Rhinology, 33, 121-125, 1995

Intranasal levocabastine for the treatment of seasonal allergic rhinitis: A multicentre, double-blind, placebo-controlled trial*

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SUMMARY

In this international, multicentre, randomized, double-blind, parallel-group, placebo-controlled trial 262 patients participated to assess the efficacy and tolerability of levocabastine nasal spray in the treatment of seasonal allergic rhinitis. Patients were randomized to receive either twice daily 0.05% levocabastine or matching placebo nasal spray with a treatment duration of four weeks. Assessments of global therapeutic efficacy favoured levocabastine. At the end of the trial, 55% of levocabastine-treated patients considered therapeutic efficacy to be excellent or good compared to 36% of those who received placebo ($p < 0.001$). The corresponding values for the investigator assessments were 54% and 37% ($p < 0.001$), respectively. Analysis of patients' diary data showed significantly lower AUCs for all parameters in the levocabastine group ($p < 0.05$). Investigator assessments revealed a trend towards a greater reduction in individual symptom severity from baseline in levocabastine-treated patients compared to placebo-treated controls. Adverse experiences were reported by 21% of levocabastine-treated patients and by 19% of those who received placebo, with no statistically significant differences in incidence or type. Headache and local reactions following application were the most frequently reported adverse events. Levocabastine nasal spray appears to be effective and well-tolerated for the treatment of seasonal allergic rhinitis and is an alternative to oral antihistamines.

Key words: levocabastine, intranasal, placebo, allergic rhinitis

INTRODUCTION

Seasonal allergic rhinitis is a common atopic condition caused by sensitivity to specific pollen, molds and spores, which affects as many as 20% of the general population for several months each year (Weeke, 1987). In susceptible individuals, exposure to the causative allergen initiates an IgE-mediated reaction resulting in the release of a number of inflammatory mediators from nasal mucosal mast cells. Although a wide range of mediators have been implicated in the pathogenesis of the allergic reaction, histamine appears to play a prominent role (White, 1990).

Nasal provocation tests have demonstrated that the majority of symptoms of seasonal allergic rhinitis are mediated by the actions of histamine at H_1-receptor sites (Kirkegaard et al., 1983). As a result, oral H_1-receptor antagonists are generally considered to be a primary treatment option (Badhwar et al., 1992). The efficacy of oral antihistamines in the treatment of allergic rhinitis is well documented (Simons and Simons, 1989). However, although these agents are generally well-tolerated, the potential for systemic adverse effects and drug interactions exists.

Topical antihistamine therapy could be beneficial. Direct application of an antihistamine to the affected site may provide more rapid relief from symptoms than oral administration. In addition, topical therapy may produce higher local concentrations of the active agent than can be achieved with systemic administration resulting in greater clinical benefits. Furthermore, topical administration would be expected to significantly reduce the potential for undesired systemic drug-related effects.

Levocabastine is a potent and highly selective H_1-receptor antagonist which has been specifically developed for the topical treatment of allergic rhinitis (Van den Bussche, 1986).

Nasal challenge studies have shown that levocabastine has a rapid onset of action providing relief from symptoms within 5 min after administration (Palma-Carlos et al., 1988), with a sufficiently long duration of action to permit a twice-daily dosing schedule (Tomiyama et al., 1993). Importantly, levocabas-

* Received for publication March 23, 1994; accepted August 30, 1994

tine appears to be well-tolerated with an adverse effect profile comparable to that of sodium cromoglycate and placebo (Dechant and Goa, 1991), with no evidence of tachyphylaxis or rebound during long-term therapy (Frostad and Olsen, 1993). Topical levocabastine, therefore, appears to be a possible alternative to oral antihistamines in seasonal allergic rhinitis. The efficacy and tolerability of levocabastine nasal spray in seasonal allergic rhinitis was assessed in this placebo-controlled trial.

MATERIAL AND METHODS

Patients aged between 12 and 70 years, with a documented history of seasonal allergic rhinitis confirmed by positive skin-prick or radioallergosorbent test (RAST) and who presented with at least two typical clinical manifestations of seasonal allergic rhinitis which had already required treatment during at least one previous season, were eligible for entry into this study. Patients also sensitive to causative allergens for perennial allergic rhinitis were not excluded. Exclusion criteria included: (1) concurrent diseases which could interfere with assessment of the study drug such as vasomotor rhinitis, rhinitis medicamentosa, active infectious sinusitis, upper respiratory tract infections or large obstructive nasal polyps; (2) concurrent therapy with corticosteroids, sodium cromoglycate, decongestants or other antihistamines; (3) concurrent hyposensitization therapy; (4) use of an investigational drug within a period of 30 days prior to entry into this trial; and (5) use of soft contact lenses (due to benzalkonium content of levocabastine eye drops). Patients with evidence of major organ disease, and pregnant and nursing women were also excluded from participation.

Study design

This was an international (Denmark, Germany, and The Netherlands), multicentre, double-blind, parallel-group trial. Patients were randomized to receive either 0.05% levocabastine or matching placebo nasal spray, administered two puffs per nostril twice daily with a treatment duration of four weeks.

Patients were required to discontinue all anti-allergic therapy prior to randomization with a wash-out period of one week for oral corticosteroids and three days for all other drugs excluded by the study protocol. However, after this time, the investigator could prescribe an ocular or nasal decongestant or oral terfenadine if required.

The study was conducted in accordance with the Declaration of Helsinki and subsequent revisions. Approval of the Ethics Committee was obtained and all patients gave informed consent, with informed parental consent for patients under 18 years of age.

Efficacy assessments

The severity of sneezing, nasal itching, rhinorrhoea, nasal congestion and concurrent eye symptoms was assessed by the patients on a daily basis, using a scale from "0" to "3" (0: absent; 1: mild [noticeable only on occasion, but not bothersome]; 2: moderate [noticeable from time to time and tending to be bothersome]; 3: severe [frequent and bothersome]) and by the investigator at the start of the trial and after two and four weeks. Patients also provided a daily assessment of the overall severity of their rhinitis using a 100-mm Visual Analogue Scale (VAS; extremes: "0": absent, and "100": very severe). In addition, both the patients and the investigator performed global evaluations of treatment efficacy at the end of the trial rating the effect of therapy as excellent, good, moderate, or poor.

Patients were required to note any adverse events in their diary and report these to the investigator at weeks 2 and 4. Vital signs (blood pressure and heart rate) were assessed at the time of entry into the trial and after four weeks of therapy. Pollen counts were measured every day at each participating centre.

Statistical methods

An intention-to-treat analysis was performed. In addition to the five individual symptoms (*vide supra*), the maximum score for symptoms of sneezing, itching or rhinorrhoea (SIR), the total nasal symptom severity score and the total overall symptom severity score were calculated and analyzed at the start of the trial and after two and four weeks of treatment. The area under the curve (AUC; expressed as a percentage of the maximum AUC and calculated using the trapezoidal rule), the percentage of days with severe symptoms and the percentage of symptom-free days were also determined for each individual symptom from the data recorded in the diaries. An analysis was performed for the entire study period and separately for days with high pollen counts (defined as >50 pollen particles/m^3/day). All intergroup differences were evaluated using the Mann-Whitney U-test or Fisher's exact test (two-tailed).

RESULTS

A total of 262 patients participated in this trial, 133 of whom were randomized to receive levocabastine nasal spray and 129 to receive placebo. As shown in Table 1, patients' demographics and baseline symptom severity were comparable in the two treatment groups. In all, 52 patients withdrew from the trial (25 levocabastine-treated patients and 27 of those who received placebo). The most frequent reasons for withdrawal are summarized in Table 2. Adverse experiences resulting in withdrawal were sneezing and rhinorrhoea, nasal burning, palpitations, and

Table 1. Patients' demographics and symptom severity at baseline in the two treatment groups.

	levocabastine	placebo
no. of patients	133	129
sex (m/f)	63/70	53/76
mean age in years (range)	31.7 (14-65)	31.6 (15-69)
weight in kg (mean±SEM)	70.5±1.10	68.5±1.08
mean baseline symptom severity:		
sneezing	2.1	2.2
nasal itching	2.1	2.2
rhinorrhoea	1.7	1.9
nasal congestion	1.7	1.9
ocular symptoms	1.5	1.6
maximum SIR*	2.5	2.6
total nasal symptoms	7.6	8.1
total all symptoms	9.2	9.7

*SIR: sneezing, itching or rhinorrhoea

Table 2. Reasons for withdrawal in the two treatment groups. (Some patients gave more than one reason for withdrawal.)

	levocabastine	placebo
no. of patients	25	27
insufficient response	13	21
lack of symptoms	7*	1
adverse experiences	4	3
other (lost to follow-up, un-cooperative, ineligibility)	7	6

*: p=0.07

common cold and stomach-ache for the levocabastine-treated patients and nasal itching, urticaria, and headache for those on placebo.

Pollen counts were considered sufficient to elicit symptoms of seasonal allergic rhinitis at all centres throughout the trial with high pollen counts recorded on 50% of study days. Compliance with the study regimens was similar in the two treatment groups. It was necessary to allow rescue medication for symptom relief during the first two weeks of the trial. The frequency of use of rescue medication was comparable in the two treatment groups and was required in 10% and 12% of treatment days in the levocabastine and placebo groups, respectively. In all, 31 levocabastine-treated patients (23%) and 36 placebo patients (28%) used rescue medication at some point during the trial with no significant intergroup differences in the type of rescue medication used.

Assessments of global therapeutic efficacy significantly favoured levocabastine (Figure 1). At the end of the trial, 55% of the levocabastine-treated patients considered therapeutical efficacy to be excellent or good compared to 36% of those who received placebo ($p < 0.001$). The corresponding values for the investigator assessments were 54% and 37% in the two groups, respectively, at this time ($p < 0.001$).

Patient assessments of symptom severity were in accordance with these findings. As shown in Table 3, mean AUCs for all parameters over the 4-week study period were significantly lower in levocabastine-treated patients than in placebo-treated controls (sneezing, rhinorrhoea, nasal itching, maximum SIR, total nasal symptoms and total all symptoms, $p < 0.001$; nasal congestion, $p < 0.01$; and ocular symptoms, $p < 0.05$). VAS ratings of the overall severity of rhinitis were also consistently significantly lower in the levocabastine- treated group (Figure 2; $p < 0.001$). Investigator assessments also revealed a trend towards a greater reduction in symptom severity from baseline in levocabastine-treated patients than in those who received placebo after two weeks of treatment and at the end of the trial (Table 4).

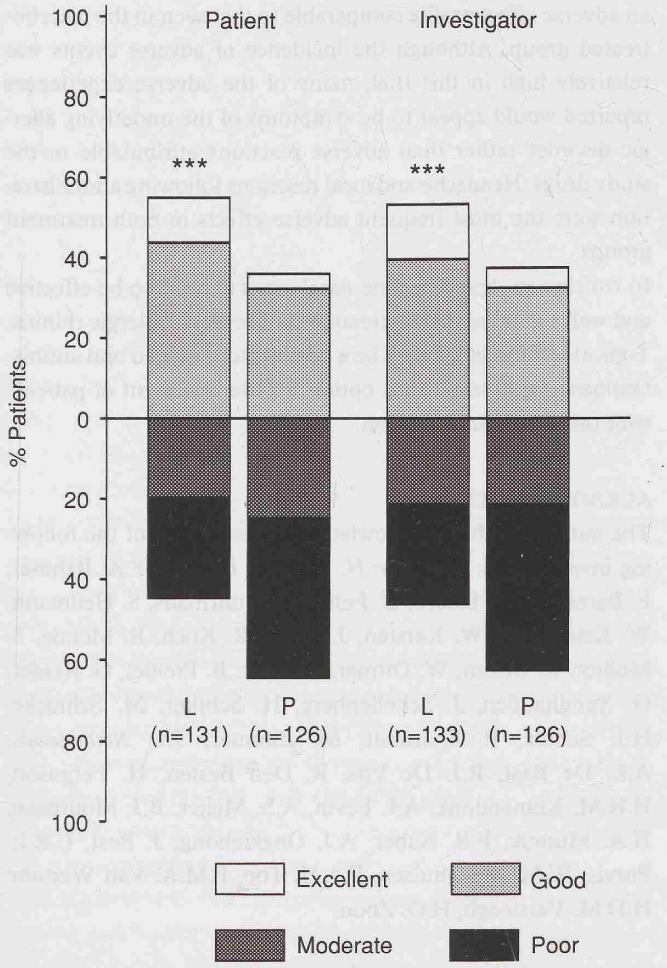

Figure 1. Patient and investigator assessments of global therapeutic efficacy at the end of the trial (L: levocabastine; P: placebo; ***: $p < 0.001$).

Table 3. Patient assessment of symptom severity at the end of the trial expressed as a percentage of the maximum AUC.

symptom	levocabastine (n=132) 4 weeks	placebo (n=129) 4 weeks	% levocabastine vs. placebo 4 weeks
sneezing	30.7***	43.9	30
rhinorrhoea	33.5***	44.6	-25
nasal itching	28.7***	41.3	-31
nasal congestion	30.0**	39.9	-25
ocular symptoms	28.0*	34.2	-18
max. SIR#	42.6***	56.3	-24
total nasal symptoms	30.8***	42.7	-28
total all symptoms	30.2***	41.1	-27
VAS (overall severity of rhinitis)	34.3***	43.5	-21

#: SIR (sneezing, itching or rhinorrhoea); *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

Table 4. Investigator assessments of symptom severity after two weeks of treatment at the end of the trial expressed as mean change from baseline values.

symptom	levocabastine		placebo	
	week 2 (n=128)	endpoint (n=130)	week 2 (n=119)	endpoint (n=124)
sneezing	-1.1*	-1.3*	-0.9	-1.0
rhinorrhoea	-1.1*	-1.2**	-0.8	-0.9
nasal itching	-0.8	-0.9	-0. 8	-0.9
nasal congestion	-0.7	-0.9	-0.6	-0.7
ocular symptoms	-0.7	-0.9	-0.5	-0.7
max. SIR#	-1.2*	-1.3**	-1.0	-1.0
total nasal symptoms	-3.8*	-4.3*	-3.0	-3.2
total all symptoms	-4.4*	-5.2*	-3.5	-3.9

#: SIR (sneezing, itching or rhinorrhoea); *: $0.05 < p < 0.1$; **: $p < 0.05$

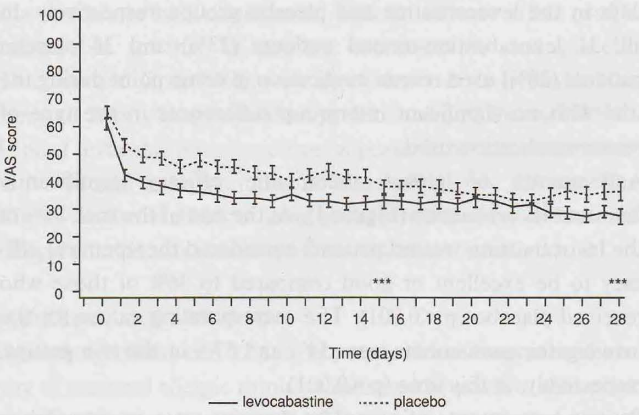

Figure 2. Patient VAS assessments of the overall severity of rhinitis (0: absent; 100: severe; ***: $p < 0.001$).

The percentage of symptom-free days was found to be significantly greater in the levocabastine group than in the group treated with placebo for all symptoms evaluated ($p < 0.01$), with levocabastine-treated patients completely free from symptoms of seasonal allergic rhinitis on 14% of treatment days compared with 5% for patients in the placebo group ($p < 0.001$). Separate analysis of intergroup differences on days with high pollen counts revealed that the percentage of symptom-free high pollen days was also greater in the levocabastine group than in the group treated with placebo, attaining statistical significance for all symptoms evaluated ($p < 0.01$). Finally, levocabastine-treated patients were found to be completely symptom-free in 15% of high-pollen days compared to 5% for patients receiving placebo ($p < 0.01$).

Adverse experiences were reported by 21% of the levocabastine-treated patients and by 19% of those who received placebo with no significant differences in the type or incidence of adverse reactions between the two treatment groups. The most frequently-reported adverse events during the course of this trial were headache (reported by seven and four patients in both groups, respectively), application site reactions (six and four patients), epistaxis (four and two patients), common cold (one and four patients) and nasal dryness (reported by four patients in the levocabastine-treated group). No significant changes in vital signs from baseline were reported in either of the two treatment groups during this trial.

DISCUSSION

The results of this study show that levocabastine nasal spray is effective and well-tolerated for the treatment of seasonal allergic rhinitis, even on days with high pollen counts. In this trial, intergroup differences in therapeutical efficacy attain statistical significance in favour of the topical antihistamine for most parameters evaluated.

Analysis of the patients' diary data revealed that the average AUC during treatment with levocabastine was 18–31% lower than that seen with placebo for all parameters evaluated. The fact that levocabastine was associated with a significant reduction in the severity of nasal congestion is somewhat surprising, as clinical experience indicates that oral antihistamines generally do not provide significant relief from this symptom (Busse, 1988; Delafuente et al., 1989). However, it is possible that topical application of this potent H_1-receptor antagonist provides higher local antihistamine concentrations than can be achieved with an orally administered drug resulting in greater clinical benefits. It would, however, be good to confirm this influence on nasal congestion by objective measurements. A significant improvement in ocular symptoms was also seen in patients treated with levocabastine nasal spray in this trial. As levocabastine plasma concentrations are extremely low following intranasal administration (Dechant and Goa, 1991), this effect is most likely due to improved ocular drainage through the lachrymal ducts, although it is also possible that following relief of their nasal symptoms, subjects tolerate ocular symptoms better than previously.

Although fewer levocabastine-treated patients resort to the use of rescue medication than the placebo controls, the difference in frequency of use between treatment groups, and between types of rescue medication used was not statistically significant. Since 23% of the levocabastine-treated patients still required rescue medication, it seems likely that a proportion of patients will benefit from more comprehensive treatment of their symptoms with adjunctive therapy using for instance, levocabastine eye-drops or an ocular decongestant.

Levocabastine nasal spray was found to be well-tolerated with an adverse effect profile comparable to that seen in the placebo-treated group. Although the incidence of adverse events was relatively high in this trial, many of the adverse experiences reported would appear to be symptoms of the underlying allergic disorder rather than adverse reactions attributable to the study drugs. Headache and local reactions following administration were the most frequent adverse effects in both treatment groups.

In conclusion, levocabastine nasal spray appears to be effective and well-tolerated for the treatment of seasonal allergic rhinitis. Topical levocabastine may be a useful alternative to oral antihistamines as a therapeutical option for the treatment of patients with this common condition.

ACKNOWLEDGEMENTS

The authors wish to acknowledge the assistance of the following investigators: *Germany:* N. Apel, C. Bachert, F.A. Bahmer, E. Barnstedt, U. Blaese, G. Felten, R. Fuhrmans, S. Heilmann, W. Kainzinger, W. Kersten, J. Knop, R. Koch, B. Mende, S. Molitor, R. Olzem, W. Ottmar, T. Peter, B. Preidel, G. Reider, G. Sundhaußen, J. Schellenberg, H. Schiller, M. Schnicke, H.J. Schulz, P. Spornraft, M. Zimmer; *The Netherlands:* A.E. De Baat, R.J. De Vos, R. Den Besten, H. Ferguson, H.H.M. Kranendonk, A.I. Levin, A.S. Meijer, B.J. Mouthaan, H.A. Munnik, F.B. Naber, A.J. Ongkiehong, J. Post, C.R.E. Purvis, W.M. Steenhuisen, P.A.H. Top, P.M.A. Van Wenum, H.D.M. Versteegh, H.O. Zoon.

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