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TREATMENT OF VASOMOTOR RHINITIS WITH INTRANASAL BECLOMETHASONE DIPROPIONATE (BECOTIDE®)

Results from a Double-Blind Cross-Over Study

By

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Local cortisone therapy with beclomethasone dipropionate must to-day be considered an established alternative in the treatment of bronchial asthma. Good therapeutic results have also been achieved in cases of hay fever, perennial rhinitis and nasal polyposis. Among the test subjects with perennial rhinitis, both allergic persons and those without evidence of allergy have been included, that is to say patients with vasomotor rhinitis*. This last group has been rather small in number. We have considered it important to test this preparation on a larger number of patients with this pathological condition than has been done earlier, using the comparatively low dosage which, according to a previous investigation, we have found to be effective against hay fever.

MATERIAL AND METHODS

The study comprised 39 patients (19 males and 20 females) aged 19-66 years (average 39 years) with a history of vasomotor rhinitis for many years. Half of

* The term vasomotor rhinitis has been assigned to those conditions characterized symptomatically by sneezing, obstruction, stuffiness, increased discharge, postnasal drip, and pathologically by the appearance of a boggy, swollen, red, sometimes pale, mucosa and where nasal allergy is excluded, (Hansel 1953 (8)).

the patients had had symptoms for more than 10 years. Their trouble was of a perennial nature in the form of obstruction, nasal drip, sneezing and nasal itching in varying degrees. Allergologic testing in the form of intracutaneous tests with 26 common extracts (6 dust extracts, 2 mould extracts, 8 animal epithelium extracts, and 10 pollen extracts) proved negative. Analysis of IgE/serum (Phadebas® IgE Test) showed the following values: < 100 ng/ml for 21 subjects, 101–200 for eight, 201–300 for four, 301–400 for two, 440, 600, 840 and 1,200 ng/ml for one patient. Estimate of eosinophilic cells in nasal secretion (7) prior to treatment showed few or fairly many eosinophils without clusters, < 10 per cent, corresponding to ($\pm$) or (+) according to Koch (10). Patients with nasal polyposis, obvious septum deviation, and bronchial asthma were not included in the material. The study originally comprised 41 patients, but two of them withdrew in the first test period owing to a suspected pregnancy and an influenza-like disease.

The study was of a double-blind cross-over type, and was continued for 9 weeks during February–April 1975. Nineteen patients started with a 4-week treatment period with beclomethasone dipropionate, followed by 1 week without medication, and finished with 4 weeks' placebo treatment. The other 20 patients were treated in the reverse order.

Beclomethasone dipropionate and placebo were distributed in identically equal packings, and were administered as a nasal spray. The beclomethasone dipropionate aerosol was the same as used for bronchial asthma, and so was the packing, apart from a special nasal adapter.

The dosage was one puff into each nostril 3 times daily both during the placebo period and during the beclomethasone dipropionate period. One puff of the active aerosol corresponds to 50 μ g of beclomethasone dipropionate, which means a total dose of 300 μ g in a 24-hour period.

Each subject recorded on a daily diary card the following symptoms: Blocking, running, sneezing and itching, on a scale 0–3 (0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe) during all 9 weeks.

Each patient was interviewed and medically examined before entry into the trial and on the last day of both the beclomethasone dipropionate and the placebo period. The condition of the nose was recorded as to the presence of lividity, redness, oedema, and purulent discharge, again on a 0–3 scale as above. Haematological analysis and bacteriological examination of the nasopharyngeal secretion were also carried out on these occasions. Estimation of cortisol/plasma (modification of the method of De Moor et al. (4, 5)) was made in 19 patients at 8 a.m. once during the last week of the placebo period and once during the beclomethasone dipropionate treatment period.

On the last day of both treatment periods, the patients' subjective evaluation of the therapeutic effect was recorded as follows: No trouble, improved, unchanged, worsened, and at the last examination, their opinion as to which of the treatment periods had given the least nasal trouble, or whether they had found no difference between the two periods.

Statistical Methods

The data obtained from the diary cards and medical examinations were subjected to statistical analysis.

"A linear nonparametric permutation test for matched pairs" was used, estimating the decreases of nasal score during the two respective periods.

Comparison between the period of beclomethasone dipropionate and the placebo period was carried out in the following way: One group (A) was treated with placebo in the first period and with beclomethasone dipropionate in the second period. The other group (B) started with beclomethasone dipropionate and afterwards received placebo. The difference in nasal score between the first and the second period was determined for each patient in both groups. These differences for group A were compared with the corresponding differences for group B using Fisher's permutation test, which is a nonparametric test.

RESULTS

Twenty-five patients out of the 39 who accomplished the investigation preferred the beclomethasone dipropionate period, whilst five patients preferred the placebo period, and nine did not find any difference between the periods.

On questioning after the beclomethasone dipropionate period, four patients considered themselves free of trouble, 25 had improved, 10 were unchanged, and no one had worsened during the period, whereas after the placebo period no one was free of trouble, 12 had improved, 20 were unchanged, and seven patients had worsened.

An investigation as to whether the trouble score decreased in either the placebo period or the beclomethasone dipropionate period, showed no significant decrease for any variable during the entire placebo period. On the other hand, a significant reduction of the trouble score for all symptoms as well as total nose score (the total of the four single symptoms) between day 1 and the average for week 1 were registered during the beclomethasone dipropionate period. This effect was sustained throughout the period of treatment.

Table 1 shows the result of a comparison of the trouble score during the respective periods, i.e. corrected for placebo effect. For the different nasal symptoms the result deviated to some extent from the one shown above, since only the

TABLE 1

Comparative Statistical Analysis of the Results from Diary Cards During the Periods of Treatment with Beclomethasone Dipropionate and Placebo. The Significant P-Values Favour Treatment with Beclomethasone Dipropionate.

Sneezing	Day 1	n.s.
	Week 1	$P < 0.05$
	Week 2	$P < 0.01$
	Week 3	$P < 0.01$
	Week 4	$P < 0.01$
Nasal catarrh	Day 1	n.s.
	Week 1	n.s.
	Week 2	$P < 0.01$
	Week 3	$P < 0.01$
	Week 4	$P < 0.01$
Itching	Day 1	n.s.
	Week 1	n.s.
	Week 2	n.s.
	Week 3	$P < 0.05$
	Week 4	$P < 0.05$
Blocking	Day 1	n.s.
	Week 1	n.s.
	Week 2	n.s.
	Week 3	n.s.
	Week 4	$P < 0.01$
Total score	Day 1	n.s.
	Week 1	n.s.
	Week 2	$P < 0.01$
	Week 3	$P < 0.01$
	Week 4	$P < 0.01$

n.s. = not significant.

therapeutic result recorded for each particular preparation was considered. Thus it was only during the second week that a significantly lower total score during the beclomethasone dipropionate treatment was observed. This effect remained throughout the rest of the period. For the individual nasal symptoms a significantly lower trouble score for the beclomethasone dipropionate period was registered as follows: for

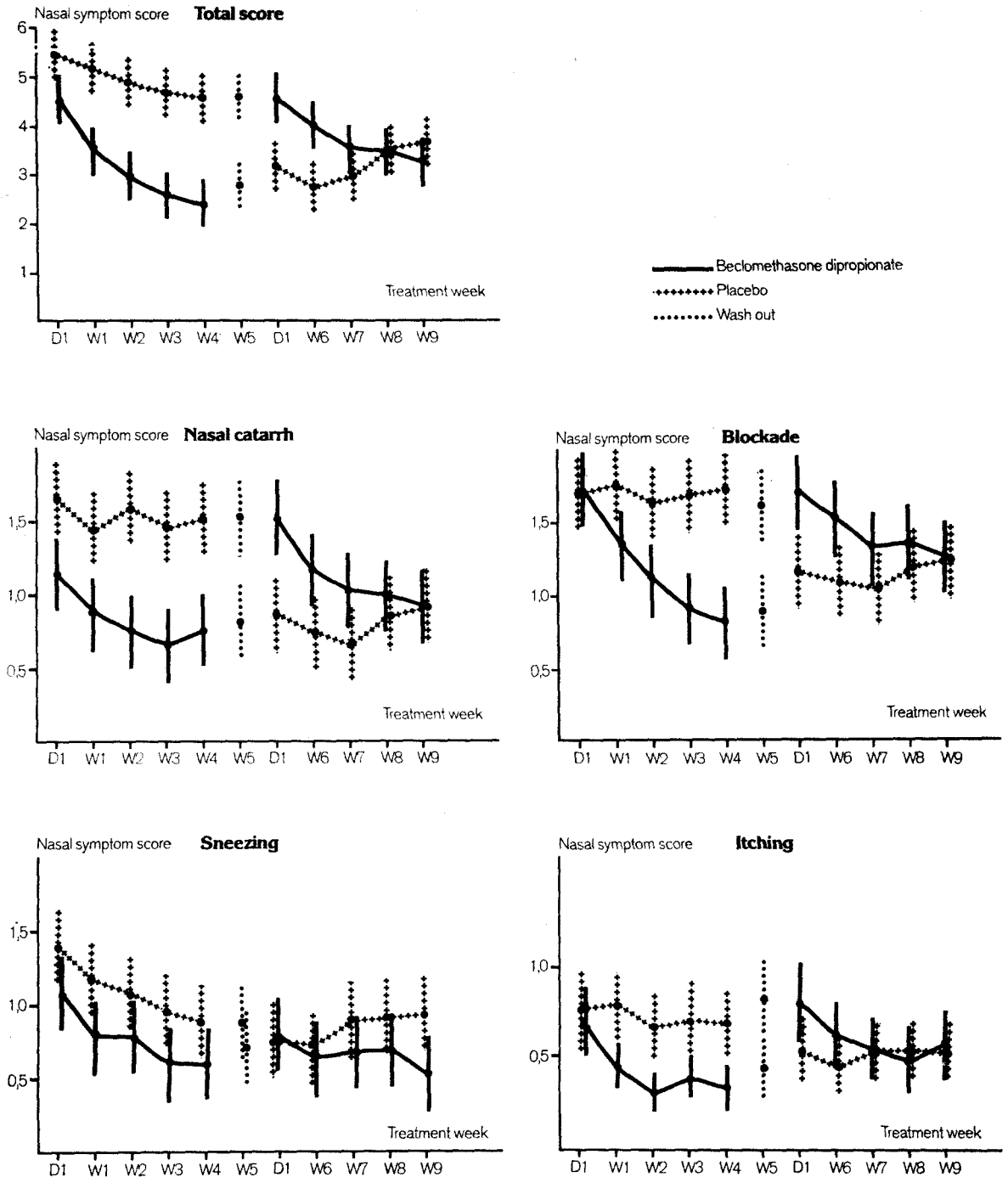


Fig. 1.

Average daily total nasal score and daily score for nasal catarrh, blockade, sneezing and itching from diary cards in 39 patients with vasomotor rhinitis treated with beclomethasone dipropionate and placebo for 4 weeks respectively. One week's wash-out period separates the two treatment periods. Data noted the first day (D_1) of both treatment periods and once a week (W_1 – W_9).

TABLE 2

Estimations of Morning Plasma Cortisol Level During the 4th Week of Treatment with Beclomethasone Dipropionate and Placebo in 19 Patients with Vasomotor Rhinitis.

Patient	Born	Sex	Cortisol level during	
			Beclomethasone dipropionate period ($\mu\text{g}/100\text{ ml}$)	Placebo period ($\mu\text{g}/100\text{ ml}$)
I.O.	1942	male	14	18
M.S.	1920	female	19	20
J.T.	1951	male	14	22
E.B.	1946	female	16	16
M.O.	1917	female	20	32
E.B.*	1953	female	29	38
B.S.	1926	male	12	12
A.T.	1946	female	20	18
G.H.	1909	male	16	20
C.F.	1937	male	19	17
B.N.	1923	female	14	19
A.O.	1931	female	17	20
I.F.	1948	male	27	20
C.S.	1952	female	19	15
I.A.	1923	female	23	19
G.S.	1947	male	32	27
L.W.*	1956	female	41	47
E.O.*	1953	female	44	53
B.P.	1946	female	18	18
Average			21.8	23.7

Normal level of plasma cortisol 8 a.m.: 10-30 $\mu\text{g}/100\text{ ml}$.

* Patient using contraceptive pills.

sneezing already during the first week, for nasal catarrh during the second week, for nasal itching during the third week, and for nasal blocking only during the fourth week of treatment.

Fig. 1 illustrates graphically the total score and the score for each nasal symptom during treatment with beclomethasone dipropionate, placebo, and the wash-out period in between.

The rhinoscopic examination showed there had been no therapeutic effect for lividity, redness, oedema, and purulent secretion.

Cultures for bacteria and *Candida albicans* from the nasopharynx were generally negative. Thus the analysis was negative for *Candida albicans* in all patients on all three test occasions. Furthermore, no pathogenic bacteria could be isolated on any test occasion in 31 patients. In four patients new bacteria growth was found after the beclomethasone treatment, whereas two patients with bacteria growth before the beclomethasone treatment were free from bacteria at the end of the period of treatment. After the placebo period, fresh growth was isolated in two patients. Diagnosed pathogenic types of bacteria were *Haemophilus influenzae*, *Neisseria catarrhalis*, plasma-coagulating staphylococci, and beta haemolytic streptococci.

The mean cortisol/plasma value was somewhat lower during the beclomethasone dipropionate period than during the placebo period, but this difference is not statistically significant. For the individual patients, definite pathological values were observed only in the three women taking contraceptive pills. For the rest, two patients were noted to have slightly elevated values, one of which was found in the beclomethasone period and the other in the placebo period. (Cf. Table 2).

No serious side effects have been observed. One patient had a blood-tinged secretion from the nose towards the end of the beclomethasone period. No certain source of bleeding was ascertained. The trouble disappeared in the medicine-free week and did not recur during the placebo period following. One patient withdrew on account of an influenza-simulating disease during the beclomethasone treatment period. A few patients experienced increased irritation from itching, sneezing, nasal catarrh, and blocking following spraying with placebo as well as beclomethasone dipropionate.

DISCUSSION

Vasomotor rhinitis is, in many respects, an aetiologically obscure pathological condition. For this reason it has become the object of a wide range of therapeutic measures, such as treatment with drugs, vaccines, and surgery (17). Corticosteroids, for oral or parenteral use, will usually relieve the symptoms (2).

The synthesis of high-grade locally active corticosteroids has opened the possibility of a successful local cortisone therapy with reduced risk of systemic hormonal side effects. Good results with beclomethasone dipropionate in varying dosages have been shown in seasonal allergic rhinitis (1, 11, 15), perennial rhinitis (6, 9, 14), and nasal polyposis (16). As a natural extension of our investigation of hay fever (11) we continued with a study of vasomotor rhinitis treated with the same dose of beclomethasone (300 μ g a day) that had proved successful in the previous trial.

The study had the character of a double-blind cross-over study, allowing an evaluation of the therapeutic effect in 39 adult patients with vasomotor rhinitis without polyposis, which is, as far as we know, the greatest number of patients with this pathological condition that has been evaluated in a special investigation.

The results must be considered encouraging. About three-quarters (74 per cent) of the patients considered themselves to be free of trouble or improved when treated with beclomethasone dipropionate. The subjective evaluation corresponded with the results obtained at the statistical processing of the trouble score. The symptom of sneezing was found to be the most easily influenced, with a reduction already within a week. A clear effect on nasal catarrh was noted during the second week of treatment, on itching during the third, and on nasal blocking during the fourth week. No serious side effects were registered, judged from analysis of cortisol/plasma, bacteriological, and partial mycological (*Candida albicans*) flora in the nasopharynx.

No previous study has been made before on this category of patients, i.e. patients with vasomotor rhinitis without polypsis. The material is therefore more uniform than material presented in other studies under the term of perennial rhinitis, where patients with both allergic and vasomotor rhinitis have been included. However, a comparison of our results with those from investigations with mixed material and investigations with allergic rhinitis might be of interest.

In the study of Gibson et al. (6) with 200 μg beclomethasone dipropionate/day, 16 patients with allergic rhinitis and nine with vasomotor rhinitis took part. The corresponding figures for Hansen & Mygind (9) and Morrison Smith et al. (14) with 400 μg /day were 15/6 and 28/17, respectively. Good results were obtained in all three investigations, with a preference for beclomethasone dipropionate rather than placebo of between 64 and 76 per cent. It is worth noting that Gibson et al. in their investigation with 200 μg /day, found an effect which was well comparable with that of other studies using double the dose.

In purely allergic cases, for instance patients with hay fever, equally good or even better results have been registered in earlier studies. Thus, in Mygind's study (15) with 400 μg beclomethasone dipropionate, 86 per cent of the patients reported a preference for beclomethasone. In a later study, Brown & Storey (1) have found 71 per cent to have good, and 7 per cent moderate control also with 400 μg of beclomethasone dipropionate/day. In a previous report, we (11) could state that 95 per cent of the subjects regarded the treatment effective against nasal symptoms with 300 μg /day.

Our treatment results presented here are consequently on a level with those reported by the above-mentioned investigators for perennial rhinitis, but somewhat less favourable than those for hay fever. It is also of interest when comparing results to note that Morrison Smith et al. (14), in their study of 17 cases of vasomotor rhinitis in a material of 45 patients, only had an improvement of about 50 per cent with beclomethasone dipropionate, i.e. considerably lower than in our study. Maybe

our more favourable results can be ascribed to a different intensity of symptoms.

In our study, the nasal symptoms differed in their resistance to therapy. Most easily influenced was sneezing, followed in descending order by nasal catarrh, itching, and nasal blocking. This is not quite in conformity with the results from the investigation by Gibson et al. (6), according to whom sneezing and itching were resistant to treatment, whereas nasal catarrh and blocking improved. The results are more in accordance with those of Hansen & Mygind (9) who recorded an effect as regards sneezing and nasal catarrh already after a few days in several patients. Since the explanation of this observation hardly seems to be connected with the duration of treatment, it may perhaps be reasonable to assign the discrepancy either to the degree of trouble or to the smaller dose used in the study of Gibson et al. (6).

In our earlier study of hay fever (11) we wished to use a smaller dose of beclomethasone dipropionate than previously in order to further reduce the risk of systemic hormonal side effects. This has also been the aim in the present study, which includes the determination of cortisol/plasma in 19 patients. As seen in Table 2, we have found a definite, but insignificant influence on the cortisol/plasma values after 4 weeks of treatment with beclomethasone dipropionate. This is perhaps of interest in cases with long-term therapy, and in this connection it is worth noting the results of Gibson et al. (6) who found no decrease of values with a dose of 200 μ g beclomethasone dipropionate.

Finally, it is evident from recent studies concerning bronchial asthma (3, 12, 13) that the risk of infection by *Candida albicans* is dependent on the dose and duration of treatment with beclomethasone dipropionate. From the results of this study it seems that 300 μ g of beclomethasone dipropionate a day for 4 weeks is too small an amount in too short a time to influence the flora of nasopharynx with regard to *Candida albicans* and bacteria.

SUMMARY

The effect of beclomethasone dipropionate (Becotide®) intranasally in vasomotor rhinitis has been studied on 39 adult volunteers in a double-blind cross-over study during 9 weeks in February–April 1975. The dose of beclomethasone dipropionate was 300 µg/day. Twenty-five patients preferred the beclomethasone dipropionate period, 5 patients the placebo period, and 9 patients had no preference. About three-quarters (74 per cent) of the patients considered themselves free of symptoms or greatly improved after the treatment with beclomethasone dipropionate. Statistical calculation of the daily nasal symptoms score confirms the improvement. The speediest effect was registered for sneezing, followed by nasal catarrh, nasal itching, and blocking. No changes in the levels of cortisol occurred during the treatment. The bacteriological and mycological findings (analysed with regard to *Candida albicans*) were fairly constant.

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