

The Effect of Nasally Administered Budesonide Respules on Adrenal Cortex Function in Patients With Chronic Rhinosinusitis

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Objectives: To evaluate whether nasal administration of budesonide in adults with chronic rhinosinusitis for 30 days suppresses adrenal function and to assess its clinical efficacy.

Design: An open-label prospective study.

Setting: Academic medical center.

Patients: We assessed adrenal function in 9 patients using the cosyntropin test before and after budesonide therapy.

Intervention: Budesonide respule therapy.

Main Outcome Measure: Scores from the Sino-Nasal Outcome Test–20 (SNOT-20), a tool for assessing

rhinosinusitis health and quality of life, were used to assess efficacy of budesonide treatment.

Results: All of our patients showed adequate adrenal response to cosyntropin stimulation before and after the budesonide trial. The mean difference in SNOT-20 scores was –1 (95% confidence interval, –1.77 to –0.23; $P = .02$), indicating clinically significant improvement after therapy.

Conclusion: Our findings suggest that using budesonide nasal wash may be clinically effective in decreasing the symptoms of chronic rhinosinusitis and does so without suppression of the hypothalamic-pituitary-adrenal axis in patients with chronic rhinosinusitis.

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CHRONIC RHINOSINUSITIS IS one of the most prevalent conditions among adults in the United States, affecting up to 14% of the population.¹ This condition has a considerable economic impact on patients' lives, which is mainly attributable to additional visits to primary care physicians and increased pharmacy fill use.²

Budesonide, as an aqueous nasal spray with anti-inflammatory properties, has been shown to have a positive impact for those with chronic rhinosinusitis³ and perennial allergic rhinitis.^{4,5} Multiple studies⁶⁻⁸ demonstrate its safety as a topical nasal steroid spray. Budesonide is also available as a respule, a small, plastic, liquid-containing device that can be easily opened and used to deliver unit-dose medications in a sterile fashion (Pulmicort Respules, 0.25 mg and 0.5 mg; AstraZeneca LP, AstraZeneca LP, Wilmington, Delaware), for the maintenance treatment of asthma and as prophylactic therapy in children aged 12 months to 8 years. Yu et al⁹ studied the use of budesonide respules as rehabilitation after functional endo-

scopic sinus surgery. They found that using budesonide respules locally was beneficial for relieving mucosal inflammation, shortening the stage of epithelialization, and accelerating the recovery of mucosa after functional endoscopic sinus surgery. Anecdotally, we are aware of many physicians who also prescribe budesonide respules for patients with chronic sinusitis, many of whom have not had sinus surgery.

The safety of inhaled budesonide respules has been assessed in 3 separate 12-week randomized clinical trials,¹⁰⁻¹² and all have demonstrated no significant systemic effects in pediatric patients with asthma. Safety was assessed in these studies through measurement of the hypothalamic-pituitary-adrenal (HPA) axis function using a corticotropin-stimulation test and observation of rates of adverse events. To our knowledge, a similar demonstration of the safety of a nasally administered budesonide wash has not been performed.

Our primary aim in this study was to evaluate whether nasal administration of budesonide in adult patients with chronic

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rhinosinusitis with or without nasal polyps for 30 days suppresses adrenal function as a result of systemic absorption. We assessed adrenal function in patients with sinusitis using the cosyntropin test.¹³ We also assessed the clinical efficacy of budesonide in treatment of chronic rhinosinusitis using the Sino-Nasal Outcome Test–20 (SNOT-20) questionnaire as a secondary outcome measure.¹⁴

METHODS

DESIGN

This was an open-label study of subjects with chronic rhinosinusitis. The enrolled subjects had their adrenal function assessed before initiating budesonide therapy. They also completed the SNOT-20 questionnaire. The patients received sufficient budesonide for 30 days of therapy and were instructed to use it on a daily basis. After 30 days of use, adrenal function was assessed again, and subjects completed the SNOT-20 questionnaire and a drug satisfaction survey.

STUDY SUBJECTS

Subjects were recruited from the offices of two of us (J.F.P. and S.E.T.) at the Department of Otolaryngology–Head and Neck Surgery, Washington University School of Medicine, St Louis, Missouri. Enrollment began January 2005 and continued until February 2006. Patients between the ages of 18 and 70 years were included and had to have a history of chronic rhinosinusitis with or without nasal polyps. Patients were excluded from the study if they met any one of the following criteria: concurrent or recent use (within the past 30 days) of systemic corticosteroids; history of pituitary disease; morbid obesity (body mass index [calculated as weight in kilograms divided by height in meters squared] >38); concurrent or recent use of medications that accelerate the clearance of cortisol, such as diltiazem, rifampin, amphetamines, or lithium carbonate; concurrent use of medications that interfere with the production of cortisol, such as ketoconazole, amphotericin B, bupropion, *Echinacea*, fluoroquinolones, itraconazole, licorice, and ma huang (*Ephedra*); use of oral contraception; use of female or male hormone therapy; a radioactive scan performed within 7 days before the test; known hypersensitivity to cortisol, corticotropin, or cosyntropin; allergic disease associated with anaphylactic reactions or breathing difficulties; or pregnancy.

We successfully enrolled 10 subjects. Subsequently, one of the subjects dropped out of the study and was excluded from all analyses. The Washington University Human Studies Committee approved this study.

DRUG ADMINISTRATION

Patients were instructed to use budesonide, 0.25 mg, 1 respule per nostril once daily, with the following protocol. First, patients poured a small amount of isotonic sodium chloride (saline) solution into a clean container or a small disposable cup. They then emptied 1 respule into a separate container or cup and mixed the contents of the respule with 5 mL of saline solution using a 5-mL syringe. They irrigated each nostril with the single respule diluted in 5 mL of saline solution in each of the following 3 positions:

1. Head down and back or head down and forward. The patient lies in a supine position with his or her head over the side of the bed. The hair should be pointing toward the floor

while the patient looks directly at a wall. The nostrils will be facing the ceiling.

2. Head in downward position. The patient turns his or her head to the same side as the nostril to be irrigated. The patient remains in position 1, yet rolls to the same side as the nostril to be irrigated.

3. The patient lies in a supine position with his or her head held flat to allow the head to tilt back at about a 45° angle.

The patients instilled the 5-mL solution in approximately 3 applications.

The patients were to hold their head in each position for 2 to 3 minutes and to sit up and rest between each position. Patients completed this process on one side and then repeated the process for the opposite nostril. They were instructed to discard syringes every other day.

MEASUREMENTS

Baseline levels of cortisol in the bloodstream were measured at the patients' first visit. Participants then received 0.25 mg of cosyntropin and 10 mg of mannitol reconstituted with 1 mL of 0.9% sodium chloride as an intramuscular injection to stimulate the adrenal cortex. The patients' stimulated levels of blood cortisol were then measured approximately 30 minutes later. This procedure was repeated on the completion of the 30 days of nasally administered budesonide therapy.

Measuring blood levels of cortisol after cosyntropin stimulation is the standard way to assess for suppressive effects on the HPA axis. If nasally administered budesonide is systemically absorbed, this will result in a reduced output of the adrenal cortex relative to that before stimulation. This, in turn, will result in inadequate cortisol levels in response to cosyntropin in the posttreatment period. However, if nasally administered budesonide is not absorbed and has no systemic effect on the HPA axis, there will be no difference in the blood cortisol stimulation between the 2 periods.

Blood cortisol levels were measured by the General Clinical Research Center Immunoassay Core Laboratory, Washington University School of Medicine. Blood insulin levels were also measured as a calibration for the blood cortisol levels. Cortisol levels were measured in micrograms per deciliter (to convert to nanomoles per liter, multiply by 27.588).

Scores from the SNOT-20¹⁴ questionnaire, a valid patient-based tool for assessing rhinosinusitis health status and quality of life, were used to assess the efficacy of budesonide treatment. Each of the 20 individual items are scored from 0 to 5, with 0 indicating no problem and 5 indicating that the particular item had the greatest burden. Each subject completed the survey at the initial and final visits. The total SNOT-20 score was calculated by adding up the response values of each individual item and dividing by the total number of items answered. The difference in total score between initial and final visit is a measure of the change in rhinosinusitis health status and quality of life. A negative change score implies improvement in rhinosinusitis health status and, based on previous research,¹⁴ a change of –0.8 or greater indicates a clinically significant improvement.

At the final visit, subjects also completed a drug satisfaction survey addressing the level of global improvement with 7 choices ranging from “very much better” to “very much worse”; adverse effects with choices ranging from “none” to “extremely severe”; and whether they would recommend nasally administered budesonide lavage therapy to a friend.

ANALYSES

The primary analysis was the observation of poststimulation blood cortisol levels before and after the administration of na-

Table 1. Description of Patient Population

Characteristic	Patients ^a (N = 9)
Age, mean (SD), y	54.5 (10.9)
Sex, female	6 (67)
Race/ethnicity, white	9 (100)
Nonsmokers	8 (89)
No previous sinus surgery	6 (67)

^aData are given as number (percentage) unless otherwise specified.

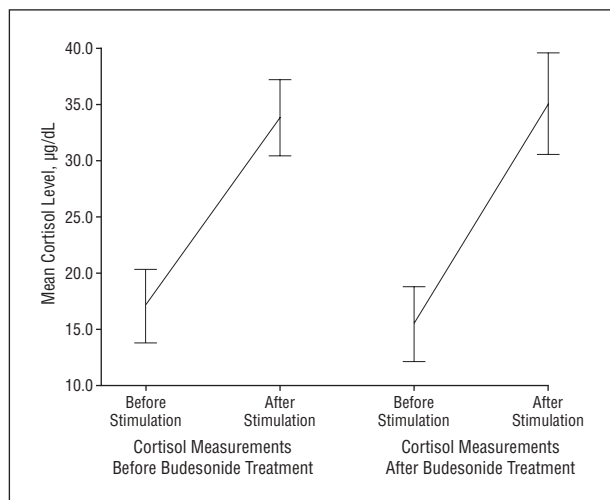


Figure. Blood cortisol levels before and after budesonide respule therapy. Error bars indicate 95% confidence intervals. To convert cortisol to nanomoles per liter, multiply by 27.588.

sally administered budesonide lavage. A poststimulation level below 20 µg/dL indicated an insufficient adrenal response to cosyntropin stimulation. The SNOT-20 scores were obtained before and after administration of budesonide, and a change score was calculated as the difference between initial and final score. We used paired sample *t* tests to determine the statistical significance of cortisol and SNOT-20 changes. All analyses were performed using SAS statistical software (SAS Corporation, Cary, North Carolina), and *P* < .05 was considered as statistically significant.

RESULTS

The majority of patients were white, nonsmoking women who had previously undergone sinus surgery (**Table 1**). The prestimulation and poststimulation cortisol levels at baseline and after 30 days of therapy are shown in the **Figure**. There was no significant difference in mean prestimulation cortisol levels between baseline and after 30 days of budesonide therapy. Cosyntropin-induced cortisol levels spike were robust at each assessment time. The poststimulation cortisol level at 30 days was slightly, although not statistically significantly, higher than the poststimulation cortisol value at baseline. At baseline, the mean poststimulation cortisol level was 33.9 µg/dL (95% confidence interval [CI], 30.50-37.28 µg/dL). After 30 days of budesonide therapy, the mean poststimulation cortisol level was 35.2 µg/dL (95% CI, 30.66-39.70 µg/dL). Overall, none of the subjects' poststimulation cor-

Table 2. Poststimulation Cortisol Levels^a

Patient No.	Cortisol Level, µg/dL	
	Before Budesonide Treatment	After Budesonide Treatment
1	34.5	43.2
2	37.3	44.0
3	39.0	34.3
4	36.9	40.0
5	24.7	29.3
6	34.4	27.7
7	36.3	33.3
8	31.6	31.7
9	30.3	33.1

SI conversion factor: To convert cortisol to nanomoles per liter, multiply by 27.588.

^aBudesonide administered as budesonide respules.

tisol level was below the critical level of 18 to 20 µg/dL, thus suggesting that daily use of budesonide nasal respules for 30 days does not suppress adrenal function to a significant degree. The peak cortisol level in response to cosyntropin stimulation is an important measure in terms of assessing adrenal insufficiency¹⁵; a peak cortisol level between 18 and 20 µg/dL is considered an adequate response indicating no adrenal insufficiency and is well supported in the literature.¹⁵⁻¹⁷ In our cohort, poststimulation levels of serum cortisol were higher than 18 µg/dL before and after the budesonide trial for all patients (**Table 2**). This further validates our findings; there were no signs of adrenal suppression in our patient population.

The total SNOT-20 score was 2.4 (95% CI, 1.7 to 3.1) at baseline and 1.4 (95% CI, 0.8 to 2.1) at the 30-day visit. This difference of -1 was both statistically and clinically significant (95% CI, -1.77 to -0.23; *P* = .02). Budesonide nasal lavage treatment resulted in 6 of the 9 patients (67%) experiencing a reduction of 0.8 point or greater.

The subjects all reported some form of overall improvement with the use of budesonide, and 6 of the 9 patients (67%) would recommend this drug to a friend (**Table 3**). Of the 10 patients enrolled in the study, 1 patient discontinued the study because of the lack of an effect. Of the remaining 9 patients, 2 patients reported nosebleeds and 1 patient reported a headache. One of the patients in this group experienced diarrhea, dyspepsia, and irritability. The 6 remaining patients reported no adverse effects. There were no unexpected safety concerns during the course of this trial.

COMMENT

In this study, we found that the use of budesonide respules as a nasal lavage in patients with chronic rhinosinusitis does not suppress the HPA axis. On the contrary, we found a slight increase in the mean level of cosyntropin-induced cortisol secretion after 30 days of budesonide lavage. In addition, we assessed the efficacy of budesonide through the use of a patient-based assessment of rhinosinusitis health status. The decrease in SNOT-20 question-

Table 3. Distribution of Secondary Outcome Measures

Secondary Outcome Measure	Patients, No. (%) (N = 9)
Global improvement	
Very much worse	0
Somewhat worse	0
Minimally worse	0
Normal	0
Minimally better	1 (11)
Somewhat better	5 (56)
Very much better	3 (33)
Recommendation of drug to friends	
Definitely yes	3 (33)
Maybe yes	3 (33)
Unsure	3 (33)
Maybe no	0
Definitely no	0
Adverse effects	
None	4 (44)
Very slight	2 (22)
Slight	2 (22)
Moderate	0
Significant	1 (11)
Extremely severe	0

naire scores was sufficient to suggest a clinically meaningful improvement when compared with historical data from a cohort of patients with rhinosinusitis.¹⁴ Without the use of a control group we cannot definitively conclude that this improvement was due to the budesonide nasal lavage. The decrease of SNOT-20 scores was consistent for all 9 patients, supporting the evidence for the clinical efficacy of this intervention. The drug satisfaction survey showed that patients were overall satisfied with this treatment for their rhinosinusitis.

A concern regarding the use of glucocorticoids is that they are unsafe because of systemic absorption. A pooled analysis¹⁸ of the 3 clinical trials^{10,11,19} of budesonide inhalation suspension has shown that, after a 52-week extension study period, baseline and corticotropin-stimulated cortisol levels were not significantly different in children compared with those receiving conventional treatments for asthma. Our study showed that adrenal function was not suppressed through nasal administration. Whether budesonide affects growth is a topic with differing opinions. In the 52-week extension studies of the clinical trials,^{10,11,19} 1 of the 3 studies showed that asthmatic children randomized to budesonide inhalation suspension experienced a significant reduction in growth velocity.¹⁸ Some studies^{20,21} reported no effect on growth with budesonide treatments, while others^{22,23} suggest that budesonide therapy may have a transient effect on growth rate. These effects should be investigated in children with sinusitis if there is widespread use of budesonide respules as a nasal wash. A recent meta-analysis²⁴ showed that corticosteroids may have an effect on bone mineral density and other bone markers in an adult patient population with asthma and chronic obstructive pulmonary disease. Whether these phenomena would occur in a chronic rhinosinusitis population when treated with budesonide respules as a nasal wash on a limited (ie, 3-month basis) remains an open question.

Our study was limited in that we did not have a control group to compare against for the SNOT-20 outcome score. Because the patients were not blinded to their treatment, this may have had an impact on the patients' assessment of their treatment.

The clinical significance of this study is that budesonide nasal respules appear safe for short-term use for the relief of symptoms associated with chronic sinusitis. Budesonide respules seem to provide an effective treatment option for the patient with chronic rhinosinusitis with minimal fear of systemic adverse effects. It should be noted that the use of budesonide as a nasal lavage constitutes "off-label" use. The Food and Drug Administration has not approved the use of budesonide for nasal lavage. The off-label use of medications is legal and an accepted part of medical practice. As with any prescription or use of a medical device, the physician has an obligation to disclose reasonable risks associated with the use of the product. This research helps to inform the discussion of medical risk.

A future study to assess the safety of budesonide nasal respules would be to measure bone mineral density in an adult chronic rhinosinusitis population. An additional future study would be to conduct a randomized placebo-controlled trial of nasal budesonide. Assuming that 30% of patients using a saline nasal wash and 66% of patients using budesonide nasal respules would receive a clinically meaningful benefit in a double-blinded, placebo-controlled, randomized clinical trial, the total sample size needed to detect a clinically significant difference would be 66 patients. Given the amount of patients with chronic sinusitis, it should not be difficult to conduct this study.

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