Azelastine and budesonide (nasal sprays): Effect of combination therapy monitored by acoustic rhinometry and clinical symptom score in the treatment of allergic rhinitis

Natalia Zanellato Fabbri, Ph.D., Eduardo Abib-Jr, Ph.D., and Ricardo de Lima Zollner, Ph.D.

ABSTRACT

The aim of this study was to objectively evaluate the effects of intranasal therapy with azelastine (AZE), budesonide (BUD), and combined AZE plus BUD (AZE/BUD) using a nasal provocation test (NPT) and acoustic rhinometry in patients with allergic rhinitis. A randomized, single-blind, crossover study with three treatment sequences was used. Thirty patients with persistent AR received the three treatments using a nasal spray twice daily for 30 days and were evaluated by an NPT with histamine before and after each period of treatment. The treatment comparison, assessed by the nasal responsiveness to histamine, was monitored based on subjective (symptom score) and objective parameters (acoustic rhinometry). The minimal cross-area 2 (MCA2) was measured by acoustic rhinometry at 1, 4, 8, and 12 minutes after NPT for each histamine concentration administered (0.5, 1, 2, 4, and 6 mg/mL) up to at least a 20% reduction in the MCA2 from baseline (NPT_{20}). The subjects were scored regarding nasal response encompassing histamine dose and time after histamine administration that caused nasal obstruction (NPT_{20} score) to assess the treatments' effects. Combination therapy produced a significant increase in baseline MCA2, viz., the improvement of nasal patency ($p = 0.005$). The symptoms score was significantly decreased after treatment with AZE ($p = 0.03$), BUD ($p < 0.0001$), and AZE/BUD ($p < 0.0001$), compared with pretreatment. The NPT_{20} score was significantly higher ($p = 0.0009$) after AZE/BUD, compared with AZE and BUD on their own. Thus, AZE therapy combined with BUD might provide more therapeutic benefits than the isolated drugs for improving nasal patency.

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Pharmacologic treatment for allergic rhinitis (AR) includes intranasal and oral antihistamines, intranasal and oral glucocorticosteroids, leukotriene receptor antagonists, cromones, ipratropium bromide, decongestants, subcutaneous-specific immunotherapy, and intranasal allergen-specific immunotherapy. Therapy guidelines for AR recommend new-generation oral H_1-antihistamines and intranasal corticosteroids as the main treatment.[1]

Antihistamines control the symptoms of AR with a rapid onset of effects.[2] The effects of H_1-antihistamines include decreased eosinophilic and neutrophilic cell infiltration, decreased eosinophil cationic protein levels, and expression of intercellular adhesion molecule 1 in nasal lavages after allergen challenge and inhibition of the allergen-induced release of mast cell mediators, histamine, and tryptase from the nasal mucosa.[3] In addition to its antihistamine and antiallergic effects, azelastine (AZE) has anti-inflammatory properties. It reduces the inflammatory mediator levels, including nasal eosinophil cationic protein, tryptase, and intercellular adhesion molecule 1. Intranasal AZE therapy decreases sneezing and nasal secretions and improves the baseline symptom scores after histamine nasal challenge.[4]

Intranasal corticosteroids are the most effective medication class for controlling the symptoms of AR.[5] Corticosteroids reduce the transcription factors that regulate gene expression, preventing several events associated with inflammatory cell recruitment and activation. Intranasal corticosteroid in continuous treatment reduces the nasal responsiveness to histamine and methacholine.[6]

Despite there being several therapies that are currently available for AR, patients do not always achieve symptom relief with a single-agent therapy.[7] Antihistamines and corticosteroids are routinely prescribed together; however, there are few clinical studies indicating that combination therapy with these agents is more effective than monotherapy.[7,8] Recently, randomized trials have studied the intranasal antihistamines and efficacy of corticosteroids, when comparing single

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and combined therapy in patients with AR. These studies[7,8] used a symptom score and quality-of-life questionnaire to evaluate the drug efficiency and verified that combined therapy had a better effect than drug monotherapy.[7–10]

Drug effectiveness can be assessed by using the nasal challenge protocol, which provides convenient access to the application of appropriate agents in the nasal chamber.[11] The nasal provocation test (NPT) is a standardized method[12] used to diagnose suspected allergies and a useful tool for studying the pathophysiological mechanisms involved in allergic inflammation. In this test, reactions are observed in response to potential allergens or to histamine placed in the nasal cavity. Among other symptoms, sneezing, nasal secretion, itchiness, lacrimation, and swelling of the nasal mucosa are considered indications of an inflammatory reaction.

Ordinarily, objective methods that monitor nasal patency include rhinomanometry and acoustic rhinometry. These techniques have been validated and are standardized for clinical use in Europe and scientific research in the United States.[13] Acoustic rhinometry measures cross-sectional areas and the volume of the nasal cavity to objectively define the structure of the nasal passage. Several topographical measurements of acoustic rhinometry have been described, such as minimal cross-sectional area (MCA), nasal volume, and distance between the nostril and nasopharynx in rhinograms. The second notch in the rhinogram, MCA 2 (MCA2), represents the anterior portions of the inferior turbinate or middle turbinate.[14]

The aim of this study was to evaluate the effects of intranasal therapy with AZE and budesonide (BUD; isolated and combined) using NPT and acoustic rhinometry in patients with AR.

MATERIALS AND METHODS

Study Subjects

Fifty patients were recruited from the University Hospital, University of Campinas, Brazil, with a history of at least 2 years of persistent rhinitis presenting significant current clinical rhinitis symptomatology. The study protocol was approved by a National Institutional Review Board of the Faculty of Medical Science of University of Campinas and conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent before participation in the study. The patients underwent a screening evaluation that included clinical history, physical examination (anterior rhinoscopy), and standardized aeroallergen (*Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Blomia tropicalis*, *Blattella germanica*, *Periplaneta americana*, cat dander, dog dander, and three regional specific fungi species) skin-prick tests (FDA Allergenic LTDA, RJ, Brazil). Patients with a diagnosis of persistent AR (based on the Allergic Rhinitis and Its Impact on Asthma[1] classification), aged between 18 and 35 years, and positive for aeroallergen skin-prick test were included in the study. The exclusion criteria were as follows: severe anatomic abnormalities in the nasal cavity (detectable by anterior rhinoscopy), significant concomitant medical condition (including severe asthma, chronic rhinosinusitis, and patients with other immunologic diseases), pregnancy or breast-feeding women, and smokers.

Nine patients were excluded because of a negative prick test, three for poor adherence to treatment, and eight did not complete the study for private reasons. The study population consisted of 30 patients (10 female and 20 male patients, aged between 18 and 32 years; mean, 25.39 years). None of the subjects had received systemic or topical corticosteroids or systemic or topical antihistamines for a period of at least 2 weeks before enrollment.

Sample Size

The sample size was determined based on the MCA2 results (mean and SD; $n = 30$ patients) of a previous pilot study, which suggested an effective size of 2.23, calculated by mean of differences (0.38 ± 0.17) with an error of 0.05 (two tailed) and overall power ($1 - \beta$) of 80%. Twenty-eight randomized subjects per treatment arm was sufficient to achieve 95% power.

Study Design

This was a randomized, single-blind, crossover study with three periods, performed in Brazil from January 2011 to November 2012.

The subjects were trained to self-administer twice daily (at awakening and at bedtime) either (A) 1 spray (0.14 mg/mL) in each nostril, or (B) 1 spray (0.64 mg/mL) in each nostril or both nasal sprays (1 spray of each drug in each nostril). Each treatment period lasted 30 days, and the washout period was 7 days. During the washout period, patients used saline solution (0.9% NaCl), as during the treatment period (Fig. 1 *A*).

During the study period, the patients were instructed not to use any other drug. Nasal responsiveness to histamine was monitored based on subjective (symptom score) and objective parameters (acoustic rhinometry) to compare the treatments (1–6 visits).

Blinding and Randomization

Subjects were randomized to the sequence of administration of each one of the three treatments AZE, BUD, or AZE/BUD. Randomization occurred in a 1:1:1 ratio and all subjects were treated with the three drugs in three different periods. Aiming for blind treatment assignment, the identities of nasal spray bottles were

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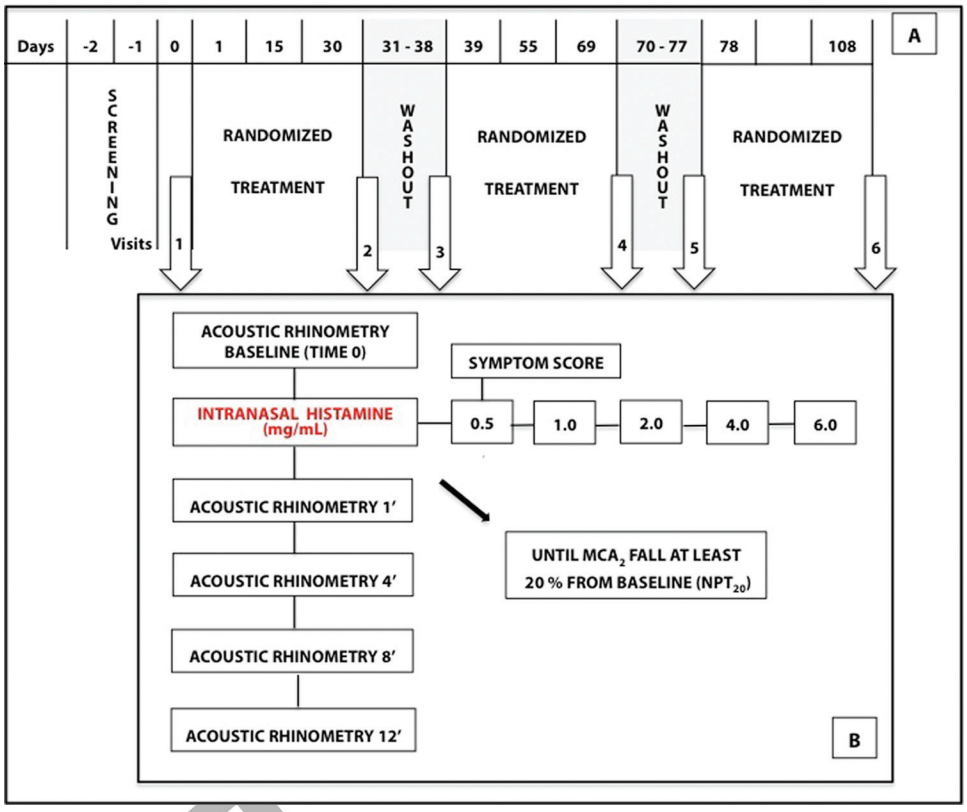

Figure 1. *(A) Study design. Screening, randomized treatments, and washout periods are shown. (B) Nasal provocation test (NPT) protocol assessment by acoustic rhinometry and clinical score are presented.*

masked. The investigator retained the blind randomization codes.

Histamine Spray Challenge

Histamine (2-[4-imidazolyl] ethylamine) diphosphate salt (Sigma-Aldrich Corp., St. Louis, MO) was dissolved in sterile saline solution (0.9% NaCl) and diluted to the following concentrations: 0.5, 1.0, 2.0, 4.0, and 6.0 mg/mL for use in the same day. After acoustic rhinometry measurements (baseline), histamine was administered in both nostrils (0.5 mg/mL per nostril) *via* nasal spray.

A second histamine dose was applied if the subject did not present nasal obstruction up to 12 minutes after the first administration, and this was continued as necessary. The histamine doses that were necessary to obtain the decreased nasal patency could be cumulative because of the addition of earlier histamine administrations (Table 1).

Acoustic Rhinometry

A properly fitted nosepiece was selected for each subject, and special care was taken not to distort the nasal valve anatomy during the assessment. Four curves of acoustic rhinometry were used to ensure the results were reproducible. The parameter analyzed was the total MCA2, *i.e.*, the right MCA2 + left MCA2. All data were supplied automatically by Naris software (GM Instruments, Ashgrove, Kilwinning, U.K.). The rhinometry procedures were performed according to the recommendations of the "Consensus Report on Acoustic Rhinometry and Rhinomanometry."[15]

Before acoustic rhinometry measurements (GM Instruments), the subjects were acclimatized for at least 30 minutes (controlled temperature and humidity), and each nostril was washed with 5 mL of saline solution warmed to 37°C. After 10 minutes, baseline acoustic rhinometry (time 0) was assessed followed by immediate histamine application. Acoustic rhinometry was performed to measure MCA2 at 1, 4, 8, and 12 minutes after NPT for each histamine dose administered until nasal obstruction occurred. MCA2 was monitored from the 1st minute after histamine administration until 64 minutes (Table 1; "time after NPT" column) according to nasal response (nasal obstruction). Histamine administration and acoustic rhinometry measurement were stopped when nasal obstruction occurred (*i.e.*, MCA2 reduction was observed).

Symptoms Score

Clinical symptom scores, based on a study by Lebel *et al.*,[16] were acquired during nasal challenge and evaluated as indicated in Table 2. The subjects were instructed by the investigator to self-evaluate their symptoms, and the number of sneezes was counted by the investigator. The compound symptom score was

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Table 1 **Schedule showing the sequence of histamine administrations in NPT, histamine concentrations administered, histamine doses, and the protocol of acoustic rhinometry measurements: Time after NPT and NPT_{20} score**

Histamine Administration	Histamine Concentration (mg/mL)	Histamine Dose	Time after NPT (min)	Score NPT_{20}
1st	0.5	0.5	1	0.5
			4	2
			8	4
			12	6
2nd	1.0	1.5	14	21
			17	25.5
			21	31.5
			25	37.5
3th	2.0	3.5	27	94.5
			30	105
			34	119
			38	133
4th	4.0	7.5	40	300
			43	322.5
			47	352.5
			51	382.5
5th	6.0	13.5	53	715.5
			56	756
			60	810
			64	864

NPT = nasal provocation test; NPT_{20} = 20% reduction in nasal patency, as defined as a fall in MCA2 from baseline.)

Table 2 **Clinical score based on a study by Lebel *et al.*[14]**

Sneezing	3–4	1
	>5	3
Rhinorrhea	Anterior moderate	1
	Posterior moderate	1
	Important anterior and posterior	3
Blockade	Breathing with difficulty	1
	One nostril is blocked	2
	Both nostrils are blocked	3
Pruritus	Nose	1
	Palate or ear	1
	Eyes	1

immediately applied after nasal challenge to evaluate the number of sneezes; amount of rhinorrhea; nasal blockade sensation; and nasal, ear, palate, and eye pruritus. The total score was recorded to compare the symptom score before and after each treatment.

Safety Assessment

Serious adverse events, vital signs, and systemic reactions were evaluated.

Study Protocol

Subjects were submitted to NPT before and after each period of treatment. Nasal histamine was administered after baseline acoustic rhinometry, and both score symptoms and acoustic rhinometry measurements were immediately applied. Histamine was administrated in progressively increasing doses and MCA2 evaluations were measured by consecutive acoustic rhinometry and maintained until a nasal response occurred (nasal obstruction; Fig. 1 *A*).

The criterion for a positive response was at least a 20% reduction in nasal patency, as defined as a fall in MCA2 from baseline (NPT_{20}). NPT was stopped when a positive response occurred.

The overall study protocol is depicted in Fig. 1 *B*.

After reaching NPT_{20}, the test was stopped and the following parameters were recorded: decrease in MCA_2 from baseline (%), histamine dose, and the time after histamine administration. These parameters represent the nasal patency variation marker. The subjects were scored regarding nasal response encompassing histamine dose and time after histamine administration, which caused NPT_{20} (NPT_{20} score) to assess the treatment effects (Table 2).

Therefore, the NPT_{20} score = total histamine dose administered × total time to obtain NPT_{20}.

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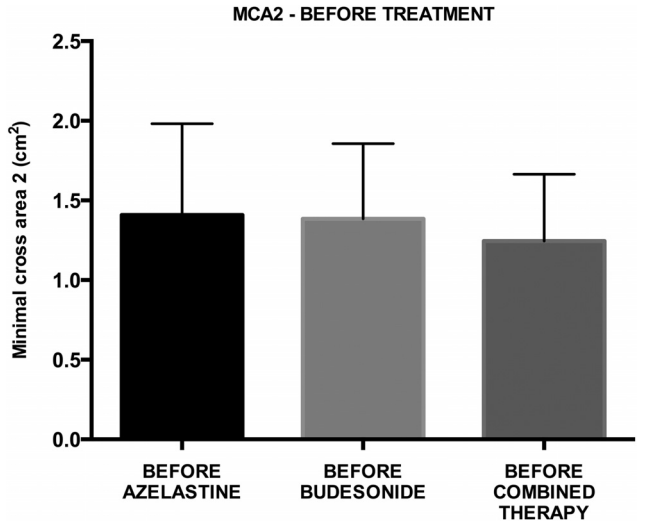

Figure 2. Minimal cross-sectional area 2 (MCA2) before treatments—statistical analyses did not indicate significant differences among the MCA2 baselines. The data were analyzed using ANOVA and Tukey's multiple comparison test.

Statistics

Data are expressed as means and SD and described between brackets for the variables. The MCA2 and symptom score data were analyzed by Wilcoxon signed-ranks test to compare pre- and posttreatments. The NPT_{20} score data were analyzed by one-way ANOVA and Dunn's multiple comparison tests to identify significant differences between treatments. All values of $p < 0.05$ were considered statistically significant using a 95% CI. Graph Pad Prism 5 software (Graph Pad, Inc., San Diego, CA) was used for statistical analysis.

RESULTS

The combined nasal sprays were well tolerated by the patients in this study; the most commonly reported adverse effect was a bitter taste (73%). No other adverse events were reported.

MCA2 Baseline Characteristics

ANOVA was used for statistical analysis of baseline MCA2 to compare nasal patency before each treatment (1, 3, and 5 visits; Fig. 1). We used this analysis to test the washout period efficacy. There was no difference between baseline MCA2 ($p = 0.07$) for the groups. Tukey's multiple comparison test did not present any difference in means (CI 95%). Therefore, there was no interference among treatments (sequence effects; Fig. 2).

MCA2 Baselines before and after Treatments

Baseline MCA2 values (before nasal challenge) were compared by Wilcoxon multiple comparison test to evaluate the treatment effects on nasal patency. The subjects treated with AZE displayed a significant decrease (before treatment mean, 1.40 ± 0.57; after treatment mean, 1.2 ± 0.41; $p = 0.004$) in baseline MCA2 in contrast to BUD treatment, which produced significant improvements (before treatment mean, 1.38 ± 0.47; after treatment mean, 1.52 ± 0.41; $p = 0.01$). Combined therapy also produced a significant increase in baseline MCA2, improving the nasal patency (before treatment mean, 1.24 ± 0.42; after treatment mean, 1.42 ± 0.35; $p = 0.005$; Fig. 3).

MCA2 after NPT

The nasal patency was evaluated during the NPT procedure and compared before and after each treatment (Fig. 4). There was a significant decrease in MCA2 after AZE therapy (before treatment mean, 1.01 ± 0.42; after treatment mean, 0.87 ± 0.29; $p = .01$), suggesting that AZE alone did not protect nasal patency after NPT. In contrast, the treatment with BUD (before treatment mean, 0.99 ± 0.35; after treatment mean, 1.10 ± 0.26; $p = 0.006$) and combined treatment (before treatment mean, 0.85 ± 0.32; after treatment mean, 1.02 ± 0.27; $p = 0.002$) significantly increased MCA (under nasal challenge) after treatment.

NPT_{20} Score after Treatment

The NPT_{20} score was significantly different ($p = 0.0009$) for AZE (13.64 ± 17.21), BUD (11.43 ± 9.96), and AZE/BUD (20.71 ± 14.54), indicating a significant increase in histamine dose and time for the histamine administration that caused NPT_{20}. Dunn's multiple comparison tests did not show rank sum differences between AZE versus BUD (4.5), but showed a significant difference between AZE and AZE/BUD (−19.50), BUD versus AZE/BUD (−24.00). The combined drugs showed a higher NPT_{20} score than AZE and BUD alone, suggesting better nasal effects (Fig. 5).

Clinical Score

All treatments were able to decrease the clinical score during NPT. There were significant differences in symptom scores after treatments with AZE (before treatment mean, 5 ± 2.43; after treatment mean, 3.82 ± 2.79; $p = 0.04$), BUD (before treatment mean, 5.85 ± 1.75; after treatment mean, 3.10, ± 1.77; $p < 0.0001$), and combined drug therapy (before treatment mean, 5.78 ± 2.57; after treatment mean, 1.96 ± 1.34; $p < 0.0001$; Fig. 6).

DISCUSSION

Pharmacologic treatment, based on the current guidelines, is not effective in all patients with AR, and around one-third of patients present uncontrolled symptoms even under treatment, particularly conjunc-

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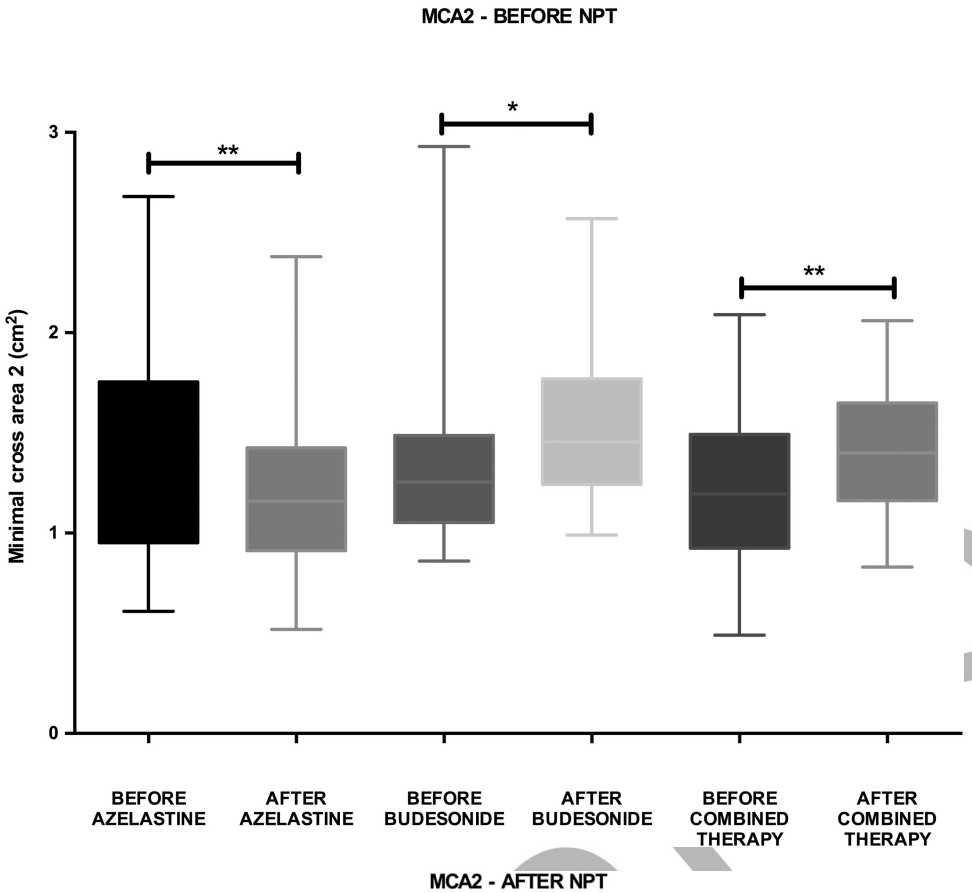

Figure 3. *Effect of treatments on nasal patency. Azelastine (AZE) produced a significant decrease in baseline minimal cross-sectional area 2 (MCA2), budesonide (BUD) treatment, and combined therapy produced significant increases in baseline MCA2, improving the nasal patency.*

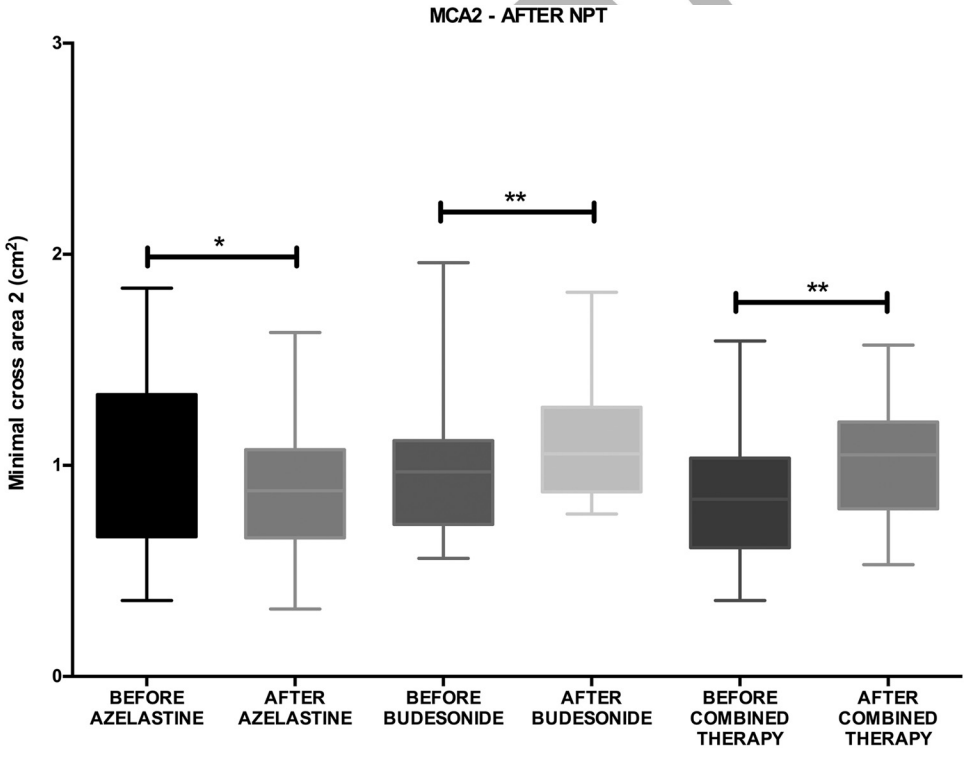

Figure 4. *Effect of treatments on nasal patency after nasal provocation test (NPT). Minimal cross-sectional area 2 (MCA2) decreases after azelastine (AZE) treatment. In contrast, budesonide (BUD) and combined therapy significantly increase MCA2 after nasal challenge.*

tivitis and nasal obstruction.[17] In 2012, the Food and Drug Administration approved a novel formulation of AZE and fluticasone[18] (delivered in the same device) for the treatment of AR, based on the results of a multicenter, randomized, double-blind, placebo-controlled trial. This study[7] showed a superior efficacy of the aforementioned formulation over intranasal fluticasone and intranasal AZE monotherapy in patients

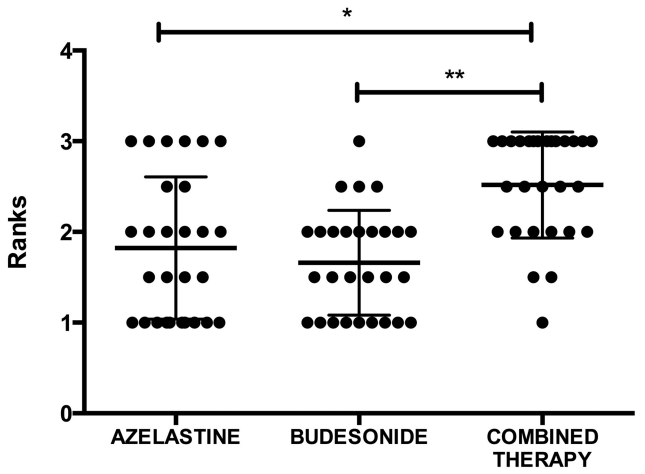

Figure 5. Twenty percent reduction in nasal patency, as defined as a fall in MCA2 from baseline (NPT_{20}) scores before and after treatments. The analysis of the scores after budesonide (BUD) and combined therapy indicates a significant increase in NPT_{20} score; however, combined therapy showed a higher statistical significance, suggesting a higher efficacy for the combined drugs, when compared with treatments for each drug alone.

with AR, as assessed using just symptom scores. In the present study, a compound clinical score was used as a subjective evaluation that assessed the overall nasal, ocular, ears, and palate symptoms. The clinical score[16] used in our study was applied with the aim of assessing the nasal response to NPT. We observed that all treatments were able to decrease scores for symptoms during NPT, but BUD and AZE/BUD decreased the score for symptoms with a higher statistical significance than AZE. The combined therapy was more effective in symptom reduction, with a 66.12% improvement versus 47% improvement when using BUD alone. Our results are in accordance with recent publications[7,8] examining combinations of nasal antihistamines and corticosteroids, as assessed by clinical scores or using a visual analog scale.

Although subjectively appraised, the effects of combined treatment with intranasal antihistaminic and corticosteroids on nasal obstruction have not been objectively evaluated in clinical trials. Nasal congestion is the most frequent complaint of patients with AR. Previous studies[19,20] have indicated that the correlation between objective evaluation and subjective perception of nasal obstruction can be contradictory. The feeling of nasal congestion is caused by a combination of factors, including nasal resistance to airflow and more subjective changes such as sinus congestion, eustachian tube function, and cool air receptors in the nasal mucosa, whereas nasal obstruction is associated with increased nasal resistance, decreased cross-sectional area, and decreased nasal cavity volume.[20]

The aim of this study was to objectively evaluate the effects of intranasal therapy with AZE and BUD (isolated and combined), highlighting the major symptom of AR—nasal obstruction. The NPT with histamine, evaluated by acoustic rhinometry, allowed the assessment of changes in nasal patency under nasal stimulation, before and after each treatment. Histamine is a good marker of the nasal vasomotor response and neuroreflex as it acts both directly at the mucosal level and through nervous reflexes on vessels and glands, producing sneezing, itching of the nose, mucosal edema and, consequently, nasal congestion.[21,22] We used a model of NPT with histamine to mimic the alterations found in atopic hypersensitivity, modifying the nasal compartment in a transitory manner to investigate the effects of treatments.

The method to objectively evaluate nasal patency used in this study is reproducible, noninvasive, fast, easy, and low cost. In addition, the procedure provides the identification of changes in the anatomic structures of the nasal cavity immediately after stimulus. Acoustic rhinometry can determine changes in the nasal chamber by measuring cross-sectional areas in the nasal cavity.[15]

The MCA2 analysis before the nasal challenge, considering pre- and posttreatment, shows that AZE was unable to improve nasal obstruction. In contrast to AZE, the analysis of the effects of BUD and AZE/BUD treatment showed a significant improvement in MCA2. However, AZE/BUD provided better results, improving nasal patency with a higher MCA2 than BUD. This result suggests that drug association decreases the time latency for nasal protection in a more efficient manner than AZE or BUD on their own.

On the other hand, after nasal challenge, the patients treated with BUD ($p = 0.02$) showed a lower reduction in nasal patency than patients treated with AZE. The MCA2 data from patients treated with AZE/BUD confirm the favorable effect of this drug association. The nasal response to NPT was much lower ($p = 0.002$) than that observed for BUD treatment. These results corroborate the hypothesis that the combination of these drugs is better than monotherapy for the control of nasal obstruction.

NPTs may induce immediate and/or late responses. The European Academy of Allergy and Clinical Immunology recommend monitoring the nasal response at 5, 10, 20, 30, 45, and 60 minutes poststimulus.[23] Our data were analyzed considering the nasal patency from the 1st minute after histamine nasal administration until 64 minutes poststimulus, with regard to the nasal response. This method allowed the characterization of the onset of action and also the maintenance of the effect of drugs on nasal patency under nasal provocation. The NPT_{20} score was used to compare two variables before and after treatments—time and histamine

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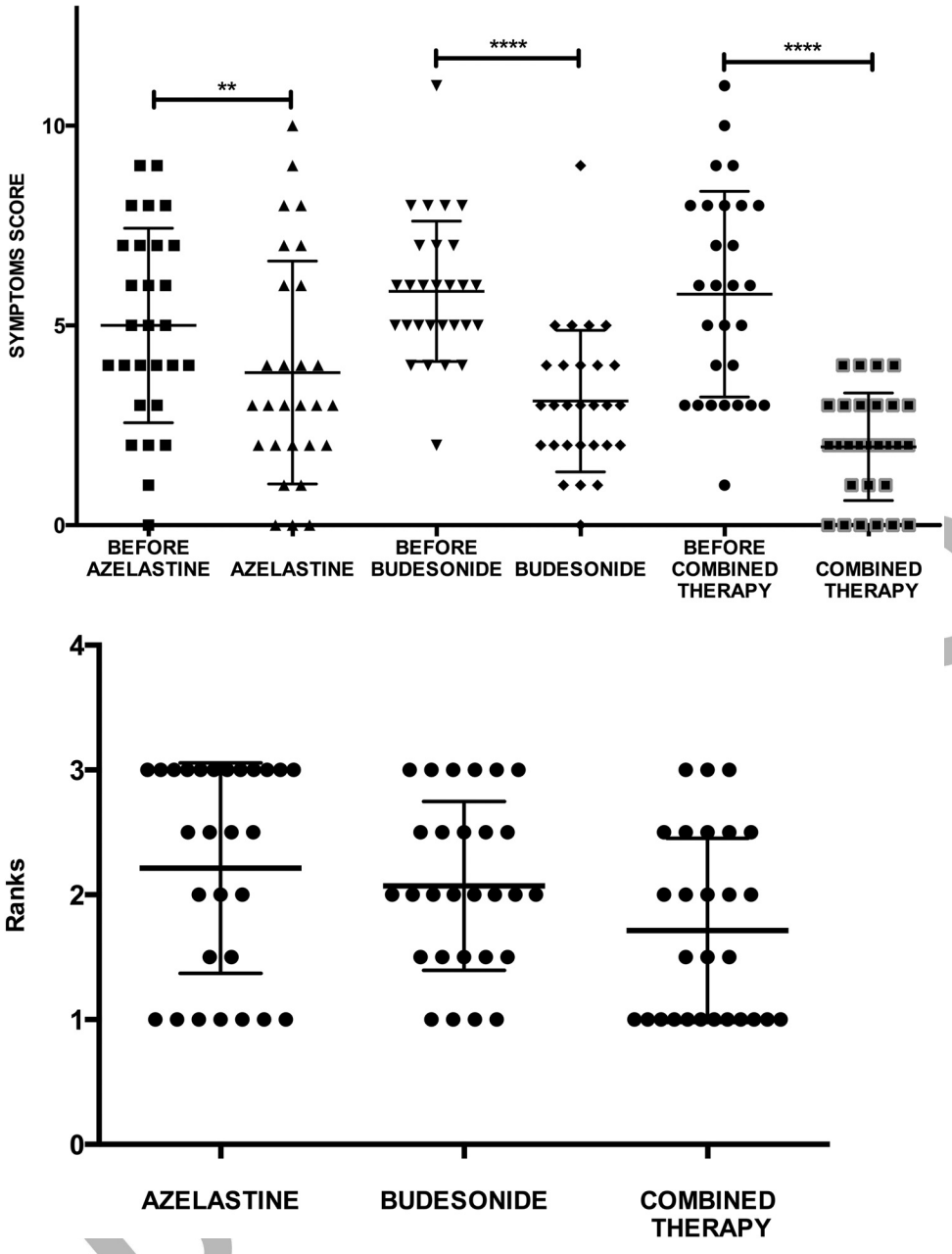

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Figure 6. *Effect of treatments on clinical scores. All treatments significantly decreased the following; number of sneezes; amount of rhinorrhea; nasal blockade sensation; and nasal, ear, palate, and eye pruritus during nasal provocation test (NPT).*

dose necessary to achieve NPT_{20}. These variables are nasal patency markers and are relevant in studies where drugs with different onsets of action are associated. As previously mentioned, AZE has a fast onset of action, whereas BUD requires extended use to reach peak efficacy. The effects of the drugs combined significantly increased the time and histamine dose necessary to achieve NPT_{20}, requiring a higher histamine dose and prolonged time to obtain nasal obstruction after treatment.

This study shows the benefits of combined therapy for reducing nasal obstruction, where there is an objective evaluation of the changes of nasal patency after treatment. The advantage of the combined treatment derives from the addition of complementary effects of two known distinct mechanisms of action. In addition to H_1-receptor antagonism, pharmacodynamic studies of AZE have shown a variety of anti-inflammatory properties, such as histamine release from mast cells and inhibition of leukotriene C4 and leukotriene B4 synthesis and release.[3] The combination of antihistamines and the anti-inflammatory effect of AZE with the anti-inflammatory effect of corticosteroid provides greater efficacy in the treatment of AR. Moreover, our results contribute to an alternative model for pharmacodynamic studies, rather than the use of large clinical trials, using a reduced number of patients and lower costs. Furthermore, we are proposing a new approach to evaluate the effects of nasal provocation considering the time and histamine dose administered.

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