

Onset and duration of action of levocabastine nasal spray in atopic patients under nasal challenge conditions

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Background: Although prior studies have documented the rapid onset of action of topical intranasal levocabastine (LEV), little is known about its duration of action under nasal challenge conditions.

Objectives: We sought to assess the onset and duration of action of escalating doses of LEV nasal spray by using a nasal allergen challenge (NAC) model.

Methods: Eighteen asymptomatic subjects with histories of seasonal allergic rhinitis were enrolled into a randomized, single-blind, placebo-controlled, dose-ranging crossover study. Each patient was randomly assigned to receive single doses of placebo and intranasal LEV 0.1, 0.2, and 0.4 mg during 2 parts of the study. In part 1 (onset of action), NAC consisted of a single dose of allergen administered 5 minutes after study drug treatment. In part 2 (duration of action), NAC consisted of increasing doses of allergen administered 0.5, 6, 12, and 24 hours on separate days after study drug treatment. Nasal symptom scores (NSSs) and nasal peak expiratory flow rates were measured after NAC in both phases of the study. Blood samples for plasma LEV concentrations were drawn after each NAC.

Results: In part 1, NSSs were significantly lower after the administration of LEV 0.1, 0.2, and 0.4 mg compared with placebo ($P < .05$). In part 2, NSSs were significantly lower after LEV doses of 0.2 and 0.4 mg compared with placebo at 0.5, 6, 12, and 24 hours after treatment ($P < .05$). The mean provocative dose of allergen required to elicit a positive nasal reaction was increased after LEV doses of 0.2 and 0.4 mg at 0.5, 6, and 12 hours after treatment. Nasal peak expiratory flow rates demonstrated no significant differences between LEV and placebo for any doses at any time points. Mean plasma LEV concentrations were low (range, 0 to 3.7 ng/mL) after all doses and did not correlate with drug efficacy.

Conclusions: Single intranasal LEV doses of 0.1, 0.2, and 0.4 mg significantly reduced the severity of the immediate nasal response to allergen when administered 5 minutes before NAC.

This protective effect against NAC continued to be present 24 hours after administration of LEV doses of 0.2 and 0.4 mg. Efficacy in blocking the reaction to NAC did not correlate with plasma LEV levels, suggesting that the inhibitory effect was due largely to topical rather than systemic effects. (*J Allergy Clin Immunol* 1999;103:574-80.)

Key words: Levocabastine, topical antihistamine, nasal allergen challenge, H_1 -receptor antagonist

Histamine plays a prominent role in the pathogenesis of allergic rhinitis and is particularly responsible for the sneezing, itching, and rhinorrhea that follow acute exposure to an allergen.¹ Although oral H_1 -receptor antagonists are used commonly for this prevalent condition, the onset of action of these agents is approximately 1 to 2 hours.²⁻⁴ Topical delivery of antihistamines directly to the nasal mucosa would theoretically allow for a more rapid onset of action and improve the therapeutic benefit of these drugs when used on an as-needed basis. Until recently, none of the available antihistamines possessed sufficient potency to allow for effective intranasal administration. Levocabastine (LEV) is a highly potent H_1 -receptor antagonist that was developed specifically as a topical formulation.⁵⁻⁷ Studies in the rat model of 48/80-induced lethality have demonstrated that LEV is approximately 15,000 times more potent than chlorpheniramine on a molar basis⁵ and that it exhibits antihistaminic activity at doses of less than 0.002 mg/kg.⁸ LEV is also highly specific for histamine H_1 -receptors,⁹ with no apparent anticholinergic, antiseroenergic, or antidopaminergic activity.¹⁰

Several previous studies of intranasal LEV have indicated a rapid onset of action in nasal provocation tests in patients with allergic rhinitis.¹¹⁻¹⁴ This study was designed to determine both the onset and duration of action of LEV by using a range of doses under nasal challenge conditions. In addition, we sought to correlate inhibition of nasal provocation reactions with plasma LEV concentrations to determine whether drug efficacy was attributable to topical or systemic effects.

METHODS

Subjects

Men and women between 18 and 55 years of age were chosen for this study. All subjects were required to have histories of at least 2

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Abbreviations used

LEV:	Levocabastine
NAC:	Nasal allergen challenge
NPEFR:	Nasal peak expiratory flow rate
NSS:	Nasal symptom score
PD5:	Provocative dose eliciting a symptom score ≥ 5

years of seasonal allergic rhinitis occurring during the late spring or summer months. All subjects had to have a positive skin prick test response (>3 mm wheal diameter) to full-strength Timothy grass and/or olive tree pollen extracts (100,000 allergy units [AU] per mL; ALK America, Milford, Conn) and a positive response to nasal allergen provocation at a dose greater than 50 AU but less than 6250 AU (see below). At the time of study, all patients were to be free of nasal symptoms and receiving no antiallergy medication. Subjects were also required to be in good general health, have no recent history of smoking, and have normal clinical laboratory values. Subjects were excluded if they had nasal pathology other than seasonal allergic rhinitis that resulted in significant nasal obstruction, had a recent history of viral upper respiratory infection or sinusitis 6 weeks before the study, or had received allergy immunotherapy during the previous 2 years. All subjects provided statements of informed consent before entry into the trial, and the protocol was approved by the Western Institutional Review Board (Olympia, Wash).

Nasal allergen challenge

Nasal allergen challenges (NACs) were performed with diluent (NaCl, 0.9%; albumin, 0.3%) followed by 5-fold increasing dilutions of Timothy grass or olive tree pollen extract (50, 250, 1250, 6250, and 31,250 AU). Each dose of challenge solution was administered as 2 sprays per nostril with a commercially available, hand-held atomizer used for topical nasal therapy (Nostilla nasal spray; Boehringer-Ingelheim, Ridgefield, Conn), which delivers 0.07 mL per actuation. Short-acting antihistamines were withheld for 3 days, loratadine for 5 days, and astemizole for 90 days before all nasal challenges.

Patients assessed the severity of their symptoms according to the scale developed by Bousquet et al¹⁵ as follows: sneezing (number of sneezes in 10 minutes): 3 or 4 = 1, greater than 5 = 2; rhinorrhea: runny nose = 1, postnasal drip = 1, both = 3; nasal blockage: breathes freely = 0, breathes with difficulty = 1, one nostril blocked = 2, both nostrils blocked = 3; pruritus: nose = 1, palate and/or ear = 1; conjunctivitis = 1 (total maximum score = 11).¹⁵ Nasal symptom scores (NSSs) were determined at baseline before NAC, 10 minutes after diluent, and 10 minutes after each dose of allergen. A positive response to challenge was defined as a score of 5 points or more after a single dose of allergen; this score has been shown to correlate significantly with the activation of mast cells and release of PGD₂ after NAC.¹⁵

Nasal patency was assessed during the challenge with a mini-Wright peak flow expiratory flow meter (Clement Clarke International, Ltd, London, England) fitted with a nasal adaptor. Nasal peak expiratory flow rates (NPEFRs) were measured in triplicate before NAC, 10 minutes after diluent, and 10 minutes after each allergen dose, and the highest value was recorded for subsequent analysis.

Study design

We used a single-blind, placebo-controlled, crossover design. Three active study treatments were evaluated: LEV 0.1 mg, 0.2 mg, and 0.4 mg (each at a concentration of 0.05 mg/mL). The study was done in a single-blind fashion because of the different number of sprays required to deliver the 3 LEV doses; however, the LEV 0.2

mg and placebo groups used the same number of sprays and were double blinded throughout the study. The study was performed during an asymptomatic period of the year.

Part 1 was designed to assess the onset of action of the study treatments. A single dose of treatment was administered at 8 AM and was followed 5 minutes later by a single-dose NAC, consisting of the cumulative dose of allergen previously shown to elicit a symptom score of 5 or more points. Ten minutes later, nasal symptoms and NPEFRs were measured. All 4 of the study treatments (placebo and LEV 0.1 mg, 0.2 mg, and 0.4 mg) were administered to all subjects in a randomized sequence at 7- to 10-day intervals. Each patient underwent a total of four NACs during part 1.

Part 2 was designed to assess the duration of action of the study treatments. A single treatment dose was given at 8 AM, and NAC was performed 0.5, 6, 12, or 24 hours after each treatment on separate days. Nasal challenges in part 2 consisted of multiple incremental doses of allergen, starting with 50 AU and followed by 5-fold increasing doses until a positive reaction was elicited. Each of the 4 time points constituted a separate cycle of testing, and all 4 of the study treatments were administered to all subjects in a randomized sequence during each cycle. All NACs were performed at 7- to 10-day intervals, with the exception of the 0.5- and 24-hour tests, which were performed on consecutive days. Each patient underwent a total of 16 allergen challenges during part 2.

Efficacy assessments

Evaluation of onset of action was based on differences in total NSS (sum of symptom scores for sneezing, rhinorrhea, blockage, pruritus, and conjunctivitis), major NSS (sum of symptom scores for sneezing and rhinorrhea), and NPEFR.

Evaluation of duration of action was based on differences in total NSS, major NSS, and NPEFR. Total and major NSSs were compared across treatment groups with the highest dose of allergen common to the 4 treatments in a given cycle, henceforth referred to as "the highest common dose of allergen."

Differences between treatment groups were also assessed by using the dose of allergen required to elicit a symptom score of 5 or more points (provocative dose 5 [PD5]). The PD5 was converted to an ordinal scale by means of a log transformation (log base 5[AU/10]).

Plasma drug concentrations

Blood samples for determination of plasma LEV concentrations were obtained 15 minutes after administration of the LEV dose during part 1 and immediately before NAC (at 0.5, 6, 12, and 24 hours after the LEV dose) during part 2. Plasma LEV concentrations were determined by RIA (lower limit of quantification of 0.2 ng/mL plasma).¹⁶

Statistics

A 4-treatment, 4-period Williams' design was used for this study. A minimum of 16 subjects (4 per treatment sequence) was considered sufficient to provide interpretable results. All tests were made at the .05 level of significance. Treatment sequences were compared with respect to categorical demographic variables by using the Cochran-Mantel-Haenszel test for general association. For continuous demographic variables (age and vital signs), a 1-way ANOVA model, with treatment sequence as the effect, was used.

For efficacy assessments, separate analyses were performed for each cycle; only subjects who completed all 4 periods were included in the analysis of a specific cycle. Analyses of total NSS, major NSS, and NPEFR in parts 1 and 2 were performed with ANOVA, including effects for treatment sequence, subject (within sequence), period, and treatment.

TABLE I. Demographic characteristics of the study population

No of patients	18
Mean age (SD) (y)	31.3 (6.52)
Mean height (SD) (in)	68.7 (3.58)
Mean weight (SD) (lb)	157.1 (25.94)
Race (%)	
White	88.9
Black	5.6
Hispanic	5.6
Sex (%)	
Male	66.7
Female	33.3

Dunnett's test for comparing multiple treatments to a single control was used to determine the statistical significance of the simultaneous comparisons of each LEV dose with placebo (2-sided test at a .05 level of significance). Fisher's least significant difference procedure was used for additional comparisons among the LEV dose groups. Descriptive statistics of prediluent and postdiluent values for total NSS, major NSS, and NPEFR in each cycle were also calculated.

Descriptive statistics of plasma LEV concentrations at each time point were calculated for each cycle, and mean plasma LEV concentrations were plotted against time after dose for each cycle. The relationships between efficacy measures and plasma LEV concentrations were assessed graphically.

RESULTS

Eighteen subjects (12 men and 6 women) with a mean age of 31 years were enrolled into the study. The demographic variables for the study population are summarized in Table I. There were no significant differences among the treatment sequences for any demographic variable. One patient discontinued the study early because of an adverse event (acute sinusitis not related to study drug), and one discontinued because of an intercurrent illness (upper respiratory tract infection of moderate severity).

Part 1: Onset of action

All patients had total and major NSSs of 0 at all prediluent and postdiluent assessments. At 15 minutes after dose administration, all doses of LEV significantly ($P \leq .023$) reduced total NSS compared with placebo, and doses of 0.2 mg and 0.4 mg significantly ($P = .01$) reduced major NSS compared with placebo (Fig 1). Although the numerical values of NPEFR were higher with LEV doses of 0.2 and 0.4 mg than for placebo, these differences did not reach statistical significance.

Part 2: Duration of action

Mean total and major NSSs at the highest common dose of allergen were evaluated for each nasal challenge. Prediluent and postdiluent symptom scores were universally low for all treatment groups at 0.5, 6, and 12 hours. After the dose of 0.1 mg, mean total and major NSSs were significantly ($P \leq .014$) lower compared with placebo at the 30-minute and 6-hour challenges, whereas

doses of 0.2 and 0.4 mg significantly ($P \leq .04$) reduced mean total and major NSSs at all challenge time points (Figs 2 and 3). There were no significant differences in NPEFR between any of the LEV doses and placebo at any of the 4 time points.

Prechallenge symptom scores were highest in the 24-hour challenge. Because there was no washout period between the 0.5- and 24-hour challenges, residual effects from the previous day's challenge appear to have been present at the 24-hour challenge. To adjust for the higher postdiluent scores observed at the 24-hour challenge, the analysis at 24 hours was repeated by using the postdiluent assessments as a covariate. After adjusting for postdiluent scores, the LEV dose of 0.4 mg was not significantly better than placebo for mean total symptom scores.

LEV doses of 0.2 and 0.4 mg increased the mean allergen PD₅ at 0.5, 6, and 12 hours, and a dose of 0.1 mg increased the mean allergen PD₅ at 0.5 and 6 hours (Fig 4).

Plasma drug concentrations

Mean plasma LEV concentrations demonstrated a dose-related relationship that was linear beginning 1 hour after drug administration (Fig 5). There was no correlation between plasma LEV concentrations and inhibition of the response to nasal challenge 15 minutes after drug administration. All 3 LEV doses were more effective than placebo 15 minutes after administration, despite very low plasma drug concentrations at this time point. There was no clear relationship between mean plasma LEV concentrations and drug efficacy at the 6-, 12-, and 24-hour time points. Although all 3 LEV doses had similar effects at 30 minutes and 6 hours after administration, plasma concentrations were higher at 6 hours than at 30 minutes for each dose. Similarly, although symptom scores increased from 6 to 12 hours after dose administration (for the LEV 0.1 mg dose), plasma concentrations were equivalent at both time points.

Safety

Single doses of intranasal LEV were well tolerated. Adverse events were reported by 8 of 17 patients receiving placebo (47%), 8 of 18 patients (44%) receiving LEV 0.1 mg, 7 of 17 patients (41%) receiving LEV 0.2 mg, and 5 of 17 patients (29%) receiving LEV 0.4 mg. Headache was the most commonly reported adverse event. Adverse events reported by at least 2 or more patients are shown in Table II. All adverse events were mild or moderate in severity and similar after all treatments; none were classified as drug related. Somnolence was reported in 1 patient after receiving LEV 0.1 mg and in another after receiving 0.2 mg, although none reported this effect after receiving the 0.4-mg dose.

DISCUSSION

The results of this study demonstrate that LEV nasal spray provides rapid, effective protection against NAC that persists for up to 24 hours. Our results are in agreement with those of other investigators who have demon-

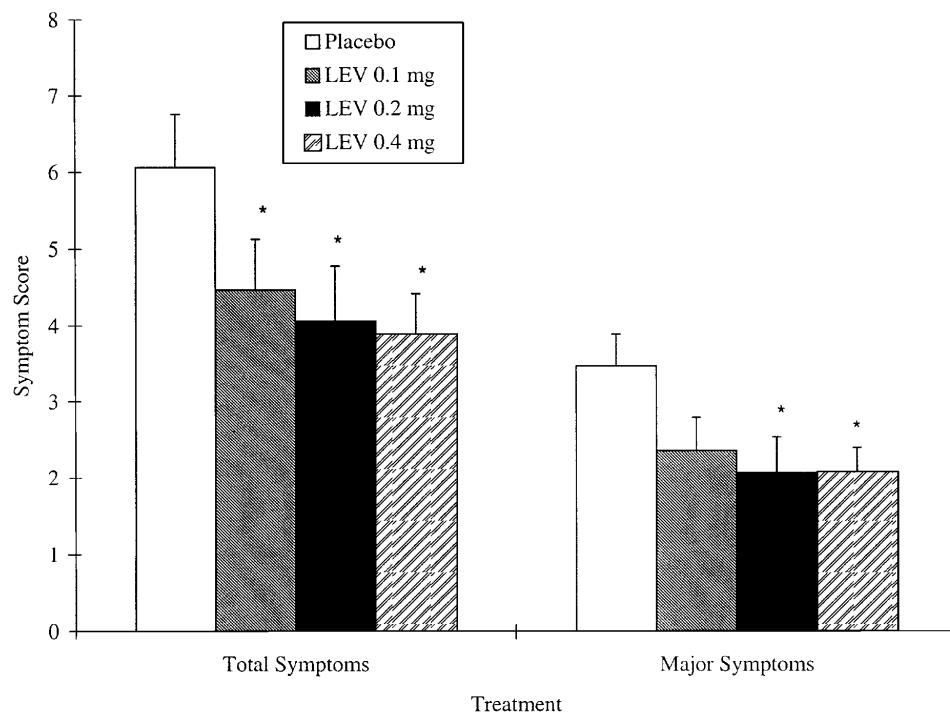


FIG 1. Onset of protective effect. Mean ($\pm$ SD) total and major NSSs 15 minutes after LEV administration and allergen challenge. *Symptom scores were significantly lower than placebo ($P \leq .05$).

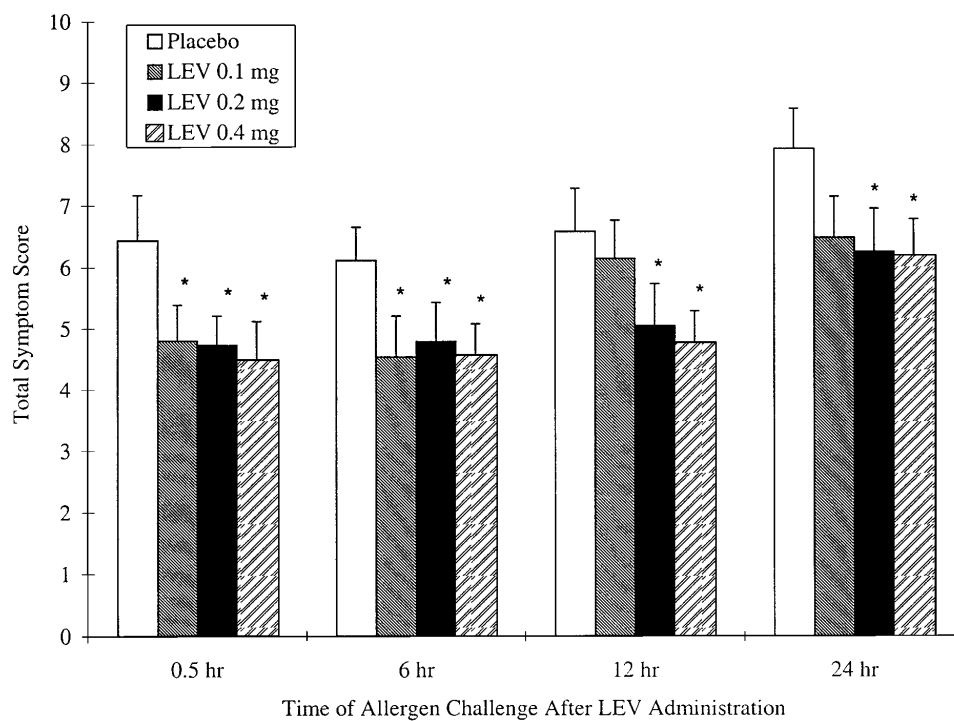


FIG 2. Duration of action. Mean ($\pm$ SD) total NSS after LEV administration and allergen challenge. *Symptom scores were significantly lower than placebo ($P \leq .05$).

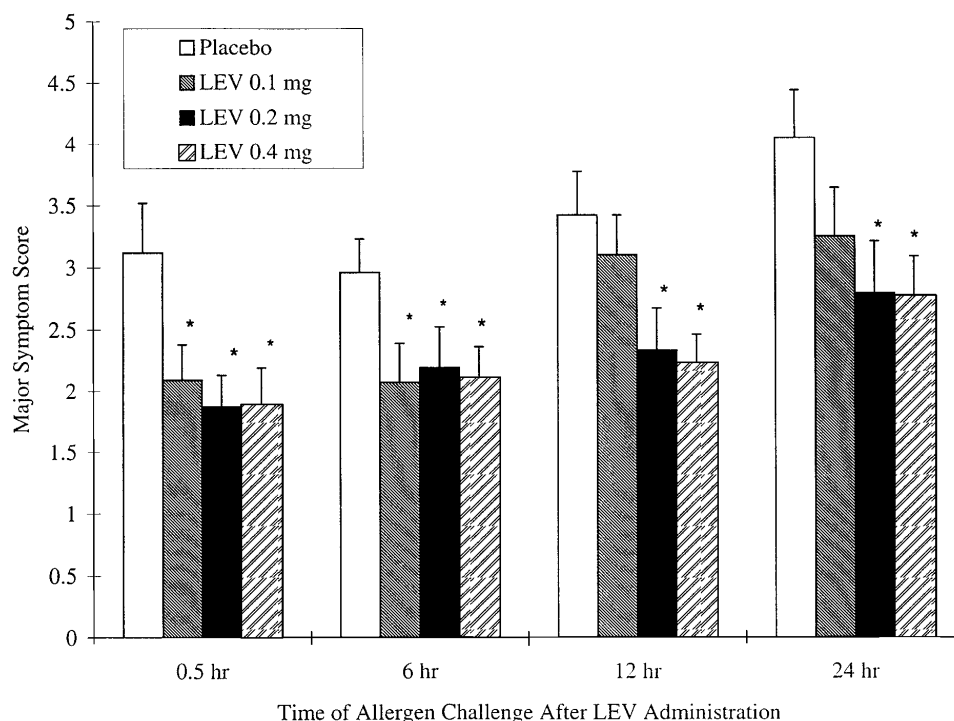


FIG 3. Duration of action. Mean ($\pm$ SD) major NSS after LEV administration and allergen challenge. *Symptom scores were significantly lower than placebo ($P \leq .05$).

TABLE II. Adverse experiences reported by 2 or more patients after any treatment

	Placebo	LEV 0.1 mg	LEV 0.2 mg	LEV 0.4 mg
Headache	2 (12%)	2 (11%)	3 (18%)	0
Chest pain	1 (6%)	0	2 (12%)	2 (12%)
URI	1 (6%)	0	2 (12%)	1 (6%)
Dizziness	0	0	2 (12%)	0
Syncope	1 (6%)	2 (11%)	0	0

URI, Upper respiratory tract infection.

strated rapid-onset protection of intranasal LEV against nasal provocation with allergen.¹¹⁻¹⁴ Previous nasal challenge studies, however, have not carefully documented the duration of the protective effect of topical LEV. Although clinical trials with LEV have shown optimal control of nasal symptoms with twice daily dosing,¹⁷⁻¹⁹ our data suggest that some patients may obtain adequate relief using intranasal LEV once per day.

The results from the current study also demonstrate that intranasal LEV significantly reduces the total symptom score after allergen challenge but does not have any significant effects on objective measures of nasal obstruction (ie, NPEFR). Although one recent clinical trial demonstrated that 4 weeks of treatment with LEV nasal spray significantly reduced nasal congestion,¹⁸

most single-dose and steady-state studies of antihistamines have shown no significant effects on subjective or objective measures of nasal obstruction.²⁰ Although most symptoms of rhinitis (rhinorrhea, pruritis, and sneezing) are mediated at least in part by the action of histamine at H_1 -receptor sites,²¹ the above studies suggest that other cell-derived products are most likely responsible for inducing nasal airway obstruction.

Plasma LEV concentrations were extremely low (<1 ng/mL) 15 minutes after drug administration, suggesting that the rapid onset of action of intranasal LEV results primarily from its topical effect on nasal tissue. Although plasma LEV concentrations increased significantly at the 6-hour time point and beyond, there was no apparent relationship between drug concentrations and responses to nasal allergen challenge at 6, 12, or 24 hours.

Our experimental design allowed us to study a wide range of drug doses across multiple time points by using a relevant model of allergic disease. The study design did not allow us to display complete dose-response curves (allergen dose vs symptom score) for the data from part II because allergen challenges were stopped when patients achieved a significant nasal response. Nonetheless, analysis of the "highest common dose" allowed us to make adequate comparisons of the LEV doses and placebo at each time point tested. Although the interval between each allergen challenge was only 7 to 10 days

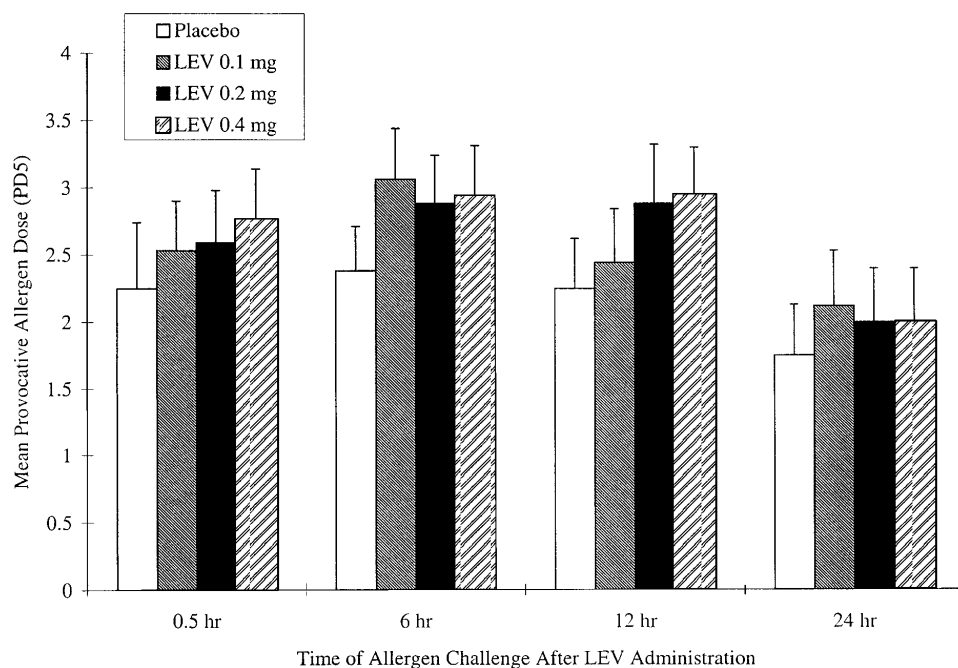


FIG 4. Mean provocative dose of allergen that elicited a symptom score of 5 or greater (*PD5*) expressed as $\log_5(\text{AU}/10)$.

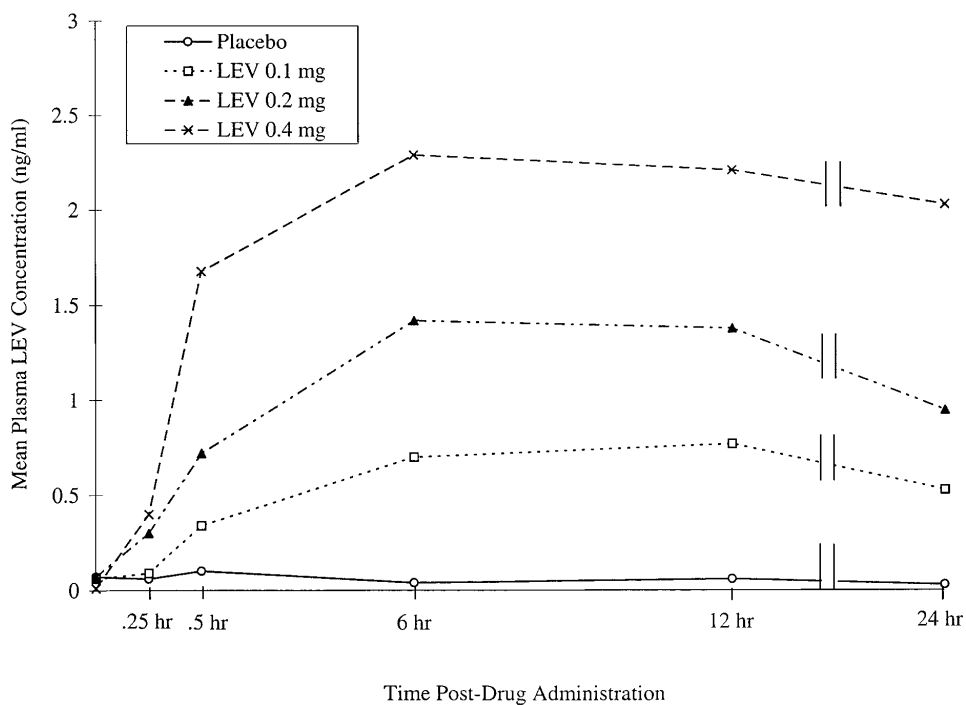


FIG 5. Mean plasma LEV concentrations in treatment sequence 3.

(with the exception of the 30-minute and 24-hour challenges), there were no significant carry-over effects noted.

In this study adverse events reported with single intranasal doses of LEV 0.1, 0.2, and 0.4 mg were comparable among the doses and similar to placebo. Headache was the most common adverse event reported, but no adverse events were considered drug related. Adverse events in other intranasal LEV nasal challenge studies have been infrequent. Extensive clinical investigations suggest that topical LEV is well tolerated in the treatment of allergic rhinitis.¹⁷⁻¹⁹

Intranasal LEV effectively reduced the nasal response to allergen provocation. This effect occurred rapidly and lasted up to 24 hours with both the 0.2 and 0.4 mg doses. The results of this study are consistent with clinical trials that have previously established the effectiveness and safety of twice daily dosing with intranasal LEV. As a potent and specific topical antihistamine with minimal systemic effects, LEV will provide a useful alternative to existing therapies for seasonal allergic rhinitis.

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