

Nasal carbon dioxide for the symptomatic treatment of perennial allergic rhinitis

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Background: Brief nasal carbon dioxide insufflation has previously been shown to provide rapid relief of the symptoms of allergic rhinitis.

Objective: To examine the safety and efficacy of nasal carbon dioxide on the symptoms of perennial allergic rhinitis.

Methods: This was a randomized, double-blind, placebo-controlled, multicenter, in-clinic study that evaluated 2 flow rates (5 or 10 mL/s) and 2 administration durations (10 or 30 seconds per nostril) for nasal carbon dioxide vs placebo. Study participants rated their symptoms in clinic for 4 hours after administration and then through 24 hours outside the clinic. A total of 348 symptomatic patients with a minimum 2-year history of perennial allergic rhinitis requiring pharmacotherapy were randomized and treated.

Results: The mean change in total nasal symptom score from baseline at 30 minutes (the primary end point) showed greater improvement in the nasal carbon dioxide-treated groups compared with placebo. This change was statistically significant in the group treated with 10 mL/s for 10 seconds per nostril: -4.69 carbon dioxide vs -2.00 placebo ($P = .03$). The effect of a single dose lasted approximately 4 to 6 hours. The mean change from baseline at 30 minutes in total nonnasal symptom score was also statistically significant (-4.06 carbon dioxide vs -2.25 placebo, $P > .029$) for this group. The most common adverse events were nasal discomfort, lacrimation, and headache.

Conclusion: The study provides further evidence that nasal carbon dioxide is a potentially efficacious treatment for the symptoms of allergic rhinitis.

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INTRODUCTION

Allergic rhinitis afflicts approximately 30 million to 60 million people in the United States¹ and is associated with medical costs of several billion dollars a year.²⁻⁴ It is associated with significant comorbidities, such as sinusitis, otitis, and asthma.^{1,5}

Current treatments of allergic rhinitis include allergen avoidance, pharmacotherapy, and immunotherapy.^{1,6} These therapies may be administered alone or in combination. In the United States, patients are most commonly treated with topical or systemic antihistamines and nasal steroids. With suboptimal responses to these therapies, immunotherapy and, rarely, systemic steroids are added to the management regimen.

Despite the wide variety of available treatments, a significant proportion of patients with allergic rhinitis are dissatisfied because of persisting symptoms and a reduced quality of life.^{1,7} Older oral antihistamines have a significant sedating effect, and although newer ones typically do not, they are no more effective. Antihistamines have a minimal effect on congestion,^{1,8} which is considered to be the most bothersome symptom by most patients with allergic rhinitis.⁹ Topical sympathomimetics provide relief from congestion, but long-term use is associated with rhinitis medicamentosa.^{1,10} Intranasal steroids are more effective but have a relatively slow onset of effect and require dosing on a regular basis.^{1,11} In addition, even though systemic exposure to nasal steroids is minimal, concerns remain for some physicians and parents about their use in the pediatric population.¹² Therefore, there continues to be a need for a safe therapy that would provide rapid and significant relief of the symptoms of allergic rhinitis even if used on an as needed basis.

Nasal carbon dioxide has previously been shown to provide rapid and sustained relief of the symptoms of seasonal allergic rhinitis (SAR).¹³ The mechanism of action is not known, although it is clear from clinical trials to date that a brief carbon dioxide insufflation of the nasal mucosa provides relief from all symptoms of allergic rhinitis.¹³ Because carbon dioxide is administered while no nasal breathing is taking place and the nostril is sealed to the outside, it is likely that a higher pressure exists in that nostril, particularly in patients who are significantly congested. This pressurized gas rinse

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Table 1. Symptom Severity Scale

Patient-rated severity	Description	Score
None	No symptom is present	0
A little	Symptom is clearly present but minimally noticeable and is easily tolerated	1
Moderate	Symptom is bothersome but tolerable	2
Quite a bit	Symptom falls between moderate and severe	3
Severe	Symptom is hard to tolerate and causes interference with daily activities and/or sleeping	4
Very severe	Symptom makes daily activities completely intolerable and does not allow normal function at all	5

likely results in local effects, such as cleansing the nasal mucosa of allergens and, in so doing, removing the stimulus for neuropeptide secretion from the trigeminal nerve endings¹⁴ and for mast cell degranulation.¹⁵ It has been postulated that the acidic nature of carbon dioxide may have a mechanistic role to play.¹⁶ However, given the transient nature of pH changes seen in the nasal mucosa after carbon dioxide administration compared with the sustained relief of symptoms observed in the earlier clinical trial, we do not believe this to be the mechanism of efficacy.

A previous study of nasal carbon dioxide in patients with SAR showed that 60 seconds per nostril of carbon dioxide at a flow rate of 10 mL/s provided a rapid and sustained relief of symptoms.¹³ This study in patients with perennial allergic rhinitis (PAR) was conducted to evaluate whether shorter durations at the same flow rate and at a lower flow rate would provide symptom relief to patients.

METHODS

Study Design

This was a randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety and efficacy of multiple dosing regimens of nasal carbon dioxide in the acute treatment of PAR. This study enrolled men and women aged 18 to 65 years with at least a 2-year history of PAR requiring pharmacotherapy and a positive skin test result to a perennial allergen (dust mite, cockroach, cat, dog, or mold) within the prior 12 months at 3 study centers: 1 academic research center and 2 private clinical research centers. Patients were screened up to 6 weeks before the randomization and treatment day. On the treatment day, patients rated their nasal and nonnasal symptoms at 60 and 30 minutes before the administration of the study treatment. Eligible study participants were required to have an average total nasal symptom score (TNSS) of 6 or greater. A 6-point scale was used (0, none; 1, a little; 2, moderate; 3, quite a bit; 4, severe; and 5, very severe). Each patient at each assessment time point self-evaluated the severity of their nasal and nonnasal symptoms using the same scale (Table 1). Eligible study participants were randomized to 1 of 6 treatment groups (Fig 1) in a 2:2:2:2:1:1 ratio (active:active:active:active:placebo:placebo).

The TNSS was derived as the sum of the average of nasal congestion, itching, rhinorrhea, and sneezing. The total nonnasal symptom score (TNNSS) was derived similarly using the nonnasal symptoms itchy eyes, watery eyes, itchy ears or throat, and eye redness. The total symptom score was derived as the sum of the TNSS and TNNSS and was regarded as missing if either the TNSS or TNNSS was missing.

Patients rated their nasal and nonnasal symptoms in clinic for 4 hours after study drug administration at 10, 20, 30, 45, and 60 minutes and at 2, 3, and 4 hours and then outside the clinic at 6, 9, 12, and 24 hours after study drug administration. The primary efficacy end point was the 30-minute posttreatment TNSS for treatment groups A, B, C, and D.

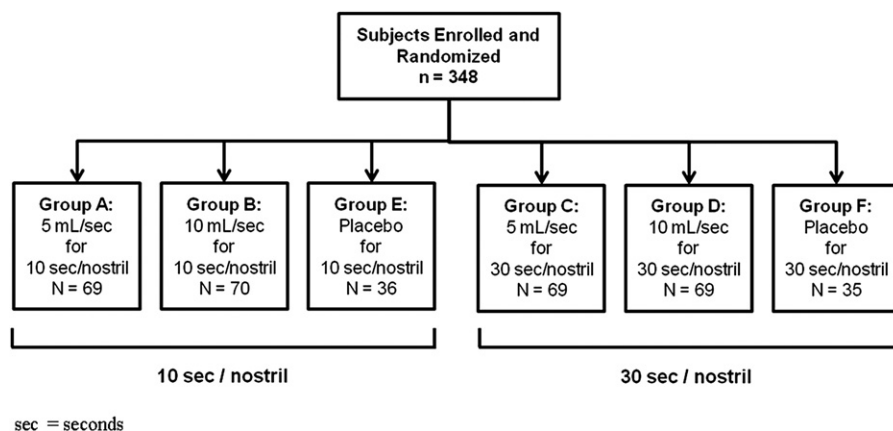


Figure 1. Study population disposition.

There was only 1 administration of study drug in this study, and patients' participation ended when they completed the 24-hour posttreatment assessment.

The study was performed in accordance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice Guidelines. Before conducting the study, each of the sites that participated in the study received the appropriate institutional review board approvals because use of nasal carbon dioxide is considered to be investigational and does not involve the use of a commercial product.

Study Participants

This study enrolled men and women aged 18 to 65 years with at least a 2-year history of PAR requiring pharmacotherapy and a positive skin test result to a perennial allergen (dust mite, cockroach, cat, dog, or mold) within the last 12 months. A positive skin test result was defined as a wheal 3 mm or larger than the diluent control for prick testing or 7 mm or larger than the diluent control with intradermal testing. Eligible study participants were required to have a TNSS of 6 or greater of a maximum of 20 before treatment. The TNSS was defined as the sum of the patients' ratings of congestion (average of the right and left nostrils), rhinorrhea, itchy nose, and sneezing scored on a 0- to 5-point scale each (Table 1).

Patients who had a history of asthma (other than mild or intermittent), other clinically significant nasal disorders, or acute or significant sinusitis or upper respiratory tract infection within 14 days of treatment were excluded from the study. Patients were not allowed to use medications that would affect the study outcomes: intranasal, inhaled, or systemic corticosteroids within 30 days of randomization, intranasal cromolyn within 14 days of randomization, loratadine within 10 days of randomization, intranasal or oral long-acting antihistamines within 7 days of randomization, leukotriene modifiers within 7 days of randomization, intranasal or systemic decongestants within 3 days of randomization, or oral short-acting antihistamines within 3 days of randomization. Patients who used concomitant medications (such as tricyclic antidepressants) that would affect assessment of the

effectiveness of study medication were excluded. Also excluded were patients with an existing serious medical condition, such as severe emphysema, to ensure that the safety and efficacy results of this early-phase study were not complicated by the potential adverse effects of a preexisting medical condition or women who were pregnant or breastfeeding and/or who planned to become pregnant or to breastfeed during study participation or within 30 days after treatment. Written informed consent was obtained from all patients before study specific screening procedures were performed.

Study Drug Delivery

Carbon dioxide was delivered via a nosepiece attached to a standard carbon dioxide cylinder fitted with a regulator by plastic tubing. The flow rate was controlled by a flow valve attached to the regulator at 0 mL/s (placebo treatment groups E and F), 5 mL/s (active treatment groups A and C), or 10 mL/s (active treatment groups B and D). The duration of carbon dioxide administration, 10 seconds per nostril or 30 seconds per nostril, was measured from the time the patient inserted the nosepiece into his/her nostril and a seal between the nostril and nosepiece was formed until a member of the study staff instructed the patient to remove the nosepiece from his/her nostril once the specified duration was completed. The placebo and active treatment apparatus were identical in appearance. Patients randomized to different treatment groups were treated in separate treatment rooms by study team members who were only informed of the duration of carbon dioxide or placebo administration. The study team members present in the treatment rooms did not participate in any other phases of the study to maintain the blind.

Statistical Analysis

The primary end point was the mean change from baseline in TNSS, which was the sum of the average of nasal congestion, itching, rhinorrhea, and sneezing at 30 minutes. An unbalanced 1-way analysis of variance (ANOVA) was used to perform the primary efficacy analysis and the analysis of each of the time points. This analysis was performed separately for each of the treatment groups. Within each ANOVA, a Dun-

Table 2. Characteristics of the Intent-to-Treat Population by Treatment Group

Characteristic	Group A (n = 69)	Group B (n = 70)	Group E (n = 36)	Group C (n = 69)	Group D (n = 69)	Group F (n = 35)
Flow rate, mL/s	5	10	0	5	10	0
Duration, seconds per nostril	10	10	10	30	30	30
Age, mean (SD), y	38.5 (12.77)	36.9 (11.27)	39.6 (12.72)	38.3 (12.77)	38.2 (12.81)	34.8 (9.47)
Female, %	72.5	67.1	63.9	60.9	71.0	71.4
White, %	76.8	75.7	77.8	82.6	76.8	77.1
Allergen, %						
Dust mite	62.3	75.7	77.8	68.1	73.9	57.1
Cockroaches	50.7	41.4	52.8	40.6	44.9	31.4
Cats	73.9	72.9	66.7	62.3	68.1	48.6
Dogs	50.7	54.3	38.9	49.3	56.5	45.7
Mold	68.1	64.3	77.8	66.7	68.1	65.7

nett 2-sided pairwise comparison test was performed to compare the active treatment groups with their placebo groups. This test performed both comparisons while maintaining an overall $\alpha = .05$. A 2×2 factorial analysis was performed to estimate and quantify the influence of flow rate and treatment duration on the TNSS mean change from baseline. No adjustments were made for multiple analyses. If a patient was missing one or more symptom assessments, the patient was not included in the analysis for that time point.

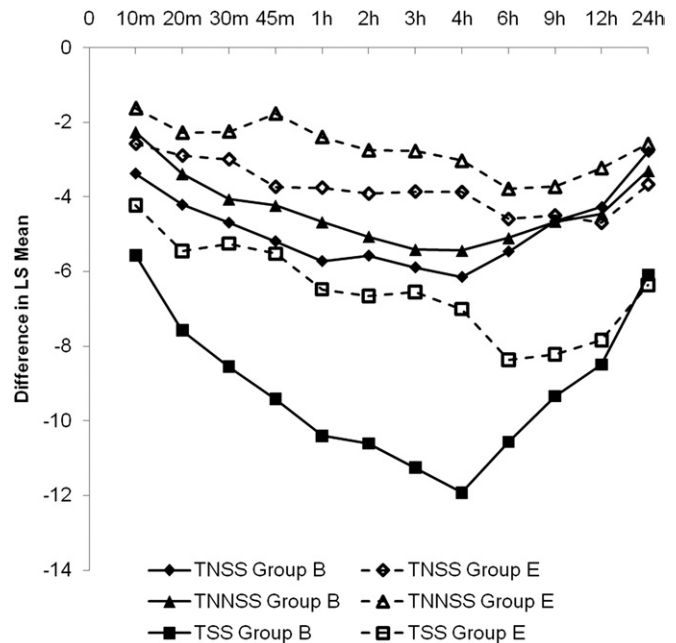
RESULTS

Patient Disposition

Three hundred forty-eight symptomatic PAR patients (TNSS ≥ 6 of 20) were randomized and treated with a single dose of carbon dioxide at 10 seconds per nostril ($n = 69$ at 5 mL/s and $n = 70$ at 10 mL/s) or placebo ($n = 36$) or carbon dioxide at 30 seconds per nostril ($n = 69$ at 5 mL/s and $n = 69$ at 10 mL/s) or placebo ($n = 35$) (Fig 1). The demographics and characteristics of the patients are presented in Table 2. There were no significant differences between groups at baseline.

Efficacy

The mean change in TNSS from baseline for each active and placebo group at 30 minutes (the primary end point) showed greater improvement with nasal carbon dioxide (Fig 2). The change was statistically significant for group B ($P = .03$). All other groups showed a numerically superior change in TNSS compared with corresponding placebo. The improvement in TNSS was rapid, with statistically significant separation from placebo at 30 minutes, and lasted for at least 4 hours. The changes were most prominent in group B (Fig 3). Statistically significant improvement compared with placebo in group B was also seen in the nonnasal symptoms, as measured by a change in TNNSS, and in total symptoms, as measured by a change in total symptom score. In each, again the improvement was rapid and was sustained for several hours (Fig 3). The pattern of improvement in group B compared with placebo



	Statistically Significant ($p < 0.05$), Group B vs. Group E									
	30 m	45 m	1 h	2 h	3 h	4 h	6 h	9 h	12 h	24 h
TNSS	X		X		X	X				
TNNSS	X	X	X	X	X	X				
TSS	X	X	X	X	X	X				

m = minute

h = hour

TNSS = Total Nasal Symptom Score

TNNSS = Total Non-Nasal Symptom Score

TSS = Total Symptom Score

Figure 3. Total nasal symptoms score (TNSS), total nonnasal symptom score (TNNSS), and total symptom score (TSS) mean change from baseline for group B (10 mL/s for 10 seconds per nostril) vs placebo (10 seconds per nostril).

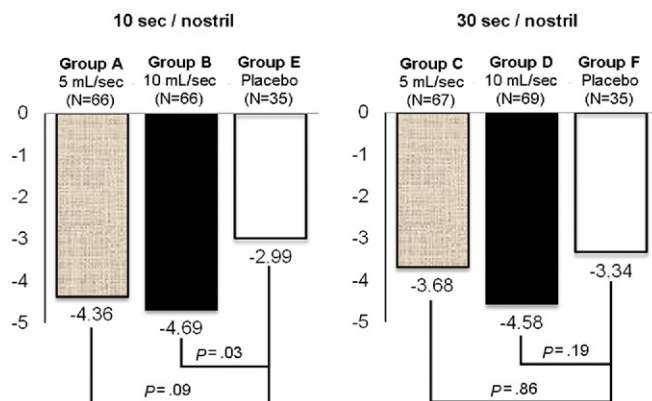


Figure 2. Total nasal symptom score change from baseline at 30 minutes after treatment for group B (10 mL/s for 10 seconds per nostril) vs placebo (10 seconds per nostril).

cebo was seen across all individual nasal and nonnasal symptoms (Fig 4).

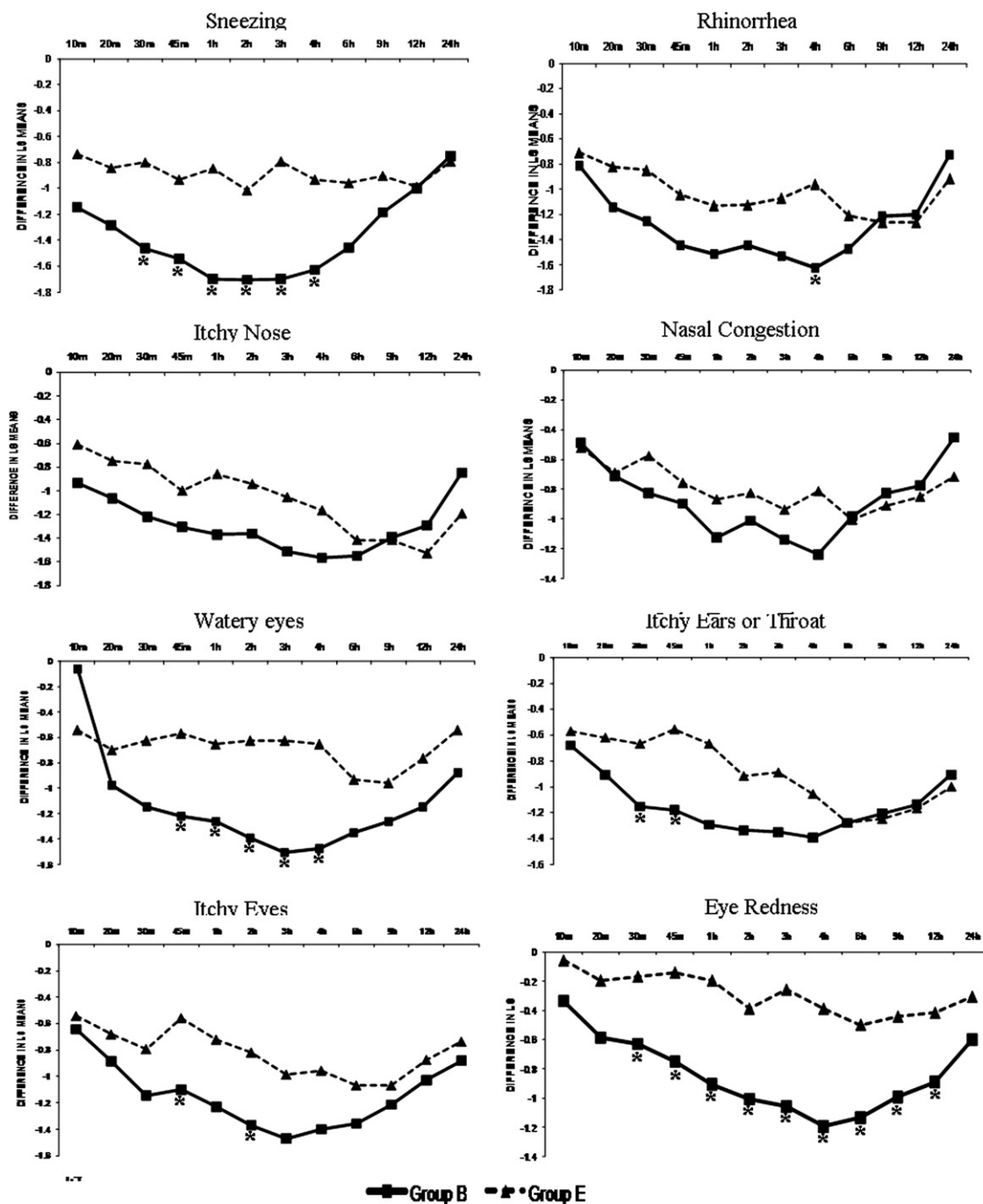
Safety

The most frequently reported adverse events were nasal discomfort, headache, and lacrimation. These events resolved on cessation of dosing, without intervention (Table 3).

DISCUSSION

Nasal carbon dioxide has been shown to be efficacious in the symptomatic treatment of SAR patients in a single-center, single-dose, randomized, placebo-controlled study.¹³ The present study is a multicenter, single-dose study to test multiple regimens of nasal carbon dioxide for the symptomatic treatment of PAR patients.

As in the SAR study, the current study shows a rapid effect of carbon dioxide with immediate separation of active and placebo groups, which remain separated for at least 4 hours.



* Statistically significant vs placebo, $P < .05$

m = minute

h = hour

Figure 4. Mean change from baseline in individual symptom scores for group B (10 mL/s for 10 seconds per nostril) vs placebo (10 seconds per nostril).

Table 3. Most Frequently Reported Adverse Events by Treatment Group

Adverse event	10 Seconds per nostril, %			30 Seconds per nostril, %			Total, % (n = 348)
	Group A (5 mL/s) (n = 69)	Group B (10 mL/s) (n = 70)	Group E (0 mL/s) (n = 36)	Group C (5 mL/s) (n = 69)	Group D (10 mL/s) (n = 69)	Group F (0 mL/s) (n = 35)	
Nasal discomfort	89.9	81.4	8.3	79.7	87.0	8.6	69.0
Lacrimation increased	21.7	27.1	2.8	29.0	20.3	2.9	20.1
Headache	20.3	8.6	13.9	8.7	15.9	2.9	12.4
Rhinalgia	1.4	8.6	2.8	14.5	8.7	0.0	6.9
Rhinorrhea	4.3	2.9	2.8	14.5	4.3	0.0	5.5
Throat irritation	2.9	8.6	0.0	4.3	10.1	2.9	5.5
Blood pressure increased	4.3	1.4	5.6	7.2	0.0	5.7	3.7
Dizziness	0.0	2.9	0.0	1.5	2.9	5.7	2.0

The primary end point of the study was met with statistically significant differences from placebo at 30 minutes observed in group B. The effect was seen across all nasal and nonnasal symptoms and was most prominent in the group receiving 10 seconds per nostril of carbon dioxide at 10 mL/s with a TNSS statistical significance seen at the 30-minute primary end point. All other groups (5 mL/s for 10 or 30 seconds and 10 mL/s) trended toward an improvement with active treatment, although without reaching statistical significance. Of note, the group receiving 30 seconds per nostril of carbon dioxide did not have as much separation from placebo as the group receiving 10 seconds per nostril of carbon dioxide even though the numerical changes in TNSS were similar, especially with the 10 mL/s group. This could at least in part be related to the small size of the placebo group and a larger response in the 30-second placebo group and the resulting skewing of the data due to TNSS changes in a small number of patients. The placebo for the study consisted of an apparatus that did not deliver anything to the patient. Although this may have been a cause of a lower treatment effect in the placebo patients, significant precautions were taken to minimize this bias. Patients were segregated in separate rooms while treatment was administered, and no patients were enrolled in the study if they had participated in any previous study with nasal carbon dioxide. Patients were told that they may or may not feel a nasal sensation with active treatment, in line with the fact that a proportion of patients do not report nasal sensation with carbon dioxide administration, whereas some placebo patients do. The active and placebo apparatuses looked and sounded identical to each other. Because the placebo groups did not have any gas delivered to the nostril, we cannot completely confirm that the efficacy could be driven by the pressure rinse with any gas. We have studied Medical Air at room temperature as a control in a previous study¹³ and found that even though a beneficial control effect was seen, the effect of carbon dioxide was statistically superior.

The data show that the major determinant of efficacy is flow rate, and increasing the duration of administration does not have a significant incremental effect. Interestingly, we also saw a marked effect on nonnasal symptoms (Fig 4). This

is likely related to the inhibition of the afferent arm of the naso-ocular reflex, which has been implicated in the causation of such symptoms.¹⁷

The significance of this study includes the ability to inhibit all of the principal symptoms of allergic rhinitis within 30 minutes by a nonpharmacologic therapy. The effect of a single dose lasted for approximately 4 to 6 hours. The duration of treatment required to positively affect both nasal and nonnasal symptoms was only 10 seconds per nostril, a marked reduction from the duration used in the previously reported study of 60 seconds.¹³ Moreover, because the amount of carbon dioxide delivered should have no systemic effects, this treatment may be especially useful in very young and very old patients who might be more susceptible to adverse effects from other allergic rhinitis treatments. Finally, because of the rapidity of onset, this could be an effective way to manage symptoms on an as needed basis. Although the need to take carbon dioxide multiple times a day may be a drawback, we believe that the episodic nature of the symptoms of allergic rhinitis will limit the need for frequent use. Further study is needed to define how this treatment best adds to our current treatment armamentarium for allergic rhinitis and whether it might also be effective for nonallergic rhinitis. In addition, the development of a hand-held device will allow its use on an as needed basis, which will be studied in upcoming clinical trials.

CONCLUSION

This study demonstrates that intranasal carbon dioxide can be efficacious for the treatment of nasal and nonnasal symptoms of PAR. Adverse effects were mainly limited to nasal administration site reactions, which resolve on cessation of dosing. Noninhaled carbon dioxide has potential as a therapeutic for the symptomatic treatment of allergic rhinitis. Future studies will determine the most effective use for the treatment of allergic rhinitis symptoms using a hand-held dispenser.

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