

# Adding Loratadine to Topical Nasal Steroid Therapy Improves Moderately Severe Seasonal Allergic Rhinoconjunctivitis

**Michel A. Drouin, M.D.**

**William H. Yang, M.D.**

Section of Allergy and Clinical  
Immunology  
Ottawa Civic Hospital  
University of Ottawa  
Ottawa, Canada

**Friedrich Horak, M.D.**

HNO University Clinic  
University of Vienna  
Vienna, Austria

**Paul H. van de Heyning, M.D.**

Department of ENT and Head  
and Neck Surgery  
University Clinic of Antwerp  
Antwerp, Belgium

**Gert H. Kunkel, M.D.**

Department of Clinical Immunology  
and Asthma O.P.D.  
University Clinic Charlottenburg of  
the Free University of Berlin  
Berlin, Germany

**Charles I. Backhouse, M.D.**

The Medical Centre  
East Horsley, Surrey, England

**Melvyn R. Danzig, Ph.D.**

Schering-Plough Research Institute  
Kenilworth, New Jersey

## ABSTRACT

This study assessed the efficacy of adding the nonsedating selective H<sub>1</sub> anti-histamine loratadine to topical intranasal beclomethasone dipropionate (BDP)

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Address reprint requests to  
Melvyn R. Danzig, Ph.D.  
Schering-Plough Research Institute  
2015 Galloping Hill Road  
Kenilworth, NJ 07033-0539

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to treat patients with seasonal allergic rhinoconjunctivitis (SAR). In a double-blind, randomized, parallel-group trial, 154 patients, ages 18 to 65, with moderately symptomatic SAR were treated with intranasal BDP (100 µg in each nostril twice daily) combined with 10 mg of loratadine or placebo for 7 days. Four nasal and four non-nasal symptoms were evaluated following 3 and 7 days of treatment, and patients recorded daily symptoms and possible adverse effects in a diary. BDP alone improved the symptoms of SAR; however, BDP plus loratadine provided further improvement. Patients treated with BDP plus loratadine achieved significantly greater ( $P<.05$ ) relief of both nasal and non-nasal symptoms than those treated with BDP plus placebo. No differences were noted in the incidence or type of adverse effects in the two treatment groups. Loratadine plus topical intranasal BDP controls SAR more effectively than does BDP alone, without any increase in adverse effects.

**Keywords:** antihistamine; topical corticosteroid; loratadine; beclomethasone dipropionate; allergic rhinitis

## INTRODUCTION

Current pharmacologic management of rhinitis provides less than complete relief of symptoms and may be associated with variable degrees of adverse effects.<sup>1</sup> Because many of the drugs currently available affect different components of the allergic response, combinations of drugs with complementary effects can maximize therapeutic efficacy.

Loratadine is an orally effective and long-acting antihistamine.<sup>2</sup> It has a high selectivity for peripheral histamine H<sub>1</sub> receptors and a low affinity for central nervous system H<sub>1</sub>, cholinergic, or alpha-adrenergic receptors in vitro or in vivo.<sup>3,4</sup> Loratadine does not readily cross the blood-brain barrier and has an incidence of sedation equal to that of placebo.<sup>5</sup> Loratadine is rapidly absorbed, with peak concentrations in serum reached within 2 hours, an effect consistent with its rapid onset of action.<sup>6</sup> Loratadine relieves most of the symptoms related to SAR<sup>2</sup> and is as effective as terfenadine,<sup>7-9</sup> astemizole,<sup>10,11</sup> and cetirizine.<sup>12</sup>

The nasal response to allergen challenge can be divided into an early reaction (occurring within minutes of allergen exposure) and a late-phase reaction (occurring 4 to 10 hours after allergen challenge in about half of patients). A rechallenge reaction may occur with a second exposure to allergen 10 hours after the first challenge, resulting in increased symptoms and associated physiologic effects.<sup>13</sup> Systemic corticosteroids reduce symptoms and mediator release in the late and rechallenge phases of the process but have little effect on the early phase. Intranasally applied steroids are effective in all three phases of the response, however.<sup>1,14</sup> Studies on their mode of action have shown that they reduce the number of eosinophils, the presence of eosinophil cationic protein, and the number of mast-cell progenitors in the nasal mucosa.<sup>1</sup>

Topical steroids, including BDP, flunisolide, budesonide, triamcinolone acetonide, fluticasone propionate, and mometasone furoate, are efficacious agents for all the nasal symptoms of SAR.<sup>1</sup> H<sub>1</sub>-receptor antagonists relieve the ocular symptoms that





accompany SAR<sup>15-18</sup> and help prevent and relieve sneezing, nasal itching, and rhinorrhea; however, they do not relieve nasal blockage.<sup>19</sup> In a recent report, Frolund<sup>20</sup> compared the effects of loratadine with those of intranasal BDP and concluded that although both medications were effective in patients with SAR, the two drugs controlled different symptoms. Patients treated with BDP had significantly less nasal blockage; those treated with loratadine had more relief of ocular symptoms. This study attempts to determine whether combination treatment with BDP and loratadine maximizes clinical efficacy.

## PATIENTS

Five medical centers participated in this double-blind, randomized, parallel-group study designed to determine the efficacy of adding 1 week of loratadine treatment to therapy with topical nasal steroids to alleviate the signs and symptoms of SAR. The centers were located in Austria, Belgium, Canada, Germany, and England. An institutional review committee at each center approved the study protocol and statement of informed consent, and each study participant gave written informed consent.

### Study Design

Outpatients between 18 and 65 years of age with a history of moderately severe SAR were admitted to the study. IgE-mediated hypersensitivity was confirmed by a positive skin prick or an intradermal test with relevant seasonal allergens.

Patients were excluded from the study if they were pregnant, lactating, or not using medically accepted birth control; had severe asthma or chronic obstructive pulmonary disease; had nasal polyps or significant nasal structural abnormalities; or had any significant current disease that might interfere with treatment evaluation. Anyone undergoing immunotherapy with pollen extracts must have been receiving a stable dose for at least 1 month before beginning the study.

Before dosage, patients were required to stop taking oral antihistamines (for 48 hours, except astemizole for 1 month), oral decongestants (for 24 hours), systemic and orally inhaled steroids (for 1 month), nasally inhaled steroids (for 72 hours), cromolyn sodium (for 1 week), and topical decongestants (for 24 hours).

Before beginning the study, patients had to have at least moderately severe SAR symptoms. They were evaluated for nasal, ocular, and ear/palate symptoms according to the following rating scale: 0 = none (not visible to physician or patient); 1 = mild (noticed by physician or patient or both but not disturbing); 2 = moderate (definitely present and disturbing to the patient some of the time); and 3 = severe (very disturbing most of the time). Nasal symptoms evaluated included rhinorrhea, stuffiness, itching, and sneezing. Ocular symptoms evaluated were itching, tearing, and redness. Ear/palate itching was also assessed. To be included in the study, patients had to demonstrate a nasal score of at least 6 (including nasal discharge and one other nasal symptom of moderate severity) and an ocular score of at least 5. Individual symptoms were summed, creating nasal, ocular, and total scores.

Patients were randomly assigned to treatment with either intranasal BDP plus loratadine or intranasal BDP plus placebo. Patients were instructed to take one

tablet of loratadine (10 mg) or matched placebo daily in the morning and two sprays (50 µg/spray) of BDP in each nostril every morning and evening for 7 days. All patients kept a daily diary of symptom severity and adverse effects between visits.

After 3 and 7 days of treatment, patients were evaluated by the investigator. In addition to scoring individual symptoms at each visit, the patient and physician made an overall global assessment of response to treatment on day 7 (or on the last day of treatment if a patient discontinued earlier than day 7), using a rating scale of 1 to 5 (1, excellent; 5, treatment failure). Adverse events were also elicited.

### Statistical Analysis

Continuous demographic variables (age, weight, duration of condition, and duration of episode) were evaluated by means of a two-way analysis of variance model. Fisher's Exact Test was used to assess the comparability of sex and race. A two-way analysis of variance was used to analyze total symptom scores, which were confirmed with the Wilcoxon rank-sum test. The incidence of adverse events (total and specific) was analyzed with Fisher's Exact Test.

## RESULTS

The study enrolled 156 patients. One patient from each group was dropped from the study for failure to return for follow-up evaluation after the initial visit. Table 1 lists the demographic information for the two study groups. Race, age, weight, and baseline total symptom scores were comparable ( $P \geq .27$ ). Sex had significant treatment-by-center interaction ( $P = .03$ ) but was determined to have no major impact on overall efficacy comparisons.

**Table 1. Demographic Information**

	Loratadine + BDP	Placebo + BDP
No. of patients	76	78
Sex, M/F	48/33	38/40
Mean age, y	31	32
Mean weight, kg	70	68
Mean duration of SAR, y	9	12
Mean duration of current episode, wk	3	4
Baseline scores (mean value)		
Total symptoms	14.9	15.1
Nasal symptoms	8.4	8.6
Ocular symptoms	5.5	5.6



## Efficacy

In general, patients treated with loratadine plus BDP showed greater clinical improvement in most symptoms of SAR than those treated with placebo plus BDP (Table 2).

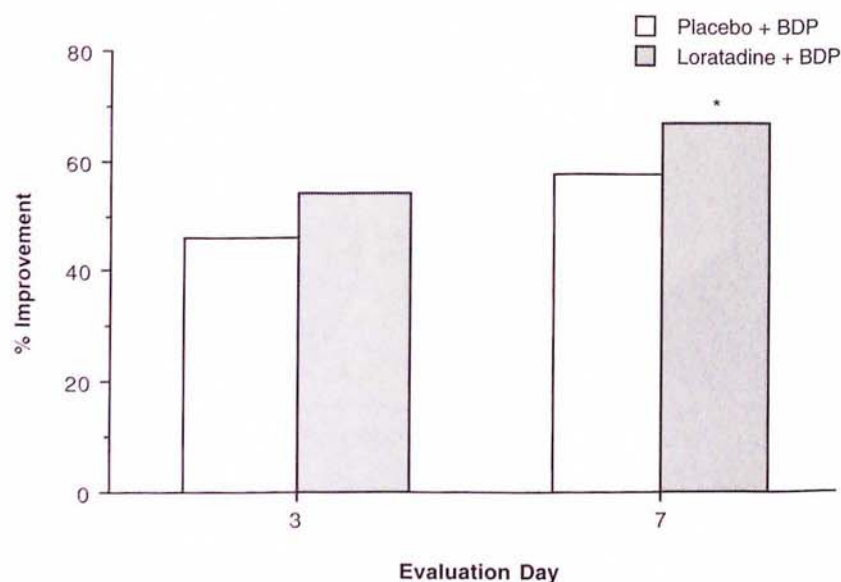
**Table 2. Improvement in Symptom Scores at Days 3 and 7**

	Evaluation Day	Loratadine + BDP, %	Placebo + BDP, %	P Value
Total symptom score	3	54	46	.08
	7	68	58	<.05
Total nasal score	3	55	48	<.05
	7	66	59	NS
Nasal discharge	3	58	52	NS
	7	67	65	NS
Nasal stuffiness	3	43	40	NS
	7	62	55	NS
Nasal itching	3	61	48	<.05
	7	72	62	<.05
Sneezing	3	57	46	<.05
	7	67	59	.07
Total ocular score	3	53	45	NS
	7	70	57	<.05
Itching	3	48	39	NS
	7	65	52	<.05
Tearing	3	56	52	NS
	7	72	61	<.05
Redness	3	53	46	NS
	7	73	54	.07
Ear/palate itching	3	60	38	<.05
	7	80	50	<.05

NS = not significant.

Patients receiving loratadine plus BDP showed significantly greater improvement in total symptom score at day 7 (Fig 1), total nasal score at day 3, and total ocular score at day 7 ( $P < .05$ ). Greater improvement with loratadine plus BDP was also noted in several individual symptoms. These included less nasal itching on days 3 and 7, less sneezing on day 3, less eye itching and tearing on day 7 ( $P < .05$ ), and decreased eye redness on day 7 ( $P = .07$ ). The two groups did not differ in effects on nasal discharge or nasal stuffiness.

Fig 1. Total symptom score.



\* $P < .05$ .

The last non-nasal score, ear/palate itching, was considerably different between the two groups at both evaluation days ( $P < .05$ ). At day 7, this symptom had improved 80% in the loratadine plus BDP group, compared with 50% in the placebo plus BDP group.

Figs 2 and 3 illustrate the physicians' and patients' global evaluation at the endpoint of the study. Physician evaluation showed that 84% of patients in the loratadine plus BDP group had a good to excellent response, compared with 71% of patients in the placebo plus BDP group ( $P < .05$ ). In the loratadine plus BDP group 34% of patients had an excellent response, compared with only 17% in the placebo plus BDP group. Similarly, patient evaluation showed that 90% of patients in the loratadine plus BDP group had a good to excellent response, compared with 73% of those receiving placebo plus BDP ( $P < .05$ ). Again, the percentage of patients who rated the treatment effect as excellent was substantially greater in the loratadine plus BDP group than in the placebo plus BDP group (39% vs 19%, respectively).

### Safety

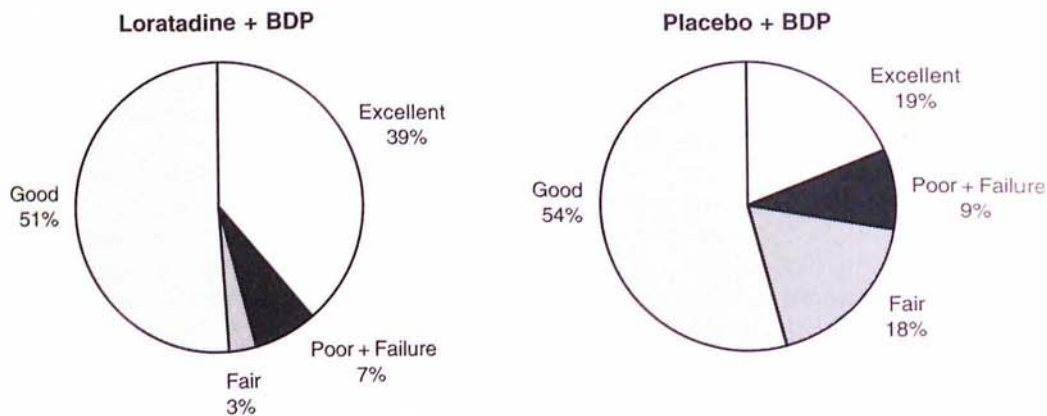
Both groups reported similar incidence and types of adverse effects (Table 3). Twenty-three (30%) patients in the loratadine plus BDP group and 20 (26%) patients in the placebo plus BDP group reported treatment-related adverse events. Somnolence was reported by 4 (5%) patients receiving loratadine and 5 (6%) patients receiving placebo. No patient dropped out of the study because of adverse effects.

**Fig 2. Physicians' global evaluation at endpoint.\***



\* $P < .05$  for comparison.

**Fig 3. Patients' global evaluation at endpoint.\***



\* $P < .05$  for comparison.



**Table 3. Adverse Experiences\***

	No. (%) of Patients	
	Loratadine + BDP (n = 77)	Placebo + BDP (n = 78)
Dry mouth	1 (1)	3 (4)
Fatigue	3 (4)	4 (5)
Headache	2 (3)	1 (1)
Nasal burning	4 (5)	4 (5)
Nasal irritation	3 (4)	1 (1)
Rhinitis	4 (5)	1 (1)
Sneezing	2 (3)	1 (1)
Somnolence	4 (5)	5 (6)

\*Treatment-related adverse experiences reported by more than one patient.

## DISCUSSION

Although some authors have found no difference in effectiveness,<sup>17,21</sup> studies in which an intranasal corticosteroid has been directly compared with a nonsedating antihistamine have generally shown that steroid nasal sprays control nasal symptoms more effectively.<sup>15,18,22,23</sup> Clinically, patients respond differently following treatment of allergic rhinitis with antihistamines or intranasal steroids. Antihistamines relieve pruritus, sneezing, rhinorrhea, and ocular symptoms but do not control nasal stuffiness. Intranasal steroids can attenuate all nasal symptoms but are most effective against stuffiness and rhinorrhea. Thus, treatment that combines an antihistamine and a steroid nasal spray may maximize clinical efficacy.

Backhouse and colleagues<sup>24</sup> found that terfenadine reduced SAR symptoms but that terfenadine plus flunisolide nasal spray relieved symptoms more effectively than did terfenadine alone. Wihl et al<sup>25</sup> showed that astemizole improved rhinitis symptoms but that astemizole plus BDP nasal spray was more effective. Juniper et al<sup>18</sup> showed that sneezing, nasal obstruction, and rhinorrhea were significantly improved in patients taking only BDP over those taking only astemizole; BDP plus astemizole did not control rhinitis better than did BDP alone. Individuals taking astemizole alone or with BDP had fewer ocular symptoms and used fewer eye drops than those taking BDP alone; eye symptoms were best controlled when patients took both medications.

This study demonstrates that the addition of an antihistamine to topical intranasal steroid therapy improved the control of most SAR symptoms. Loratadine plus intranasal BDP improved the symptoms of moderately severe SAR to a greater degree than did BDP plus placebo. Patients had significantly improved responses in total symptom score as well as in overall nasal and ear/palate itching scores when the two agents were combined. The addition of loratadine also improved ocular symptoms. This is not surprising, as nasally administered steroids, because of their



localized site of action, cannot be expected to provide control of conjunctivitis, even if some studies of intranasal steroids have revealed partial relief of eye symptoms.<sup>26</sup> Patients using BDP plus loratadine had increased symptomatic control of SAR but had no more adverse effects than did patients using only BDP.

## CONCLUSION

Oral loratadine added to intranasal BDP improves the treatment of patients with SAR. Each drug apparently compensates for the other's shortcomings and enhances therapeutic outcome without producing any limiting adverse effects.

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