

Original article

Intranasal noninhaled carbon dioxide for the symptomatic treatment of seasonal allergic rhinitis

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Background: Noninhaled intranasal carbon dioxide (CO₂) has been shown to be effective in the abortive treatment of migraine headache. Migraine headache is associated with trigeminal neuronal activation and release of calcitonin gene-related peptide, events also implicated in allergic rhinitis. Intranasal CO₂ might inhibit trigeminal neuronal activation and suppress the release of calcitonin gene-related peptide.

Objective: We studied whether noninhaled intranasal CO₂ would be effective in the treatment of seasonal allergic rhinitis. **Methods:** We conducted a single-center, randomized, double-blind, placebo-controlled, parallel-group study. Treatment consisted of either CO₂ (verum) or air (placebo) at a 2:1 ratio administered in each nostril for 60 seconds per nostril at a flow rate of 10 mL/s. The primary efficacy end point was the change from baseline in total nasal symptom score (TNSS), the sum of congestion, rhinorrhea, itching, and sneezing scored on a 0- to 5-point scale, at 30 minutes.

Results: Eighty-nine subjects received treatment, 60 with CO₂ and 29 with placebo, and all subjects completed the study. CO₂ resulted in a statistically significant improvement in TNSS at 30 minutes over placebo (absolute changes of 5.0 for CO₂ and 2.2 for placebo, $P = .00019$). Improvement from baseline in TNSS (CO₂ vs placebo) was statistically significant at 10 minutes and remained so for 24 hours.

Conclusion: Two 60-second intranasal CO₂ treatments resulted in rapid (10 minutes) and sustained (24 hours) relief of seasonal allergic rhinitis symptoms.

Clinical implications: Noninhaled intranasal CO₂ has potential as a safe and effective treatment for seasonal allergic rhinitis. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Carbon dioxide, topical nasal administration, clinical trial, allergic rhinitis

Abbreviations used

ANCOVA: Analysis of covariance
CGRP: Calcitonin gene-related peptide
TNSS: Total non-nasal symptom score
TNSS: Total nasal symptom score

Allergic rhinitis afflicts 9% to 16% of the population, approximately 40 million persons in the United States, making it the sixth most common ailment.^{1,2} It significantly affects the quality of life through upper airway symptoms and contributes to other conditions, such as rhinosinusitis, otitis media, and asthma.^{2,3} The medical costs associated with allergic rhinitis are estimated at 6 billion dollars annually in the United States alone,^{4,5} with an even higher societal burden when indirect costs are factored in as well.

The treatment of allergic rhinitis includes allergen avoidance, pharmacotherapy, allergen immunotherapy, and, more recently, immunomodulators.¹⁻³ The goals of treatment are relief of symptoms, improvement of the patient's functionality, and prevention of complications. Typically, treatments are combined, with the pharmacotherapy applied topically, systemically, or both. Topical pharmacotherapies include intranasal corticosteroids, anticholinergics, antihistamines, sympathomimetics, and chromones. Systemic pharmacotherapies include oral antihistamines, sympathomimetics, antileukotrienes, and, in particularly severe cases, corticosteroids. Patients who either respond inadequately or experience bothersome side effects with these pharmacotherapies are often treated with allergen immunotherapy.

However, despite the available treatments, a significant proportion of patients with allergic rhinitis continue to have symptoms and experience impaired quality of life.^{6,7} Furthermore, there is no treatment currently available that provides truly rapid relief of symptoms, other than the topical sympathomimetics for nasal congestion.¹⁻³ However, the chronic use of these medications is not recommended because this can lead to the development of rhinitis medicamentosa.

Noninhaled intranasal carbon dioxide (CO₂) has been shown to be effective in the abortive treatment of migraine

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headache.^{8,9} The onset of the effect is rapid, with one third to two thirds of the 2-hour pain-free benefit achieved within 30 minutes. Migraine headache is associated with trigeminal neuronal activation and the release of calcitonin gene-related peptide (CGRP), as evidenced by increased CGRP levels in external-jugular venous blood¹⁰ and stimulated (by applying 2% citric acid to the tip and sides of the tongue) saliva.¹¹ CO₂ administered to cultures of trigeminal neurons in buffered media has been shown to inhibit both neuronal activation and CGRP release.¹²

Rhinitis results from allergen-induced degranulation of mast cells and the subsequent release of histamines and other inflammatory mediators, which cause changes in neuronal activity.¹³ Mediators either directly or indirectly increase neuronal activation, causing neuropeptide release,¹⁴ and recent work has shown that CGRP levels are increased in patients with allergic rhinosinusitis and migraine, both between and during attacks.¹¹ In addition, allergen exposure in patients with allergic rhinitis has been shown to increase the CGRP content of nasal lavage fluid.^{15,16} Hence trigeminal neuronal activation seems to occur here as well, probably caused by mediators released from activated mast cells.¹⁷ This activation of peripheral neurons in the nasal mucosa likely plays a role in the mediation of symptoms like itching and sneezing, whereas the released CGRP causes vasodilation and glandular secretion, thereby potentially contributing to symptoms such as congestion. Therefore we hypothesized that non-inhaled intranasal CO₂ would be effective in the treatment of the nasal symptoms of allergic rhinitis. To test this hypothesis, we conducted a randomized, double-blind, placebo-controlled, parallel-group study.

METHODS

Subjects

The study was conducted at Creighton University in Omaha, Neb, and the protocol and informed consent document were reviewed and approved by its institutional review board.

We enrolled subjects 18 to 75 years of age, with a minimum of a 2-year history of seasonal allergic rhinitis requiring pharmacotherapy. The subjects were required to have a positive skin prick test response to the seasonal grass or mold allergens prevalent in Omaha, Nebraska, in May 2005. A positive skin prick test response was defined as a wheal exceeding by more than 3 mm in diameter that of the diluent control. The exclusion criteria were as follows: asthma, other than mild and intermittent; the use of intranasal, inhaled, or systemic corticosteroids within 30 days of the study; the use of concomitant medications that could affect study outcome, such as intranasal chromones, intranasal or systemic sympathomimetics, and intranasal or systemic antihistamines; clinically significant nasal disorders, such as deviated septum, nasal polyposis, or chronic rhinosinusitis; a history of an upper respiratory tract infection within 14 days of the study; and rhinitis medicamentosa.

Study design

After an initial screening visit to determine eligibility, the subjects returned to the clinic for a 1-day treatment and efficacy assessment. On the day of treatment, the subjects evaluated the intensity of 4 nasal symptoms (ie, congestion, rhinorrhea, itching, and sneezing) to

determine final eligibility. The nasal symptoms were scored on a 0-to 5-point scale (0, none; 1, little; 2, moderate; 3, quite a bit; 4, severe; 5, very severe); for nasal congestion, the average was taken of the 2 nostrils. The subjects qualified if they had a total nasal symptom score (TNSS) of 6 or more, with the maximum being 20 (4 × 5). The baseline scores were taken 60 and 30 minutes before treatment and averaged to determine eligibility. The non-nasal symptoms (ie, eye itching, eye tearing, eye redness, and itching of the ears or palate) were scored by using the same 0- to 5-point scale but were not used to qualify the subjects for randomization. The scores were added to generate the total non-nasal symptom score (TNNSS).

After randomization and treatment, the subjects evaluated their nasal and nonnasal symptoms at 10, 20, 30, 45, and 60 minutes after treatment, as well as hourly thereafter while in the clinic. At discharge from the clinic, 4 hours after treatment, the subjects were given diaries for symptom recording at 6, 12, and 24 hours after treatment, which they returned to the clinic by mail.

Treatment

The treatment consisted of either CO₂ (verum) or air (placebo), with a randomization ratio of 2 to 1. The gases were delivered from large-capacity compressed gas cylinders fitted with regulators and flow control valves that were set to deliver gas at a constant 10 mL/s (by using a flow meter). Both gas sources were connected to a 3-way selection valve, which allowed for the selection of the "off" position or the positions A or B, blinded for CO₂ or air. The 3-way valve was connected to a length of tubing that ended in a disposable nosepiece. The subjects administered the gases themselves under the guidance and supervision of the study coordinators. The subjects administered the gases intranasally twice for 60 seconds at a rate of 10 mL/s, for a total dose of approximately 1200 mL. The doses were separated by an interval of less than 5 minutes and were administered to alternate nostrils. The subjects avoided inhaling the gas by breathing through the mouth, allowing the gas to flow in 1 nostril, pass through the nose and sinus cavities, and pass out through the other nostril.

Study end points

The primary efficacy end point was the change from baseline in TNSS at 30 minutes after treatment. The secondary end points included the change from baseline in TNSS at each time point; the change from baseline of the individual, nasal, and non-nasal symptom scores at each time point; the percentage of responders at 30 minutes with a TNSS improvement of more than 25%, 50%, or 75%; and adverse event occurrence.

Statistical analysis

The power calculation was based on the TNSS and assumed a 3.3-point difference in the mean absolute change from baseline between CO₂ and placebo. With 66 subjects in the CO₂ group and 34 in the placebo group (2:1 randomization) and an α value of .05 (2-sided), the power of the study was calculated to be 67.6%. The mean, absolute, and percentage changes from baseline in individual and composite symptom scores were compared by using the Student *t* test. We also conducted a sensitivity analysis using an analysis of covariance (ANCOVA), with the baseline TNSS score as the covariate.

Adverse events were coded to preferred term, higher-level term, and system/organ class by using the MedDRA dictionary. An adverse event reported more than once by a subject was counted once at the maximum intensity reported and with the strongest relationship to treatment. The last-observation-carried-forward method was used for imputing missing data, and an α value of .05 was considered the minimal level of statistical significance.

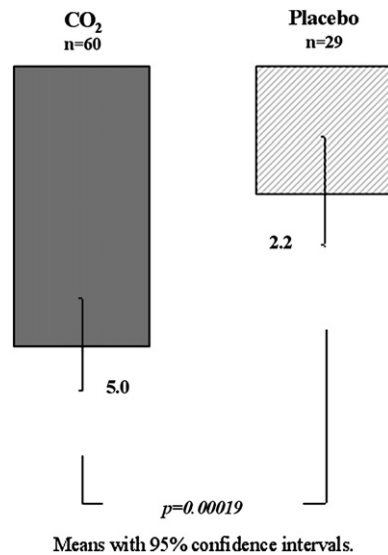


FIG 1. Absolute improvement from baseline in TNSS at 30 minutes after treatment: noninhaled intranasal CO₂ versus placebo.

RESULTS

Baseline characteristics

For the study, we screened 171 subjects, of whom 146 (82.5%) were determined eligible for participation. Of these 146 subjects, 136 (93.2%) came to the clinic for the 1-day treatment and efficacy assessment. Of these 136 subjects, 89 (65.4%) met the randomization criterion of a minimum baseline score of 6 (TNSS) determined 60 and 30 minutes before treatment and averaged. Of these 89 subjects, 60 were randomized to the CO₂ treatment and 29 to the placebo treatment, and all of them completed the study. The baseline demographic characteristics were similar between the 2 groups, CO₂ and placebo, with respect to age (38.1 ± 13.2 vs 41.7 ± 15.6 years), sex (female: 63.3% vs 75.9%), and ethnicity (white: 90.0% vs 86.2%). The TNSS was 9.3 ± 3.0 in the CO₂ group and 7.8 ± 2.2 in the placebo group ($P = .014$). However, the only nasal symptom with a significant baseline imbalance was sneezing (1.3 vs 0.6 , $P = .004$). Baseline TNNSS for CO₂ was 7.5, and that for placebo was 6.5 ($P = .227$). All patients had a positive skin test response, predominantly to grass (91.7% vs 86.2%) and mold (85.0% vs 82.7%) but some to tree or weed. Nasal congestion was the most bothersome symptom on the day of the treatment (28.3% vs 34.5%), followed by rhinorrhea in the CO₂ group (26.7%) and itchy eyes in the placebo group (27.6%).

Primary efficacy

CO₂ improved the TNSS more than placebo, with the absolute changes from baseline at 30 minutes after treatment being 5.0 and 2.2, respectively ($P = .00019$, Fig 1). The ANCOVA results also showed a statistically significant difference in TNSS between the groups at all early time points, including the primary analysis time point of 30 minutes ($P = .0044$).

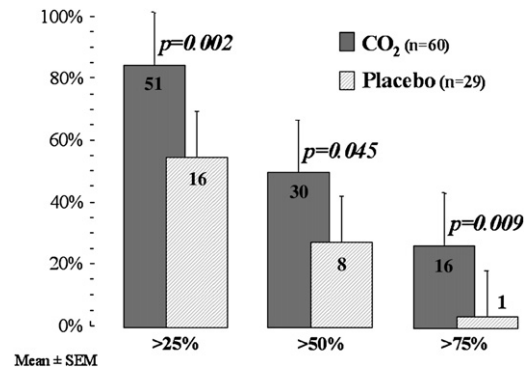


FIG 2. Responders with more than 25%, 50%, or 75% improvement in TNSS from baseline at 30 minutes after treatment: noninhaled intranasal CO₂ versus placebo.

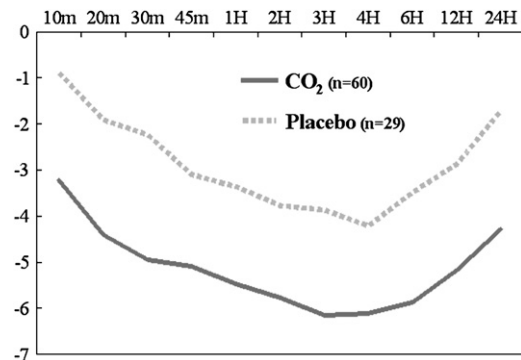


FIG 3. Improvement from baseline in TNSS over the 24 hours after treatment: noninhaled intranasal CO₂ versus placebo. Differences between the CO₂- and placebo-treated groups were significant at a P value of less than .05 at all assessment time points.

Secondary efficacy

A responder analysis at 30 minutes after treatment is presented in Fig 2, showing the percentage of subjects with more than 25%, 50%, or 75% improvement in TNSS. Fifty percent of the subjects in the CO₂ group achieved an improvement in TNSS of more than 50% compared with 27.6% in the placebo group ($P = .045$). For an improvement in TNSS of more than 75%, these numbers were 26.7% and 3.4%, respectively ($P = .009$).

At 30 minutes, all individual nasal symptoms showed benefit with CO₂ treatment. The changes were statistically significant for rhinorrhea ($P = .007$), itchy nose ($P = .001$), and sneezing ($P = .001$). Changes in congestion were significant at 20 minutes ($P = .015$) and showed a trend toward significance ($P = .069$) at 30 minutes.

TNSS changes in the CO₂ group showed a statistically significant benefit over placebo at every time point measured (10 minutes to 24 hours, Fig 3). Improvement from baseline in TNSS (CO₂ vs placebo) was statistically significant at 10 minutes (3.2 vs 0.9, $P = .0005$) and remained different until the 24-hour time point (4.2 vs 1.7, $P = .0022$).

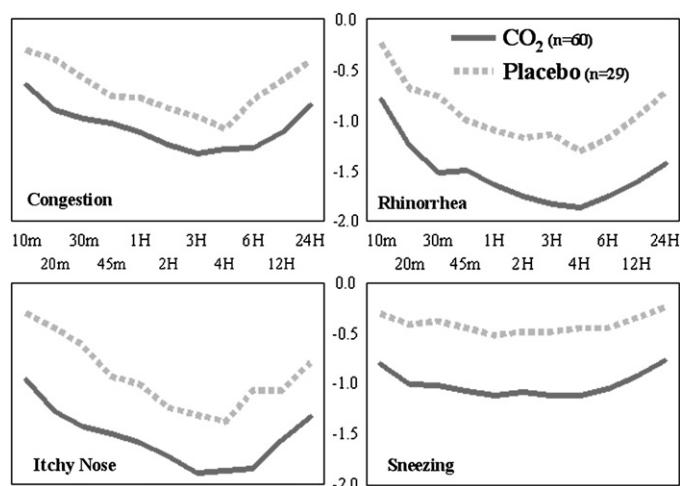


FIG 4. Improvements from baseline in individual nasal symptom scores over 24 hours after treatment: noninhaled intranasal CO₂ versus placebo.

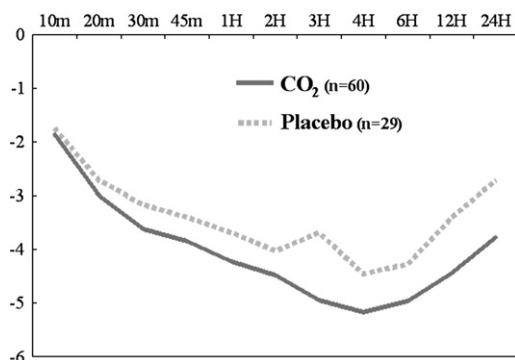


FIG 5. Improvement from baseline in TNNSS over the 24 hours after treatment: noninhaled intranasal CO₂ versus placebo. Differences between the CO₂- and placebo-treated groups were not significant at any assessment time point.

Because there was a statistically significant difference in TNNSS between the 2 groups at baseline (9.3 ± 3.0 in the CO₂ group and 7.8 ± 2.2 in the placebo group, $P = .014$), the percentage improvement in TNNSS was also analyzed. Statistical significance was again seen starting at the earliest time point measured (10 minutes), with a change of 31.6% in the CO₂ group and 12.5% in the placebo group ($P = .002$). The difference between the 2 treatment groups remained statistically significant over the assessment period, with the exception of the 4-hour time point ($P = .091$) and the 24-hour time point ($P = .057$).

Interestingly, the baseline imbalance in TNNSS was driven by a statistically significant difference in sneezing ($P = .004$). However, all symptoms showed improvements from baseline with CO₂ compared with placebo over the 24-hour evaluation period (Fig 4).

The individual nonnasal symptoms, as well as the TNNSS, also showed benefit with CO₂ treatment compared with placebo (Fig 5), although the changes were not statistically significant.

TABLE I. Most common adverse events

	Nasal stinging		Watery eyes	
	CO ₂ (n = 60)	Placebo (n = 29)	CO ₂ (n = 60)	Placebo (n = 29)
None	5.0%	55.2%	21.7%	72.4%
Mild	15.0%	27.6%	16.7%	20.7%
Moderate	33.3%	10.3%	40.0%	3.4%
Severe	46.7%	7.0%	21.7%	3.4%

Adverse events

Serious adverse events did not occur during the study and neither did adverse events of medical significance.

In earlier studies intranasal noninhaled CO₂ was found to cause nasal stinging or burning and watery eyes.^{8,9} These were the most common adverse events observed in this study as well (Table I). The adverse events were limited to the duration of the gas administration and were often relieved before the gas administration was terminated. In addition to the above, 5 of the 89 subjects reported nonserious adverse events, 2 in the CO₂ group and 3 in the placebo group. The events were all rated by the subjects as mild in intensity and consisted of a “swimmy” feeling, sore throat, headache, laryngitis, and stomach cramps. Only the latter 2 events occurred in the CO₂ treatment group.

DISCUSSION

This is the first report to document the therapeutic potential of intranasal noninhaled CO₂ for the symptomatic treatment of allergic rhinitis. The study met its primary end point, a reduction in TNNSS at 30 minutes after treatment. The two 60-second treatments administered within 5 minutes maintained the TNNSS improvement over that of placebo for the entire 24-hour assessment

period (Fig 3). Furthermore, the CO₂ treatment also improved each of the individual nasal symptom scores (Fig 4).

Although intranasal CO₂ showed improvement in the nonnasal symptoms of allergic rhinitis (Fig 5), the differences from placebo were not statistically significant. This could in part be due to baseline values that were relatively low (baseline TNNSS for CO₂ was 7.5 and for placebo was 6.5). The rapid and sustained improvement in nasal symptoms, however, indicates that this novel treatment potentially has an important therapeutic role for this common condition. The oral antihistamines and antileukotrienes have little or no effect on nasal congestion, and in addition, their onset of action in relieving the other nasal and nonnasal symptoms of allergic rhinitis is relatively slow.^{1-3,18}

The mechanism of action involved in the therapeutic effect of CO₂ in allergic rhinitis was not examined in this study. However, *in vitro* experiments have shown that the gas, when administered in a buffered medium, inhibits both neuronal activation and the release of CGRP, possibly by causing intracellular acidosis.¹² Trigeminal neuronal activation has been implicated in the pathogenesis of allergic rhinitis, accompanied by mast cell activation and the release of inflammatory mediators. The trigeminal neuronal activation, in turn, causes the local release of neuropeptides, including CGRP, a potent vasodilator.¹¹ It is additionally plausible that the effect of CO₂ on neuronal activation is nonspecific and that CO₂ similarly affects mast cell degranulation, targeting the center-stage cell in the pathogenesis of allergic rhinitis. Future studies will have to address this issue and might help further define the therapeutic potential of CO₂ in allergic rhinitis and other (craniofacial) inflammatory conditions.

The administration of intranasal CO₂ did result in moderate or severe nasal stinging and watery eyes in the majority of subjects. It is possible that this could have adversely affected the blinding of the study subjects. However, each patient was dosed in a separate closed-door room so that other subjects and study staff making treatment assessments could not witness the dosing procedure. Furthermore, all subjects were instructed not to discuss any adverse events or improvements with other subjects. Finally, adverse effects of the CO₂ were prominent only during administration and subsided very rapidly after the treatment was completed. Nonetheless, further studies are needed to determine whether changes in flow rate or flow duration decrease the occurrence of these adverse events while maintaining the positive treatment effect. The proved safety of noninhaled administration of CO₂ for surgical procedures provides indirect support for the overall safety of noninhaled intranasal CO₂. For example, laparoscopic procedures entail the intra-abdominal administration of many liters of the gas under moderate pressure for up to several hours, with little or no effect on patient safety.

There are some limitations to the present single-dose and clinic-based study, with no natural exposure to seasonal allergens over the initial 4 hours of efficacy

assessment. However, requiring minimal allergic rhinitis symptom scores for randomization (TNSS ≥ 6) partly addresses this concern. There was a statistically significant difference in TNSSs between the 2 treatment groups at baseline, with the placebo-treated subjects having a lower score. It is conceivable that this could have resulted in a "floor" effect, limiting the symptom changes in the placebo group. However, this is unlikely to be the case given the substantial improvement seen in the placebo group. In addition, the effect of CO₂ appears robust, with different statistical approaches (eg, using percentage change from baseline and ANCOVA analyses) all showing significant effects. Moreover, when we analyzed the differences between the active and placebo cohorts, eliminating sneezing (the only symptom to differ between the 2 groups at baseline), there was still a positive treatment effect as quickly as 10 minutes ($P = .001$) and as long as 24 hours ($P = .011$) after treatment. Another limitation was that the study did not include an active comparator to gauge the beneficial effect of the CO₂ treatment relative to other treatments, such as oral or intranasal antihistamines. Finally, the large-capacity, compressed gas cylinders used to administer the gases in the present study are not practical for widespread application. A small hand-held device has been used to examine the therapeutic effect of noninhaled intranasal CO₂ in migraine headache and will be used in future allergic rhinitis studies.

Despite the above minor limitations, the data show that noninhaled intranasal CO₂ has great potential as a safe and effective treatment for seasonal allergic rhinitis. The rapid onset (<30 minutes) and long duration (24 hours) make this novel approach especially appealing as treatment, in addition to its inherent safety. Future studies will have to determine the best dosing regimen, weighing efficacy against tolerability, and will have to define its application as acute treatment, chronic treatment, or both of allergic rhinitis.

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