A pilot study of the effects of intranasal budesonide delivered by NasoNeb® on patients with perennial allergic rhinitis

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Background: **We investigated whether nebulization of budesonide via a NasoNeb® device would treat perennial allergic rhinitis.**

Methods: **We performed a parallel, randomized, double-blind, placebo-controlled, pilot study in subjects (n = 40) with perennial allergic rhinitis. After recording baseline symptoms, subjects were randomized to budesonide respules (0.25 mg) or an equivalent placebo for 26 days. Nasal peak inspiratory flow (NPIF) and nasal symptoms (graded on a 0–3 scale) were recorded by the subjects twice daily. Rhinoconjunctivitis quality of life (RQOL) as well as nasal volume, measured by acoustic rhinometry, was obtained at baseline, after 2 weeks, and at the end of treatment.**

Results: **The average change from baseline in symptoms over the treatment period was greater for the group on budesonide (−3.33) compared to placebo (−1.98) ($p = 0.45$). When the average change from baseline over the treatment period was compared between the groups, budesonide resulted in higher NPIF (36.4 L/min) than placebo (18.7 L/min), $p = 0.094$. QOL improved in both groups compared to baseline with no significant difference between the groups. Although acoustic rhinometry indicated a larger volume in the group treated with budesonide on the last trial visit, the differences between the groups were not significant when accounting for the baseline values.**

Conclusion: **Compared to placebo, administration of nebulized budesonide in subjects with perennial allergic rhinitis resulted in improvements in symptoms and objective measures of nasal congestion which approached but did not achieve statistical significance. A higher dose of active agent, a less effective placebo and a larger number of subjects might have improved statistical significance.** © 2013 ARS-AAOA, LLC.

Key Words:
rhinitis; perennial; nebulized; budesonide

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Allergic rhinitis affects up to 400 million people worldwide and has a marked impact on patients' quality of life (QOL) both at school and in the workplace.[1] It is 1 of the top 10 reasons that patients visit their primary care physician. It has also been shown to cause significant decreases in sufferers' productivity in the workplace which, in addition to the cost of medical treatment for the disease, amounts to a significant socioeconomic burden.[2]

While current treatments are effective, national surveys of patients suggest there is a need for better treatments.[3–6] Intranasal steroids are considered the gold standard for the treatment of moderate to severe allergic rhinitis, although many patients do not comply with the treatment and many require adjuvant treatment to improve efficacy. Intranasal steroids have been shown to improve all nasal symptoms in clinical trials of seasonal and perennial allergic rhinitis and also improve QOL.[7] The standard form of administration of these intranasal agents has been in the form of an aqueous metered dose spray and more recently as an hydrofluoroalkane (HFA) aerosol. Unfortunately, only about 60% of patients report the treatment as being excellent.[8] One potential reason for this result is that the drug is not well

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distributed through the nose. This consideration has led to several studies examining novel distribution methods of intranasal therapies.[9–14] Several studies have demonstrated promising results for the efficacy of nebulized medication and its distribution of solution throughout the nasal cavity as well as into the paranasal sinuses.[15–17] The initial studies that looked at nebulized distribution in the nose were in vitro/in vivo studies performed on models, cadavers, or healthy subjects.[18] The subsequent clinical investigations have focused on treating patients with chronic rhinosinusitis with or without nasal polyps, with a focus on post–endoscopic sinus surgery patients presuming delivery to be enhanced in postsurgical sinus cavities.[19,20] Further investigation is therefore warranted in more diverse clinical settings for different nasal diseases. We hypothesized that nebulization would provide a superior method of delivering intranasal corticosteroids compared to the metered dose spray and would lead to superior control of the symptoms of perennial allergic rhinitis. The NasoNeb® device has been U.S. Food and Drug Administration (FDA)-approved for the delivery of intranasal medications. As a first step in addressing our hypothesis, we performed a placebo-controlled study evaluating the efficacy of an intranasal steroid, delivered via the NasoNeb device, in controlling the symptoms of perennial allergic rhinitis. The obvious next step to prove our hypothesis would be a head-to-head comparison of the same intranasal steroid, delivered by the 2 different methods, on the control of symptoms.

Patients and methods

Study design

We performed a 4-week, randomized, double-blind, placebo-controlled, parallel, clinical trial in 40 patients with perennial allergic rhinitis. Initial screening included an allergy questionnaire, a skin prick test to confirm a positive response to a perennial allergen (cat, dog, dust mite, or indoor mold), and a nasal symptom score recording in which patients ranked their symptoms over the past 12 hours from 0 to 3 for sneezing, runny nose, nasal congestion, and itchy nose. Participants who had a positive skin prick test and a total score $\geq$4 and congestion score $\geq$2 then underwent a decongestant test. This was performed as follows: nasal peak inspiratory flow (NPIF) was measured, 2 sprays of oxymetazoline 0.05% were then delivered to both nostrils, followed, 10 minutes later, by another NPIF measurement. Participants with a 35% or greater increase in response to the decongestant were then enrolled into the study. This was based on a previous study that showed that participants who fulfilled the symptom and decongestant criteria above were more responsive to therapy and that these tests eliminated volunteers with confounding issues.[21]

Eligible participants then filled out an Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)[22] and underwent measurement of nasal volume by acoustic rhinometry prior to starting the study. They were then randomized to receive either Pulmicort Respules (budesonide) at a dose of 0.25 mg or placebo (saline) once daily delivered by NasoNeb. This dose is equivalent to giving Rhinocort AQUA (4 sprays (32 μg/spray) in each nostril once daily [QD]; total dose = 0.256 mg). The investigator assigned patients in a sequential randomized fashion to either study treatments in groups of 4. The subjects all received nebulized treatments via the NasoNeb device and neither them nor the administering investigator were privy to the medications received as the medication packets were blinded. Participants were instructed to record symptom diary cards twice daily and measure NPIF twice daily. Participants were instructed to take the study medication once daily in the evening after recording their symptoms and NPIF. Before starting study medication, subjects recorded 1 morning and 1 evening set of parameters that were used as baseline for all the measurements. Participants were seen in the laboratory every 2 weeks over the 4 week study to check their diaries, replace medications, and repeat acoustic rhinometry and RQLQ surveys. At the conclusion of their 4 weeks they returned the NasoNeb machine and medication, turned in their diaries, filled out their final RQLQ, and had their final acoustic rhinometry measurement taken. The study was approved by the Institutional Review Board of the University of Chicago and all participants signed informed consent. The trial was registered with clinical trials.gov (NCT01270256).

Subjects

Healthy adults between the ages of 18 and 55 years with perennial allergic rhinitis were recruited between February 14, 2011 to June 25, 2012. All patients had a positive skin prick test to a perennial allergen and symptoms of perennial allergic rhinitis. Patients with positive skin prick test to cat and dog had symptoms related to exposure and had the relevant pets in their homes. Exclusion criteria were as follows: patients with physical signs or symptoms suggestive of renal, hepatic, or cardiovascular disease; pregnant or lactating women; participants treated with systemic steroids within the past 30 days; participants treated with topical (inhaled, intranasal, or intraocular) steroids, Nasalcrom, or Opticrom within the past 30 days; participants treated with oral antihistamine/decongestants within the past 7 days; participants treated with topical (inhaled or intraocular) antihistamine/decongestants within the past 3 days; participants treated with immunotherapy during escalation of their dose; participants on chronic antiasthma medications; participants with nasal polyps or a significantly deviated septum; participants with a history of an upper respiratory infection within 14 days of study entry. Rescue medications were not allowed during the trial. Ultimately 41 participants were enrolled in the study and 40 completed it.

Symptom score

Severity of sneezing, rhinorrhea, nasal congestion, and itchy nose were recorded on a scale from 0 to 3 (0 = none,

1 = mild, 2 = moderate, and 3 = severe). Subjects were asked to record their symptoms reflective of the previous 12 hours in the morning (reflecting the nighttime symptoms) and again in the evening (reflecting the daytime symptoms). The reflective total daily nasal symptom score consisted of the sum of the morning and evening scores.

NPIF

NPIF was measured objectively in liters per minute with an In-Check Peak & Inspiratory Flow Meter (Ferraris Medical Inc, Orchard Park, NY). Subjects obtained 3 readings every morning and every evening and the greatest of the 3 measures were recorded. Total daily NPIF was calculated by adding the morning and evening values each day.

Acoustic rhinometry

Acoustic rhinometry, a quantitative measurement of nasal volume, was performed with an ECCOVISION acoustic rhinometer (Hood Laboratories, Pembroke, MA). We used the measurement of nasal volume between 2 and 8 cm from the nasal vestibule. Each participant underwent 3 measurements on each side and the average was used for data analysis. The sum of nasal volume for the right and left sides were reported.

Statistical analysis

The primary outcome measure was the change in NPIF over the treatment period. Secondary outcome measures were the changes from baseline in daily individual and total symptoms, QOL, and nasal volumes measured by acoustic rhinometry. QOL and acoustic rhinometry data are normally distributed and were analyzed using parametric statistics. For each treatment arm, we performed an analysis of variance (ANOVA) and if the p value was significant, post hoc testing was performed using the Student paired t test to compare differences between the 3 visits within treatments. We then compared the differences between treatments by calculating the change from baseline for both visit 2 and visit 3 and comparing the deltas between therapies usng unpaired t tests. We also compared the baselines between the 2 treatment groups using unpaired t tests.

NPIF and symptom score data were not normally distributed and were analyzed using nonparametric statistics. We first examined the overall change within each treatment arm by Friedman ANOVA and, if there was a significant treatment effect, we compared all treatment days to the baseline using the Wilcoxon signed ranks test. We then calculated the change in scores from baseline for each treatment day within each treatment arm. The average of the change from baseline for all 26 treatment days was then used to compare the 2 treatments and was analyzed by the Mann Whitney U test for unpaired comparisons.

TABLE 1. Baseline subject characteristics

Parameter	Budesonide	Placebo	p
Number	20	20	
Age (years), mean (range)	33.3 (18–55)	32.3 (18–52)	0.77
Sex (M/F)	13/7	9/11	NS
Race/ethnicity (%)			
Caucasian	35	50	NS
African American	40	45	NS
Asian	20	0	NS
Hispanic	5	5	NS
Number with positive skin tests			
Dust mites	16	18	NS
Mold and/or cat	19	13	NS
Total nasal symptoms, median (range)[a]	6.5 (4–11)	7.0 (4–11)	0.52
Nasal volume (cm^3), mean (SEM)[b]	15.62 (1.1)	13.98 (1.09)	0.3
RQLQ, mean (SEM)	3.08 (0.26)	3.03 (0.21)	0.9
NPIF (L/min), median (range)	100 (70–160)	90 (50–200)	0.26

[a]Total nasal symptoms are 12-hour reflective.
[b]Nasal volume = measured by acoustic rhinometry.
F = female; M = male; NPIF = nasal peak inspiratory flow; NS = not statistically significant; RQLQ = rhinoconjunctivitis quality of life; SEM = standard error of the mean.

Results

Subjects

We screened 83 patients and entered 41 subjects into the study. One subject failed to complete the study due to noncompliance and 40 patients completed the study. The groups were matched at entry for age, sex, race, allergies, baseline symptoms, nasal volume, QOL (using the RQLQ), and airflow (Table 1). There were no adverse events to report. There were 4 asthmatics within the trial and 5 patients who had previously taken immunotherapy, last in 2006. The patients in these categories were randomly separated between the treatment groups and their individual data did not seem to be different from the group data.

NPIF

Total NPIF was obtained by adding the morning and evening recordings. Baseline total NPIF was similar in both treatment groups ($p = 0.26$; Fig. 1). There was a significant overall increase in NPIF over the duration of the trial only in the active treatment group (budesonide ANOVA: $p = 0.03$, placebo ANOVA: $p = 0.08$). Post hoc analysis was therefore performed only in the budesonide treatment group and showed that nebulized budesonide led to a consistent significant increase in total daily NPIF compared to baseline on days 2 to 26 of the trial ($p < 0.005$ vs baseline). When the average of the change from baseline in NPIF for

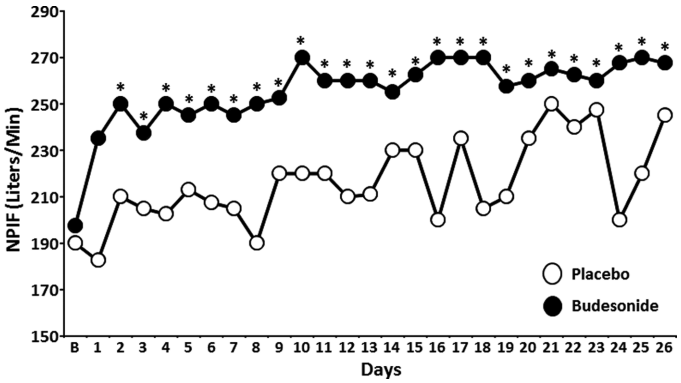

FIGURE 1. Daily nasal peak inspiratory flow on treatment. Median values are depicted. The x-axis shows the study timeline with B = baseline measurement. *$p < 0.005$ vs baseline for the group on budesonide.

all days of treatment was compared between groups, there was a larger increase in the budesonide treatment group (median = 36.4 L/min, range = −15.4 to 123.2 L/min) compared to placebo (median = 18.7 L/min, range = −50.4 to 88.1 L/min) that almost reached statistical significance ($p = 0.09$).

Total nasal symptom scores

Baseline total nasal symptom scores (TNSS) were similar in both treatment groups ($p = 0.56$, Fig 2). There was a significant overall reduction in TNSS over the duration of the trial in both treatment groups (budesonide ANOVA: $p = 0.005$; placebo ANOVA: $p = 0.022$). Post hoc analysis showed that nebulized budesonide led to a consistent significant reduction in TNSS compared to baseline on days 2 to 26 ($p < 0.05$). In the placebo-treated group, there was a statistically significant reduction of TNSS compared to baseline only on days 4 to 5, 11 to 16, 18, and 20 to 22 ($p < 0.05$). When the average of the change from baseline in TNSS for all days of treatment was compared between groups, there was a larger reduction in the budesonide treatment group (median = −3.33; range, −13.8 to 2.2) compared to placebo (median = −1.98; range, = −12.5 to 4.9) but this did not reach statistical significance ($p = 0.45$).

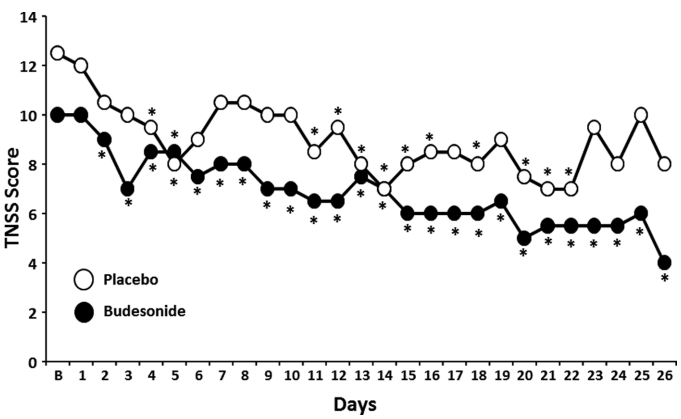

FIGURE 2. Daily TNSS on treatment. Median values are depicted. The x-axis shows the study timeline with B = baseline measurement. *$p < 0.05$ vs respective baselines within treatment groups. TNSS = total nasal symptom scores.

TABLE 2. Average change from baseline in individual nasal symptom scores[a]

Parameter	Budesonide	Placebo	*p*
Sneezes	−0.37(−2.4, 1.3)	−0.37 (−3.8, 2.4)	0.75
Stuffy nose	−0.63 (−3.5, 1.4)	−0.65 (−4.5, 2.8)	0.85
Runny nose	−0.85 (−4.8, 1.0)	−0.33 (−2.9, 1.6)	0.5
Itchy nose/throat	−1.25 (−5.0, 1.4)	0.12 (−3.9, 2.0)	0.46

[a]Data are the median change from baseline over all treatment days. Results shown are median (range).

Individual nasal symptom scores

Individual symptoms showed similar findings to the total nasal symptom scores. However, when comparing the average change from baseline across the trial days between treatments, there were no statistically significant differences between the treatment groups (Table 2).

Acoustic rhinometry

Nasal volume measured by acoustic rhinometry was obtained at 3 points throughout the trial: at baseline, after 2 weeks of treatment and at the end of the trial. There was no significant difference in the subjects' baseline acoustic rhinometry values ($p = 0.3$) (Fig. 3). There was also no overall significant differences between visits within either the steroid-treated (ANOVA: $p = 0.58$) or placebo-treated groups (ANOVA: $p = 0.9$). Although the baselines were not statistically different, they were numerically different between the groups. Therefore, to analyze treatment effect, we calculated the change from baseline on visit 2 and visit

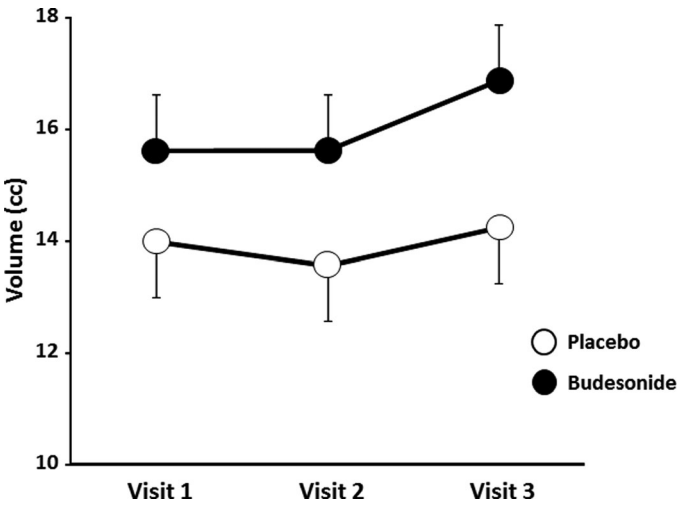

FIGURE 3. Acoustic rhinometry measures for the 3 treatment visits. No significant differences were detected. Data depicted as means ± SEM. SEM = standard error of the mean.

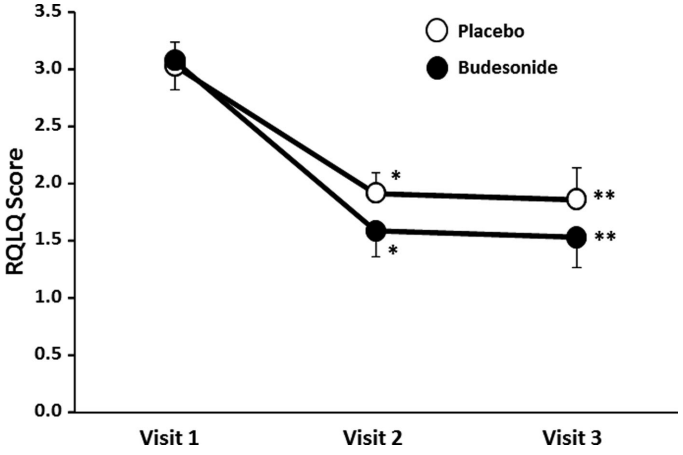

FIGURE 4. Rhinoconjunctivitis quality of life. The overall domain of the RQLQ is shown here at the baseline and treatment visits. Data depicted as means ± SEM. *$p < 0.0002$ and **$p < 0.0003$ vs respective baselines. RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; SEM = standard error of the mean.

3 (by subtracting the baseline from the respective visit 2 and 3 values) within each group and then compared the 2 groups by unpaired *t* test. There were no significant differences between the treatment groups on either the second visit ($p = 0.52$) or the third visit ($p = 0.3$).

RQLQ

The RQLQ was obtained at 3 points in the study, at the initial visit, the 2-week visit and the 4-week visit. The results of the overall domain (average of all other domains) are discussed here. There was no significant difference in the subjects' baseline RQLQ scores ($p = 0.9$, Fig 4). Both the budesonide and the placebo group demonstrated statistically significant improvements of their overall score on the RQLQ compared to baseline at the 2-week time point ($p < 0.0002$) and the 4 week time point ($p < 0.0003$). There was no statistically significant difference between the two treatment groups at either visit 2 or visit 3 ($p > 0.3$). To analyze treatment effect, we calculated the change from baseline on visit 2 and visit 3 (by subtracting the baseline from the respective visit 2 and 3 values) within each group and then compared the 2 groups by unpaired *t* test. There were no significant differences between the treatment groups on either the second visit ($p = 0.33$) or the third visit ($p = 0.41$).

Discussion

Although the current study is small, we feel that our results demonstrate promise for treating patients with perennial allergic rhinitis with nebulized intranasal corticosteroids. Subjects treated with nebulized budesonide (selected because there is an FDA-approved nebulized product with the same dose as the currently used budesonide aqueous intranasal spray) demonstrated improvement in NPIF, nasal volume, and symptom scores when compared to the placebo treatment group. Patients in the budesonide treatment arm also demonstrated significant improvement on a daily basis during the trial in their total symptom scores in comparison to their baseline score. Considering our small sample size of 20 subjects per treatment arm, we feel that a larger study would likely demonstrate convincing statistical improvements in total nasal symptoms, nasal volumes, NPIF as well as in subjects' QOL reflected by the RQLQ.

The typical perennial allergic rhinitis study enrolls between 200 and 300 patients per arm to show statistical difference in total nasal symptoms scores. In fact, based on the results of this pilot study with respect to NPIF, a power calculation shows that it would require a sample of 116 subjects per group to show a statistically significant effect of budesonide over placebo with a power = 80% and alpha = 0.05. Although an increased duration of therapy and a longer trial might have shown better effects, we chose the duration of 4 weeks based on the literature and FDA recommendations for clinical trials in perennial allergic rhinitis.

The approximate increase of 50 L/min in peak flow from baseline in the actively treated group compares favorably with increases in peak flow from other studies in seasonal allergic rhinitis.[23] Consistent with peak flow, which was measured daily, was the increase in nasal volume, which was measured at the different study visits and exhibited similar trends for improvement in the actively treated group.

The baseline scores for the RQLQ were typical for subjects entering into allergic rhinitis trials. Both groups improved with slightly more improvement in the active treatment group. The improvement in QOL in the placebo group was more than the improvement in the placebo groups in the ciclesonide HFA trial of perennial allergic rhinitis.[24] A significant improvement in the placebo arm of the TNSS parallels this observation in QOL. The large improvement we saw in our placebo group may reflect the fact that the placebo arm of this trial is not 2 actuations from a metered dose inhaler but a nebulization of saline. The placebo in prior studies is less than 50 μL whereas in this study the volume of placebo (saline) was 2 mL. Recent data has shown that large volume saline irrigations are beneficial not only in the treatment of chronic rhinosinusitis but also in patients with allergic rhinitis.[25]

In summary, our pilot study suggests that delivering an intranasal steroid in nebulized fashion is effective in the treatment of allergic rhinitis. This is the first time that an FDA-approved device for the delivery of intranasal medications has been tested for efficacy of the delivered medication. We believe that this pilot data can now be used to design a clinical trial to compare the effectiveness of an aqueous intranasal steroid with a nebulized steroid to test whether nebulization leads to better intranasal delivery and hence better effectiveness in the olfactory and sinus regions.

As discussed previously, numerous studies have demonstrated improved intranasal distribution of tracers administered via a nebulizer in comparison to the standard metered dose spray. Therefore, it stands to reason that administering intranasal corticosteroids, which have been shown

effective time and again as a treatment for perennial allergic rhinitis, would prove to be even more effective when delivered in this novel way. Despite our limitations with a small study which was not powered enough to demonstrate statistical significance in all parameters, we believe that our subjects demonstrated clinically significant improvements which warrants further investigation and continued interest by clinicians in this mode of delivery. This study also re-emphasizes the power of the placebo effect.[26] Theoretically all medical devices used to deliver drugs should be tested in clinical trials to show efficacy before widespread clinical use.

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