Original Article

Nasal Carbon Dioxide Used As Needed in the Symptomatic Treatment of Seasonal Allergic Rhinitis

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What is already known about this topic? Nasal, noninhaled carbon dioxide (CO_2) has been shown to be effective for the treatment of symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis in single application studies.

What does this article add to our knowledge? On the basis of the results of this study, it appears that the nasal, noninhaled CO_2 device is effective for the as-needed treatment of all principal SAR symptoms with a rapid and large effect size.

How does this study impact current management guidelines? The nasal, noninhaled CO_2 device represents a novel option for a safe and rapidly effective addition to the medical armamentarium for as-needed relief of SAR symptoms.

BACKGROUND: Nasal, noninhaled carbon dioxide (CO_2) was shown to be effective for the treatment of symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis in single application studies.
OBJECTIVE: To assess the efficacy of as-needed treatment with nasal, noninhaled CO_2 in patients with SAR.
METHODS: Fifty-six ragweed-allergic patients were enrolled at 3 sites in this study. After a 3- to 7-day run-in, 32 eligible patients who had an instantaneous total nasal symptom score of 8 or more out of a maximum of 12 in at least 2 SAR episodes per day were randomized to the CO_2 group (n = 19) or to the placebo group (n = 13). A 10-second/nostril application was used as needed for 14 days (maximum 6 times/d). Patients evaluated their symptoms before and 30 minutes after each application. All symptoms were scored on a 0 to 3 scale.
RESULTS: Analysis of all treated episodes (CO_2 = 816, placebo = 516) showed a statistically significant beneficial change in total nasal symptom score from baseline (effect size = −0.51; $P < .001$). The effect size was larger with more severe baseline symptoms (baseline severities of ≥6 = −0.98; ≥8 = −1.14; and ≥10 = −1.61; all $P < .001$). CO_2 was well tolerated, with transient nasal discomfort as the most common adverse event reported. There were no serious adverse events, serious adverse device effects, or early discontinuations.
CONCLUSIONS: Nasal, noninhaled CO_2 is effective for the as-needed treatment of SAR symptoms. The effect is rapid and the effect size is large. It represents a novel potential option for the as-needed treatment of rhinitis symptoms. **© 2017 American Academy of Allergy, Asthma & Immunology** **(J Allergy Clin Immunol Pract 2017;■:■-■)**

Key words: *Carbon dioxide; Nasal; Noninhaled carbon dioxide; CO_2; Seasonal allergic rhinitis; Treatment*

Allergic rhinitis (AR) affects between 10% and 30% of the population.[1] The prevalence of AR continues to increase worldwide.[1] The disease is associated with significant morbidity, reduced productivity, lost school days, and cost. In the United States alone, the total direct and indirect annual costs associated with AR are more than $11 billion.[2]

Rhinitis is characterized by the presence of 1 or more of the nasal symptoms of congestion, rhinorrhea, sneezing, and itching. Nonnasal symptoms such as itchy ear and throat, lacrimation, itchy eyes, and eye redness are often present as well. Other associated symptoms include headache, postnasal drip, fatigue, cognitive impairment, and sleep disturbance. Comorbid conditions such as asthma, sinusitis, and sleep apnea often exist as well.[3,4]

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This study was funded by Capnia Inc. (Redwood City, Calif).
Conflicts of interest: T. B. Casale has received consultancy fees and research support from Capnia Inc and is employed by the American Academy of Allergy, Asthma & Immunology as Executive Vice President. R. F. Onder has received research support from Capnia Inc. P. E. Korenblat has received financial support from the Clinical Research Center and has received consultancy fees and research support from Capnia Inc. R. B. Berkowitz declares no relevant conflicts of interest. All the authors were principal investigators on grants received from Capnia Inc to perform the study; however, they do not own stock in the company.
Received for publication December 20, 2016; revised May 1, 2017; accepted for publication May 16, 2017.
Available online ■■
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2213-2198
© 2017 American Academy of Allergy, Asthma & Immunology
http://dx.doi.org/10.1016/j.jaip.2017.05.028

Abbreviations used
AR- Allergic rhinitis
AE- Adverse event
CO_2- Carbon dioxide
SAR- Seasonal allergic rhinitis
TNNSS- Total nonnasal symptom score
TNSS- Total nasal symptom score

AR fundamentally involves nasal mucosal inflammation as a result of exposure to allergens. Seasonal AR (SAR) results from exposure to seasonal allergens (such as ragweed, cedar, and grass), whereas perennial AR results from exposure to allergens such as dust mites, occupational allergens, and molds. The early-phase symptoms are typically sneezing, itching, and rhinorrhea, whereas congestion is predominantly a late-phase symptom.[3]

An investigational product to deliver nasal, noninhaled carbon dioxide (CO_2) has been studied for the treatment of AR. Rapid relief from symptoms has been seen after single doses in symptomatic patients with SAR[5,6] and perennial AR.[7] The primary mode of action appears to be mechanical in nature. A brief 10-second wash per nostril cleanses the nasal passage and displaces allergens much like other washes. A longer duration of exposures may lead to chemical changes but does not appear to be the mechanism for such rapid relief of symptoms.[8,9] In this study, we assessed whether the nasal CO_2 device used only as needed would provide relief to patients for symptoms of SAR over a 2-week period.

METHODS

This was a randomized, double-blind, placebo-controlled, multicenter, parallel group, pilot study (ClinicalTrials.gov identifier: NCT 00917020) conducted in the United States at 3 clinical research centers: Atlanta Allergy and Asthma Research Department (Woodstock, Ga), the Clinical Research Center (St Louis, Mo), and Midwest Clinical Research, LLC (St Louis, Mo). The Sterling Institutional Review Board (Atlanta, Ga) reviewed/approved this study and protected the rights and welfare of the participants throughout the study. All patients signed an approved informed consent form before any study procedures. This study evaluated the efficacy and safety of a nasal, noninhaled CO_2 application (nasal CO_2 device) used as needed, up to 6 times a day, in patients with SAR. Approximately 50 patients who met the eligibility criteria were to be enrolled into this study to ensure that approximately 30 patients completed the study.

During a 3- to 7-day run-in period, patients rated their SAR symptoms in a paper diary during at least 2 SAR episodes per day (the interval in between episodes must be at least 2 hours). Patients were instructed to assess episodes that they believed had symptoms that were severe enough to warrant treatment. In addition, patients rated their SAR symptoms in the morning (eg, when they woke up) and in the evening (eg, before they went to sleep). These morning and evening diaries were reflective and were to indicate how patients felt over approximately the last 12 hours.

After the run-in period, patients returned to the clinical research center for a review of their diary data and to assess eligibility for randomization. Once eligibility was confirmed, patients were randomized to 1 of 2 treatment groups in an approximate 2:1 (active:placebo) ratio in blocks of 6. A 2:1 randomization was selected to provide the opportunity for more patients to be assigned and exposed to the CO_2, the active arm. The randomization list was generated using an SAS program (SAS Institute, Cary, NC) by a statistician independent from the study. Only the independent statistician and the clinical supply organization had access to the randomization list during the conduct of the study. Unblinding occurred after the completion of study assessments for all patients and after the database had been locked. The clinical supply organization generated a treatment kit assignment log for each site, which consisted of a list of treatment kits based on the order of treatment arm assignment (CO_2 or placebo). Once the site confirmed that a patient was eligible, they would assign the treatment kits to eligible patients in sequential order. Two treatment kits were dispensed to each patient so that the first set of 2 treatment kits (eg, 1a and 1b) was dispensed to the first patient randomized at the site, the second set of 2 treatment kits (eg, 2a and 2b) was dispensed to the second patient randomized at the site, and so on. The treatment kits consisted of a handheld device containing CO_2. The active nasal CO_2 device was calibrated to deliver CO_2 at 0.5 standard liters per minute. The placebo for the nasal CO_2 device was identical in appearance to the active device but was designed not to dispense the CO_2 to the nasal cavity.

TABLE I. Symptom scores

Symptom score	Symptoms used to determine symptom score*	Minimum score	Maximum score
TNSS	Average of left nostril nasal congestion and right nostril nasal congestion, runny nose, itchy nose, and sneezing	0	12
TNNSS	Lacrimation, eye redness, ear/throat itching, and eye itching	0	12

*Each symptom was rated on the basis of a 0-3 scale: none (0) = no sign/symptom evident; mild (1) = sign/symptom clearly present, but minimal awareness; easily tolerated; moderate (2) = definite awareness of sign/symptom that is bothersome but tolerable; severe (3) = sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping.

Patients used the nasal CO_2 device or placebo for 10 seconds/nostril, once on day 0 in the clinic. They then used the nasal CO_2 device or placebo for 10 seconds/nostril, as needed up to 6 times a day (the interval in between uses was required to be at least 2 hours), on days 1 to 14 inclusive. They documented their use (ie, date, time, and duration of application to each nostril) in the patient diary.

On day 0, randomized patients completed instantaneous symptom assessments immediately before (ie, no more than 10 minutes before) the use of the nasal CO_2 device or placebo; at 10, 30, and 60 minutes; and 4 and 6 hours after use of the nasal CO_2 device or placebo. On days 1 to 14, patients assessed their symptoms in a paper diary immediately before each use and approximately 30 minutes after each use. In addition, patients rated their SAR symptoms in the morning (eg, when they woke up) and in the evening (eg, before they went to sleep).

All SAR episode-related assessments, preuse assessments, and 30-minute postuse assessments were instantaneous assessments (ie, the symptom severity rating at the time of the assessment). The morning and evening assessments were reflective assessments (ie, the symptom severity rating since the previous reflective assessment; assessments were ~ 12 hours apart).

Patients self-rated the severity of their nasal (runny nose, congestion, sneezing, and itching) and nonnasal (lacrimation, eye redness, ear/throat itching, and eye itching) symptoms as well as postnasal drip and headache. Total nasal symptom scores (TNSS) and total nonnasal symptom scores (TNNSS) were calculated on the basis of the ratings and are presented in Table I.

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