA-NASAL
BECLOMETHASONE DIPROPIONATE

Short-Term Trials and Long-Term Follow-Up

By

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Corticosteroids are known to be highly effective in allergic conditions, whether taken orally, given parenterally or applied locally. These routes of administration have also been employed for several years in the treatment of chronic allergic rhinitis, but even with local application it has not been possible to eliminate their systemic side effects (3, 4, 16).

With a relatively new, locally acting corticosteroid, beclomethasone dipropionate (Becotide®), no suppression of the hypothalamic-pituitary-adrenal axis has been observed in short-term studies when beclomethasone dipropionate is used in therapeutic doses (8, 11, 12). Controlled long-term studies have shown that inhaled beclomethasone exerts a beneficial effect in bronchial asthma (2, 6, 10). Intra-nasal beclomethasone dipropionate has also proved to be very effective in the treatment of perennial and seasonal rhinitis, in adults as well as children (5, 14, 18). It has also been possible to show that beclomethasone dipropionate applied intra-nasally slows down the growth of polypi (15). However, there is as yet no information on the long-term treatment of nasal allergy with beclomethasone dipropionate.

In 1974, clinical trials were started in the Ear, Nose and

Throat Hospital of Helsinki University, the aim being to obtain additional information on the role of intra-nasal beclomethasone dipropionate in the symptomatic treatment of allergic rhinitis, and to carry out a long-term follow-up of patients suffering from perennial allergic rhinitis. In the long-term follow-up attention was focussed on subjective tolerance and side effects, maintenance dosage for these patients, and possible macroscopic and/or microscopic changes in the nasal mucous membrane.

MATERIAL AND METHODS

Ninety-two patients suffering from chronic allergic rhinitis were admitted to the trials. On the basis of the duration of the symptoms, the patients were divided into two main groups:

- 1) 42 patients with seasonal allergic rhinitis
- 2) 50 patients with chronic perennial rhinitis.

The characteristics of the patients in both groups are shown in Table 1.

TABLE 1
Age and Sex Distribution.

		Perennial rhinitis	Seasonal rhinitis
Total no. of patients		50	42
Age	mean	32	27
	range	13-67	11-63
Sex	male	14	17
	female	36	25

There were more women than men in both groups. The age range of the patients was wide, but there were few children in the material, most of the patients being over 25 years of age.

When selecting the patients for the groups, their allergic status was carefully determined by history, skin tests, nasal challenge and IgE determination. The dominant allergens in the seasonal rhinitis group were various kinds of grass (23 patients), birch pollen (11 patients) and mugwort (8 patients). The patients with perennial symptoms were divided into two subgroups; 37 patients with

extrinsic allergies, mostly house dust and/or animal danders and 13 with intrinsic rhinitis.

Nine patients had to be excluded from the analysis of the short-term trial results. Thus altogether 39 patients with seasonal and 44 with perennial rhinitis symptoms completed the short-term trial.

The patients with pollen allergy entered a simple double-blind trial, half of them receiving the active drug and the other half placebo, for a period of 3 weeks each.

The perennial rhinitis patients were given both the active drug and placebo in random order each for two 3-week periods. In order to avoid any carry-over effect, there was an interval of 1 week at the crossover point.

In order to acquire information on long-term use of beclomethasone dipropionate the 44 patients with perennial symptoms who had completed the short-term trial were instructed to continue to use beclomethasone when needed. They reported to a follow-up examination 1 year after the beginning of the trial. Four patients failed to report to the follow-up examination.

The drug was administered from a pressurised aerosol, as used for the control of asthma, but fitted with a special nozzle for ease of delivery to the nostrils. The dose was 50 µg beclomethasone dipropionate four times daily into each nostril. The placebo contained inert propellants only.

At the start of the trial the clinician graded each of the nasal symptoms of blocking, running, sneezing and itching on a 0-2 scale as mild, moderate or severe. In the seasonal rhinitis group 25 patients had severe and 13 patients moderate symptoms. The corresponding figures in the perennial rhinitis group were 20 and 18, respectively.

During the trials each patient recorded the daily occurrence of each of these symptoms on a diary card, again on a 0-2 scale (nil, mild or disturbing symptoms). All patients were allowed to take antihistamine ad libitum. The number of tablets taken had to be recorded on the diary card.

Clinical investigations were carried out at the beginning and end of each treatment period. This investigation comprised rhinoscopy, nasal smears and cultures (also fungi), rhinomanometric measurements to determine the total nasal resistance and in some patients measurement of plasma cortisol level. The plasma samples were analysed by the competitive protein-binding assay (13). Histological changes were studied by means of biopsies, taken before therapy, at the end of the treatment periods and after 1 year's use of beclomethasone dipropionate. At the end of the short-term trials the patients in the seasonal group were asked to express their opinion as to the effectiveness or otherwise of the treatment, and, correspondingly in the perennial group a possible preference for either of the coded drugs. When a patient was unable to make a definite statement, this was recorded as 'unclear' and 'no preference', respectively.

A survey of the parameters used is given in Table 2.

The entire material was checked statistically by the use of the conventional χ^2 test. The interpretation of the significance of the results followed border

values in general use, according to which $0.05 \geq P > 0.01$ is almost significant, $0.01 \geq P > 0.001$ is significant, and $0.001 \geq P$ highly significant.

TABLE 2
Clinical Parameters.

1. Clinical symptoms:
sneezing, itching, running, blocking
2. Rhinoscopic findings
3. Nasal smear and culture
4. Rhinomanometry
5. Biopsy
6. Plasma cortisol measurement
7. Symptom score cards
8. Patient opinion and preference data

RESULTS

Short-Term Trial Results

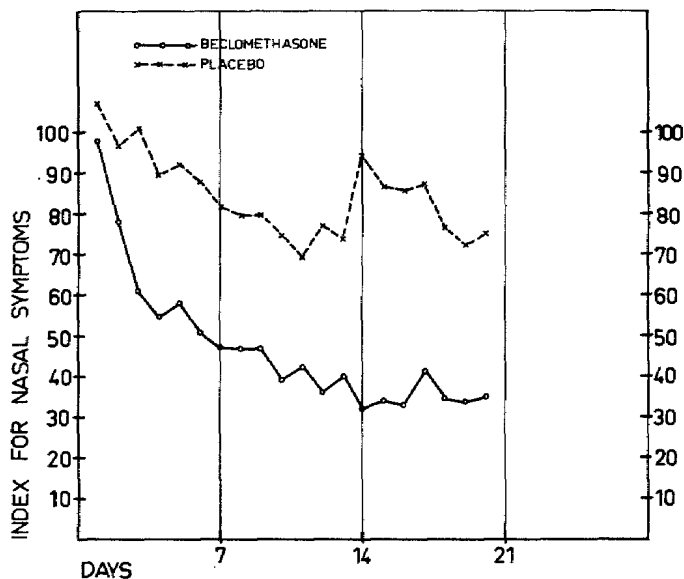


Fig. 1.
Total median symptom score—seasonal rhinitis.

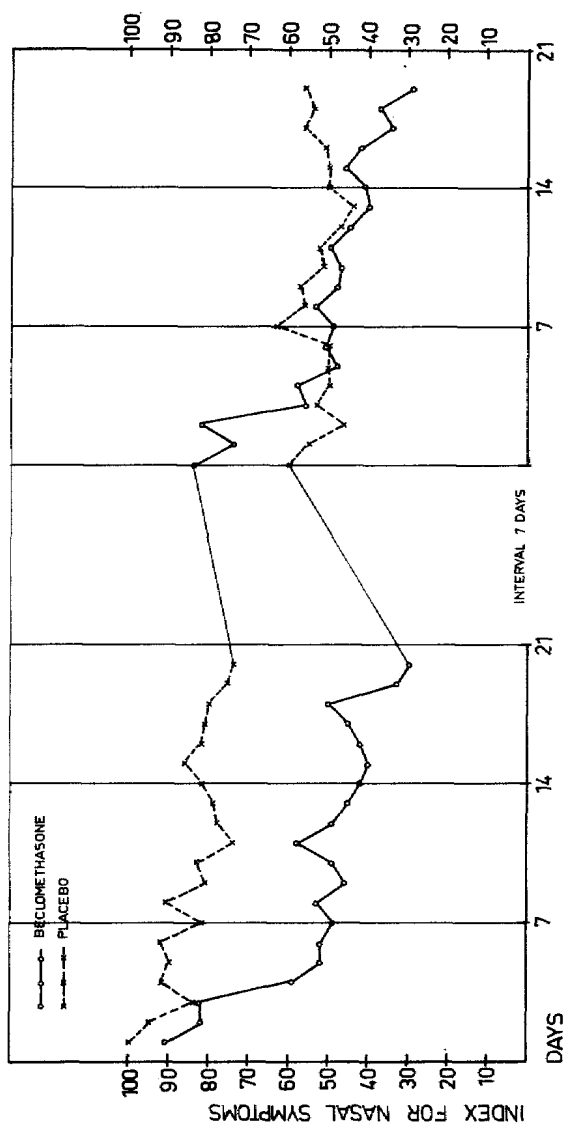


Fig. 2.
Total median symptom score—perennial rhinitis.

Total median symptom scores are shown in Figs. 1 and 2. In the seasonal rhinitis group there is a distinct difference in favour of intra-nasal beclomethasone dipropionate. In the Figure for perennial rhinitis the difference is distinctly in favour of beclomethasone during the first 3-week period, but in the second period which began after 1 week's break in the treatment, the difference between placebo and beclomethasone dipropionate does not reach the same degree of significance.

The average use of antihistamine during the trials was very low (see Discussion). Table 3 shows the opinions of the patients in the seasonal group regarding the effectiveness of intra-nasal beclomethasone dipropionate.

TABLE 3
Patient Opinion—Seasonal Rhinitis

	Active drug	Placebo	Total
Effective	15	5	20
No effect or unclear	4	15	19
$P < 0.001$.			

The difference in favour of beclomethasone dipropionate is statistically highly significant ($P < 0.001$). In the perennial rhinitis group a highly significant number of preferences for the active drug were expressed ($P < 0.001$) (Table 4).

TABLE 4
Patient Preference Data—Perennial Rhinitis.

Active drug preferred	34
Placebo preferred	6
No preference	4
$P < 0.001$.	

When the rhinoscopic findings were analysed, a distinct decrease in the swelling of the conchae and in the volume of

secretion was noted in the patients receiving the active drug as compared with those receiving the placebo. No changes in the lividity of the mucosa were observed in either group. Positive signs of atrophy or dryness of the mucosa were not observed in any patient. Table 5 shows changes in the occurrence of eosinophils in both the seasonal and the perennial groups.

TABLE 5
Effect on Secretion Eosinophils.

	Eosinophils		(+	++	+++)	
	neg.	pos.				
<i>Seasonal rhinitis</i>						
<i>beclomethasone</i>						
Before therapy	3	13	(8	3	2)	$P = 0.01$
After therapy	10	6	(6	0	0)	
<i>placebo</i>						
Before therapy	2	15	(4	5	6)	
After therapy	2	15	(3	8	4)	
<i>Perennial rhinitis</i>						
<i>beclomethasone</i>						
Before therapy	5	39	(11	19	9)	$P < 0.001$
After therapy	18	26	(19	6	1)	
<i>placebo</i>						
Before therapy	9	33	(16	11	6)	$P = 0.69$
After therapy	6	36	(19	13	4)	

A distinct decrease in the number of eosinophils in the smears taken after intra-nasal beclomethasone dipropionate therapy is evident, the decrease being statistically significant. Conversely, in the placebo groups, the number of eosinophils remained virtually the same. No distinct difference was noticed in the occurrence of leucocytes and bacteria in the nasal smears and cultures taken from the patients who were treated with beclomethasone and placebo.

Changes noted in the nasal resistance among the patients with perennial rhinitis are given in Table 6. The improvement in air flow of these was quite marked following intra-nasal beclomethasone therapy ($P < 0.001$).

TABLE 6
Changes in Nasal Resistance during Trial-Perennial Rhinitis.

Nasal resistance	Beclomethasone dipropionate	Placebo
Improved air flow	22	7
Unchanged air flow	7	8
Impaired air flow	5	18
$P < 0.001$.		

Rhinomanometric data were obtained from 14 patients in the seasonal rhinitis group. No clear difference was noticeable in the nasal resistance between those patients treated with beclomethasone and those treated with placebo.

Results of 1-Year Follow-Up

At the follow-up examination 1 year after the start of the trial 21 patients out of 40 still used intra-nasal beclomethasone dipropionate as can be seen from Table 7.

TABLE 7
One Year Follow-Up.

Present at the examination 40/44			
Patients who used intra-nasal beclomethasone dipropionate all the time		Patients who did not use intra-nasal beclomethasone dipropionate	
3-4 times daily	2	No effect	5
1-2 times daily	14	No or mild symptoms	11
Occasionally	5	Other reasons	3
	21		19
(two used antihistamines)		(two used antihistamines)	

Sixteen of the 21 patients used the drug regularly one to four times each day, the other five patients using the treatment but occasionally. Nineteen patients had stopped medication for various reasons.

No signs of atrophy or drying of the nasal mucosa were noticed in the rhinoscopic examination of the patients who had used intra-nasal beclomethasone dipropionate more or less regularly for 1 year. Histological examination of biopsies taken from 11 patients, four biopsies in each case, revealed that tissue eosinophils had markedly decreased or even totally disappeared following beclomethasone dipropionate therapy. No significant changes were seen in the epithelium.

The plasma cortisol content was measured before the beginning of the trial and after 1 year's use of intra-nasal beclomethasone dipropionate in 13 of the patients. The data obtained showed that the mean plasma cortisol levels (0.32 $\mu\text{Mol/L}$) were of the same order both before and after beclomethasone treatment.

TABLE 8
Side Effects.

Side effect	Short-term treatment		Long-term treatment
	Perennial rhinitis 44 patients Seasonal rhinitis 39 patients		Perennial rhinitis 21 patients
	Active drug	Placebo	Active drug 1 year
Nasal irritation	21	31	7
Drying	1	—	4
Nose bleeding	5	6	5
Nausea	3	3	1
Other	1	3	—
No. of patients with complaints	27	33	13

Side Effects

At the end of each treatment period any side effects noted by the patients were recorded (summary in Table 8). The most common complaint was nasal irritation. In the short-term

trials the irritation occurred slightly more frequently with placebo than with the active drug. The difference is not statistically significant ($P = 0.10$).

In the entire material there were five patients who complained of drying of the nasal mucosa: one after short-term use of beclomethasone and four after using beclomethasone for 1 year. A slight nose bleed was reported by five patients after short-term use and by five patients who had taken beclomethasone dipropionate for 1 year.

DISCUSSION

In the symptomatic treatment of allergic rhinitis antihistamines, sodium cromoglycate and steroids are probably the most commonly used drugs. Antihistamines frequently exert a highly undesirable somnolent effect which somewhat limits their use; in addition their therapeutic effect is comparatively uneven. Sodium cromoglycate insufflated into the nostrils is of value, but only in some 70 per cent of patients (9). In most cases systemic corticosteroids effect the most dramatic results, but their use, especially in long-term treatment, must be limited because of the possibility of suppression of adrenal function.

In this trial the effect of intra-nasal beclomethasone dipropionate was observed in patients suffering from seasonal allergic rhinitis and in patients suffering from perennial rhinitis. Only nine patients out of 92 interrupted the short-term treatment. In the seasonal group two patients defaulted during the placebo period, and one patient failed to return the diary card. In the perennial group six patients were excluded from the analysis. One patient defaulted during the placebo period, one patient failed to return after receiving the active drug, and one patient contracted thrombocytopenic purpura during the placebo period. Of the remaining three patients, one left the area, one had a maxillary sinusitis and one had to be put onto oral cortisone therapy because of a severe allergic skin reaction unconnected with beclomethasone dipropionate therapy. Forty out of 44 patients with perennial rhinitis were

examined in a follow-up control 1 year after the start of the trial. These patients have continued to use beclomethasone dipropionate for a second year and follow-up examinations have been carried out. The results of the 2-year follow-up will be reported later.

Only 12 per cent of the patients in the 1-year follow-up group reported having stopped using the drug because of its apparent lack of effect. However, 27 per cent of the patients had stopped treatment as their symptoms had completely disappeared or were so mild that medication was no longer required. Prior to the start of the trial, these particular patients' symptoms were classed as follows: three displayed mild symptoms, four moderate and four severe symptoms. It is evident that the daily dose of 400 μ g of intra-nasal beclomethasone dipropionate can be reduced once the symptoms have decreased. One possible reason for this is that the defense mechanism of the nose begins to function correctly again, once the patient has escaped from his vicious symptom-circle. It should be emphasized, however, that in order to obtain maximum benefit from this drug, continuous use, even in small doses, is important.

The patients with pollen allergy could not be subjected to a crossover trial, because the pollen season in Finland is very short; instead a simple double-blind trial was carried out. Despite the fairly small number of patients in this group, some interesting conclusions can be drawn. Seventy-nine per cent of the patients using intra-nasal beclomethasone dipropionate considered the drug effective in relieving their symptoms, the corresponding figure for the placebo group was only 25 per cent. The superiority of beclomethasone as compared with placebo is also evident from the symptom index drawn up on the basis of the patients' diary cards.

In the perennial group 77 per cent of the patients expressed a preference for beclomethasone. The symptom score index also shows that the group taking the active drug had significantly fewer symptoms in the first 3-week period. The difference between the two groups as to occurrence of symp-

toms is not as distinct in the second 3-week period, however. Although there was 1 week's interval without medication between the periods, this was obviously not sufficient to prevent a carry-over effect from the first period to the second. No such carry-over effect was noticed in Mygind's crossover trials with seasonal and perennial rhinitis patients (14, 18).

Few patients used the antihistamine tablets they had been given even when symptoms did occur, probably because most patients had earlier taken large numbers of these preparations without any alleviation of their symptoms. Thus the antihistamine use is of no value in rating the efficacy of intranasal beclomethasone dipropionate in this trial.

In both the seasonal and perennial rhinitis groups the effect of beclomethasone was observed within a few days by the patients. This observation differs from that made by Mygind et al. (7, 14) in their trials where a decrease in the symptoms was not distinctly noticed until the second week of medication.

Alleviation of subjective symptoms agreed with the objective observations made by the clinician. The swelling of the mucous membrane decreased as did the volume of nasal secretion. Among the perennial rhinitis patients a distinct improvement in the nasal air flow was noticed when the active drug was used. No such clear distinction was apparent among the patients suffering from seasonal rhinitis. This clear lack of noticeable improvement in nasal air flow among these patients may well be accounted for by the brevity of the pollen season and by the rapid changes in nasal obstruction in patients suffering from pollen allergy. In both groups a marked decrease in the occurrence of secretion and tissue eosinophils was observed in the patients following beclomethasone therapy.

No changes indicative of atrophy of the mucous membrane were observed when the patients who had used beclomethasone dipropionate for 1 year were subjected to rhinoscopic examination. Likewise, histological examination of the biopsy sections taken from treated patients failed to reveal any changes indicative of mucosal membrane atrophy. These latter findings

are in agreement with the results obtained by Andersson & Smidt (1) in an investigation of the bronchial mucous membrane, and by Poynter (17, unpublished) in histological investigations of the nasal mucous membrane. Histological findings will be discussed in greater detail when the results of the 2-year control, which has just been carried out, are presented.

Side effects attributable to intra-nasal beclomethasone dipropionate therapy were few and extremely mild. Nasal irritation, probably caused by the propellant gases was reported by 21 of the patients in the short-term trial, but conversely 31 patients reported nasal irritation when using placebo. Five patients using the active drug, and six patients using placebo complained of a slight nose bleed. It is considered that the propellants might be the causative factors in these patients and it was not necessary to discontinue treatment. It should be noticed that the applicator used in this trial was a modified lung-applicator, where the gas volume was larger than in the nasal beclomethasone applicators in present use.

Nasal candidiasis was not seen in any patient on active treatment. A possible explanation might well be the protection that the cilia and nasal defense mechanism afford to the nasal mucous membrane.

The results of the present rhinitis trials support the earlier bronchial findings that even in long-term treatment, intra-nasal beclomethasone dipropionate does not disturb the normal function of the H.P.A. axis system (1).

SUMMARY

The effect of locally acting intra-nasal beclomethasone dipropionate was observed in 42 patients suffering from seasonal allergic rhinitis and 50 patients suffering from perennial rhinitis. The study consists of three parts:

- 1) a simple double-blind trial in seasonal rhinitis,
- 2) a double-blind crossover trial in perennial rhinitis,

3) a 1-year follow-up of the perennial group.

The active drug was significantly superior to placebo when comparing subjective symptoms, nasal resistance and secretion eosinophilia in the patients. In long-term use it was possible to reduce the initial dose considerably. On objective examination no significant changes were seen in the epithelium following long-term use. No suppression of the hypothalamic-pituitary-adrenal axis was observed after 1 year's regular use of beclomethasone dipropionate. The side effects were mild, the most common complaint being irritation of the nasal mucous membrane, apparently caused by the propellant gas.

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