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Intranasal levocabastine provides fast and effective protection from nasal allergen challenge*

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SUMMARY

A total of 22 asymptomatic patients with a documented history of allergic rhinitis participated in this single-centre, double-blind, randomized, placebo-controlled, cross-over trial undertaken to assess the efficacy and tolerability of levocabastine nasal spray (0.5 mg/ml) in the prevention of allergen-induced nasal symptoms. Objective assessment of nasal symptoms revealed that the severity of sneezing was significantly lower following treatment with levocabastine ($p<0.001$), with rhinorrhoea also tending to be less severe in the levocabastine-treated group ($0.05<p<0.1$). Rhinomanometry and acoustic rhinometry failed to reveal any significant intergroup differences, and there were no differences in nasal albumin concentrations between the two treatment groups. Patients' VAS ratings revealed significant differences in favour of levocabastine for sneezing ($p<0.001$) and itching ($p<0.05$), with the severity of rhinorrhoea also tending to be lower during treatment with this topical antihistamine ($0.05<p<0.1$). The mean total symptom score was also significantly lower in levocabastine-treated patients ($p<0.05$). Levocabastine was well tolerated. Only two adverse events were reported: fatigue in one patient, and vesicular rash with facial oedema and urticaria in another. In conclusion, intranasal levocabastine provided effective protection from nasal allergen challenge and would appear to be a valuable therapeutic approach in patients with allergic rhinitis.

Key words: levocabastine, topical antihistamine, allergic rhinitis, nasal allergen challenge

INTRODUCTION

The central role of H_1-receptor antagonists in the treatment of allergic rhinitis is well documented (Simons and Simons, 1989; Badhwar and Druce, 1992). However, although oral antihistamines have proven to be effective in the treatment of this atopic condition and are generally well-tolerated, topical antihistamine therapy may be a more logical therapeutical approach. Onset of action is likely to be more rapid following topical administration as the drug is applied directly to the affected site. Furthermore, any potential for systemic adverse effects is likely to be considerably reduced with a topical agent as compared to an orally administered drug, due to the low concentration of actual drug required for topical administration.

Until recently, however, none of the available antihistamines have been sufficiently potent to permit topical single-agent therapy. Levocabastine is a highly potent and selective H_1-receptor antagonist which has been specifically developed for topical use (Van den Bussche, 1986). Studies in the rat model of 48/80-induced lethality have shown that this agent is approximately 15,000 times more potent than chlorpheniramine on a molar basis, expressing antihistaminic activity at doses of less than 0.002 mg/kg (Van Wauwe, 1989). The present study has been undertaken to assess the efficacy and tolerability of intranasal levocabastine by means of nasal allergen provocation. Although environmental studies are widely used to assess the efficacy of drug therapy in the treatment of allergic rhinitis, such trials are limited to a certain extent by inter-patient variation in the degree of pollen exposure, arising from differences in regional pollen counts and the amount of time spent outdoors (Connell, 1986). Nasal provocation is a useful method of evaluating the efficacy of anti-allergic drug therapy, permitting a more controlled and uniform allergen exposure as well as enabling the use of more objective measures of therapeutical efficacy.

MATERIAL AND METHODS

Study population

Asymptomatic adult patients with at least a 3-year history of seasonal allergic rhinitis and positive skin prick or RAST tests for birch, grass or weed pollen, were eligible for inclusion into the trial. Exclusion criteria included: (1) concurrent disease

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which might complicate evaluation of the studied drug, such as perennial allergic rhinitis, vasomotor rhinitis, rhinitis medicamentosa, acute nasal infection or sinusitis, nasal polyps, upper respiratory tract infections or asthma; (2) concomitant therapy which could interfere with the assessment of the studied drug with a wash-out period of 1 month for systemic corticosteroids, 2 weeks for topical corticosteroids and sodium cromoglycate, and 3 days for nasal decongestants, antihistamines, anti-depressants and any other medication with potential anti-allergic activity, with the exception of astemizole for which a 6-week wash-out period was required; (3) use of an investigational drug within 1 month prior to entry into the trial; (4) hyposensitization therapy within 9 months of study entry; (5) known hypersensitivity to benzalkonium chloride; and (6) concurrent cardiovascular, pulmonary, renal, hepatic, neurological, and malignant disease. Pregnant, nursing and fertile women without adequate contraception were also excluded.

Study design

This was a single-centre, double-blind, randomized, placebo-controlled, cross-over trial consisting of two treatment periods separated by a wash-out period of at least 2 weeks, both of which were out of the pollen season. Study medication consisted of levocabastine nasal spray (0.5 mg/ml) and matching placebo (0.9% physiological saline).

Nasal lavage was performed at the start of each treatment period. Study medication was administered 10 min later at a dose of 0.2 ml per nostril, followed by nasal provocation using a commercial test solution (Allergopharma, Reinbek; 5,000 BU/ml each of birch, grass and weed pollen) 15 min later at a dose of 0.08 ml per nostril, according to the German Guidelines for Nasal Provocation Testing (Gonsior et al., 1990).

The study design was approved by the Local Ethics Committee and all patients provided written informed consent.

Assessments

To permit objective evaluation of nasal symptom severity, the incidence of sneezing and rhinorrhoea (measured by weighing paper tissues before and after use) were assessed at 10-min intervals for 30 min following allergen challenge. In addition, nasal obstruction was assessed by means of anterior rhinomanometry and acoustic rhinometry, immediately before allergen challenge and 30 min after. Albumin concentrations in nasal lavage fluid were also measured at these times (by radioimmunoassay) to permit assessment of any changes in vascular permeability. Patients were requested to assess the severity of sneezing, itching, rhinorrhoea and nasal congestion 30 min after allergen challenge by means of a Visual Analogue Scale (VAS; 0: absent, 100: very severe). Patients were also asked to report any adverse reactions to the investigator at the end of each treatment period.

Statistical analysis

An intention-to-treat analysis was performed. In addition to the individual parameters listed above, the maximum VAS score for symptoms of sneezing, itching and rhinorrhoea (SIR) and the mean total symptom score were calculated and analyzed. All intergroup differences were evaluated using the Mann-Whitney U-test. The non-parametric method of Koch (1972) for the analysis of a two-way cross-over trial was also performed.

RESULTS

Key demographic parameters for the 22 patients who participated in this study are summarized in Table 1.

All patients tested positive for grass pollen allergy, with 95% allergic to birch pollen and 55% to weeds. All patients were asymptomatic prior to allergen provocation.

Two patients were excluded from the efficacy analysis (uncooperative), however, data from all patients have been included in the safety analysis. Appropriate analyses did not reveal any significant residual effects at cross-over and consequently the data from both treatment periods have been combined.

Table 1. Patients' demographics.

number of patients:	20
male/female ratio:	15/5
age (years):	27.5
range:	19.0-41.0
weight (kg):	74.95
range:	51.0-108.0
height (cm):	178.25
range:	159.0-193.0

Objective assessments

The incidence of sneezing was significantly lower following treatment with levocabastine than with placebo (Figure 1), with a mean of 3.1 and 8.7 sneezes in the two groups, respectively, in the 30 min following allergen challenge ($p<0.001$). Rhinorrhoea was also found to be less severe following treatment with levocabastine (Figure 2), although intergroup differences did not

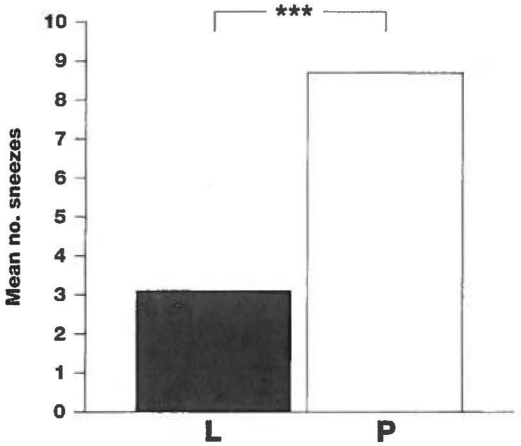

Figure 1. Severity of sneezing (L: levocabastine; P: placebo; ***: $p<0.001$).

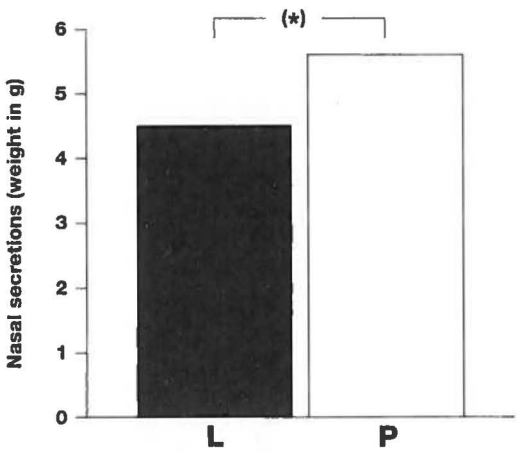

Figure 2. Severity of rhinorrhoea assessed by weight of nasal secretions (L: levocabastine; P: placebo; (*): 0.005<p<0.1).

attain statistical significance (0.05<p<0.1). The mean weight of nasal secretions during the 30-min period after allergen challenge was 4.5 g with levocabastine and 5.6 g with placebo. Rhinomanometry and acoustic rhinometry failed to reveal any significant intergroup differences. Similarly, there were no apparent differences in the albumin concentrations in nasal lavage fluid in the two treatment groups.

Subjective assessments

As shown in Table 2, patients' VAS ratings revealed that the severity of sneezing and nasal itching were significantly lower 30 min after allergen challenge in the levocabastine group as compared to placebo-treated controls ($p<0.001$ and $p<0.05$, respectively). A non-significant trend in favour of levocabastine was also apparent for rhinorrhoea ($0.05<p<0.1$). However, the severity of congestion did not differ significantly between the two treatment groups. Analysis of the maximum VAS score for symptoms of sneezing, itching and rhinorrhoea and the mean total symptom score also significantly favoured levocabastine ($p<0.01$ and $p<0.05$, respectively).

Table 2. Mean patients' VAS ratings of symptom severity (levocabastine *versus* placebo).

symptom	levocabastine	placebo
sneezing	19.7***	47.6
nasal itching	25.8*	46.4
rhinorrhoea	30.5(*)	39.2
nasal congestion	70.8	66.0
maximal SIR	42.9**	66.6
total symptoms	36.7*	49.8

SIR: sneezing, itching and rhinorrhoea
(*): 0.05<p<0.1; *: p<0.05; **: p<0.01; ***: p<0.001

Adverse events

Only two patients reported adverse events during the course of this study. One patient reported fatigue while on levocabastine, with another experiencing vesicular rash, facial oedema and urticaria during the wash-out period following treatment with levocabastine.

DISCUSSION

The results of this study demonstrate that levocabastine nasal spray provides fast and effective protection from nasal allergen provocation. Objective and subjective measures of treatment efficacy have revealed that topical antihistamines provide greater protection than placebo from all allergen-induced nasal symptoms, with the exception of nasal congestion, with a rapid onset of action. These findings are not unexpected and are in agreement with those of previous challenge studies (Kolly and Pecoud 1986; Palma-Carlos et al., 1988; Holmberg et al., 1989). Although nasal provocation tests have demonstrated that the majority of symptoms of allergic rhinitis are mediated by the action of histamine at H_1-receptor sites (Kirkegaard et al., 1983), it appears that other mediators may be involved in the pathogenesis of nasal congestion (Druce and Rutledge, 1990; Jankowski et al., 1993). The lack of effect of levocabastine on nasal obstruction, as determined by anterior rhinomanometry and acoustic rhinometry, is consistent with this concept. Treatment with intranasal levocabastine would generally be expected to have a greater effect on rhinorrhoea than seen in this study. Although a trend favouring levocabastine was apparent, intergroup differences just failed to attain statistical significance. The short interval between administration of study medication and allergen challenge may have influenced the results. With a longer interval, it is likely that the severity of rhinorrhoea would be significantly reduced. However, it is again possible that mediators other than histamine may also play a role in the production of allergen-induced nasal secretions (Druce and Rutledge, 1990; Jankowski et al., 1993). The high response rate associated with the use of a topical placebo should also be taken into consideration when evaluating the results of this study, as it is possible that this may have masked intergroup differences in therapeutic efficacy to some extent (Cornell, 1986). In a recent multicentre trial, levocabastine nasal spray administered twice daily for 4 weeks was significantly more effective than placebo for the treatment of all symptoms of seasonal allergic rhinitis, including nasal congestion (Dahl et al., 1995). Similarly, clinical experience in both adults and children available to date also demonstrates that topical levocabastine is at least as effective in the treatment of allergic rhinitis as the oral antihistamines, terfenadine and loratadine (Livostin Study Group, 1993; Søhoel, et al., 1993; Bahmer and Ruprecht, 1994; Swedish GP Allergy Team, 1994), and significantly superior to the topical mast-cell stabilizer, sodium cromoglycate (Palma-Carlos et al., 1991; Schata et al., 1991; Vermeulen and Mercer, 1994). Levocabastine nasal spray would also appear to be as effective as intranasal steroids in the relief of nasal symptoms, with the exception of nasal congestion (Bende and Pipkorn, 1987; Van de Heyning et al., 1988). The lack of apparent differences in albumin concentration in nasal lavage fluid during treatment with levocabastine as compared to placebo is also surprising. The available data clearly demonstrate that treatment with an H_1-receptor antagonist should significantly reduce albumin

levels following allergen challenge, presumably due to reduction of H_1-mediated increases in vascular permeability (Druce and Rutledge, 1990; Jankowski et al., 1993). It is possible that the timing of sampling was responsible for the lack of effect observed in this study. In the present study, levocabastine nasal spray was found to be well-tolerated.

In conclusion, levocabastine nasal spray provides effective protection from nasal allergen challenge with a rapid onset of action. Levocabastine would appear to be a valuable therapeutic approach in patients with allergic rhinitis.

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