

A Comparative Study of Dexchlorpheniramine Maleate Sustained Release Tablets and Budesonide Nasal Spray in Seasonal Allergic Rhinitis

E. P. MUNCH,¹ M. SØBORG,² T. T. NØRRESLET³ and N. MYGIND⁴

¹ Allergy Clinic, Frederiksberg Hospital, ² Dept. of Internal Medicine B, Hillerød Hospital, ³ Dept. of Otorhinolaryngology, Bispebjerg Hospital, ⁴ Dept. of Otorhinolaryngology, Rigshospitalet, Copenhagen, Denmark

It was the aim of the study to compare the efficacy and side effects of oral antihistamine and nasal glucocorticoid therapy in seasonal allergic rhinitis. In a double-blind, double-dummy, group-comparative study, 61 adult grass pollen allergic patients were either treated with dexchlorpheniramine maleate sustained release tablets (6 mg b.d.), or with budesonide nasal spray (200 µg b.d.). After a 1-week run-in period, treatment was given for 3 weeks in the grass pollen season. Patients treated with budesonide showed significantly less nasal blockage than those who received dexchlorpheniramine ($P < 0.05$), but there was no difference in the number of sneezes and nose blowings. Patients treated with budesonide used a larger quantity of antihistamine-vasoconstrictor eye drops ($P < 0.01$). Drowsiness occurred in the group that was treated with dexchlorpheniramine, but mainly during the first week of treatment. The side effects caused by the budesonide spray were few and insignificant. The patients' overall assessment of the treatment favoured the glucocorticoid spray ($P = 0.06$).

Key words: antihistamine; glucocorticoid; allergic rhinitis.

Accepted for publication 14 May 1983

Oral antihistamine and topical glucocorticoid are both widely used in the treatment of allergic rhinitis. The choice between these two types of therapy will be based on chance and personal preference, if it cannot be founded on published reports of double-blind comparisons of effect and side effects. Harding & Heath (8) have compared a glucocorticoid (steroid) spray (betamethasone valerate 200 µg b.d.) with a combined antihistamine (triprolidine 2.5 mg t.i.d.) and vasoconstrictor (pseudoephedrine 60 mg t.i.d.) preparation in patients with perennial rhinitis, allergic and non-allergic. In this cross-over study, the patients' preferences were significantly in favour of the aerosol, 22 preferring the steroid and five the antihistamine ($P < 0.01$). As the inclusion of non-allergic patients has probably favoured the steroid preparation, we have found it relevant to compare these two

types of treatment in patients with seasonal allergic rhinitis.

In this study, we have used dexchlorpheniramine maleate as sustained release tablets, and budesonide nasal aerosol. Dexchlorpheniramine maleate was chosen because it is a widely used antihistamine with a potent H_1 -antihistamine effect and little sedative effect (5). Budesonide is a potent glucocorticoid; the non-halogenated budesonide molecule is more efficiently inactivated in the liver than the halogenated steroids (3). Compared with the steroid which is more widely used for topical application in the airways, beclomethasone dipropionate, budesonide has an increased ratio between anti-inflammatory and systemic potencies (3, 9). It is too early to say whether this will be reflected in the efficacy and safety of hay fever treatment; but budesonide seems to be at least

as effective as beclomethasone dipropionate in hay fever (13).

PATIENTS AND METHODS

Patients

Hay fever patients, allergic to grass pollen, were included in the trial if they fulfilled all the following criteria: a) aged 15 years and over, b) rhino-conjunctivitis in June–July, which had required treatment for the last two seasons, c) positive skin prick test to timothy grass (at least of the same size as that of the histamine test (1 mg/ml)), d) stayed in Denmark during the entire period, and e) gave informed consent.

Applicants were not included if: a) they were of childbearing potential, b) had perennial rhinitis or asthma, c) had severe seasonal asthma, d) had marked hay fever symptoms in the birch pollen season (April–May), e) had anatomical abnormalities, hindering the use of a nasal spray, f) had recurrent-chronic infectious rhinosinusitis, and g) were treated with other drugs, or had received glucocorticoids for the last 2 weeks (4 weeks for depot-injections).

Treatment was initiated in 61 patients, and completed by 60, 29 in the antihistamine and 31 in the glucocorticoid group; 30 were female and 30 male. The mean age was 29 years (range 16–56).

Drugs

Dexchlorpheniramine maleate (referred to as dexchlorpheniramine) was given as slow-release tablets of 6 mg (Polaramine Duplex®), one tablet in the morning and one in the evening. In the case where a patient might become too heavily sedated, he was allowed to reduce the daily dose, and take the evening tablet only. Vials with 50 tablets and vials with identical placebo tablets were manufactured by Schering Corporation, Kenilworth, U.S.A., and supplied in coded form by Essex Pharma, Denmark.

Budesonide was given as two puffs of 50 µg into each nostril morning and evening; the daily dose was 400 µg. Patients were instructed to: a) check the patency of the nostril before spraying,

b) hold the canister in the sagittal plane, and c) direct one puff towards the upper and one puff towards the lower part of the nasal cavity. Budesonide was administered as an aerosol from a pressurized canister (valve size, 25 µl) (Rhino-cort®) (Fig. 1). Active drug and placebo were supplied as coded aerosols from Draco, Lund, Sweden, via Astra, Denmark.

To check patient compliance the used aerosols and tablet vials were returned by the patients to one of the departments (Hillerød), and the doses actually used were calculated on the basis of weighing and counting before and after treatment.

Study design

The study was started on the 1st of June, 1982 with a 7-day pretreatment period, followed by a treatment period of 21 days. The patients were randomized into two parallel groups. All patients received both a coded tablet vial and a coded aerosol, containing either active tablets and placebo aerosol, or vice versa. The trial was thus undertaken with a double-blind, double-dummy design. It was carried out as a multi-centre study in four departments in and around Copenhagen.

Pollen count

Pollen was collected in a Burkard trap, placed 15 m over ground level in the City of Copenhagen. The daily pollen count, published in the

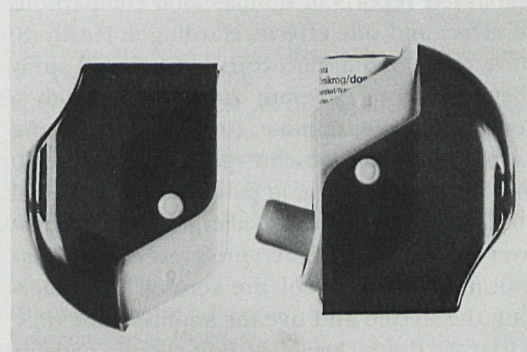


Fig. 1. The pressurized aerosol, used for budesonide (Rhino-cort®).

Danish Pollen Bulletin, was used with permission of the Aerobiological group, Danish Asthma-Allergy Association.

Symptom recording

Throughout the study, each volunteer carried a diary card on which he noted all sneezes and nose blowings (or similar procedures) in 2-h periods. Every morning and evening, he estimated the degree of sneezing, (0 = no symptoms; 1 = slight; 2 = moderate; 3 = severe symptoms) rhinorrhea and blockage according to a rating scale. These symptoms were compiled to form a total nasal symptom score. Throat itching during the day was evaluated on a rating scale (0–3), and eye itching on a 100 mm visual analogue scale (0 = no itching; 100 = the worst itching ever experienced).

Additional therapy

In the run-in period, patients were allowed to take their ordinary antihistamines for nasal symptoms and Antistin-Privin® eye drops (Ciba-Geigy) for eye itching. Whenever necessary, these drops were also used during the treatment period. If the nasal symptoms became very severe during the treatment period, the patient could get in touch with the investigator and obtain 20 prednisolone tablets of 5 mg (1–2 tablets per day). All use of additional therapy was noted on the diary card.

Recording of side effects

On the diary card, the patients were asked daily whether they had experienced haemorrhagic nasal secretion, dryness in mouth, headache, or any other symptom, which might be related to the treatment. Sedation was evaluated morning and evening (for the daytime) on a 100 mm visual analogue scale (0 = completely awake and alert; 100 = very tired and sleepy).

Overall evaluation

At the end of the trial each patient answered the question: "What do you think of the hay fever

treatment this year"? on a 100 mm visual analogue scale (0 = very unsatisfactory; 100 completely satisfactory).

Statistical methods

It was stated in the protocol that the two groups should be directly compared using a non-parametric test for unpaired data (Wilcoxon), provided the two groups had comparable symptoms in the pretreatment week. However, as seen from the figures, the two groups did not exhibit identical symptom severity. Although the differences were not statistically significant with regard to any of the symptoms ($P > 0.05$), it was decided to take the pretreatment values into account when making the statistical comparisons between the two treatments. A stratified, two-sided Wilcoxon test was therefore employed. On the basis of the symptom score (sneezing, discharge, blockage, itching of the palate) in the pretreatment week, the patients were allocated to three strata: Slight symptoms (0–2.99), moderate symptoms (3–5.99), severe symptoms (≥ 6). The use of the stratified method implied that only patients belonging to the same stratum are compared. Inter-group comparisons concerning drug efficacy were only made on the basis of mean scores for the entire treatment period, not for single days and weeks. In respect to drowsiness (morning and evening) a mean score in the pretreatment week was calculated for each patient, and this was compared with the corresponding score for the first, second, and third week of the treatment (Wilcoxon test for paired data). All P -values were calculated for two-sided alternatives.

RESULTS

Use of the test drugs

The used aerosols and vials were returned by 21 patients as requested. They had taken an average of 6.3 puffs/day of placebo and 7.1 of budesonide, while 1.98 placebo tablets had been used per day and 1.79 dexchloropheni-

DIURNAL VARIATION OF HAY FEVER DURING THE RUN-IN PERIOD

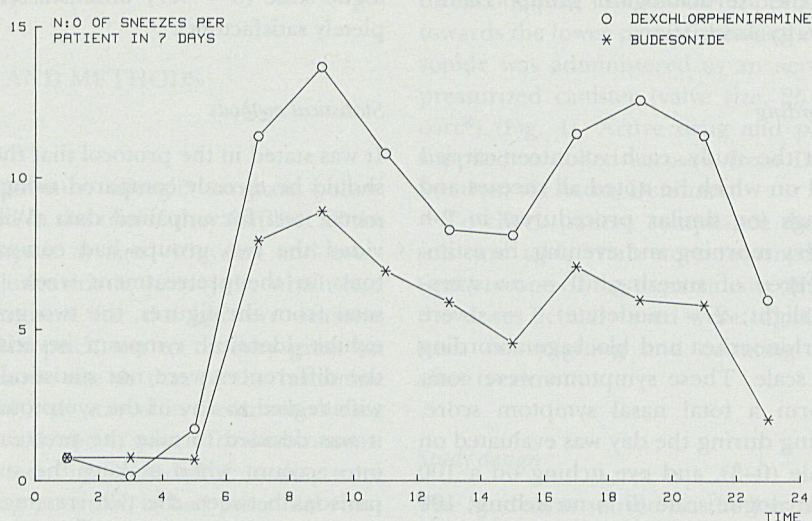


Fig. 2. Diurnal variation of sneezing in two groups of untreated hay fever patients.

DIURNAL VARIATION OF HAY FEVER DURING THE TREATMENT PERIOD

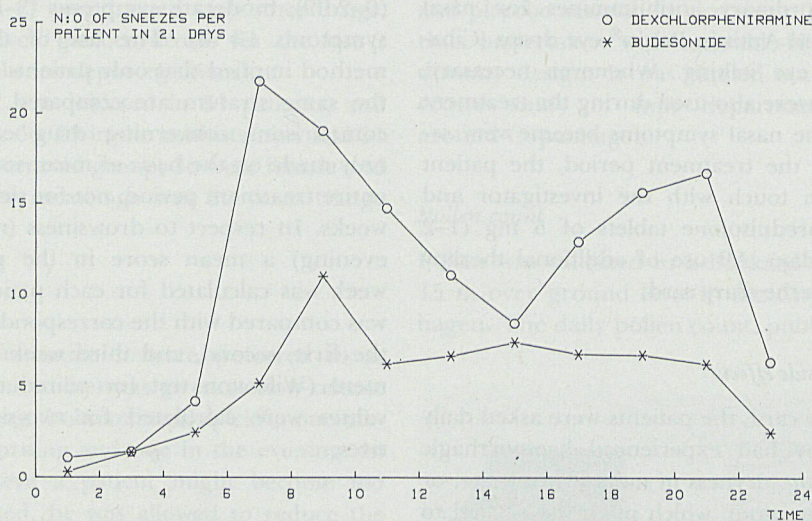


Fig. 3. Diurnal variation of sneezing during treatment with dexchlorpheniramine and with budesonide.

ramine (prescribed daily doses were 8 puffs and 2 tablets).

Diurnal symptom variation

Fig. 2 shows that a marked diurnal variation

occurred in the pretreatment period with regard to the number of sneezes, with a peak in the morning and a second increase in the evening. Sneezing approached zero during sleep. While the diurnal variation was unchanged during antihistamine therapy, there was a clear ten-

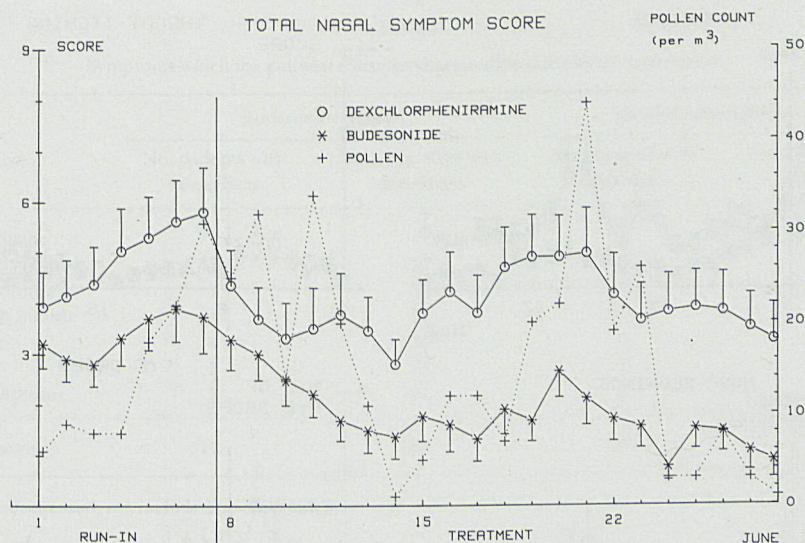


Fig. 4. Means of all nasal symptoms in the two organs, related to the pollen count.

dency towards a reduction of the morning and especially evening symptom peaks for sneezing during steroid therapy (Fig. 3). Similar results were obtained for number of nose blowings.

Nasal symptoms

The total nasal symptom score (sneezing, discharge, blockage) was significantly lower ($P < 0.05$) in the group treated with budesonide than in the dexchlorpheniramine group (Fig. 4). This is the result for the whole treatment period, using stratification on run-in values as described above. The curves indicate that the antihistamine was more effective than the steroid on treatment days 1–3, that they were equally active on days 4–7, and that the steroid was superior to the antihistamine on days 8–21. There were no significant differences between the two groups with regard to the number of sneezes (Fig. 5) and the number of nose blowings (Fig. 5), but patients treated with budesonide had the lowest score for nasal blockage morning and evening ($P < 0.05$) (Fig. 5). There were no significant differences for itching of the palate (Fig. 6), but the trend was in favour of budesonide.

Eye symptoms

There was no statistically significant difference between eye itching in the two treatment groups (Fig. 6), but this is probably due to the higher use of eye drops in the budesonide group ($P < 0.01$) (Fig. 6).

Additional therapy

During the run-in period, two patients in the dexchlorpheniramine group used a total of 31 antihistamine tablets, and two patients in the budesonide group took 10 tablets altogether. One patient in the dexchlorpheniramine group needed 10 prednisolone tablets during the treatment period.

Side effects

Patients on dexchlorpheniramine treatment had a quick increase in sedation (Fig. 6). During the day (the assessment being recorded in the evening) this side effect was only statistically significant during the first week ($P < 0.01$), and had disappeared after 10 days of treatment. Sedation in the morning was also particularly

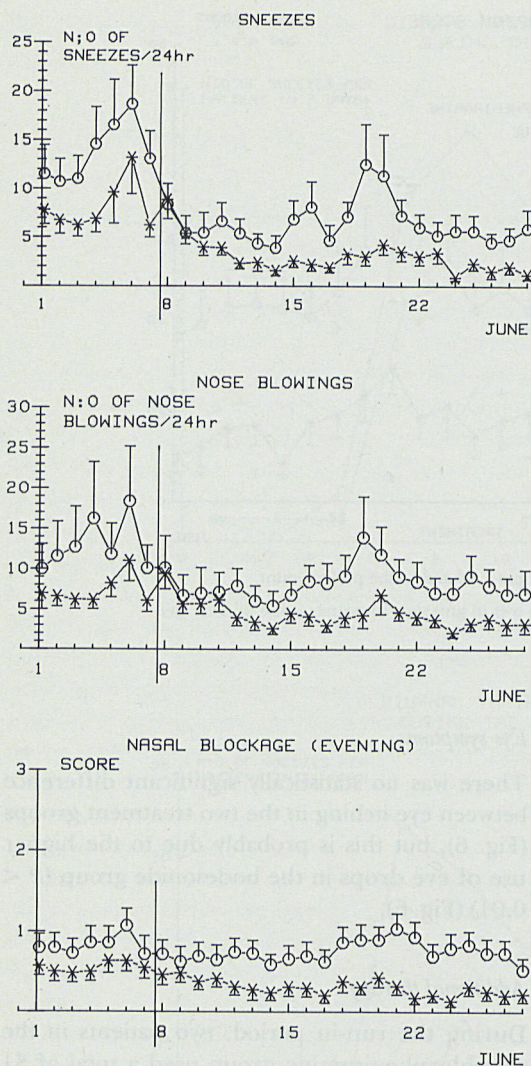


Fig. 5. Specified nasal symptoms during run-in period (7 days) and treatment period (21 days) in the dexchlorpheniramine (O—O) and the budesonide group (x—x).

noticeable in the first week ($P < 0.01$); but a slight increase in sedation tended to persist throughout the entire treatment period ($P > 0.05$ for weeks 2, 3 and 4).

One patient in the antihistamine group (a physician) discontinued the treatment after a few days due to sedation, which interfered with his work. His data are not included in the statistical calculations. Also due to sedation, two patients in the same group halved the tablet dose.

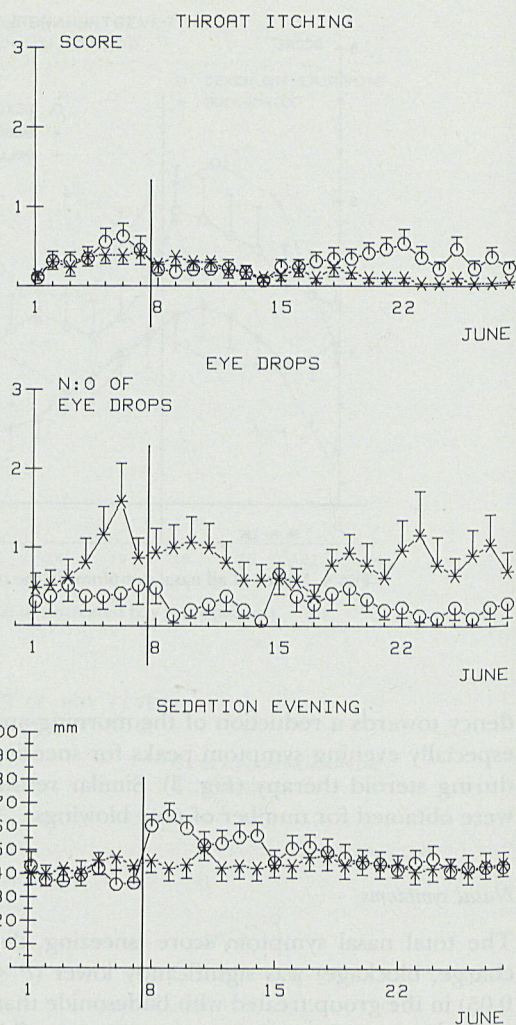


Fig. 6. Other symptoms and side effects. Text as Fig. 5.

Other possible side effects (Table 1) were few and equally distributed between the two groups, with the exception of mouth dryness, which tended to be more frequent in the dexchlorpheniramine group.

Overall assessment

The patients' assessment of the treatment was in favour of the steroid spray: the average scores for budesonide and for dexchlorpheniramine were 82 and 62 respectively ($P = 0.06$; one drop-out due to sedation from dexchlorpheniramine is not included). This overall as-

Table 1
Symptoms which the patients considered as possible side effects to treatment

	Budesonide group		Dexchlorpheniramine group	
	No. patients with side effects	Total No. days with side effects	No. patients with side effects	Total No. days with side effects
Haemorrhagic nasal secretion	7	20	5	14
Dryness in nose	7	35	5	49
Dryness in mouth	4	29	11	83
Headache	4	35	8	51
Sedation*	3	19	7	37
Other symptoms	7	24	2	13
All symptoms	17	166	20	249

* Information volunteered, not included on diary cards.

essment score combines the effect on nose symptoms, the effect on eye symptoms, any systemic side effects, and local steroid side effects, but not side effects due to the freon spray itself (used in both groups), patient compliance to spray or tablet treatment, or economy.

DISCUSSION

Our study was undertaken in a rather cold and rainy summer with a relatively low pollen count. The mildness of the disease in most patients may have rendered the design less sensitive in detecting differences between the two treatments; so may the inequality between the groups in the run-in period. Although there were no statistically significant differences between the dexchlorpheniramine and budesonide groups for sneezing and discharge, there was a tendency towards a better control of these symptoms under steroid treatment in the last two treatment weeks (see Fig. 5).

It is interesting that the steroid tended to smooth out the two-humped diurnal curve for sneezing and rhinorrhoea, while the antihistamine did not have this effect, although it was given in sustained-release form. This observation suggests that the morning and evening symptom peaks are not direct results of histamine release, but are more likely to reflect a normal diurnal rhythm (12), amplified by allergen-induced mucosal hyper-reactivity (1, 2).

The 24-h curves for sneezing and rhinorrhoea confirmed the clinical experience that these reflex-mediated symptoms (11) are almost eliminated during sleep, although pollen deposition and histamine release do not stop. This observation indicates that the central processing of afferent nerve impulses is of great importance for reflex-mediated nasal symptoms. This may be the reason why psychosedatives are reported to be effective in some rhinitis patients (6), and general anaesthesia has been used in the management of severe asthma.

Although the design of the present study did not enable us to show significant differences between the effects of antihistamine and steroid spray on sneezing and nose blowings, the difference in favour of the spray was clear and statistically significant in respect to nasal blockage. The poor antihistamine effect on this symptom, which is in accordance with earlier studies (4, 15), can have a dual cause. First, the H_1 antihistamine has no effect on histamine H_2 receptors, which seem to play a role in histamine-induced vasodilatation and oedema formation (14). Second, antihistamines have no effect on nasal blockage due to cellular infiltration, and on vasodilatation caused by other biochemical mediators (arachidonic acid metabolites) (10).

Our finding of a significant difference between the two treatments with regard to the use of antihistamine-vasoconstrictor eye drops, but not in respect to eye itching, shows that the eye

drops have mainly been used prophylactically. An effect of the budesonide spray on eye symptoms is not expected, as this new steroid molecule gives an even better dissociation between topical and systemic activity than beclomethasone dipropionate (3, 9). While the risk of local side effects after long-term use of budesonide is still debatable, the only "side effect" of any significance when the spray is used for a short pollen season is its lack of effect on eye itching. Prescription of antihistamine-vasoconstrictor and/or sodium cromoglycate eye drops is therefore necessary.

On the other hand, the antihistamine, dexchlorpheniramine, produced side effects: sedation and mouth dryness. But considering the rather high daily antihistamine dose, the sedation was less than we had expected, and the treatment was generally well tolerated. There was a clear tendency towards a reduction of sedation after 1 week of treatment. It is uncertain whether this is due to a development of tolerance to the side effect, or caused by liver enzyme induction and hence quicker drug metabolism.

In conclusion: 1) The budesonide nasal spray is somewhat more efficient than dexchlorpheniramine sustained release tablets and has less side effects. Hence, it seems to be the best choice for basic treatment of nasal hay fever symptoms. 2) The advantage of the steroid spray is most significant in patients with nasal blockage. 3) Antihistamine tablets are a good first choice in patients with severe eye itching. 4) Oral antihistamine is preferable when quick relief is needed, and when treatment lasts for a week or less.

Further controlled studies of these two types of hay fever therapy in patients exposed to high pollen counts, are needed; so are studies of additive use in patients with severe symptoms.

REFERENCES

1. Borum, P. & Mygind, N.: Inhibition of the immediate allergic reaction in the nose by the beta-2 adreno-stimulant fenoterol. *J. Allergy Clin. Immunol.* 66, 25–32, 1980.
2. Borum, P., Grønborg, H., Brofeldt, S. & Mygind, N.: Nasal reactivity in rhinitis. *Eur. J. Respir. Dis.* 64 Suppl. 128, 65–71, 1983.
3. Brattsand, R., Thalén, A., Roempke, K., Källström & Gruvstad, E.: Development of new glucocorticoids with a very high ratio between topical and systemic activities. *Eur. J. Respir. Dis.* 63; Suppl. 122, 62–73, 1982.
4. Connell, J. T.: A novel method to assess antihistamine and decongestant efficacy. *Ann. Allergy* 42, 278–282, 1979.
5. Douglas, W. W.: Histamine and 5-hydroxytryptamine (serotonin) and their antagonists. In Goodman Gilman, A., Goodman, L. S. & Gilman, A. (eds.): *Goodman and Gilman's: The pharmacological basis of therapeutics*, pp. 609–646. MacMillan Publishing Co., New York, 1980.
6. Foxen, E. H. M.: A placebo-controlled trial of imipramine in nonspecific vasomotor rhinitis. *Br. J. Clin. Pract.* 26, 363–366, 1972.
7. Goth, A.: Antihistamines. In Middleton, Jr. E., Reed, C. E. & Ellis, E. F. (eds.): *Allergy: principles and practice*, pp. 454–463. The C. V. Mosby Company, Saint Louis, 1978.
8. Harding, S. M. & Heath, S.: Intranasal steroid aerosol in perennial rhinitis: comparison with an antihistamine compound. *Clin. Allergy* 6, 369–372, 1976.
9. Johansson, S.-Å., Andersson, K.-E., Brattsand, R., Gruvstad, E. & Hedner, P.: Topical and systemic glucocorticoid potencies of budesonide, beclomethasone and prednisolone in man. *Eur. J. Respir. Dis.* 63; Suppl. 122, 74–82, 1982.
10. Kay, A. B.: Basic mechanisms in allergic asthma. *Eur. J. Respir. Dis.* 63; Suppl. 122, 9–16, 1982.
11. Mygind, N.: Mediators of nasal allergy. *J. Allergy Clin. Immunol.* 70, 149–159, 1982.
12. Mygind, N. & Thomsen, J.: Diurnal variation of nasal protein concentration. *Acta Otolaryngol. (Stockh.)* 82, 219–221, 1976.
13. Pipkorn, U. & Rundcrantz, H.: Budesonide and beclomethasone dipropionate in hay fever – a single blind comparison. *Eur. J. Respir. Dis.* 63; Suppl. 122, 211–220, 1982.
14. Secher, C., Kirkegaard, J., Borum, P., Maansson, A., Osterhammel, P. & Mygind, N.: Significance of H₁ and H₂ receptors in the human nose: rationale for topical use of combined antihistamine preparations. *J. Allergy Clin. Immunol.* 70, 211–218, 1982.
15. Wong, L., Hendeles, L. & Weinberger, M.: Pharmacologic prophylaxis of allergic rhinitis: Relative efficacy of hydroxyzine and chlorpheniramine. *J. Allergy Clin. Immunol.* 67, 223–228, 1981.

Address:

Niels Mygind, M.D.

Department of Otorhinolaryngology

Rigshospitalet

DK-2100 Copenhagen

Denmark

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.