

Original article

Effect of loteprednol etabonate nasal spray suspension on seasonal allergic rhinitis assessed by allergen challenge in an environmental exposure unit

Background: Loteprednol etabonate (LE) is a novel soft steroid that was designed to improve the benefit/risk ratio of topical corticosteroid therapy. This study assesses the clinical efficacy and safety of three different doses of LE nasal spray in seasonal allergic rhinitis (SAR).

Methods: In this single-center, double-blind, placebo-controlled, parallel-group trial 165 subjects with SAR to grass pollen received daily single doses of either 100, 200, 400 µg LE nasal spray, or placebo for 14 days. The patients underwent three 4-h allergen challenges with grass pollen in an environmental exposure unit at a screening visit (baseline) and on days 7 and 14 of treatment. Standardized nasal symptom scores were obtained every 20 min. Nasal flow, nasal secretions, and FEV₁ were measured every hour during allergen challenges.

Results: After 14 days of treatment, patients who received 400 µg LE had significantly lower total nasal symptom scores compared with those receiving placebo ($P = 0.007$). LE400 reduced rhinorrhea, nasal congestion, nasal itching, the amount of nasal secretions, and improved nasal flow as compared with placebo ($P < 0.05$). LE100 and LE200 were not significantly different from placebo. All treatments were well tolerated.

Conclusions: Loteprednol 400 µg once daily is superior to placebo and the only effective dose tested in improving nasal symptoms and objective parameters in patients with SAR.

**N. Krug¹, J. M. Hohlfeld¹,
H. Geldmacher¹, M. Larbig¹,
R. Heermann², N. LaVallee³,
D. T. Nguyen⁴, U. Petzold⁴,
R. Hermann⁴**

¹Fraunhofer Institute of Toxicology and Experimental Medicine, Hannover, Germany; ²Department of Otolaryngology, Hannover Medical School, Hannover, Germany; ³PROMETRIKA, LLC, Cambridge, MA, USA; ⁴VIATRIS GmbH & Co. KG, Clinical Development, Frankfurt, Germany

Key words: allergen challenge; environmental exposure unit; grass pollen; loteprednol etabonate; nasal corticosteroids; seasonal allergic rhinitis.

Norbert Krug
Fraunhofer Institute of Toxicology and Experimental Medicine
Nikolai-Fuchs-Str.1
30625 Hannover
Germany

Accepted for publication 7 June 2004

Seasonal allergic rhinitis (SAR), now classified as intermittent according to ARIA guidelines (1) affects about 20% of the United States and European population and has the greatest prevalence of any respiratory disease (2). Intranasal glucocorticosteroids (GCS) are considered to be the most effective pharmacologic treatment for allergic rhinitis (3, 4). Because of their local inhibition of mucosal inflammation, they relieve symptoms with a relatively low risk of systemic side effects, such as hypothalamic pituitary adrenal axis or growth suppression (5). In recent years, new GCS such as budesonide, fluticasone propionate, and mometasone furoate have been developed that offer greater topical activity with lower systemic exposure. In particular, fluticasone propionate and mometasone furoate demonstrated low bioavailabil-

ity, longer retention time in the nasal tissue, and almost complete hepatic first-pass elimination of the dose fraction swallowed (3). However, fluticasone, for example, still has a systemic availability of 2–5% (6, 7) and has been reported to have a suppressive effect on adrenal function (8) and serum osteocalcin (9). Thus, concerns about the general safety of inhaled and intranasal GCS remain (10).

An innovative approach to decrease systemic side effects of GCS is the development of 'soft steroids' (11). In contrast to traditional GCS, 'soft steroids' are designed to be rapidly inactivated once absorbed from the site of action into the systemic circulation. Loteprednol etabonate (LE), one of the first representatives of this class of drugs, was synthesized by chemically modifying an inactive metabolite of prednisolone (12, 13). The resulting LE molecule showed topical GCS action comparable with that of betamethasone but was nearly devoid of activity in studies that evaluated systemic drug potency (14–16). As LE, in contrast to other GCS, had no effect on

Abbreviations: FEV₁, forced expiratory volume in 1 s; GCS, glucocorticosteroids; LE, loteprednol etabonate; PEF, peak expiratory flow; PLA, placebo; SAR, seasonal allergic rhinitis; TNSS, total nasal symptom score.

intraocular pressure, it is currently marketed for topical treatment of inflammatory eye disorders and seasonal allergic conjunctivitis. Preclinical studies in rodent models of allergic rhinitis showed reduced vascular permeability and rhinorrhea after intranasal administration of LE (17). Thus, a randomized, placebo-controlled, double-blind, single-center trial was conducted to compare efficacy and safety of three doses of loteprednol nasal spray (100, 200, 400 µg) to placebo during allergen provocation in an environmental exposure unit.

Methods

Subjects

A total of 165 adult subjects (aged 18–65 years) were recruited out of tree and grass pollen season. **Inclusion criteria:** history of SAR due to grass pollen for ≥ 2 years, asymptomatic or with mild symptoms at the time of inclusion and before each allergen challenge with a total nasal symptom score (TNSS) of ≤ 3 with a score for each symptom < 2 (TNSS defined below), positive skin prick test to grass pollen within 12 months of enrollment, and a TNSS of at least 6 of 12 on at least two assessments during allergen challenge at the screening visit. **Exclusion criteria:** structural nasal defect, large nasal polyps (excluded by nasal endoscopy), infection of the upper airways 2 weeks before study entry, sinusitis, asthma, with the exception of mild intermittent asthma, pregnancy, breastfeeding, and use of any medication that could affect the study outcome. For antihistamines, steroids, cromolyn, and antidepressants the washout periods were 12–96 h, 4 weeks, 2 weeks, and 2 weeks, respectively.

Written consent of the study approved by the Hannover Medical School Ethics Committee was given by each subject. All recommendations of the Division of Pulmonary Drug Products, Center of Drug Evaluation and Research, US-FDA were adopted.

Study design

This was a randomized, placebo-controlled, double-blind, single-center trial, in which 165 adult patients with SAR received LE nasal spray suspension or matching placebo for 14 days. The primary objective was to assess the clinical efficacy of three different once-daily doses of LE nasal spray (100, 200, or 400 µg) to determine the most appropriate dose for further clinical development. The secondary objective was to evaluate the dose-related safety of LE nasal spray. The participants administered each dose of LE or placebo from day 1 to day 14 at the study center (spray, two puffs, before 11 AM). Administration occurred at the same time every day under the surveillance of clinical staff. The participants were exposed to grass pollen (4000 grains/m³ air of orchard grass, *Dactylis glomerata*; Biopol Laboratory Inc., Spokane, WA, USA) in the environmental exposure unit, which has previously been described (18), for 4 h at a screening visit (baseline) and starting 2 h after treatment on days 7 and 14 (Fig. 1). During this study temperature (mean $\pm$ SD; $20.5 \pm 0.2^\circ\text{C}$), relative humidity ($39.8 \pm 0.1\%$) and pollen count (4027 ± 368 grains/m³) were kept constant.

Assessment of efficacy

Nasal symptoms (rhinorrhea, nasal congestion, sneezing, and nasal itching) and non-nasal symptoms (eye itching, eye tearing,

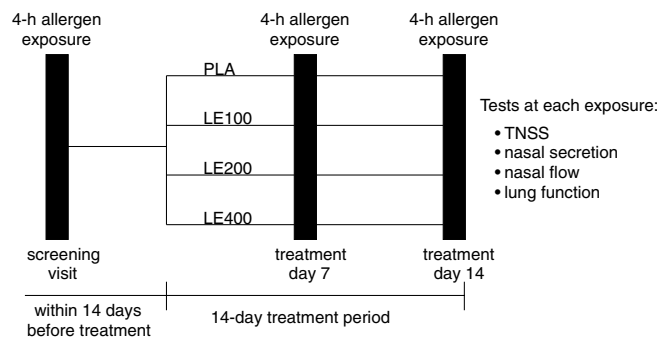


Figure 1. Study design. PLA, placebo; LE, loteprednol; TNSS, total nasal symptom score.

and ear/palate itching) were self-assessed before and every 20 min throughout the allergen challenge. For each symptom the subjects recorded scores on diary sheets according to the following 4-point severity scale: 0 = none; 1 = mild; 2 = moderate; 3 = severe. TNSS was calculated by adding the scores of the four individual nasal symptoms.

Nasal secretion was collected using paper tissues. Used and unused tissues were saved in a plastic bag by each participant, collected every 60 min, and weighed. The patients were provided with a new package after each tissue collection.

The nasal flow rate was measured before challenge and every 60 min during allergen exposure using rhinomanometry (Jaeger Master Scope Rhino; Jaeger GmbH, Wuerzburg, Germany). Flow rates at 150 Pa were separately obtained for the right and left nostrils (cm³/s). The sum of the flow rates of both nostrils was calculated from the two measurements.

Assessment of safety

Physical and nasal examination and clinical laboratory tests were conducted at the screening visit and at a final visit. Vital signs were measured at the screening visit, and on days 1, 7, and 14. At each day during the treatment period subjects were asked by study personnel whether or not they had experienced any adverse event or deterioration in their well-being or medical condition since the start of treatment. Any use of concomitant medication was recorded.

Lung function (FEV₁) was measured according to standard procedures (19) before and every 60 min during allergen challenge using spirometry (Jaeger Masterscope; Jaeger GmbH).

Participants measured their peak expiratory flow rate (PEF) using a Mini-Wright peak flow meter (Clement Clarke, Essex, UK) before exposure, 1 h after exposure, and every 2 h until bedtime. Values were recorded on diary sheets.

Statistical analysis

The primary predefined efficacy endpoint of the study was the average TNSS score during the last 2 h of allergen challenge on day 14.

Treatment group means were compared overall using analysis of variance (ANOVA). Paired treatment mean comparisons were performed using two-sided independent samples *t*-tests. Values of $P < 0.05$ were considered to be significant for both tests. Statistics were calculated using SAS® Proprietary Software (SAS Institute, Inc., Cary, NC, USA).

Results

Study subjects

Table 1 demonstrates that the loteprednol and placebo groups were comparable with regard to sex, age, body weight, and duration of SAR.

Assessment of efficacy

Table 2 shows the mean TNSS during the last 2 h of allergen exposure at the screening visit (baseline), day 7,

Table 1. Demographic and baseline characteristics

Variable	PLA	LE100	LE200	LE400
Subjects (n)				
Screening (n = 165)	41	41	42	41
Day 7 (n = 164)	40	41	42	41
Day 14 (n = 158)	38	40	42	38
Sex, n (%)				
Male	23 (56.1)	23 (56.1)	18 (42.9)	20 (48.8)
Female	18 (43.9)	18 (43.9)	24 (57.1)	21 (51.2)
Age (years)				
Mean $\pm$ SD	25.8 $\pm$ 6.2	25.3 $\pm$ 4.9	26.8 $\pm$ 6.1	27.6 $\pm$ 7.0
Range	18–45	19–47	19–47	20–52
Body weight (kg)				
Mean $\pm$ SD	71.8 $\pm$ 11.0	74.4 $\pm$ 15.7	71.0 $\pm$ 14.3	74.2 $\pm$ 15.1
Range	48–94	46–115	51–104	52–113
Duration of SAR to grass pollen (years)				
Mean $\pm$ SD	14.8 $\pm$ 6.8	15.4 $\pm$ 6.7	13.9 $\pm$ 7.9	15.8 $\pm$ 9.1
Range	4–30	3–34	3–33	4–43

PLA, placebo; LE, loteprednol; SD, standard deviation.

Table 2. Average symptom scores during the last 2 h of allergen challenge assessed by patients, mean $\pm$ SD

Day	PLA	LE100	LE200	LE400
TNSS				
Screening	6.6 $\pm$ 1.6	6.3 $\pm$ 1.5	6.5 $\pm$ 1.3	6.4 $\pm$ 1.4
Day 7	5.9 $\pm$ 2.1	5.7 $\pm$ 1.6	5.2 $\pm$ 1.7	5.2 $\pm$ 1.9
Day 14 (* <i>P</i> = 0.038)	5.7 $\pm$ 2.3	5.5 $\pm$ 1.8	5.1 $\pm$ 1.8	4.5 $\pm$ 1.8 († <i>P</i> = 0.007; ‡ <i>P</i> = 0.025)
Rhinorrhea				
Screening	1.9 $\pm$ 0.5	1.7 $\pm$ 0.6	1.7 $\pm$ 0.5	1.7 $\pm$ 0.6
Day 7	1.7 $\pm$ 0.6	1.5 $\pm$ 0.5	1.4 $\pm$ 0.6 († <i>P</i> = 0.012)	1.5 $\pm$ 0.6
Day 14 (* <i>P</i> = 0.004)	1.7 $\pm$ 0.6	1.5 $\pm$ 0.5	1.3 $\pm$ 0.5 († <i>P</i> = 0.013)	1.2 $\pm$ 0.6 († <i>P</i> = 0.001; ‡ <i>P</i> = 0.021)
Nasal congestion				
Screening	2.1 $\pm$ 0.6	2.0 $\pm$ 0.4	2.0 $\pm$ 0.6	2.1 $\pm$ 0.6
Day 7	1.8 $\pm$ 0.6	1.8 $\pm$ 0.5	1.6 $\pm$ 0.5	1.7 $\pm$ 0.8
Day 14	1.8 $\pm$ 0.7	1.7 $\pm$ 0.6	1.6 $\pm$ 0.6	1.5 $\pm$ 0.7 († <i>P</i> = 0.039)
Sneezing				
Screening	1.1 $\pm$ 0.6	1.1 $\pm$ 0.6	1.3 $\pm$ 0.5	1.2 $\pm$ 0.5
Day 7	1.1 $\pm$ 0.8	1.1 $\pm$ 0.7	1.0 $\pm$ 0.5	0.9 $\pm$ 0.5
Day 14	1.0 $\pm$ 0.7	1.1 $\pm$ 0.6	1.0 $\pm$ 0.6	0.8 $\pm$ 0.6
Nasal itching				
Screening	1.5 $\pm$ 0.6	1.5 $\pm$ 0.6	1.6 $\pm$ 0.7	1.4 $\pm$ 0.5
Day 7	1.3 $\pm$ 0.7	1.2 $\pm$ 0.7	1.3 $\pm$ 0.7	1.2 $\pm$ 0.6
Day 14	1.3 $\pm$ 0.8	1.2 $\pm$ 0.6	1.2 $\pm$ 0.7	1.0 $\pm$ 0.5 († <i>P</i> = 0.045)

PLA, placebo; LE, loteprednol; TNSS, total nasal symptom score; SD, standard deviation. *P*-values are given next to the corresponding means.

*Significant overall treatment effect, ANOVA.

†Significant paired treatment difference to PLA group, Student's *t*-test.

‡Significant paired treatment difference to LE100 group, Student's *t*-test.

and day 14 for all treatment groups. A significant overall effect of treatment was observed on day 14 (*P* = 0.038). Only the participants of the LE400 group had significantly lower mean TNSS than those in the placebo or LE100 group (*P* = 0.007 and *P* = 0.025, respectively). Figure 2 shows the mean TNSS over the entire course of the 4-h allergen challenge of the LE400 and placebo groups. When individual nasal symptoms were evaluated severity scores for rhinorrhea, nasal congestion, and nasal itching were significantly lower on day 14 for subjects treated with 400 μ g loteprednol than for those treated with placebo (Table 2). Rhinorrhea scores were also significantly lower in the LE400 group in comparison with the LE100 group. There were no significant differences in non-nasal symptom severity scores (eye itching, eye tearing, and ear/palate itching) in participants treated with any LE dose compared with placebo (data not shown).

Consistent with changes in the TNSS the objective parameters nasal secretion and nasal flow rate were significantly different only between the LE400 and the placebo group on day 14 (Table 3). Figure 3 shows the mean nasal flow rates over the entire course of the 4-h allergen challenge of the LE400 and placebo groups.

Assessment of safety

Treatment emergent adverse events did not occur more frequently in the LE groups than in the placebo group (PLA 58.5%, LE100 68.3%, LE200 57.1%, and LE400 46.3% of subjects experienced at least one adverse event)

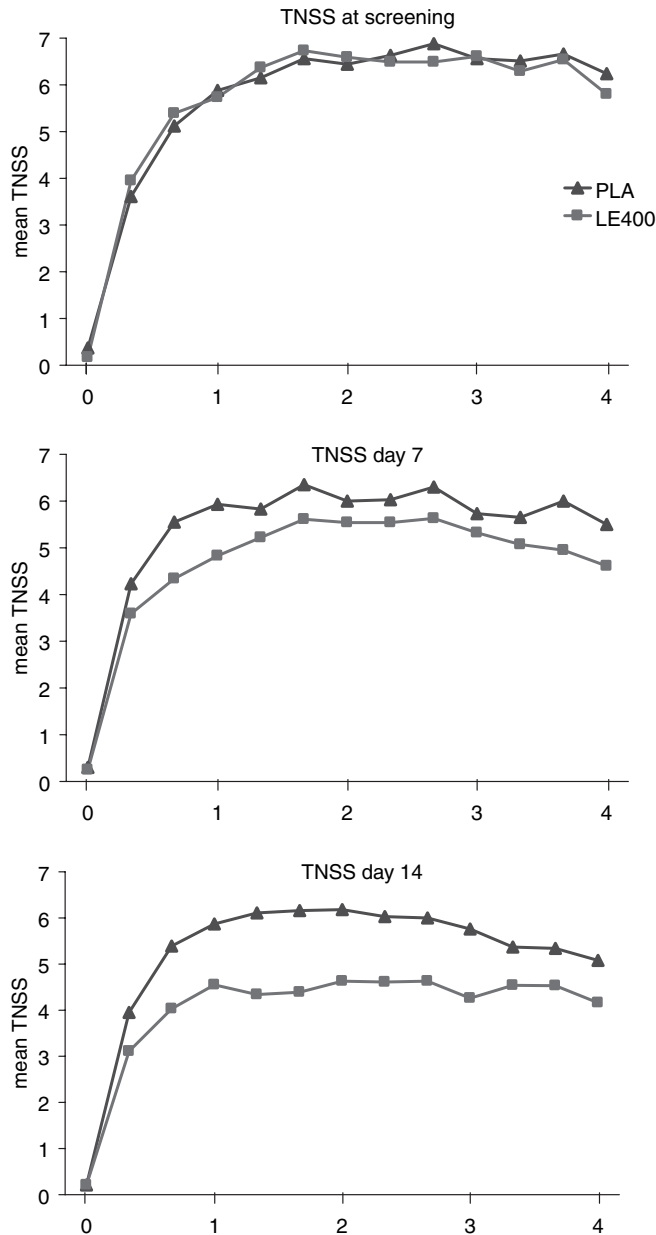


Figure 2. Loteprednol treatment improved total nasal symptom score (TNSS). Mean TNSS over time are shown for PLA and LE400 at the screening visit, day 7, and day 14. Rhinorrhea, nasal congestion, sneezing, and nasal itching were self-assessed before and every 20 min during the allergen challenge in the environmental exposure unit according to a 4-point severity scale (0 = none; 1 = mild; 2 = moderate; 3 = severe). The TNSS was calculated by adding the four nasal symptom severity scores. PLA, placebo; LE, loteprednol.

and were mainly related to the allergen challenge. Serious adverse events did not occur in any group. LE nasal spray neither had a clinically relevant effect on lung function, vital signs, nor on the results of laboratory tests, or physical and nasal examinations.

Table 3. Effect of treatment on nasal secretion and nasal flow rate during 4 hour allergen challenge, mean $\pm$ SD

Day	PLA	LE100	LE200	LE400
Average nasal secretion (g/h)				
Screening	6.8 $\pm$ 4.4	6.8 $\pm$ 3.8	7.1 $\pm$ 4.4	6.8 $\pm$ 4.5
Day 7	8.1 $\pm$ 4.6	7.6 $\pm$ 3.6	7.0 $\pm$ 4.4	6.6 $\pm$ 4.7
Day 14	8.7 $\pm$ 4.7	8.2 $\pm$ 3.2	7.4 $\pm$ 5.0	6.4 $\pm$ 4.7
(* <i>P</i> = 0.023)				
Average nasal flow rate (cm ³ /s)				
Screening	279 $\pm$ 177	249 $\pm$ 167	257 $\pm$ 151	303 $\pm$ 183
Day 7	300 $\pm$ 170	276 $\pm$ 166	288 $\pm$ 148	338 $\pm$ 200
Day 14	263 $\pm$ 166	304 $\pm$ 176	281 $\pm$ 157	349 $\pm$ 161
(* <i>P</i> = 0.024)				

PLA, placebo; LE, loteprednol; SD, standard deviation. The *P*-values are given below the corresponding means.

*Significant paired treatment difference to PLA group, Student's *t*-test.

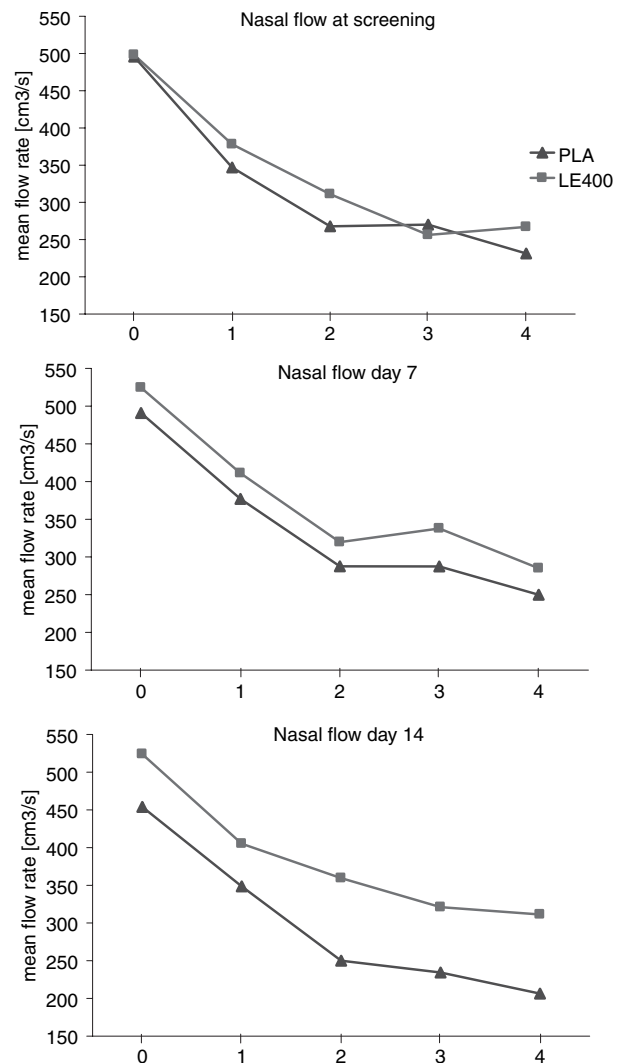


Figure 3. Improvement of nasal flow rate after loteprednol treatment. Mean nasal flow rates over time are shown for PLA and LE400 at the screening visit, day 7, and day 14. The nasal flow rate was measured before challenge and then every 60 min during the exposures. PLA, placebo; LE, loteprednol.

Discussion

In this randomized, placebo-controlled, double-blind, single-center study the dose-related efficacy and safety of LE nasal spray, a novel GCS, were assessed in patients with SAR. This was done by repeated allergen provocations in an environmental exposure unit, which is a specially designed challenge room that ensures a highly controlled and standardized aeroallergen exposure (18).

In our study a significant treatment effect regarding the primary efficacy variable TNSS was detectable after 14 days of treatment with loteprednol. Paired comparisons showed that patients who received 400 µg LE had significantly lower TNSS compared with those who received placebo. This was also true for the individual symptoms rhinorrhea, nasal congestion, and nasal itching. Improvement in subjective parameters was supported by objective measurements, namely nasal secretion and nasal flow rate. Both improved significantly after 14 days of treatment with LE400 nasal spray compared with placebo. In the placebo group, there was an increase of nasal secretion after allergen challenge at day 7 and day 14 compared with the screening visit. This phenomenon is most likely due to a priming effect that has previously been reported after repeated allergen exposures (20–22). This priming effect was prevented in the

LE400 group and it was not observed for TNSS and nasal flow.

Like other modern nasal GCS, LE nasal spray did not cause notable drug-related adverse events or any serious adverse events. The incidence of adverse events in the present study did not show any dose-relationship and was not considered different between LE- and placebo-treated patients. Furthermore, most adverse events reported were assessed as related to the procedure of allergen challenge rather than to the treatments. Similar adverse event patterns have been reported in studies with other nasal steroids (5).

In conclusion, this allergen challenge study in subjects with SAR demonstrated that loteprednol 400 µg once daily was superior to placebo and the only effective dose tested in improving nasal symptoms and objective parameters of nasal secretion and nasal obstruction. Based on the data from our study it appears to be the proper dose for further characterization of this GCS treatment of SAR in future clinical trials.

Acknowledgments

The study was supported by ASTA Medica AG (now VIATRIS GmbH & Co. KG), Frankfurt/Main, Germany. The help of Birgit Luettig, PhD, in writing the manuscript, is gratefully acknowledged.

References

1. Bousquet J, van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;**108**:S147–S334.
2. Schoenwetter WF. Allergic rhinitis: epidemiology and natural history. *Allergy Asthma Proc* 2000;**21**:1–6.
3. Trangsrud AJ, Whitaker AL, Small RE. Intranasal corticosteroids for allergic rhinitis. *Pharmacotherapy* 2002;**22**:1458–1467.
4. Dykewicz MS, Fineman S, Skoner DP, Nicklas R, Lee R, Blessing-Moore J et al. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. American Academy of Allergy, Asthma, and Immunology. *Ann Allergy Asthma Immunol* 1998;**81**:478–518.
5. Lumry WR. A review of the preclinical and clinical data of newer intranasal steroids used in the treatment of allergic rhinitis. *J Allergy Clin Immunol* 1999;**104**:S150–S158.
6. Wiseman LR, Benfield P. Intranasal fluticasone propionate. A reappraisal of its pharmacology and clinical efficacy in the treatment of rhinitis. *Drugs* 1997;**53**:885–907.
7. Daley-Yates PT, Baker RC. Systemic bioavailability of fluticasone propionate administered as nasal drops and aqueous nasal spray formulations. *Br J Clin Pharmacol* 2001;**51**:103–105.
8. Wilson AM, McFarlane LC, Lipworth BJ. Effects of repeated once daily dosing of three intranasal corticosteroids on basal and dynamic measures of hypothalamic–pituitary–adrenal-axis activity. *J Allergy Clin Immunol* 1998;**101**:470–474.
9. Knutsson U, Stierna P, Marcus C, Carlstedt-Duke J, Carlstrom K, Bronnegard M. Effects of intranasal glucocorticoids on endogenous glucocorticoid peripheral and central function. *J Endocrinol* 1995;**144**:301–310.
10. Lipworth BJ, Jackson CM. Safety of inhaled and intranasal corticosteroids: lessons for the new millennium. *Drug Saf* 2000;**23**:11–33.
11. Bodor N, Buchwald P. Soft drug design: general principles and recent applications. *Med Res Rev* 2000;**20**:58–101.
12. Druzgala P, Hochhaus G, Bodor N. Soft drugs–10. Blanching activity and receptor binding affinity of a new type of glucocorticoid: loteprednol etabonate. *J Steroid Biochem Mol Biol* 1991;**38**:149–154.
13. Hochhaus G, Chen LS, Ratka A, Druzgala P, Howes J, Bodor N et al. Pharmacokinetic characterization and tissue distribution of the new glucocorticoid soft drug loteprednol etabonate in rats and dogs. *J Pharm Sci* 1992;**81**:1210–1215.
14. Novack GD, Howes J, Crockett RS, Sherwood MB. Change in intraocular pressure during long-term use of loteprednol etabonate. *J Glaucoma* 1998;**7**:266–269.
15. Buris LF, Bodor N, Buris L. Loteprednol etabonate, a new soft steroid is effective in a rabbit acute experimental model for arthritis. *Pharmazie* 1999;**54**:58–61.
16. Hermann R, Locher M, Siebert-Weigel M, LaVallee N, Derendorf H, Hochhaus G. Intranasal loteprednol etabonate in healthy male subjects: pharmacokinetics and effects on endogenous cortisol. *J Clin Pharmacol* 2004;**44**:510–519.

17. Szelenyi I, Hochhaus G, Heer S, Küsters S, Marx D, Poppe H et al. Loteprednol etabonate: a soft steroid for the treatment of allergic diseases of the airways. *Drugs Today* 2000;**36**:313–320.
18. Krug N, Hohlfeld J, Larbig M, Buckendahl A, Badorrek P, Geldmacher H et al. Validation of an environmental exposure unit for controlled human inhalation studies with grass pollen in patients with seasonal allergic rhinitis. *Clin Exp Allergy* 2004;**34**:1667–1674.
19. American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995;**152**:1107–1136.
20. Horak F, Stubner P, Zieglmayer R, Kavina A, De Vos C, Burtin B et al. Controlled comparison of the efficacy and safety of cetirizine 10 mg o.d. and fexofenadine 120 mg o.d. in reducing symptoms of seasonal allergic rhinitis. *Int Arch Allergy Immunol* 2001;**125**:73–79.
21. Day JH, Briscoe MP, Rafeiro E, Ellis AK, Pettersson E, Akerlund A. Onset of action of intranasal budesonide (*Rhinocort aqua*) in seasonal allergic rhinitis studied in a controlled exposure model. *J Allergy Clin Immunol* 2000;**105**:489–494.
22. Connell JT. Quantitative intranasal pollen challenges III. The priming effect in allergic rhinitis. *J Allergy* 1969;**43**:33–44.