Loratadine and montelukast administered in combination produce decongestion in an experimental feline model of nasal congestion

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ABSTRACT

Background: *Histamine and leukotrienes act to exert numerous local and systemic effects that contribute to the pathophysiology of allergic rhinitis. The aim of these experiments was to evaluate the nasal decongestant effects of loratadine and montelukast alone and in combination in a feline model of nasal congestion. We also studied the decongestant actions of the alpha-agonist adrenergic agonist D-pseudoephedrine with and without desloratadine.*

Methods: *Acoustic rhinometry was used to determine nasal cavity dimensions after intranasal compound 48/80. Cats were given D-pseudoephedrine (0.3 mg/kg) alone or in combination with desloratadine (5 mg/kg) 1 hour before nasal provocation with compound 48/80 (1%, 75 microliters) to either the left or right nasal passageway. Using a similar design, the nasal decongestant effects of montelukast (1 mg/kg) and loratadine (10 mg/kg) were studied alone and in combination.*

Results: *The addition of desloratadine to D-pseudoephedrine did not improve decongestant efficacy compared with each drug given individually. In contrast, when montelukast (1 mg/kg) was given in combination with loratadine (10 mg/kg), the decongestant activity was greater than when these drugs were administered separately. Sixty minutes after compound 48/80 provocation the nasal cavity volume ratio (volume ratio of the compound 48/80 treated/untreated nasal passageway) for the control, montelukast alone, loratadine alone, and the montelukast plus loratadine–treated groups were 0.20 ± 0.03, 0.24 ± 0.01, 0.28 ± 0.03, and 0.50 ± 0.03.*

Conclusion: *Concomitant montelukast plus loratadine produces a greater degree of nasal decongestion compared with montelukast or loratadine alone in an experimental model of nasal congestion.*

(Am J Rhinol Allergy 23, e17–e22, 2009; doi: 10.2500/ajra.2009.23.3365)

Key words: Acoustic rhinometry, allergic rhinitis, antihistamine, compound 48/80, desloratadine, histamine H_1-antagonist, leukotriene receptor antagonist, loratadine, montelukast, nasal decongestion

Allergic rhinitis is characterized by several symptoms including rhinorrhea, sneezing, pruritus, and nasal congestion. Prevalence of allergic rhinitis in the U.S. population ranges between 8 and 22%.[1,2] Untreated rhinitis often leads to sinusitis, otitis media, nasal polyps, and aggravation of bronchial asthma.[3] Additionally, the disease has a sizable impact on sleep, cognitive performance, and overall quality of life.[4–6] Several inflammatory cell types including eosinophils, basophils, T lymphocytes, and mast cells likely contribute to the complex and multifaceted pathophysiology of allergic rhinitis.[7] Mast cells, in particular, have been long recognized as playing an important role in type I hypersensitivity reactions. Mast cell mediators, including histamine and leukotrienes exert numerous local and systemic effects that contribute to the pathophysiology of allergic rhinitis.[8] In the upper airways, histamine plays a pivotal role in the early phase allergic nasal responses such as sneezing, rhinorrhea, pruritus, edema, and nasal obstruction.[9] Additionally, this biogenic amine acts as a stimulatory signal for the production of cytokines that contributes to late-phase inflammatory responses.[10,11] At least four histamine receptors subtypes (termed H_1, H_2, H_3, and H_4) are likely to contribute to the nasal actions of histamine. However, most of histamine-related upper airway symptoms are attenuated by H_1-antihistamines.[12–16]

Leukotrienes (including leukotriene B_4 [LTB_4] and cysteinyl leukotrienes; LTC_4, LTD_4, and LTE_4), like histamine, are involved in both early and late-phase allergic responses.[17] There are four distinct G-protein coupled receptors that mediated the actions of leukotrienes.[18,19] For LTB_4 there is BLT_1 and BLT_2. For the cysteinyl leukotrienes there is $CysLT_1$ and $CysLT_2$. Most of pathophysiological actions of leukotrienes relevant to allergic respiratory disease (in particular asthma) are mediated by activation of $CysLT_1$.[20,21] In the nasal passageways, cysteinyl leukotrienes elicit vascular leakage, vasodilatation, and edema.[22] Moreover, cysteinyl leukotrienes by (1) promoting inflammatory cell recruitment and activation (such as eosinophils) and (2) enhancing production of various cytokines are potent proinflammatory agents.[22] Intranasal challenge with LTD_4 in healthy subjects increases nasal airway resistance without causing pruritus or sneezing.[23] In ragweed-sensitive individuals challenged with antigen, nasal lavage concentrations of LTC_4, LTD_4, and LTE_4 are significantly increased.[24] The importance of leukotrienes in allergic rhinitis was underscored in a proof of concept study with a 5-lipoxygenase inhibitor almost 20 years ago when Knapp showed that zileuton attenuated allergen-induced nasal congestion in subjects with allergic rhinitis.[25] Subsequent studies with cysteinyl leukotrienes antagonists such as montelukast, pranlukast, and zafirlukast have indicated that these drugs decrease subjective symptoms assessment and objective measures of allergic rhinitis.[26–28] Recently, montelukast was given expanded approval (in addition to its asthma use) by the Food and Drug Administration for treatment of allergic rhinitis.[29,30]

Histamine and cysteinyl leukotrienes have complementary pathological contributions to early and late-phase upper airway allergic responses. We sought to explore the potential additive actions of cysteinyl leukotriene and histamine blockage on nasal cavity dimensions in an animal model of nasal congestion involving compound 48/80-induced mast cell mediator liberation.[31]

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MATERIALS AND METHODS

Measurement of Nasal Cavity Volume Using Acoustic Rhinometry

Male cats (4.0–6.5 kg; Harlen Sprague–Dawley, Madison, WI) were anesthetized with methohexital sodium (5 mg/kg. i.v. and supplemented with 0.5–1.0 mg/kg as required). Estimates of nasal

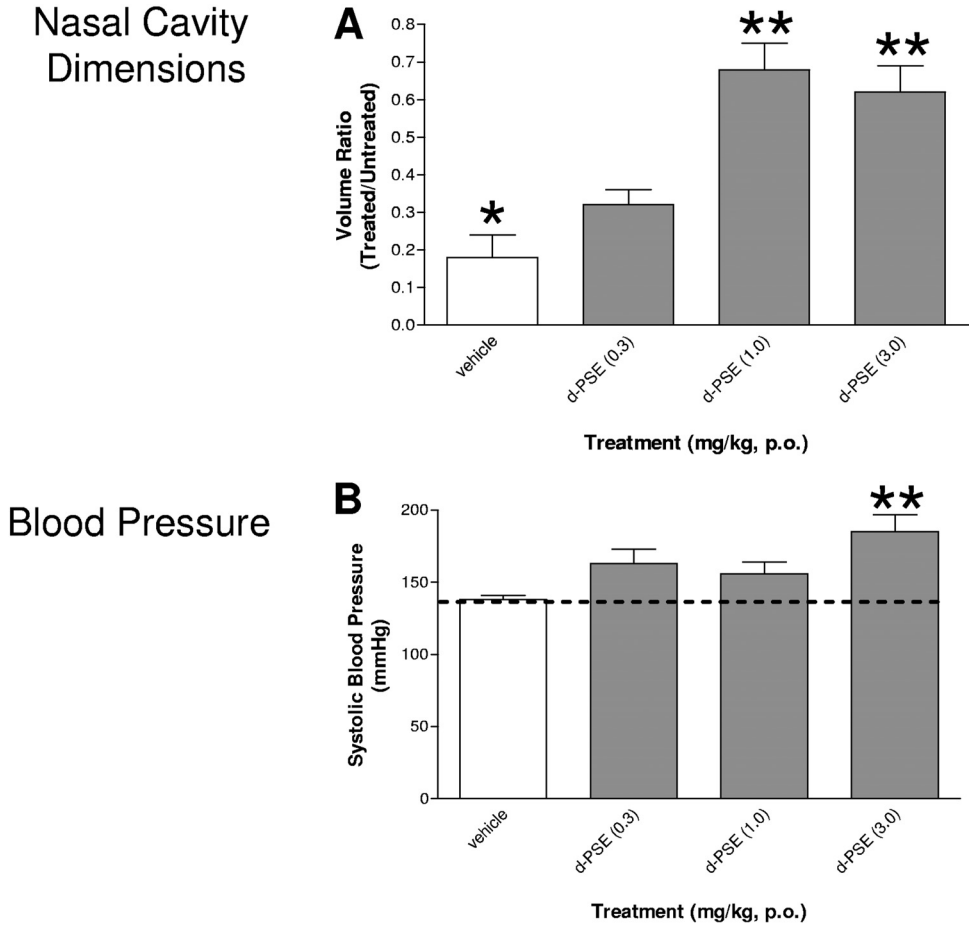

Figure 1. *Effect of D-pseudoephedrine (D-PSE) on the decrease in nasal cavity volume produced by intranasal compound 48/80. (A) Illustration of the effect of D-PSE (0.3–3.0 mg/kg, p.o.) on nasal cavity volume ratios 2 hours after oral administration* (i.e., *60 minutes after topical compound 48/80 application). (B) D-PSE (3.0 mg/kg, p.o.) significantly increased systolic blood pressure. Each bar represents the mean ± SEM (*$p < 0.05$ compared with time 0, which is not shown; **$p < 0.05$ versus vehicle group at 60 minutes post–compound 48/80 provocation, respectively; n = 4–6 animals/group).*

volumes were determined according to the methods of McLeod *et al*.[32] Briefly, the method involves evaluating the activity of nasal decongestants by studying decreases in nasal cavity volumes evoked by intranasal application of compound 48/80 (1%, 75 μL). Assessment of nasal dimensions was performed using an acoustic rhinometer purchased from NADAR (Aarhus, Denmark). Reflected sound waves from the nose were amplified and recorded. The data obtained were converted to area–distance function curves and were used to provide estimates of nasal volumes and minimum cross-sectional areas. The length of the nose piece was 3.2 cm. The distance measured from the nostril opening into the nasal cavity was 3.0 cm and was based on measurements of cast impressions made of the cat nasal passageways.[33]

Test drugs were given as a gelatin capsule (size 1; Torpac, Inc., Fairfield, NJ) 1 hour before nasal provocation with compound 48/80 to either the left or the right nares. Acoustic measurements were performed immediately before compound 48/80 was given (baseline) and 60 minutes after baseline. Consequently, the time frame for our efficacy measurement was 2 hours postoral treatment. Systolic blood pressure was measured at 2 hours after oral drug treatments using an ultrasonic Doppler flow detector (model 811-B; Park Medical Electronics, Inc., Aloha, OR). Blood samples were taken 0.5, 1.0, 1.5, and 2.0 hours posttreatment for analysis of plasma concentrations of montelukast, loratadine, and desloratadine.

In the first set of experiments, the ability of the α-adrenergic agonist decongestant, D-pseudoephedrine (0.3–3.0 mg/kg), to attenuate the nasal actions of compound 48/80 (1%), was examined. Next, we determined if the coadministration of an antihistamine with an α-adrenergic agonist could enhance decongestant efficacy compared with the nasal activity of these drugs given separately. Thus, in the second study, the effect of D-pseudoephedrine (0.3 mg/kg, p.o.) and desloratadine (5 mg/kg, p.o.) were evaluated alone and in combination. The dose of desloratadine selected for this study was based on the drug's ability (at the current dose level) to block topical histamine-induced nasal obstruction by 70% (data not shown). The dose of D-pseudoephedrine (0.3 mg/kg, p.o.) was chosen because it displayed submaximal nasal decongestant activity. The primary focus of our experiments was to examine the potential additive or synergistic nasal decongestant activity of an LTD_4 antagonist and a histamine H_1-receptor blocker. Thus, third, we gave increasing doses of montelukast (1.0–10 mg/kg, p.o.) to show the dose–response decongestant characteristics of this LTD_4 antagonist. Afterward, we studied the actions of a submaximum dose of loratadine (10 mg/kg, p.o.) and montelukast (0.3 mg/kg) administered separately and concomitantly.

Determination of Montelukast and Loratadine Plasma Concentrations

An ultra–performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) procedure has been developed. An Acquity UPLC BEH C18 column (50 × 2.1-mm interior diameter, 1.7 μm) was used as the analytical column. The mobile phase consisted of A (20/80 methanol/water, 0.01 M ammonium acetate) and B (0.01 M ammonium acetate in methanol + 0.6 mL/L of 10% acetic acid). A 1.0-minute gradient from 5% B to 95% B was used at a flow rate of 0.6 mL/minute. Under these conditions, montelukast, loratadine, desloratadine, and the internal standard eluted at 0.85, 0.82, 0.68, and 0.73 minutes, respectively. The UPLC eluant passed through a divert valve

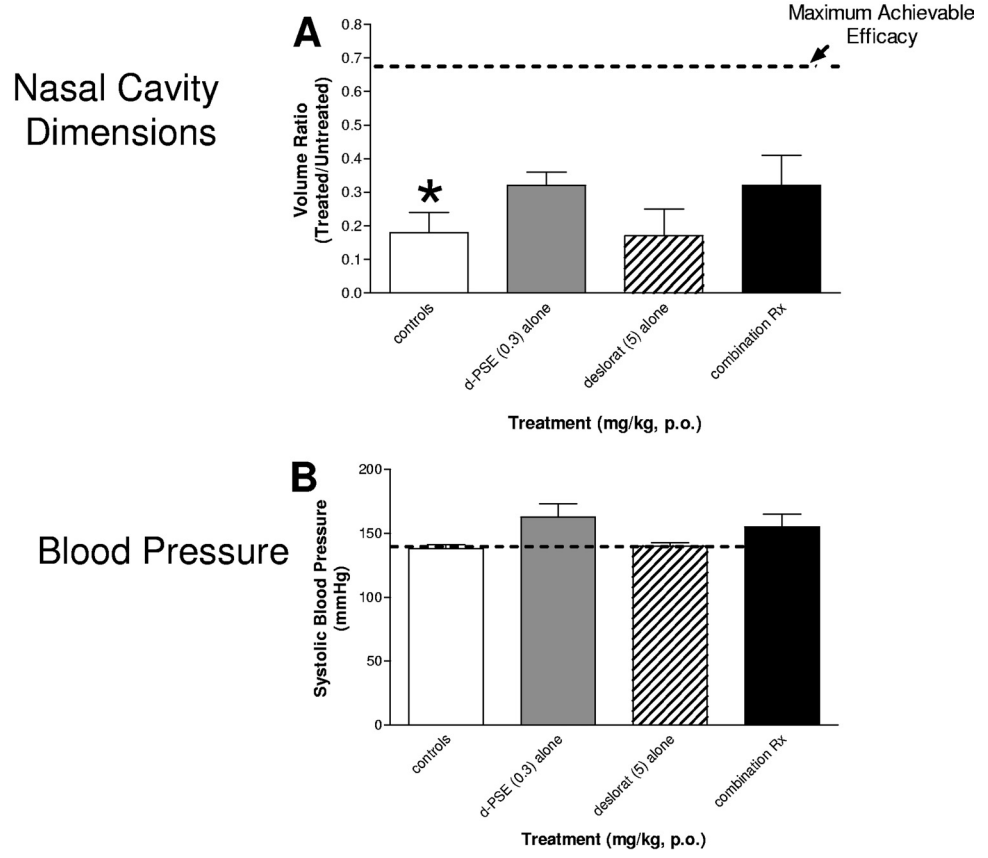

Figure 2. *Effect of combined oral desloratadine and D-pseudoephedrine (D-PSE) on nasal congestion due to compound 48/80. (A) Illustration of the effect of the desloratadine (5 mg/kg, p.o.) and D-PSE (0.3 mg/kg, p.o.) alone and in combination on decreases in nasal cavity volume ratios evoked by compound 48/80 provocation. (B) Display of the effect of combined desloratadine (5 mg/kg, p.o.) and D-pseudoephedrine treatment on systolic blood pressure. Each bar represents the mean ± SEM (*$p < 0.05$ compared with time 0, which is not shown; **$p < 0.05$ versus vehicle group at 60 minutes post–compound 48/80 treatment, respectively; $n = 4$–6 animals/treatment group; $n = 8$ in the control group).*

and was then introduced directly into the mass spectrometer source. The UPLC-MS/MS measurements were performed using a Sciex 4000 QTrap system linking with a Waters Acquity system. The mass spectrometer was operated in the positive electron spray ionization mode. The MS/MS measurements were performed using the selected reaction monitoring mode. The selected reaction monitoring transitions were selected by subjecting the protonated molecules to collision-induced dissociation in the collision cell with transitions of 586.3–568.3, 383.2–337.0, and 311.1–259.2 for montelukast, loratadine, and desloratadine, respectively. A protein precipitation procedure with a 1:6 plasma–acetonitrile ratio was used in the sample preparation. The limit of quantitation of this method reached 3 ng/mL based on a sample volume of 10 μL. This method shows good linearity between 3 and 1000 ng/mL. Plasma concentration-time data were subjected to pharmacokinetic analysis by noncompartmental methods using LIMS software (Watson, Philadelphia, PA).

Drugs

Compound 48/80 and D-pseudoephedrine was purchased from Sigma Chemical Co. (St. Louis, MO). Desloratadine and loratadine were synthesized at Schering-Plough Research.

Statistics

Nasal volumes were expressed as the ratio of the volume of the compound 48/80–treated nares versus the untreated nares.[31] Values displayed in the table and the figures represent the mean ± SEM of four to five animals per group. Data were evaluated using a nonparametric Kruskal-Wallis and Mann-Whitney *U* test. Statistical significance was set at $p < 0.05$.

RESULTS

Nasal Decongestant Effect of Desloratadine Combined with Pseudoephedrine

The D-pseudoephedrine (0.3–3.0 mg/kg) produced a dose-dependent nasal decongestion (Fig. 1 *A*). At 3 mg/kg, D-pseudoephedrine increased systolic blood pressure (Fig. 1 *B*) to 185 ± 12 mmHg compared with 138 ± 3 mmHg (control group). In the desloratadine/D-pseudoephedrine combination study, treatment groups included cats orally treated with D-pseudoephedrine (0.3 mg/kg), desloratadine (5 mg/kg), D-pseudoephedrine (0.3 mg/kg) plus desloratadine (5 mg/kg), and vehicle control. The baseline volume ratios of the experimental groups were not different from the control group. D-Pseudoephedrine (0.3 mg/kg, p.o.) produced a slight, nonsignificant increase in nasal patency (Fig. 2). Desloratadine alone did not inhibit nasal cavity volume reductions because of compound 48/80 challenge (Fig. 2 *A*). The combination of desloratadine/D-pseudoephedrine did not produce decongestant activity greater than D-pseudoephedrine alone (Fig. 2).

Nasal Decongestant Effect of Loratadine Combined with Montelukast

The nasal decongestant effects of increasing doses of oral montelukast are displayed in Fig. 3. Montelukast (10 mg/kg) was decongestive with no effect on blood pressure. In the loratadine/montelukast combination study, treatment groups included cats orally treated with montelukast (1.0 mg/kg) alone, loratadine (10 mg/kg) alone, montelukast (1.0 mg/kg) plus loratadine (10 mg/kg), or vehicle control. The baseline left/right nasal cavity volume ratios (before compound 48/80 provocation) for the control, montelukast (1.0 mg/

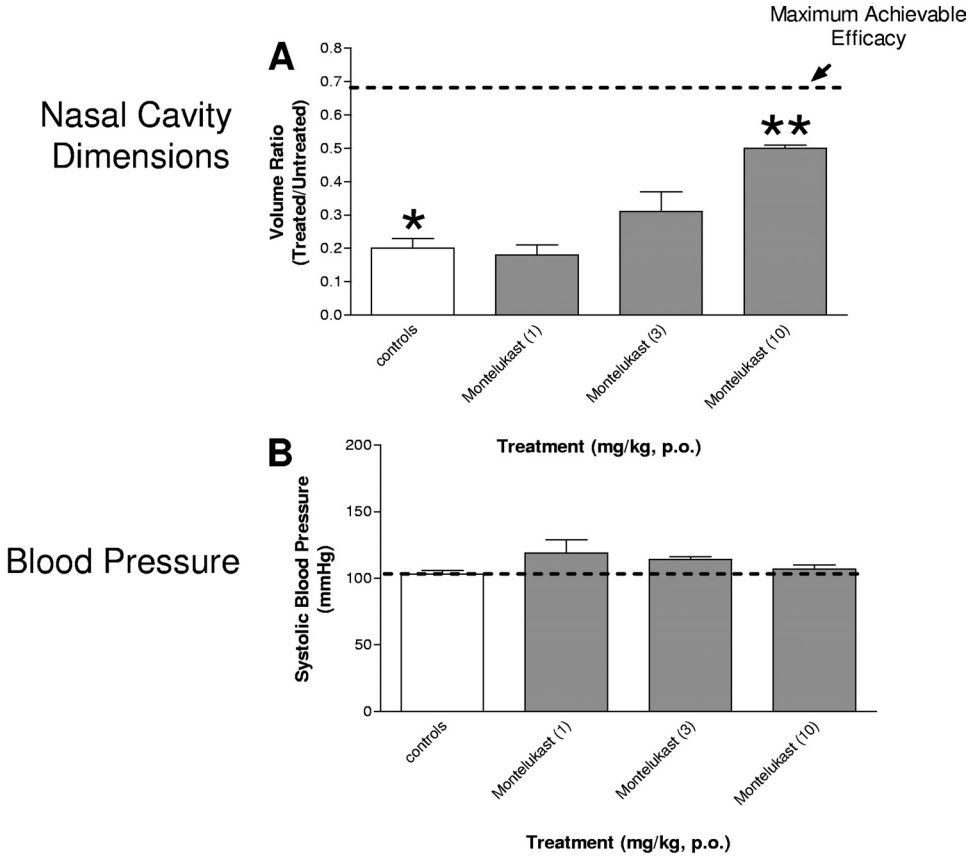

Figure 3. *Nasal decongestant effect of montelukast. (A) Illustration of the effect of montelukast (1.0–10 mg/kg, p.o.) on nasal cavity volume ratios 2 hours after oral administration* (i.e., *60 minutes after topical compound 48/80 application). (B) Montelukast did not significantly alter systolic blood pressure. Each bar represents the mean ± SEM (*$p < 0.05$ compared to time 0, which is not shown; **$p < 0.05$ versus vehicle group at 60 minutes post–compound 48/80, respectively; $n = 4$–6 animals/group).*

kg), loratadine (10 mg/kg), and montelukast (1.0 mg/kg) plus loratadine (10 mg/kg) experimental groups were 1.02 ± 0.02, 0.95 ± 0.02, 1.00 ± 0.04, and 0.96 ± 0.04, respectively, and were not statistically different from each other. Montelukast (1.0 mg/kg) and loratadine (10 mg/kg) administered separately failed to produce nasal decongestion (Fig. 4 *A*). However, in animals treated with montelukast (1.0 mg/kg) plus loratadine (10 mg/kg), nasal decongestion was evident. Table 1 shows that the montelukast/loratadine combination improved minimum cross-sectional areas.

DISCUSSION

We studied the potential decongestant additive effects of an histamine H_1-antagonist and an α-adrenergic agonist. Our results suggest that no greater decongestant benefit is derived from coadministration of an antihistamine with an α-adrenergic agonist relative to each drug class given separately. However, the main objective of our studies was to examine the possible additive or synergistic nasal decongestive activity of loratadine and montelukast in an experimental feline model of nasal congestion.[32,34,35] We found that montelukast produced a dose-dependent nasal decongestion in the cat. More interesting, we show that a low dose of montelukast when combined with loratadine attenuates the decreases in nasal volumes produced by compound 48/80. The magnitude of this decongestant activity was greater than the effects of these drugs given separately. Our data stand in contrast to a few clinical studies addressing the question of possible additive effects of montelukast plus loratadine treatment.[36–39] For example, Nayak *et al.*, in a multicenter, randomized, double-blinded, parallel, placebo-controlled trial, in patients with fall seasonal allergic rhinitis, montelukast combined with loratadine treatment did not show added nasal decongestion efficacy over singularly administered montelukast or loratadine.[38] In a similar study, Meltzer *et al.* found that concomitant montelukast plus loratadine improved rhinorrhea, nasal itching, and sneezing but did not significantly affect nasal congestion compared with montelukast or loratadine administration alone.[37] On the other hand, our findings are supported by Ciebiada *et al.*[39] who showed that in persistent allergic rhinitis patients a combination of montelukast plus desloratadine did produce a small but significant improvement in nasal congestion scores relative to either montelukast or loratadine alone.

The mechanism(s) underlying the improved decongestant effect of montelukast plus loratadine in our experiments is unknown and will require additional study. It is conceivable that combination treatment with an H_1-receptor antagonist and a leukotriene blocker could work collectively at several locations along the early phase and/or late-phase allergic pathways to produce additive or potentially synergistic nasal decongestant efficacy. Additional mechanisms beyond the effects montelukast plus loratadine on early and late-phase responses can be suggested to explained the enhanced nasal decongestant efficacy (over each drug administered alone) observed in our feline experiments. However, these proposals are less likely. For example, changes in the pharmacokinetic profiles of either loratadine or montelukast after combined administration could contribute to altered pharmacologic effects of these agents. However, we found that the plasma concentrations of montelukast, loratadine, and desloratadine (an active metabolite of loratadine) were not different when montelukast or loratadine were administered individually or in combination (Table 2). Thus, the enhanced nasal decongestant activity of montelukast plus loratadine is not related to altered plasma exposure of these drugs after coadministration. It is interesting to note that the plasma concentrations (Cmax) achieved in the cat after montelukast (1.0 mg/kg) or loratadine (10 mg/kg) were comparable with human exposures after therapeutic doses of these drugs.[40,41]

In summary, we studied the combined nasal decongestant effects of loratadine and montelukast, which blocks two prominent mast cell

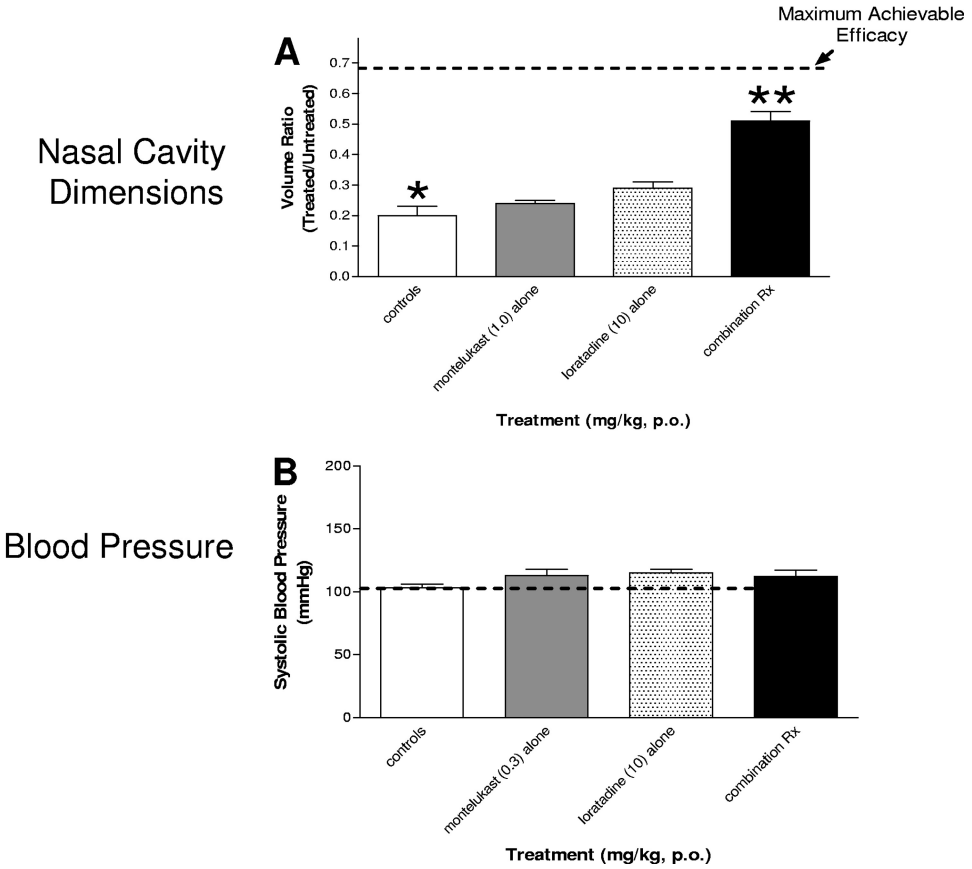

Figure 4. *Effect of combined oral montelukast and loratadine on compound 48/80–mediated nasal congestion. (A) Illustration of the effect of the montelukast (0.3 mg/kg, p.o.) and loratadine (10 mg/kg, p.o.) alone and in combination on decreases in nasal cavity volume ratios evoked by compound 48/80 challenge. Combined treatment with montelukast plus loratadine produced greater nasal decongestant activity compared with the decongestant effect of these drugs administered individually. (B) Montelukast (0.3 mg/kg, p.o.) and loratadine (10 mg/kg, p.o.) alone or in combination had no effect on systolic blood pressure. Each bar represents the mean ± SEM (*$p < 0.05$ compared with time 0, which is not shown; **$p < 0.05$ versus vehicle group at 60 minutes post–compound 48/80 provocation, respectively; n = 4–6 animals/group).*

Table 1 **Effect of montelukast and loratadine alone and in combination on nasal minimum cross-sectional areas**

Treatment Group	*n*	Baseline Values (cm^2)	Treatment Effect (cm^2)
Vehicle	6	0.045 ± 0.001	0.022 ± 0.004*
Montelukast (1.0) alone	4	0.046 ± 0.002	0.024 ± 0.003
Loratadine (10) alone	5	0.045 ± 0.004	0.029 ± 0.004
Combination Rx	5	0.045 ± 0.002	0.036 ± 0.002**[a]

Values represent the mean ± SEM.
*$p < 0.05$ compared with baseline values; **$p < 0.05$ vs vehicle group; [a]$p < 0.05$ compared with montelukast alone.*

Table 2 **Pharmacokinetic profile of montelukast and loratadine (Cmax values)**

Treatment Group	Montelukast (μM)	Loratadine (μM)	Desloratadine (μM)
Montelukast (1.0) alone	0.07 ± 0.01	—	—
Loratadine (10) alone	—	0.18 ± 0.14	0.07 ± 0.03
Combination Rx	0.03 ± 0.02	0.11 ± 0.05	0.08 ± 0.03

Values represents the mean ± SEM (n = 4–5) Cmax values determined over the course of the experiment.

agents, histamine and leukotrienes, respectively. Our studies indicate that, in an experimental nasal congestion model, combination oral treatment with montelukast and loratadine produces greater nasal decongestion efficacy compared with when these drug are given separately.

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