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INTRA-NASAL BECLOMETHASONE DIPROPIONATE IN VASOMOTOR RHINITIS

By

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After 1972, when Morrow Brown et al. (6) demonstrated good effects on the symptoms of bronchial asthma with inhaled beclomethasone dipropionate aerosol (BDA), it was not long before local treatment with this corticosteroid was also tried in allergic diseases of the nose. Investigations made in 1973 and later showed that patients with seasonal (5, 7, 8) and perennial rhinitis (2, 3) improved considerably when treated with BDA administered intranasally. In these types of rhinitis, allergens can as a rule be demonstrated and a specific hyposensitization can be performed, which in many cases markedly reduces the symptoms. The need for symptomatic treatment is more pronounced in patients with vasomotor rhinitis, since in accordance with the definition in this country no relevant allergens can be found in these cases. The aim of this study was therefore to find out if BDA administered intranasally is also effective in patients with vasomotor rhinitis. As the daily dose in the earlier investigations was 200, 300 or 400 μ g, it also seemed reasonable to perform a dose-response study with observations of the local side-effects and the possible influences on the adrenal function.

MATERIAL AND METHODS

The study is based on a material of 21 out-patients; 12 women and 9 men with an average age of 36 years (range 18-61 years). For more than 1 year all of the patients had suffered from one or more of the symptoms—nasal blockage,

watery secretion and sneezing. On the basis of clinical history, skin sensitivity to prick testing, and provocation testing, no relevant allergens were found in any of the patients. BDA was administered with commercial Becotide® aerosol used for asthma but equipped with a special adaptor. Each puff yielded 50 μg but the patients did not receive that much, as according to Hansen et al. (3) about 30 per cent of this dose is retained in the holder and the nasal adaptor. Placebo was given by an identical procedure. In double-blind fashion the patients were divided into four groups, where each group and patient took 200, 400 and 800 μg daily of the active drug or placebo for four 2-week periods as scheduled in Fig. 1. As each puff yielded 50 μg BDA the patients had to take one puff in each nostril twice a day for 200 μg , one puff four times a day for 400 μg , and two puffs four times a day for 800 μg . In order to secure the double-blind effect the daily number of placebo puffs had to be varied. The patients were asked to record daily on a diary card the intensity of the symptoms—nasal blockage, watery secretion, sneezing and eye irritation and also intake of other kinds of medicine capable of reducing the symptoms. The degree of intensity of the symptoms was recorded on an arbitrary scale from 0 to 3. The symptoms were also recorded during the week previous to the trial.

Group	Period			
	1	2	3	4
1	A	B	C	D
2	D	C	B	A
3	B	A	D	C
4	C	D	A	B

A = Placebo, B = 200 μg , C = 400 μg , D = 800 μg of BDA.

Fig. 1.

Plan showing how the 21 patients divided into four groups entered the trial.

During the 9 weeks of recording each patient was examined five times: at the end of the first week without BDA and placebo treatment, and at the end of each of the four 2-week periods. On these occasions, which always occurred at the same hour for each patient, the nasal mucosa was examined and secretion samples taken for culture of bacteria and fungi and count of eosinophil cells. The amount of eosinophils compared with other leucocytes was judged as less than 10 per cent, between 10 and 50 per cent and more than 50 per cent. At the same time, samples for an estimate of 24-hour secretion of 17-hydroxycorticosteroids in urine and of cortisol in serum were also taken. 17-Hydroxycorticosteroids were assessed with a spectrophotometric method described by James et al. (4), and cortisol with a fluorometric method described by Clark et al. (1).

The symptom scores and the laboratory values were estimated statistically on

the basis of a more rigorous method than traditional paired comparisons, in which the sequence of given drugs or given amounts of a drug are not taken into account. Owing to this, the effects of systemic deviations between the periods, e.g. those caused by weather conditions, were reduced. Fisher's non-parametric permutation test was used as a statistical test (9). The P -values were estimated by a method based on the so-called Edgeworth development. To avoid or reduce effects of BDA lingering on from previous periods of treatment, the statistical evaluation of the symptom scores was limited to the last week of each period.

RESULTS

For two of the symptoms, namely nasal blockage ($P < 0.01$) and watery secretion ($P < 0.05$) the patients had significantly lower symptom scores during the period of treatment with placebo than during the week before any treatment. When the period of placebo was compared with the periods of BDA in the different doses, it appeared that BDA in all doses was significantly more effective than placebo in reducing the nasal blockage ($P < 0.05$). However, no differences in effectiveness between the three BDA doses were found. Also the watery secretion was more effectively treated with BDA in all doses than with placebo ($P < 0.05$), but was more effective with 800 μg than 200 μg ($P < 0.05$). The most pronounced differences in effect between BDA and placebo appeared in the case of sneezing ($P < 0.01$), but none of the doses of BDA was better than the others in reducing this symptom. The mean values $\pm$ S.E.M. of the weekly scores of the three nasal symptoms are also shown in Fig. 2, which also includes the eye symptom scores. These latter symptoms were mainly the same before treatment, during placebo treatment and during treatment with BDA.

Ten out of the 21 patients used antihistamine tablets or α -adrenoceptor stimulating nose drops during the week before treatment with placebo and BDA. This number of patients is too limited to allow statistical evaluation of the use of these drugs in the different periods. During the week before treatment with placebo and BDA, however, the patients used altogether 80 tablets, during the week with placebo 20, and

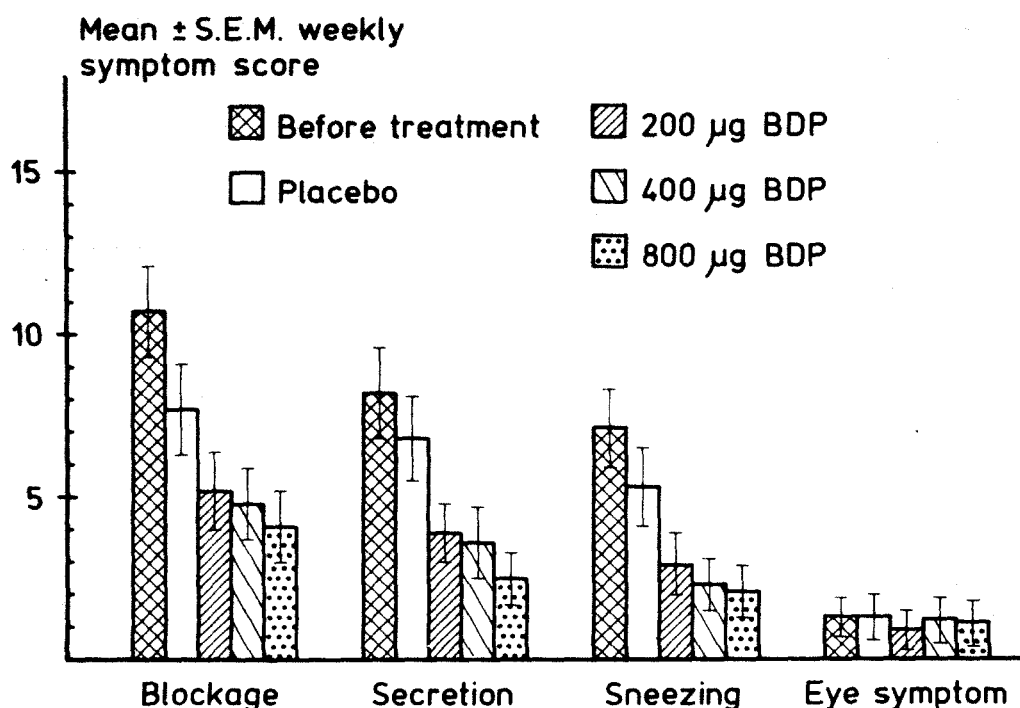


Fig. 2.

Mean values and standard error of means for symptom scores in each second week of every 2-week period of trial and the pretrial week.

during the week with 200, 400 and 800 μ g BDA, 13, 8 and 9 tablets respectively.

In certain patients, the aerosol initially provoked transient irritation in the nose followed by sneezing. Eight of the patients reported that on one or a few occasions they had noted streaks of blood in the nasal secretion. There seemed to be no difference between BDA and placebo treatment in this respect. In no case did these findings make the patients stop the trial.

No significant differences were found in 17-hydroxycorticosteroids in urine and in cortisol in serum between the samples from the different periods. Mean values $\pm$ S.E.M. are seen in Fig. 3.

Eighteen out of the 21 patients had more than 10 per cent eosinophil leucocytes in the nasal secretion in the week before treatment. During the period with placebo this figure was reduced to 10, and during treatment with BDA, to 8, 5

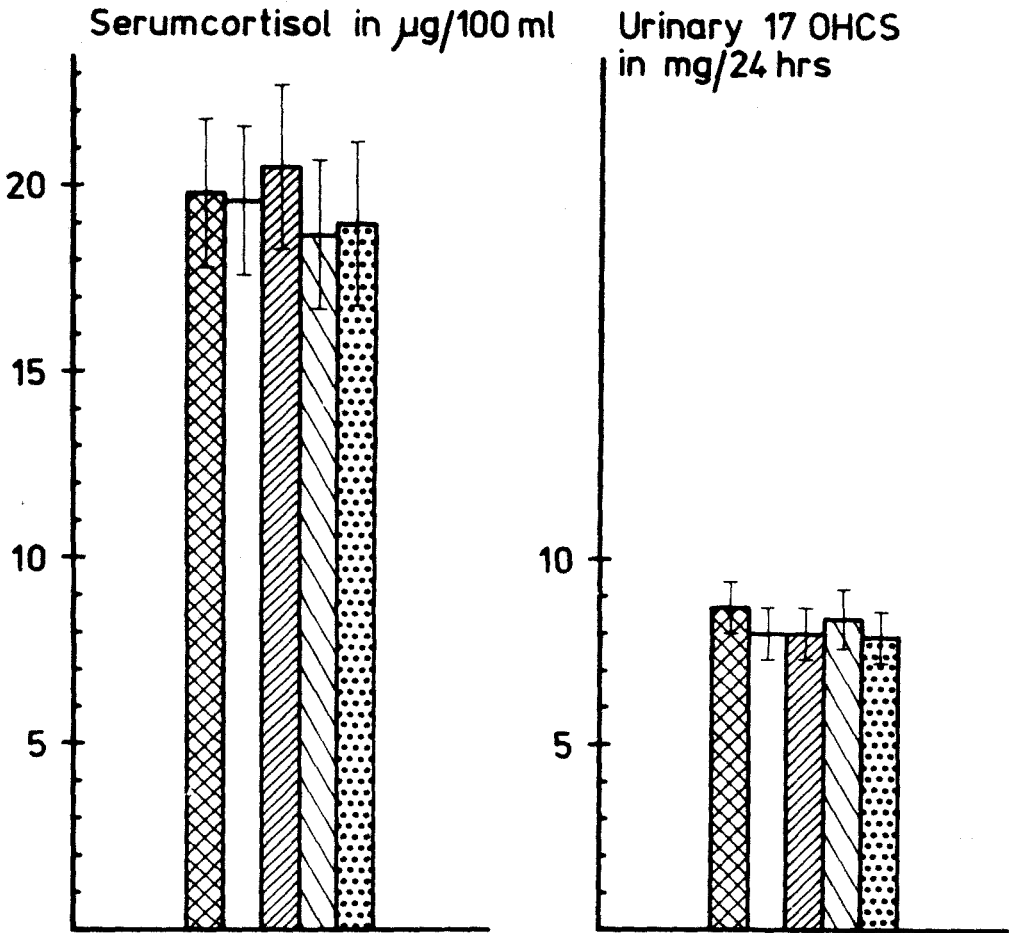


Fig. 3.

Mean values and standard error of means for cortisol in serum and 17-hydroxycorticosteroids in 24-hour urine measured at the end of each 2-week period and at the end of the pretrial week.

and 8 for 200, 400 and 800 μg , respectively. No bacteria could be found in the nasal secretion in about 25 per cent of the cultures. In the others, bacteria which normally exist in nasal secretion were observed. Pathogenic bacteria grew only in a few cultures. These bacteria did not seem to occur more often when the patients took BDA than otherwise. Nor could an increased frequency of fungi be observed during BDA treatment.

DISCUSSION

Patients with vasomotor rhinitis comprise a heterogeneous group. The main symptom in some cases is nasal blockage, while other patients are more troubled by watery secretion and sneezing. In the English literature this has led to a division of these patients into two groups—blockers and sneezers. The discomfort from the symptoms, however, differs widely from one patient to another, so the evaluation of the results has been done for each one of the symptoms.

It was obvious from this investigation that the nasal symptoms were reduced by intra-nasally administered BDA in the three doses 200, 400 and 800 μg as compared with placebo. Hardly any differences in effect were found between the three doses of BDA. This may either mean that all the doses were supramaximal in their possible effect, or that the chosen doses were too close to each other to make possible a dose-response curve. If this is the case another investigation with other doses, tentatively lower, is necessary, since the symptoms in bronchial asthma are successfully treated with doses of 400 μg BDA (6), and since the bronchial mucosa has a much larger surface than the nasal one.

This investigation also showed that nasal blockage and secretion gave significantly less trouble during treatment with placebo than during a week when no treatment at all was given. These results contradict those of Mygind (8), who found no effect with placebo in patients with seasonal rhinitis. The effectiveness of the placebo treatment in the present investigation may be due to a comparatively protracted effect with BDA and to the way in which this investigation was performed with its four consecutive 2-week periods and with the different sequences of the three doses of BDA and placebo. Another reason for such an explanation is the fact that eosinophil cells appeared less often in the nasal secretion during treatment with placebo than they did with no treatment. If such an explanation is valid the symptoms during BDA treatment could be compared with those before any treatment as

well as with those during placebo treatment. Such a comparison, as seen in Fig. 2, shows that all the doses of BDA reduced the weekly nasal symptom scores by more than 50 per cent.

The effects of BDA seemed to last in this investigation for more than a week, whereas for example Mygind (8) found that the symptoms of patients with seasonal rhinitis recurred or increased again just a few days after they had stopped taking BDA and switched to placebo. The explanation for these divergent results may be found in differences between allergic and vasomotor rhinitis. In seasonal allergic rhinitis the patients' symptoms, often for a relatively short time, are elicited by one or more specific allergens and the picture of the disease is then very distinct. In vasomotor rhinitis it is more likely that unspecific trigger mechanisms and psychological factors are of far greater importance, and these contribute to making the symptoms fairly constant for long periods of time. If such a pattern of reactions can be broken, rebuilding it again may be expected to take some time. This seems to be confirmed by the fact that several of the patients were free from symptoms as much as a couple of weeks after the tests were completed.

No undesirable side-effects of intra-nasally given BDA such as pathogenic bacteria or fungi in the nasal secretion were observed. Some patients noted streaks of blood, but these did not cause them to stop taking BDA or placebo. As the periods of treatment were relatively short, no efforts were made to look for possible atrophy of the nasal mucosa.

No systemic effects of intra-nasal BDA were found. The eye symptom scores were not changed by the treatment. Statistically, no suppression of the adrenal function by any of the three doses of BDA could be demonstrated in either the placebo or the pre-treatment values. Absence of significant differences, however, does not necessarily mean that the corticosteroid given intra-nasally lacks systemic effects. It is therefore advisable to recommend the lowest therapeutic dose in this investigation for treatment of patients with vasomotor

rhinitis. A dose of 200 μg implies a daily administration of about 140 μg to the patient. If necessary, the daily dose may be increased to 800 μg for up to a couple of days. Since, however, the present investigation does not answer the question as to what other possible local side-effects, for instance atrophy, may result from lengthy use of intra-nasal BDA, pauses for about a week now and then may be recommended in the use of BDA.

After completion of the tests many of the patients wanted very much to go on taking BDA intra-nasally and now, half a year later, 14 of them take 200 μg BDA daily with apparently good effect. This dose, which implies one puff in each nostril twice a day, is found convenient. They have interrupted the treatment for short periods without any appreciable increase of the symptoms.

It is often difficult to relieve the symptoms of patients with vasomotor rhinitis even if many of them get some help by antihistamines, sympathomimetic drugs and sodium cromoglycate. The present investigation suggests that for such patients intra-nasal BDA is a valuable form of treatment which can be used when the above-mentioned drugs are insufficient. Furthermore, the need for such therapy has apparently increased owing to the fact that patients with intrinsic bronchial asthma have unmasked nasal symptoms after switching from oral to inhaled corticosteroid treatment.

SUMMARY

Twenty-one patients with vasomotor rhinitis, with no relevant allergens known, completed a special double-blind trial of beclomethasone dipropionate aerosol (BDA) and placebo intra-nasally. Each patient took 200, 400 and 800 μg BDA and placebo during four consecutive 2-week periods and in different sequences. The symptom scores of the last week of each period of nasal blockage, watery secretion and sneezing were significantly reduced by all doses of BDA as compared with placebo. There were no differences between the effects of the different doses of BDA except for secretion, which was reduced more by using 800 than 200 μg . Cortisol in serum and

17-hydroxycorticosteroids in 24-hour urine were not significantly changed by BDA treatment and no increased frequency of pathogenic bacteria or fungi could be demonstrated in the nasal secretion. For treatment of patients with vasomotor rhinitis, intra-nasal BDA in a daily dose of 200 μ g can be recommended when antihistamines, sympathomimetic drugs and sodium cromoglycate are not sufficiently effective.

ACKNOWLEDGEMENTS

Our thanks are due to Glaxo Läkemedel AB, Sweden for the supply of aerosols, and to Nils-Gunnar Persson, Chalmers University of Technology, Gothenburg, for the statistical analysis.

REFERENCES

1. Clark, B. & Rubin, R. (1969): New fluorometric method for the determination of cortisol in serum. *Analyt. Biochem.* 29, 31-39.
2. Gibson, G. J., Maberly, D. J., Lal, S., Ali, M. M. & Butler, A. G. (1974): Double-blind cross-over trial comparing intranasal beclomethasone dipropionate and placebo in perennial rhinitis. *Brit. med. J.* 4, 503-504.
3. Hansen, I. & Mygind, N. (1974): Local effect of intranasal beclomethasone dipropionate aerosol in perennial rhinitis. *Acta allergol.* 29, 281-287.
4. James, V. H. P. & Caie, E. (1964): Determinations of urinary 17-hydroxycorticosteroids and their relations to cortisol secretion. *J. clin. Endocr.* 24, 180-186.
5. Löfkvist, T. & Svensson, G. (1975): An open assessment of Becotide® (Beclomethasone Dipropionate) nasal spray in seasonal allergic rhinitis. *Acta allergol.* 30, 227-238.
6. Morrow Brown, H., Storey, G. & George, W. H. S. (1972): Beclomethasone dipropionate: a new steroid aerosol for treatment of allergic asthma. *Brit. med. J.* 1, 585-590.
7. Morrow Brown, H. & Storey, G. (1974): Beclomethasone dipropionate aerosol in the treatment of seasonal asthma and hay fever. *Clin. Allergy* 4, 331-341.
8. Mygind, N. (1973): Local effect of intranasal beclomethasone dipropionate in hay fever. *Brit. med. J.* 4, 464-466.
9. Odén, A. & Wedel, H. (1975): Arguments for Fisher's permutation test. *Ann. Statistics* 3, 518-520.

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