

From the E.N.T. Department, University Hospital, Lund, Sweden.

AN OPEN ASSESSMENT OF BECOTIDE®  
(BECLOMETHASONE DIPROPIONATE) NASAL  
SPRAY IN SEASONAL ALLERGIC RHINITIS

By

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The treatment of allergic diseases in the respiratory tract sometimes also includes cortisone therapy. A local application of cortisone on the shock organ should imply a reasonable possibility of preventing the systemic side-effects often observed in connection with prolonged peroral or parenteral steroid treatment. With this in view, cortisone, hydrocortisone, prednisolone, and dexamethasone—among other drugs—have been tried (3, 5, 6, 8, 17, 18, 19, 20, 21, 22), but all of them have proved to have an insufficient effect in doses without systemic resorption. There was renewed interest in the local application mode of treatment with the introduction of beclomethasone dipropionate and betamethasone valerate. In reports on the treatment of bronchial asthma by Brown et al. (1), and of allergic rhinitis by Mygind (15), the good therapeutic effect of beclomethasone dipropionate has been brought out. The preparation has been evaluated as a high-grade, locally active gluco-corticoid which is effective without any considerable side-effects. On the basis of prior investigations, we did not find the recommendations of dosage established. It is desirable to aim at still lower dosage while maintaining the effect of a drug. In the present report, results are given of trials with beclomethasone dipropionate against hay fever in lower dosage than in earlier investigations.

## MATERIAL AND METHODS

The trial was conducted over a 4-week period between mid-June and mid-July during the summer of 1974. Data on pollen counts were obtained from the Aero-biological working group, Sweden. The apparatus used was a Burkard® slit sampler.

In all, 38 patients (23 male and 15 female), aged between 14 and 68 years (average 31 years) were included in the trial, all of them being sensitive to grass pollen, as shown by positive skin test or positive provocation test (10), and all having suffered from hay fever during at least the last two seasons. Any patient exhibiting nasal polyps or asthmatic symptoms was excluded. We did not take into consideration whether they had earlier been hyposensitized or not. Beclomethasone dipropionate was administered by nasal spray as an aerosol of 0.06 per cent beclomethasone dipropionate in oleic acid, difluoridichlormethane, and fluortrichlormethane. The aerosol is the same type used for bronchial asthma, as is the equipment, except for a special nasal adaptor. The dose was one puff into each nostril three times every day, i.e.  $50\text{ }\mu\text{g}$  beclomethasone dipropionate  $\times 3 = 150\text{ }\mu\text{g}$  beclomethasone dipropionate/day to each nostril. A supply of antihistamine tablets (dexchlorpheniramine—Polaramine® prolongatum) and eye drops (naphazolin.nitr. and antazolin.sulf.—Antasten®—Privin®) was issued to each patient with instructions to take them only if symptoms were so severe as to make that medication indispensable.

Each subject recorded the following symptoms on a daily diary card: sneezing, running, blocking, itching, and eye-symptoms, on a scale 0–3 (0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe). If it was necessary to take antihistamines (Polaramine® prolongatum) or eye drops (Antasten®—Privin®), the number of tablets or eye drops was also entered on the diary card.

Each patient was interviewed and medically examined before entry into the trial and after 4 weeks of treatment. The condition of the nose was recorded as to the presence of oedema and mucus, again on a 0–3 scale as above. Full hematological analysis and bacteriological examination of the nasal and throat secretions were carried out. The data obtained from the diary cards and medical examinations were subjected to statistical analysis.

At the final examination, answers were recorded to the following questions:

- 1) Were your nasal symptoms adequately controlled?
- 2) Were your nasal symptoms less marked than during last summer?
- 3) Do you wish to continue treatment with the spray for the rest of the summer?
- 4) Would you use the spray next summer if it were available?
- 5) Was the mode of the treatment acceptable?
- 6) Do you regard the treatment with the spray as a success or a failure?

In addition, the trialists also recorded their opinion as to the success or failure of the treatment.

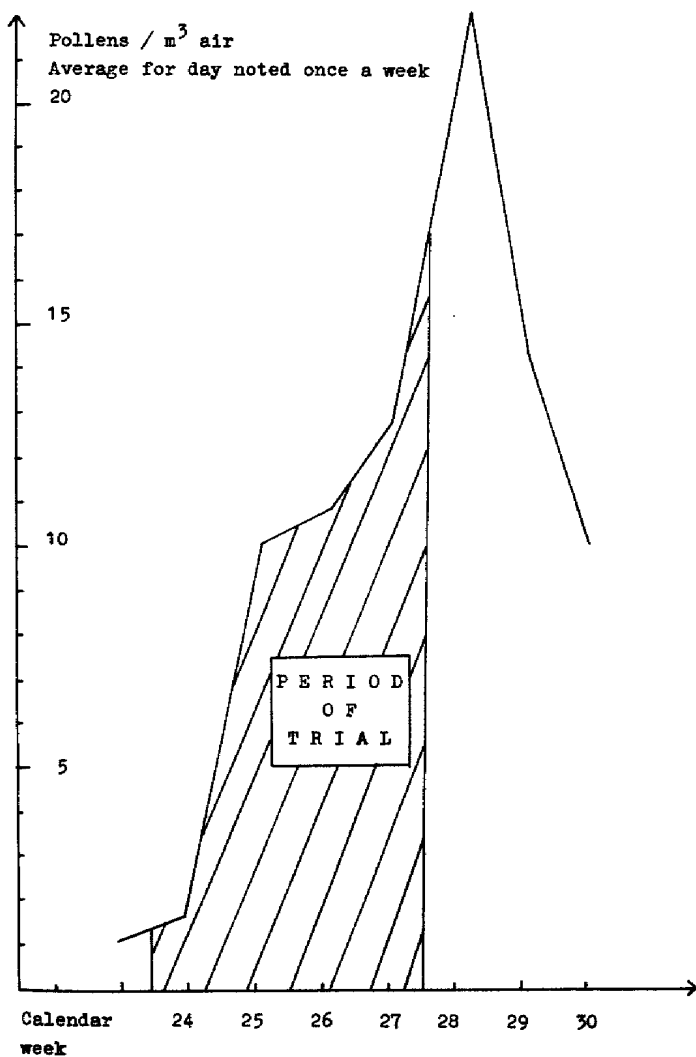


*Fig. 1.*  
Pollen count for the period of the trial.

TABLE 1

*Evaluation of Patients and Trialists after 4 Weeks' Treatment with Beclomethasone Dipropionate.*

| Question                                                                        | Answer         | Significance |
|---------------------------------------------------------------------------------|----------------|--------------|
| 1. Were your nasal symptoms adequately controlled?                              | yes 35<br>no 3 | 0.01         |
| 2. Were the nasal symptoms less pronounced than last summer?                    | yes 32<br>no 6 | 0.01         |
| 3. Do you want to continue treatment with the spray for the rest of the season? | yes 34<br>no 4 | 0.01         |
| 4. Would you use the spray next summer (if you could get it)?                   | yes 34<br>no 4 | 0.01         |
| 5. Was the mode of treatment acceptable?                                        | yes 30<br>no 8 | 0.01         |
| 6. Do you find the treatment with the spray successful?                         | yes 36<br>no 2 | 0.01         |
| 7. The trialists' evaluation of success.                                        | yes 36<br>no 2 | 0.01         |

## RESULTS

The summer of 1974 can be regarded as medium-good with respect to weather. The grass pollen season began at the normal time, and the start of this investigation coincided with the beginning of the pollen season (Fig. 1). During the trial period, a progressively increasing amount of pollen was recorded. After the termination of the trial too, the amount of pollen in the air continued to increase, and reached its maximum 1 week later. All 38 patients participating in the trial completed treatment, with one exception. After the trial period, 36 patients considered the treatment to have been successful (Table 1, question 6), which was also the opinion of the trialists (Table 1, question 7). Thirty-five patients considered the nasal symptoms adequately controlled (Table 1, question 1). In 32 patients, the nasal symptoms

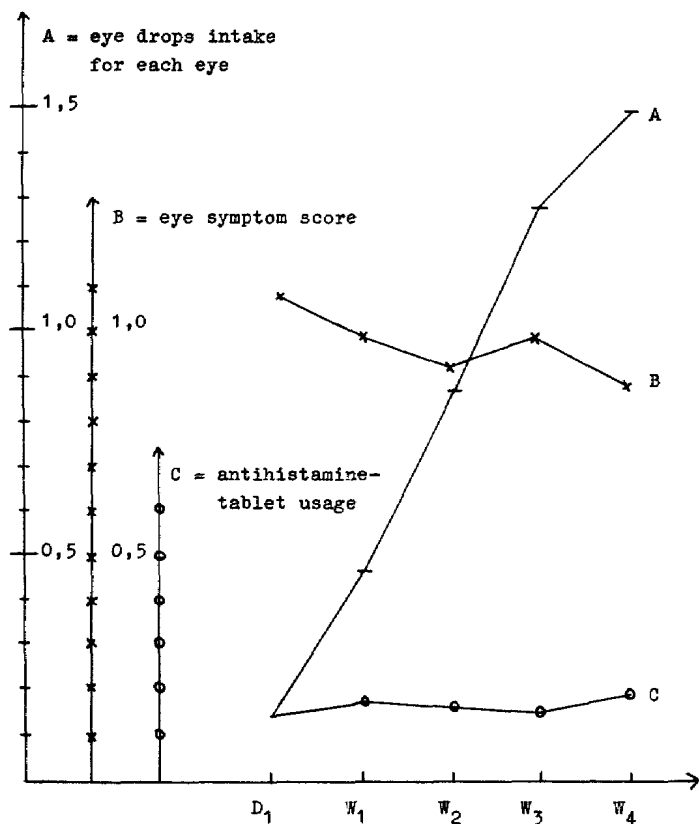


Fig. 2.

Eye drops intake\*, antihistamine tablet usage\*\* and eye symptom score from diary card data in 38 hay fever patients treated with beclomethasone dipropionate. Average for subject and day noted at entry (D<sub>1</sub>) and the 4 treatment weeks (W<sub>1</sub>-W<sub>4</sub>).

\* Antasten®-Privin®.

\*\* Polaramine® prolongatum.

were less pronounced than last summer (Table 1, question 2). Three out of the six remaining patients had received cortisone as injection or in tablet form in the previous year, and two had been given antihistamine treatment; whereas one had received no therapy. Thirty-four patients wished to continue the treatment with beclomethasone dipropionate after the termination of the trial period in the summer of 1974 (Table 1, question 3). Furthermore, 34 patients wanted to continue this form of therapy next summer (Table 1, question 4). Eight of the test subjects were not quite satisfied with the mode of administration (Table 1, question 5). They found the frequency of treatment especially troublesome, but some of them had also noted

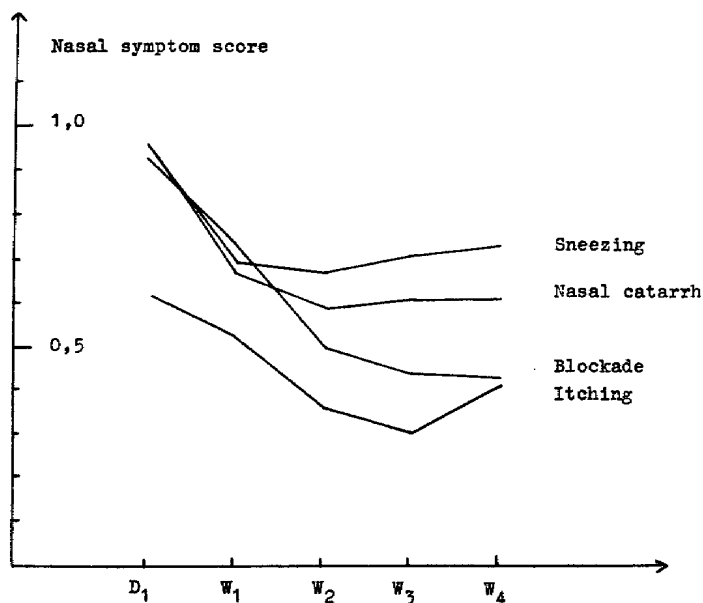


Fig. 3.

Nasal symptom score from diary card data in 38 hay fever patients treated with beclomethasone dipropionate. Average for subject and day noted at entry (D<sub>1</sub>) and the 4 treatment weeks (W<sub>1</sub>-W<sub>4</sub>).

irritative sensations from the nasal mucous membrane directly following the spraying.

Eye-symptoms were found in almost all patients to such an extent as to necessitate treatment with eye-drops. With this aid, however, the troubles could be reduced to the intensity level "1" on the scale used, i.e. "mild", during the entire trial period. To achieve this, however, a progressively increasing quantity of eye-drops was necessary in the course of the trial period (Fig. 2). There was also a certain consumption of anti-histamines, amounting to approximately 0.2 tablets per patient/day. One single patient accounted for half of this consumption.

Fig. 3 shows the scoring as far as the different nasal symptoms are concerned. The mean value of each individual symptom at the beginning of the treatment ( $D_1$ ) corresponded to the intensity "mild". After introduction of the treatment, the troubles of sneezing, nasal catarrh, and blockade decreased rapidly to a significantly (Wilcoxon's test) lower intensity ( $W_1$  = daily average for week 1). For the rest of the period of treatment the effect on nasal catarrh and sneezing did not change. A further improvement, however, was recorded as regards blockade (statistical significance  $W_4$  = week 4 compared with  $W_1$  = week 1). The effect with regard to itching was not equally conspicuous. Initially, a certain decrease in these troubles was observed, but towards the end of the trial period a relapse became apparent.

At the rhinoscopic examination a significant decrease was observed both as regards oedema ( $P < 0.01$ ) and mucus ( $P < 0.001$ ) during the period of treatment. Cultivation with respect to bacteria and *Candida albicans* from the nasopharynx as well as the pharynx did not reveal any obvious disturbance of the flora by the treatment. The analysis thus proved negative in respect of bacteria and *Candida* for 20 patients both before and after treatment; and five patients showed growth of the same bacterium or fungus on both occasions of examination. In five out of 10 patients with growth of bacteria in nasal or pharyngeal secretion prior to treatment, there were

no such findings afterwards. In eight patients, fresh growth of bacteria was found at the end of the period of treatment; and in two patients, fresh growth of *Candida albicans* was isolated. Diagnosed types of bacteria were: *Haemophilus influenzae*, meningococci, *Neisseria catarrhalis*, pneumococci, plasmacoagulating staphylococci, and beta streptococci.

No serious side-effects were recorded. Two patients complained of headache, possibly connected with the treatment, and three patients reported that the spraying sometimes initiated sneezing and nasal catarrh.

#### DISCUSSION

Inhaled beclomethasone dipropionate is beneficial in the treatment of bronchial asthma in doses that do not affect adrenal function (1, 2, 4, 7, 9, 12, 13, 16). It is also effective in patients with hay fever in an intranasal dose of 400  $\mu\text{g}/\text{day}$  without producing evident adrenal suppression; this is according to Mygind (15), who registered a lower, but not significantly lower, mean value of 17-ketogenic steroids in urine during the beclomethasone treatment period than in the period of placebo treatment. The purpose of the present investigation was to study the effectiveness of intranasal beclomethasone dipropionate in a dosage lower than that of Mygind. It was performed as an open assessment with concomitant registration of the content of pollen in the air.

The pollen counts were performed by means of a Burkard slit sampler giving the amount of pollen/ $\text{m}^3$  air. The sampler was placed in open country without trees, 100 metres from the South coast of Sweden. The pollen count showed a sharply rising tendency of the pollen content during the trial period, confirming that the trial period chosen was the right one.

At the start of the treatment with beclomethasone dipropionate, the patients had mild eye and nasal symptoms of allergic type. With a rising pollen content, an increasing intensity of the symptoms was to be expected in the absence of treatment. During the trial period, however, reduced nasal

troubles were recorded, which fact must be ascribable to the treatment with beclomethasone dipropionate. It is true that the patients were allowed to take antihistamine in the form of Polaramine prolongatum (if necessary), but the amount used per person (0.1–0.2 tablets/day) was too small to cause the reduction in the symptoms.

The effect on nasal catarrh, sneezing, and nasal blockade was obtained during the first days of treatment, and was then maintained during the continued treatment, notwithstanding the increasing pollen content. This rapid onset of the effect of beclomethasone dipropionate was also observed in Mygind's (15) investigation, with significantly less nasal symptoms by the second day of treatment. As far as the nasal blockade is concerned, a further significant recession was seen for the rest of the period of treatment. The patients' diminished troubles have also been registered objectively as less oedema in the nasal mucous membrane and less mucus at rhinoscopy. The effect manifested in the form of reduced oedema has encouraged us to further investigations, in which especially patients with non-allergic, vasomotorial rhinitis have been studied (11).

The patients' eye-symptom scores were not significantly changed during the period of treatment, in spite of the increasing aerial pollen content. To secure this result, the patients progressively increased their consumption of eye-drops. This seems to indicate that there have been allergic reactions in the eyes, and that these reactions have been neutralized by an increased intake of eye-drops. The increasing consumption of eye-drops may, therefore, be regarded as an indicator of a successively increasing intensity of troubles from hay fever in the patients during the period of treatment.

The interview at the end of the treatment period resulted in a positive evaluation of the preparation. Only two patients considered the treatment a failure. One of them, a botanist, suspended treatment after 1 week, because 1 spraying/hour was required for relief. The other patient who considered the treatment a failure had an ordinary pollen exposition. Treat-

ment with 40 mg of triamcinolone (Kenacort®-T) intramuscularly made this patient completely free of troubles after 2 days. Fourteen patients had been treated systemically with various cortisone preparations in the preceding summer. Six of them considered local beclomethasone therapy superior to a systemic cortisone therapy as far as symptomatic relief is concerned, whilst seven were of a contrary opinion, pointing out that the eye symptoms were not influenced. Altogether, 34 patients were nevertheless in favour of continued treatment with beclomethasone dipropionate for the rest of the season; and 34 also favoured this treatment in the next season.

No certain side-effects were observed. Two patients reported that during the period of treatment they had sometimes had headache in the forehead. In three patients, the spraying sometimes initiated sneezing and nasal catarrh as an expression of irritation. Any increased bleeding tendency from the nasal mucous membrane, as described by Mygind, was not observed.

During local cortisone therapy, bacterial and/or fungal superinfection may be expected. Long-term treatment with beclomethasone dipropionate in cases of bronchial asthma has proved to involve an increased risk especially of fungal infection—in the first place, *Candida albicans* (14). Up to as many as 40 per cent of these patients have become carriers of this fungus. A clinical fungal infection, however, is only seen in some 5–10 per cent, and there are only a very few cases where the beclomethasone treatment must be suspended. The risk of superinfection is obviously dose-dependent (13), and in the administered dosage of beclomethasone dipropionate—less than 400 µg/24 hours—the risk is considerably reduced. In our study, however, with the use of 300 µg of beclomethasone dipropionate no patient reported or showed any clinical signs of nasal or pharyngeal infection. Bacteriological analysis showed a growth of the common pathogens in the upper respiratory tract. No obvious difference in the flora before and after treatment was observed.

## SUMMARY

The effect of beclomethasone dipropionate (Becotide®) intranasally on hay-fever has been studied in 38 adult volunteers with grass pollen allergy. The trial was carried out as an open assessment with simultaneous pollen count during the months of June and July, 1974. With the dose 300 µg/day intranasally, 95 per cent of the subjects regarded the treatment as successful for the nasal symptoms. No effect on eye symptoms was recorded, and no evident side-effects were noted.

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