Spectrum of Seasonal Allergic Rhinitis Symptom Relief with Topical Corticoid and Oral Antihistamine Given Singly or in Combination

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ABSTRACT

Sixty ragweed-sensitive volunteers participated in a 2-week study that compared symptom profiles during treatment with antihistamine (loratadine, LOR) alone, topical corticoid (beclomethasone, BEC) alone, or the two drugs combined. For 5 days commencing shortly after the beginning of the ragweed bloom, patients took no treatment while we collected baseline data. They were then randomized to one of the three treatments, receiving that treatment for the balance of the 2-week study term. Twice each day they recorded the severity of congestion, eye symptoms, running and blowing, itching, and sneezing. At the end of the study they provided an estimate of overall symptom relief, which favored combined treatment (vs LOR P = *0.001, vs BEC* P = *0.042). To gain an estimate of disease severity and treatment effectiveness over time, and to smooth out day-to-day variation, we divided symptom diary reports into three segments (days 2–4, 5–7, and 8–10) for analysis. Combined treatment controlled symptoms better than antihistamine alone in nearly all study segments. Corticoid alone or combined with antihistamine provided similar control of congestion, running and blowing, and eye complaints. Combination therapy controlled itching and sneezing better, especially through the study segments 1 and 2. Patient preference for combined treatment seems to relate to control of itching and sneezing and rapid onset of effect.* (American Journal of Rhinology 10, 193–199, 1996)

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In several previous studies we have examined profiles of individual symptoms in allergic rhinitis and the selective effects of various treatments on these profiles. We showed that, compared to placebo, terfenadine suppressed sneeze, itch, and eye symptoms, benefitted congestion marginally, and failed to improve running and blowing. Of these, only control of sneezing appeared quickly after introduction of the drug in midseason.[1] Another study intended to establish minimal effective doses of oral methylprednisolone found, at 6 mg per day, significant suppression of congestion, postnasal drainage, and eye symptoms, but not itching, sneezing, and running.[2] These findings could be a clinical expression of the reported inability of systemic corticoid to prevent release of mediators from human mast cells.[3]

It appeared that the symptoms most responsive to antihistamine treatment responded least well to low dose corticoid and vice versa, providing a rational basis for combination of the two drug types for seasonal allergic rhinitis

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treatment. We have carried out preliminary studies documenting additive protection with combined antihistamine/corticoid treatment, and the equivalence of oral and topical corticoid when given as part of the combination.

Others have studied symptom control with combined antihistamine/topical corticoid treatment and have reported variable findings.[4–7] Most reported a more modest increment of patient-perceived benefit with combined treatment than our preliminary studies led us to expect.

The goal of the study reported here was to compare profile and severity of individual symptoms, and overall patient perception of benefit during seasonal allergic rhinitis treatment with antihistamine (loratadine, Claritin, Schering-Plough, LOR) alone, topical nasal corticoid (beclomethasone, Vancenase AQ, Schering-Plough, BEC) alone, and the two drugs in combination. The study did not contain a concurrent placebo control group, but all study participants entered the treatment comparison from an untreated baseline observation period.

STUDY DESIGN AND EXECUTION

Subject Selection

Sixty subjects enrolled in and completed the study. Each treatment group contained 20 people; sex distribution in the LOR group was 10M/10F, whereas the BEC and the LOR/BEC groups both had 7M/13F. The three treatment groups were roughly comparable in age, height, and weight. All had reliable histories of seasonal rhinitis compatible with ragweed seasonal allergic rhinitis and strongly positive ragweed skin (prick) tests. Many had participated in previous studies and had provided records of the severity of their seasonal symptoms. None had evidence of significant complicating disease on history, physical examination, or screening laboratory testing; women had negative pregnancy tests on entry and again in mid-study. All alleged that they understood the design, demands, and risks of the study and signed their consent to participate. The Bronson Hospital Human Use Committee reviewed and approved the study design and documents.

Treatment Schedule

In this community, ragweed typically begins to bloom around August 15. Subjects came under study observation on 18 August (Thursday) and were seen each Monday and Thursday through 1 September. From August 18 to 22 they used no treatment; this provided baseline information documenting seasonal allergic rhinitis severity at the beginning of the observation period. After 22 August they used their randomly assigned therapy, remaining on the same treatment through 1 September. At all visits we reviewed and verified hay fever symptom severity diaries, checked apparent study drug consumption, and inquired for possible treatment side effects or other medical events.

Table I shows the pollen counts obtained during the study confirming the appearance of reasonable levels by mid-August. (James L. McDonald, M.D., provided aeroallergen counts obtained from a rotobar sampler located at an elevated urban site about one mile from the clinic where we ran the study.) Absolute counts never exceeded 169 grains per cubic meter, relatively low compared with prior years' experiences. However, they seemed to provide an adequate allergic stimulus, both in study subjects and nonstudy patients under our care.

Experimental Drug Treatment

We randomly allocated volunteers to three drug treatment groups consisting of:

1. Loratadine (Claritin, Schering-Plough) (LOR) 10 mg once a day, plus a placebo spray twice a day.
2. Beclomethasone (Vancenase AQ, Schering-Plough) (BEC) two sprays (about 84 mcg) each side of the nose twice a day, plus placebo LOR.
3. BEC twice a day plus LOR once daily.

During the treatment comparison, subjects took no other treatment that might affect their hay fever.

TABLE I

Ragweed Pollen Grain Count in Particles Per CU Meter. Counts Made Using A Rotobar Sampler Running Intermittently on a Downtown Rooftop

Study Segment	Date	Ragweed Count	Study Segment	Date	Ragweed Count
	August 12	1	1	August 23	83
	August 13	6	1	August 24	162
	August 14	19	1	August 25	169
	August 15	14	2	August 26	95
	August 16	16	2	August 27	144
	August 17	40	2	August 28	144
	August 18	71	3	August 29	116
Baseline	August 19	27	3	August 30	76
Baseline	August 20	14	3	August 31	67
Baseline	August 21	59		September 1	45
	August 22	23		September 2	19

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Observations and Evaluations

Symptom Severity Diaries recorded the level of discomfort perceived by the subjects for each of five classes of seasonal allergic rhinitis symptoms. The diary has served us well in earlier studies.

All subjects made twice daily entries for the following hay fever-related problems:

- Congestion
- Running and blowing
- Sneezing
- Itching
- Eye symptoms

For each symptom the diary contained a scale specifically describing five levels of severity. The diary also provided space for recording use of study drug, need for any intercurrent medications, possible adverse reactions to the study drugs, and amount of time spent in air-conditioning.

Global Assessment

On the final treatment day, we asked all subjects to rate their response to treatment as excellent, good, fair, or poor. Although crude and subjective, this approach has clearly differentiated among treatments in past studies.

DATA HANDLING AND STATISTICAL ANALYSIS

We omitted symptom severity scores from the first and last days, as these typically included half day reports only, as well as the first full treatment day, feeling that it still reflected a transition day providing questionable data. To allow comparison with baseline and perception of developing trends, we collapsed symptom severity reports into four intervals; days −3 to −1 (pretreatment), and treatment days 2–4, 5–7, and 8–10. We averaged AM and PM scores and calculated change from mean pretreatment score for each subject and each follow-up day. Each symptom change score was analyzed using a repeated measures analysis of variance model incorporating factors associated with treatment, subject nested within treatment, study day, and treatment by day interaction. In addition, the mean pretreatment response was used as a covariate. We used contrast statements to make treatment comparisons within each of the 3-day follow-up periods. A pooled error term containing both the within- and between-subject errors was used in testing. All analyses were done using SAS (SAS Institute, Cary, NC).

RESULTS

Symptom Severity During Baseline

Table II contains overall mean symptom severity scores collected during the baseline period. During this interval, the volunteers took no medications to suppress their rhinoconjunctivitis. Diaries allowed description of symptoms on a discrete scale from 1 (no symptoms) to 5 (maximum symptoms). Baseline values largely between 2 and 3 suggest that patients experienced mild to moderate symptoms during this time and that symptom severity was reasonably homogeneous across the three groups.

TABLE II

Mean (± STD DEV) Severity Scores By Symptom and Treatment Group for the Untreated Baseline Period

	BEC	LOR	(BEC & LOR)
Congestion	2.78 ± 1.00	2.90 ± 0.77	2.72 ± 0.61
Eye symptoms	2.35 ± 0.89	2.28 ± 0.79	1.93 ± 0.72
Running/ blowing	2.83 ± 1.07	2.28 ± 0.83	2.62 ± 0.55
Itching	2.30 ± 0.79	2.00 ± 0.88	2.44 ± 0.96
Sneezing	2.48 ± 0.70	2.23 ± 0.69	2.22 ± 0.76

Overall Patient Assessment

At the last clinic visit, on the last day of study-imposed therapy, we asked each subject for an overall estimate of the effectiveness of the treatment they had just completed. Their options were excellent, good, fair, or poor; we did not qualify these further.

Table III contains results of the patient ratings. Combination treatment provided superior symptom control with 19/20 reporting good (8) or excellent (11) results. The combination was significantly superior to topical steroid alone ($P = 0.042$), and to antihistamine alone ($P = 0.001$). BEC alone appeared to protect slightly better than LOR alone, but statistical testing did not confirm the significance of this trend ($P = 0.122$).

Diary Symptom Severity Scores

Figures 1 through 5 show mean changes in symptom severity from pretreatment to the indicated treatment segment. We looked for treatment effect by determining symptom severity decrements from baseline and testing these for significance using the paired *t*-test.

The figures show several patterns. Antihistamine alone (LOR, L) produced relatively modest benefit, almost always less than that seen with either of the topical corticoid-

TABLE III

Overall Patient Assessment of Treatment Effectiveness Statistical Testing

Treatment Result	Treatment		
	BEC	LOR	(BEC + LOR)
Excellent	6	4	11
Good	9	5	8
Fair	4	9	1
Poor	1	2	0

(BEC & LOR) vs BEC $P = 0.042$; (BEC & LOR) vs LOR $P = 0.001$; BEC vs LOR $P = 0.122$.

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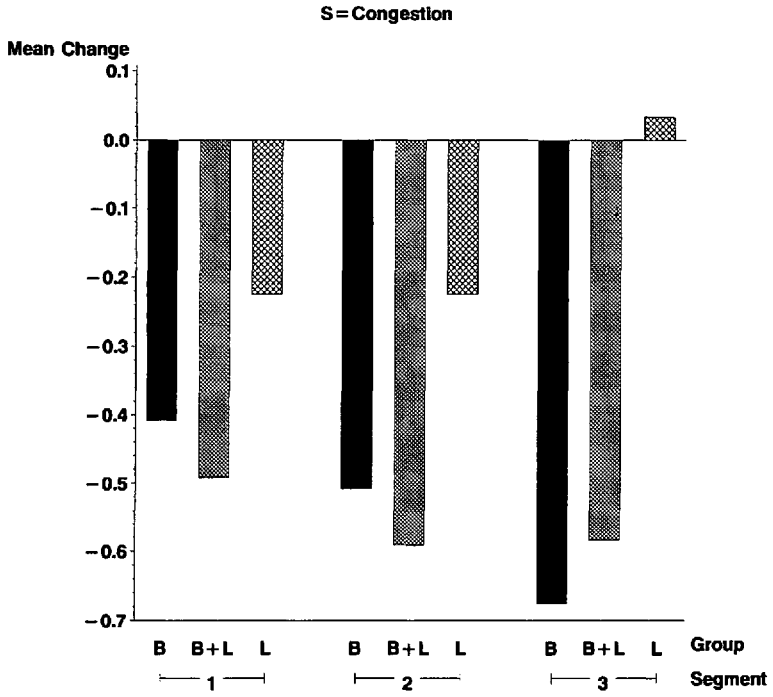

Figure 1. Congestion Mean Change by Treatment Group and Study Segment. B = Beclomethasone alone, L = Loratadine alone, B+L = Combined Beclomethasone and Loratadine. Segment 1 = Treatment Days 2–4, Segment 2 = Treatment Days 5–7, Segment 3 = Treatment Days 8–10.

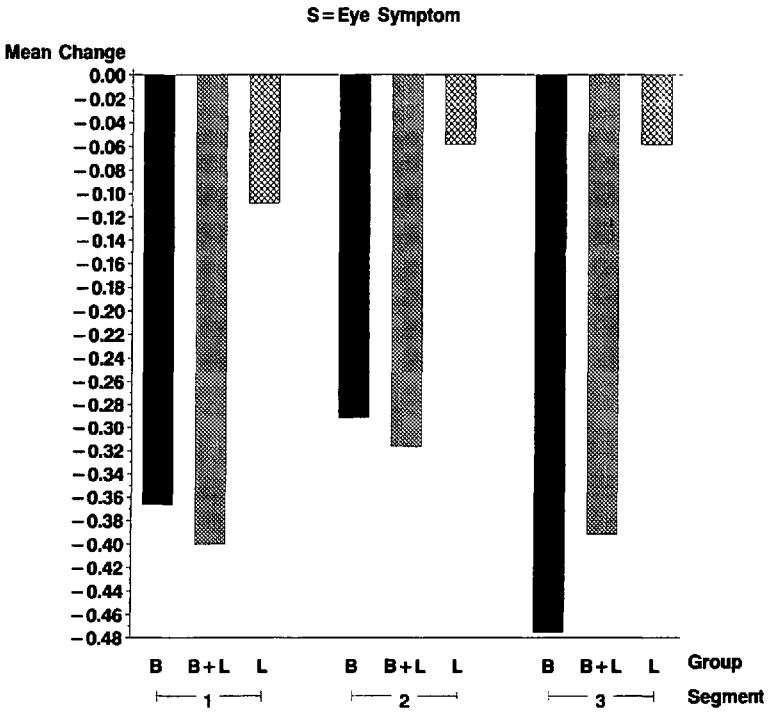

Figure 2. Eye Symptoms Mean Change by Treatment Group and Study Segment. Group and Segment as in Figure 1.

containing regimens. Antihistamine benefitted congestion (Fig. 1) slightly in segments 1 and 2, and not at all in segment 3. Eye symptoms (Fig. 2) improved minimally though never significantly, while running and blowing (Fig. 3) showed no LOR-induced improvement. Itching (Fig. 4) showed consistent and significant lessening during LOR treatment, whereas sneezing (Fig. 5) improved in segments 1 and 2, but not 3.

Comparing among the treatments, three diary entries, congestion, eye symptoms, and running/blowing showed

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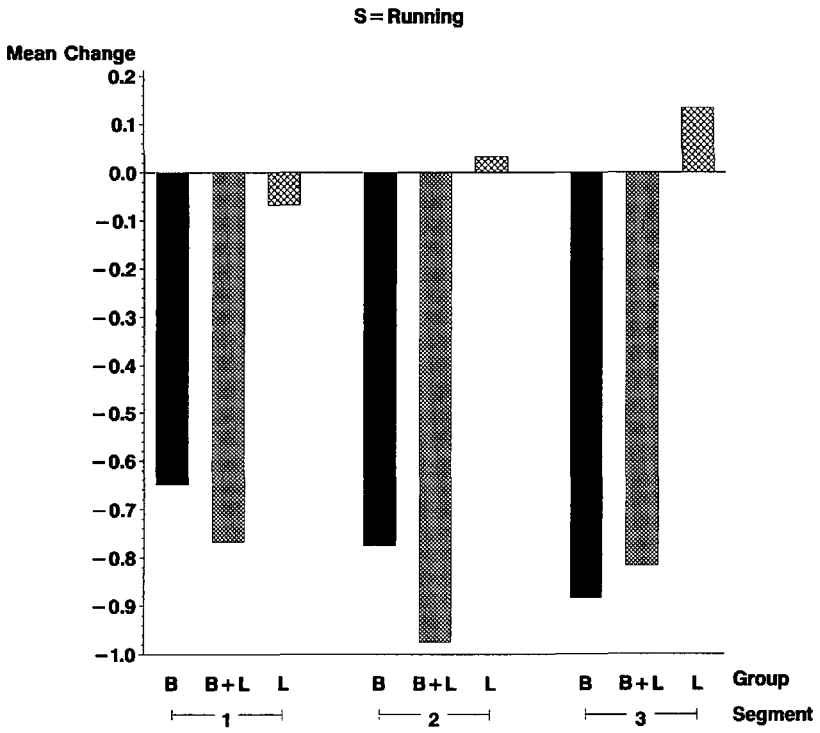

Figure 3. Running/Blowing Mean Change by Treatment Group and Study Segment. Group and Segment as in Figure 1.

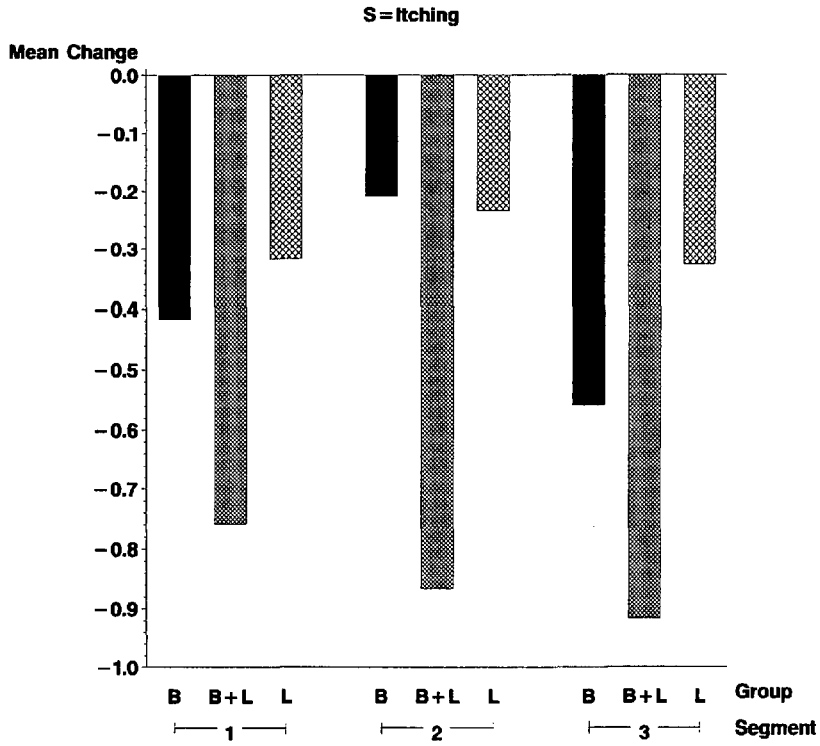

Figure 4. Itching Mean Change by Treatment Group and Study Segment. Group and Segment as in Figure 1.

similar improvement with BEC and BEC/LOR combined treatment. Combined treatment benefitted sneezing and itching significantly better than BEC alone (see Table IV) in most of the treatment segments. With BEC alone suppression of sneezing increased gradually from Segments 1 through 3, though the difference from baseline was significant in all segments. With combined BEC/LOR sneeze suppression appeared promptly and already was maximum in Segment 1; by Segment 3, BEC and BEC/LOR provided similar suppression of sneezing (albeit

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