

Effect of combined montelukast and desloratadine on the early asthmatic response to inhaled allergen

Beth E. Davis, BSc, David C. Todd, MD, FRCP(C), and Donald W. Cockcroft, MD, FRCP(C)

Saskatoon, Saskatchewan, Canada

Background: The early asthmatic response (EAR) to inhaled allergen results from IgE-mediated release of multiple mast-cell mediators, including leukotrienes and histamine, both of which cause bronchoconstriction. Combination therapy directed at blocking the effects of both mediators might protect against the EAR better than either therapy alone.

Objective: We sought to evaluate the effect of desloratadine and montelukast, administered alone and in combination, on the EAR to inhaled allergen.

Methods: Ten adults with mild-to-moderate atopic asthma participated in a randomized, 4-way crossover study design comparing placebo, 5 mg of desloratadine, 10 mg of montelukast, and the combination administered at 26 hours and 2 hours before each allergen challenge conducted at least 7 days apart. The primary end point was the concentration of allergen that resulted in a 20% decrease in FEV₁ (PC₂₀).

Results: The geometric mean allergen PC₂₀ (mean log ± SEM) for combination therapy, montelukast, desloratadine, and placebo was 697 U/mL (2.8433 ± 0.3253), 338 U/mL (2.5295 ± 0.2979), 123 U/mL (2.0883 ± 0.2102), and 104 U/mL (2.0166 ± 0.2553), respectively (n = 9; P < .00001, ANOVA). Montelukast increased the allergen PC₂₀ 4.8-fold, and combination therapy increased the allergen PC₂₀ 8.9-fold. The effect of the combination was greater than that with montelukast alone (P < .02). Desloratadine treatment was no different than placebo.

Conclusions: The early response to inhaled allergen was unchanged after desloratadine therapy and partially inhibited with montelukast therapy. The combination of desloratadine and montelukast provided superior efficacy to either blocker administered alone. Investigations into the possible mechanisms of the enhanced inhibition are necessary. (J Allergy Clin Immunol 2005;116:768-72.)

Key words: Antihistamine, leukotriene antagonist, allergen inhalation

The response of the airways to inhaled allergen in individuals with atopic asthma is an IgE-mediated mast-cell degranulation process leading to the early asthmatic response (EAR), which peaks about 15 to 30 minutes after inhalation and is often followed by a late asthmatic response (LAR) developing 3 to 8 hours after inhalation. The degranulation process results in the release of multiple mediators, including the leukotrienes and histamine. The EAR is thought to be due to airway smooth muscle contraction, mediated in part by histamine on histamine receptor subtype 1 (H₁) receptors and leukotrienes on cysteinyl leukotriene receptor subtype 1 receptors. It follows that blocking the activity of these mediators might prevent bronchoconstriction. Investigations of the effect of H₁ blockers on the EAR have produced variable and inconclusive results.¹⁻⁵ Leukotriene modifiers have been shown to provide reasonable inhibition of the EAR and LAR but do not completely abolish the response.⁶⁻¹⁰ The idea that a mechanism involving multiple mediators might require multiple interventions continues to attract interest in the role of combination therapies for the treatment of atopic asthma. Desloratadine is an antihistamine that has not been clinically investigated in atopic asthma and the response to inhaled allergen. Montelukast is effective in partially attenuating the response to inhaled allergen. There are no published data reporting the effect of the combination of these 2 therapies on allergen-induced airway responses.

METHODS

Subjects

Ten healthy atopic asthmatic subjects older than 18 years and with a baseline FEV₁ of 65% of predicted value or greater participated in the study (Table I). Subjects had no respiratory infection or allergen exposure for 4 or more weeks before enrollment. The protocol was approved by the University of Saskatchewan Biomedical Ethics Research Board, and subjects provided written consent.

Salbutamol (n = 10) was withheld before testing for 8 or more hours. Fluticasone was used (stable dose for 3 months) by one subject. No subjects used any other asthma therapies or antihistamines.

Study design

This was a randomized, 4-way crossover, placebo-controlled (thiamine, 100 mg) investigation. Matching placebo tablets were

From the Division of Respiratory Medicine, Department of Medicine, University of Saskatchewan, Royal University Hospital.

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Reprint requests: Donald W. Cockcroft, MD, FRCP(C), Division of Respiratory Medicine, University of Saskatchewan, Ellis Hall, Rm 551, 5th Floor, Saskatoon, SK S7N 0W8 Canada. E-mail: cockcroft@sask.usask.ca.

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TABLE I. Patient demographics

Subject no.	Sex	Age (y)	Height (inches)	Baseline FEV ₁ (L)	% Predicted	Allergen	MPC ₂₀ (mg/mL)	Medications
1	M	57	66	2.46	73	Grass*	0.5	S, prn
2	M	29	70	3.87	87	HDM†	2	S, prn
3	M	27	71	3.67	86	Cat‡	0.67	S, prn
4	F	24	62	2.66	83	Cat‡	0.28	S, prn
5	M	25	72	4.07	85	Cat‡	2	S, prn
6	M	40	72	2.86	65	Grass*	1.8	S, prn
7	F	25	66	3.12	89	HDM†	2.5	S, prn; F, 125 µg bid
8	M	43	68	3.44	88	Grass*	16	S; prn
9	F	27	64	3.35	101	Cat‡	0.86	S; prn
10§	M	26	72	4.59	96	Cat‡	0.75	S; prn
Mean		32	68	3.41	85		2.7	

S, Salbutamol; prn, as required; F, fluticasone propionate; bid, twice daily.

*Grass mix 10 (40,000 protein nitrogen units/mL).

†Standard mite mix (10,000 allergy units/mL).

‡Standardized cat pelt (10,000 bioequivalent allergy units/mL).

§Not included in analysis.

Abbreviations used

- AUC: Area under the curve
- EAR: Early asthmatic response
- H₁: Histamine receptor subtype 1
- LAR: Late asthmatic response
- LTRA: Leukotriene receptor antagonist
- PC₂₀: Concentration of allergen that causes a 20% decrease in FEV₁

unavailable. Subjects were provided with 2 small brown envelopes containing either 2 placebo tablets, 1 desloratadine tablet (5 mg) and 1 placebo tablet, 1 montelukast tablet (10 mg) and 1 placebo tablet, or 1 desloratadine tablet and 1 montelukast tablet. Subjects were instructed to ingest the contents of one envelope without looking at them 26 hours before and the other 2 hours before allergen challenges, which were scheduled at intervals of 7 days or longer. No subject had previously used desloratadine, and only one subject had previously used montelukast. The investigator was blind to the treatments.

Allergen challenges

Subjects were challenged during the nonpollen season (ie, December through March) with the allergen that produced the largest response on skin prick testing. Serial 2-fold dilutions were prepared from 1:8 stock solutions diluted with sterile isotonic saline containing 0.4% phenol. Starting concentrations for inhalation were determined with the use of an algebraic prediction of allergen PC₂₀ by using the skin test end point and airway responsiveness to methacholine.¹¹ Allergen challenges began with the same concentration for each individual on each occasion. Allergens (Western Allergy Services, Victoria, British Columbia, Canada; see Table I) were aerosolized through a Wright Nebulizer (Roxon Medi-tech Ltd, Montreal, Quebec, Canada) calibrated to deliver 0.13 mL/min. Each concentration was inhaled during 2 minutes of tidal breathing through a mouthpiece and with nose clips in place. Ten minutes after each inhalation was completed, 2 technically acceptable FEV₁ maneuvers were performed 60 seconds apart. Inhalations were continued until

the highest postinhalation FEV₁ was at least 15% lower than the highest baseline FEV₁ (obtained from 3 reproducible flow-volume loops after a ≥20-minute rest period) or until the top concentration had been administered. The FEV₁ measurement was repeated at 10-minute intervals until no further decrease was observed.¹² The allergen PC₂₀ was then calculated algebraically.¹³ Salbutamol (200 µg) was administered to reverse the acute bronchoconstriction. Fluticasone (500 µg) was administered to prevent the late response and associated increase in airway responsiveness.¹⁴

Data analysis

Baseline FEV₁ data and log-transformed allergen PC₂₀ data were analyzed by using 2-way ANOVA, followed by pairwise comparison (least-squared difference) of means if applicable (Statistix Version 7.0; Analytical Software Corp., Tallahassee, Fla). Power calculation¹⁵ showed a 98% power to detect a 1 doubling concentration difference in allergen PC₂₀ in 10 subjects (and a 97% power in 9 subjects).

RESULTS

All 10 subjects completed the study with no adverse events. A post hoc decision to exclude the data of 1 subject (no. 10) was made on the basis of the observation that the screening allergen challenge and the placebo treatment allergen challenge were not reproducible. The overall significance of the data was not affected.

Mean ± SD baseline FEV₁ measurements after placebo (3.24 ± 0.55 L), desloratadine (3.25 ± 0.54 L), montelukast (3.27 ± 0.54 L), and combination (3.31 ± 0.57 L) therapy were not significantly different from each other (*P* = .19, ANOVA).

Comparison of geometric mean allergen PC₂₀ differences between combination (697 U/mL), montelukast (338 U/mL), desloratadine (123 U/mL), and placebo (104 U/mL) treatments was highly significant (*P* < .00001, ANOVA; Fig 1). The mean ± SEM log values after combination, montelukast, desloratadine, and placebo

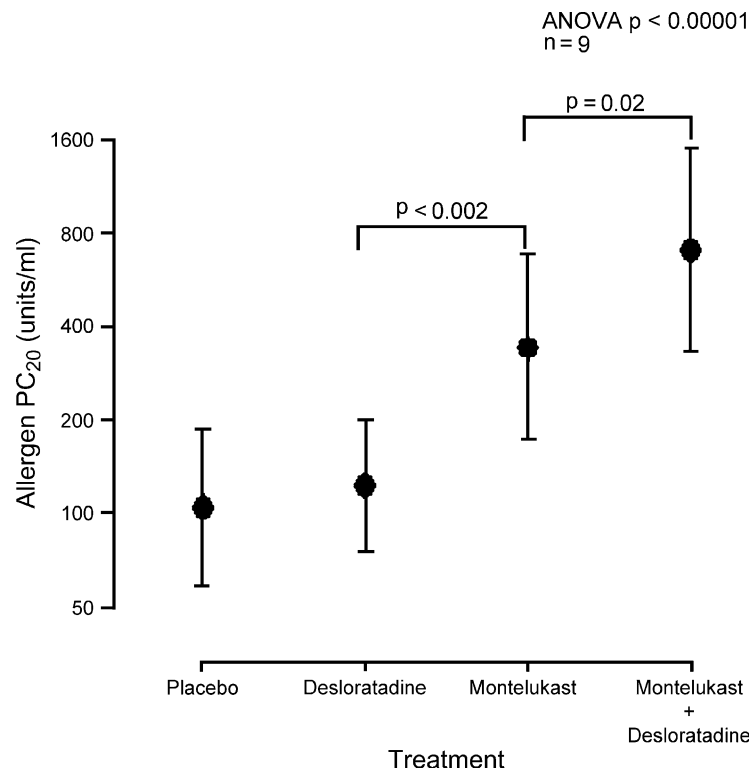


FIG 1. Allergen PC₂₀ (geometric mean) for each treatment. Extract units are generically identified as units per milliliter. Error bars represent SEM.

treatments were 2.8433 ± 0.3253 , 2.5295 ± 0.2979 , 2.0883 ± 0.2102 , and 2.0166 ± 0.2553 , respectively. Compared with placebo (least-squared difference comparison of means), combination therapy and montelukast therapy significantly increased allergen PC₂₀ ($P < .001$ for both). Allergen PC₂₀ with combination therapy was significantly greater than with montelukast alone ($P = .02$), and that with montelukast alone was significantly greater than that with desloratadine alone ($P < .002$). Desloratadine and placebo treatments produced similar results ($P > .2$). Analysis of individual fold increases in allergen PC₂₀ (combination vs placebo, montelukast vs placebo, and desloratadine vs placebo) indicated mean fold increases of 8.9-, 4.8-, and 1.4-fold or 3.2, 2.3, and 0.49 doubling concentrations, respectively.

DISCUSSION

We have demonstrated that 5 mg of desloratadine administered 26 hours and 2 hours before allergen inhalation does not protect against the EAR. We have also demonstrated that 10 mg of montelukast administered 26 hours and 2 hours before allergen inhalation increases allergen PC₂₀ by 2.3 doubling concentrations, whereas the combination increases allergen PC₂₀ by 3.2 doubling concentrations.

Desloratadine is the principal metabolite of the second-generation antihistamine loratadine. Although loratadine

had previously been shown to be ineffective in decreasing the EAR,¹⁶ desloratadine possesses superior pharmacokinetic and pharmacodynamic properties, has an excellent safety profile, and has been shown to exert anti-inflammatory effects.¹⁷ The lack of efficacy after desloratadine therapy reported here suggests that desloratadine alone does not protect against the EAR by blocking H₁ receptors on airway smooth muscle.

Montelukast is a leukotriene receptor antagonist (LTRA) with proved efficacy in asthma and exercise-induced bronchoconstriction¹⁸ and has been shown to significantly decrease the EAR to inhaled allergen.¹⁹⁻²¹ Our data are consistent with those in the existing literature on the effect of montelukast on the EAR, although we do show a slightly greater inhibition of the EAR after montelukast when changes in the maximal decrease in FEV₁ are equated to changes in doubling concentrations. In our study montelukast shifts the dose-response curve versus placebo more than 2 doubling concentrations. This is equivalent to a 75% decrease (vs an average of around 55% reported previously¹⁹⁻²¹) in the maximal decrease in FEV₁.

It is logical to postulate that the EAR to inhaled allergen could be additively or synergistically blocked by combining cysteinyl leukotriene receptor subtype 1 and H₁ receptor antagonist therapies. This effect was demonstrated *in vitro* more than 10 years ago in isolated human bronchi.²² Since then, only 2 studies investigating the effect of combination (antihistamine plus LTRA) therapy on the EAR could be identified. Roquet et al²³ investigated

the combination of high-dose zafirlukast (80 mg twice daily) and loratadine (10 mg twice daily) administered for 8 days on the EAR and LAR and found that combination therapy was more effective at inhibiting the EAR than either drug alone; however, the difference between the inhibition after zafirlukast was not significantly different from the inhibition after combination therapy. A more recent *in vitro* investigation of the H₁ antihistamine chlorpheniramine and the LTRA MK-571 documented a synergistic effect of the combination versus either drug alone in allergic isolated human bronchi.²⁴ We could identify no published data describing the effect on allergen-induced airway responsiveness after montelukast in combination with an antihistamine.

We provide evidence that the combination of 5 mg of desloratadine with 10 mg of montelukast administered at 26 hours and 2 hours before allergen inhalation increases allergen PC₂₀ by 3.2 doubling concentrations (8.9-fold) versus placebo. This is the first evidence of clinically significant inhibition of the EAR with clinically relevant doses of the combination of an antihistamine and an LTRA that is significantly greater than the inhibition with an LTRA alone. Because no effect was observed with desloratadine alone, the significantly greater combined efficacy is difficult to interpret. The magnitude of inhibition is similar to that achieved with 10 mg of inhaled sodium cromoglycate (76%), lower than that with 200 µg of salbutamol (97%), and substantially greater than that with single-dose (200 µg) beclomethasone dipropionate (<1%) reported as maximal decreases in FEV₁,²⁵ suggesting mast-cell stabilization as a possible mechanism.

There are several methods to assess the EAR, including area under the curve (AUC_[0-3h]), maximal decrease in FEV₁, and allergen PC₂₀. These differences in methodology present difficulties in data comparison and reinforce the issue of method standardization. Efficacy reported as AUC_(0-3h) represents changes in the airway that are occurring over 180 minutes, two thirds of which represents the spontaneous recovery portion of the EAR and one third of which represents the development of and the maximal response to the sensitizing agent. Comparison of AUC_(0-3h) data with data reported as changes in the maximal decrease in FEV₁ or allergen PC₂₀, both of which measure changes occurring in the first 60 minutes, is therefore extremely difficult. Reporting the EAR as maximal changes in FEV₁ requires the same dosing regimen and occasionally single-dose administration of allergen. Although single-dose administration protocols might raise concerns surrounding subject safety, the change in maximal decrease in FEV₁ can, at least in theory, be compared with the algebraic determination of allergen PC₂₀. Assuming a linear dose response, we estimate that a shift of 1 doubling concentration is approximately equivalent to a 50% change in the maximal decrease in FEV₁, a shift of 2 doubling concentrations is approximately a 75% change, a shift of 3 doubling concentrations is approximately an 87.5% change, and so on. Therefore allergen PC₂₀ reporting provides a more

precise discrimination between treatments that generate a 50% or greater change in the maximal decrease in FEV₁. The one major limitation to assessing airway response to inhaled allergen with this method is that it cannot be used to assess the LAR. Therefore the relevance of these data to the clinical features and management of asthma remains to be determined.

We present *in vivo* data supporting a synergistic effect of the combination of montelukast and desloratadine on the early response to inhaled allergen. The mechanism or mechanisms underlying the apparent synergism and the effect of the combination of montelukast and desloratadine on the LAR and associated events require further investigation.

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