

Safety analysis of long-term budesonide nasal irrigations in patients with chronic rhinosinusitis post endoscopic sinus surgery

Ethan Soudry, MD^{1,2}, Jane Wang, NP¹, Reza Vaezaefshar, MD¹, Laurence Katznelson, MD^{3,4} and Peter H. Hwang, MD¹

Background: Although the safety of topical nasal steroids is well established for nasal spray forms, data regarding the safety of steroid irrigations is limited. We studied the effect of long-term budesonide nasal irrigations (>6 months) on hypothalamic-pituitary-adrenal axis (HPAA) function and intraocular pressure (IOP) in patients post-endoscopic sinus surgery.

Methods: This was retrospective case series. Adrenal function was assessed by using the high-dose cosyntropin stimulation test.

Results: A total of 48 patients were assessed, with a mean duration of budesonide irrigations of 22 months. Stimulated cortisol levels were abnormally low in 11 patients (23%). None reported to have symptoms of adrenal suppression. Three of 4 patients who repeated the study being off budesonide for at least 1 month returned to near normal levels. Logistic regression analysis revealed that concomitant use of both nasal steroid sprays and pulmonary steroid inhalers was significantly associated with HPAA suppression ($p = 0.024$). Patients with low stimulated cortisol levels were able to continue budesonide irrigations under the supervision of an endocrinologist without frank clinical

manifestations of adrenal insufficiency. IOP was within normal limits in all patients.

Conclusion: Long-term use of budesonide nasal irrigations is generally safe, but asymptomatic HPAA suppression may occur in selected patients. Concomitant use of both nasal steroid sprays and pulmonary steroid inhalers while using daily budesonide nasal irrigations is associated with an increased risk. Rhinologists should be alerted to the potential risks of long-term use of budesonide nasal irrigations, and monitoring for HPAA suppression may be warranted in patients receiving long-term budesonide irrigation therapy. © 2016 ARS-AAOA, LLC.

Key Words:

budesonide; corticosteroid; safety; HPAA suppression; intraocular pressure; irrigation; chronic rhinosinusitis

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Corticosteroids are widely used in the management of chronic rhinosinusitis (CRS) to address the underlying

ing inflammatory disorder. To avoid the potential adverse effects of systemic steroids, topical nasal steroids are typically used for long-term maintenance therapy in these patients, often indefinitely, in order to avoid exacerbations. Topical nasal steroid sprays have been shown to have an excellent safety profile in multiple studies¹⁻⁴ in terms of hypothalamic-pituitary-adrenal axis (HPAA) suppression and intraocular pressure (IOP).⁵⁻⁹

In recent years it has become increasingly common to deliver topical nasal steroids via high-volume saline irrigations (typically 240 mL), specifically in the post-endoscopic sinus surgery (ESS) patient group. Studies have shown that in postsurgical patients there is a significantly improved penetration of the sinus cavities with high-volume low-pressure irrigations compared with nasal sprays or atomizers.¹⁰⁻¹³ Budesonide, in the respule form, has been commonly added to these high-volume irrigations in doses ranging from 0.25 mg to 2 mg daily. In comparison, the standard dose of

¹Department of Otolaryngology–Head and Neck Surgery, Stanford University School of Medicine, Stanford, CA; ²Department of Otolaryngology–Head and Neck Surgery, Rabin Medical Center, Tel Aviv University, Tel Aviv, Israel; ³Department of Neurosurgery, Stanford University School of Medicine, Stanford, CA; ⁴Department of Medicine, Stanford University School of Medicine, Stanford, CA

Correspondence to: Peter H. Hwang, MD, Department of Otolaryngology–Head and Neck Surgery, Stanford University School of Medicine, 801 Welch Road, Stanford, CA 94305; e-mail: hwangph@stanford.edu

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budesonide delivered via nasal spray metered dose inhaler is significantly lower and typically ranges from 64 μg to 256 μg . Consequently, there has been much interest in studying the safety profile of this delivery method. The vast majority of these studies addressed short term (up to 8 weeks) use of nasal steroid irrigations.^{14–19}

In this study we were interested in studying the safety profile (HPAA suppression and IOP) of long-term (6 months or longer) use of budesonide nasal irrigations. HPAA suppression was assessed by the 250 μg cosyntropin stimulation test, which evaluates the response (cortisol production) of the adrenal gland to exogenous adrenocorticotrophic hormone (ACTH) administration.

Patients and methods

This study was approved by the Institutional Review Board (IRB) of Stanford University. Since September 2012, we have offered testing of stimulated cortisol levels and IOP to all patients in our clinic who have received budesonide sinus irrigations, 0.5 mg budesonide in 240 mL saline once or twice daily, for at least 6 months. Patients undergoing stimulated cortisol testing were asked to discontinue budesonide rinses 24 to 48 hours prior to the test to allow clearance of any budesonide from the body. The tests were conducted in the early morning (8:00 AM to 10:00 AM) whenever possible. An intramuscular injection of 250 μg of cosyntropin was administered, followed 30 minutes later by blood draw to measure non-fasting serum cortisol and albumin levels. IOP was measured with the Tono-Pen® XL Applanation Tonometer (Reichert Inc., Buffalo, NY) topical anesthesia of the cornea. Patients were questioned for the frequency and dosage of budesonide irrigations and any additional use of other medications. Adverse effects of both irrigations and cortisol stimulation test were recorded as well.

The medical records were reviewed for all patients undergoing cortisol and intraocular pressure testing between 2012 and 2014. Only patients who had undergone ESS were considered. The following information was retrieved: patient demographics, duration and cumulative dose exposure of budesonide irrigation usage, IOP, stimulated cortisol levels, and use of other medications. Exclusion criteria included known pituitary disease, concurrent or recent (<30 days) use of systemic glucocorticoids (oral/intravenous/intramuscular), use of oral estrogens in women, morbid obesity (body mass index [BMI] >38), concurrent pregnancy, and use of medications that affect cortisol production or clearance. Patients found to have low stimulated cortisol levels were re-tested early in the morning if previous measurement had been done in the afternoon. Patients with abnormally low stimulated cortisol levels in the morning were offered re-test when they were 30 days off budesonide rinses.

Statistical analysis

Data were analyzed using IBM SPSS 22.0 statistical software (IBM Corp., Armonk, NY). Chi square was used

to analyze statistical differences between categorical variables. An independent 2-tailed *t* test or Mann-Whitney test were used to analyze continuous variables as determined following normality analysis using the Shapiro-Wilk test. Logistic regression was used for multivariate analysis to identify clinically significant factors associated with HPAA suppression. Values of $p < 0.05$ were considered significant.

Results

A total of 48 patients were included in the study, including 20 females and 28 males. Mean age of patients was 54.5 years (range, 27–77 years); 28 (58%) of our patient were Caucasians, 8 were Asians (17%), 9 were recorded as “other,” 1 was African American, and in 2 data was missing. In 40 patients (83%) all sinuses were operated on; in 7 a minimum of bilateral max antrostomy and total ethmoidectomy were performed.

Patients received budesonide irrigations for a mean of 22 months (range, 6–66 months) with a mean daily dose of 0.75 mg. Thirty-two (67%) patients were concurrently using other forms of topical steroids (15, nasal spray; 10, pulmonary inhaler; 1, ophthalmic drops; and 6, both nasal spray and pulmonary inhaler).

Adrenal suppression testing

Of the 48 patients, 11 (23%) had abnormally low stimulated cortisol levels (<18 $\mu\text{g}/\text{dL}$). No patient with an abnormal stimulated cortisol result reported any symptoms of adrenal suppression (weakness, fatigue, dizziness, muscle aches, nausea, vomiting, and diarrhea). Four of these 11 patients repeated the cosyntropin stimulation test being at least 30 days off budesonide irrigations. One remained with low levels and in the other 3 patients stimulated cortisol levels increased significantly (patient #1: 12.2 to 16.4 $\mu\text{g}/\text{dL}$; patient #2: 14.6 to 17.5 $\mu\text{g}/\text{dL}$; and patient #3: 16.6 to 17.6 $\mu\text{g}/\text{dL}$). Interestingly, when patient #1 resumed budesonide rinses, stimulated cortisol levels decreased again to 13.5 $\mu\text{g}/\text{dL}$. All patients with abnormally low cortisol levels were evaluated by an endocrinologist (L.K.) who, based on presenting symptoms, recommended continuation of budesonide irrigations, owing to the symptomatic benefit gained from the therapy, and observation for clinically evident adrenal insufficiency. For the 3 patients who remained with significantly low stimulated cortisol levels (<16 $\mu\text{g}/\text{dL}$), steroid irrigations were maintained, but the patients were also recommended to receive stress dose steroids as needed for medical or surgical indications.²⁰ To date, there have been no adverse clinical events related to adrenal insufficiency in any of our patients maintained on budesonide irrigations.

Comparison between the group of patients with abnormally low stimulated cortisol levels to those with normal levels did not demonstrate statistically significant differences in terms of duration of budesonide irrigation therapy, average daily budesonide dose, or cumulative budesonide dose. Concomitant use of both nasal steroid sprays

and pulmonary steroid inhalers was significantly higher ($p = 0.021$) in the group of patients with low stimulated cortisol levels. However, concurrent use of only 1 other form of steroid spray or inhaler was not associated with lower stimulated cortisol levels. Although no differences were seen with respect to age, there was a higher proportion of males in the abnormally low stimulated cortisol level group, which reached a nearly significant value of $p = 0.07$. Logistic regression analysis including all of the above parameters revealed that only concomitant use of both nasal steroid sprays and steroid inhalers in addition to the budesonide rinses was significantly associated with HPAA suppression ($p = 0.024$; odds ratio [OR] = 30.4; 95% confidence interval [CI], 1.57 to 588). Albumin levels were within normal limits in all patients, and none of the patients had any documentation of renal insufficiency, thus indicating the reliability of the stimulated cortisol levels.

IOP

IOP was tested in 46 of 48 patients and was found to be within normal limits in all of these patients (range, 13–18 mmHg; mean, 16 mmHg).

Discussion

Topical corticosteroids have been widely used in the treatment of CRS. After ESS, topical nasal steroids have been shown to reduce the rate of polyp recurrence, increase the time to polyp recurrence, reduce systemic steroid rescues, improve ostial patency and improve endoscopy scores.^{21–24}

Recent studies have shown that high-volume irrigations have a significantly better penetration of the paranasal sinuses, predominantly in the post-ESS cavity, compared to other delivery methods.^{10–13} The addition of budesonide respules to high-volume saline irrigations has been increasingly used in order to improve the topical delivery of these steroids to the sinus cavities. This practice of delivering higher doses of topical steroids intranasally through irrigations and thus minimizing the use of systemic steroids and avoiding their potential systemic adverse effects has gained wide acceptance among rhinologists. Studies have shown that this practice leads to improved post-ESS quality of life scores and endoscopy scores.^{25,26} Given that significantly higher doses of steroids are delivered using this method, there has been concern regarding the safety profile of this practice in terms of systemic steroid absorption, HPAA suppression, and elevated IOP.

Budesonide irrigations and HPAA suppression

Identifying patients with HPAA suppression, even if mild, is important because life-threatening hypotension may occur during periods of stress (eg, illness, trauma, surgery) and the condition is totally preventable if supplemental glucocorticoids are administered. Plasma cortisol testing has low sensitivity and is often nondiagnostic due to the cyclical

variability of endogenous cortisol levels. Twenty-four-hour urinary free cortisol levels are often nondiagnostic as well, due to lack of sensitivity at low levels; ie, low cortisol excretion may be normal.²⁷ Consequently, dynamic testing is preferred to diagnose adrenal insufficiency. The advantage of dynamic testing is that it provides information regarding the function, reserve capacity and, hence, the ability of the adrenal gland or of the entire HPA axis to respond to stress. The high-dose cosyntropin test is the most commonly used dynamic diagnostic test.^{27–29} A supraphysiologic dose (250 μ g) of synthetic ACTH (cosyntropin) is administered via the intramuscular or intravenous routes and cortisol levels are measured either 30 minutes (intramuscular) or 60 minutes (intravenous) after ACTH administration. This is a simple, fast, and inexpensive test that can be performed in the outpatient clinic. At 30 minutes poststimulation, blood cortisol levels above 18 μ g/dL are considered normal. In suspected secondary adrenal insufficiency, stimulated cortisol levels below 16 μ g/dL have been suggested to better predict abnormal function of the HPAA²⁹; nonetheless, the 18- μ g/dL cutoff is still more commonly used in many centers.

Multiple studies have assessed HPAA suppression associated with chronic intranasal steroid use.^{1–4} Pipckorn et al.⁴ investigated HPAA suppression through stimulated cortisol levels and found that intranasal budesonide spray in the dose of 200 to 400 μ g/day is safe for up to 5.5 years of treatment of perennial rhinitis.

Intranasal budesonide irrigations have been studied as well, but follow-up times have been limited to 12 months or less. In unoperated patients, doses of up to 2 mg budesonide daily for 4 to 12 weeks were not shown to be associated with HPAA suppression.^{14,17,18} In post-ESS patients, Welch et al.¹⁹ found normal serum and urinary cortisol levels in 10 patients after 6 weeks treatment of a total of 1 mg per day budesonide irrigations.¹⁹ Man et al.¹⁵ found normal salivary cortisol levels in 23 patients treated with a total of 6 mg fluticasone daily. Rotenberg et al.¹⁶ studied 20 patients treated with 1 mg budesonide daily for 12 months and found normal ACTH levels. Measurement of ACTH levels alone, however, is considered insufficient in the diagnosis of secondary HPAA suppression.²⁷

In our study group we observed that approximately one-quarter of patients receiving long-term budesonide nasal irrigations for the management of CRS developed subclinical adrenal insufficiency. We did not assess baseline adrenal function measurements, so we cannot determine whether the adrenal insufficiency was incidental to or caused by the initiation of budesonide nasal irrigation therapy. Nonetheless, with this relatively high incidence of adrenal insufficiency we can infer that budesonide irrigations had at least some contributing role. Strengthening our assumption were the findings that 3 out of 4 patients with adrenal hypofunction showed significantly increased stimulated cortisol levels after discontinuing budesonide rinses; furthermore, when 1 of these patients resumed budesonide rinses, his stimulated cortisol levels deteriorated again.

Because serum cortisol can be modulated by degree of circulating globulins (including cortisol binding globulin), we measured albumin to serve as a surrogate marker of protein levels.³⁰ Serum albumin levels were normal in our subjects, suggesting that the serum cortisol was accurately measured.

Our analysis of risk factors for HPA suppression showed that daily budesonide dosage, duration of use, cumulative dose, and patient demographics were not associated with increased risk, except for a near-significant association with male gender. However, the concomitant use of both nasal and pulmonary topical steroids in addition to budesonide rinses was associated with a significant risk for subclinical HPA suppression. In patients who are on both nasal and pulmonary steroids in addition to budesonide rinse, close monitoring for HPA suppression is warranted with a low threshold to discontinue topical steroid treatment. The use of a single additional form of steroid inhaler or spray was not associated with a higher risk of HPA suppression. Of note, none of our patients with low stimulated cortisol levels complained of fatigue or nausea, or other typical symptoms of adrenal insufficiency.

Budesonide irrigations and IOP

Ocular hypertension, as diagnosed by IOP above 21 mmHg, is associated with a higher risk of developing glaucoma, which is the leading cause of blindness in the United States. Early detection, risk prevention and proper treatment are thus invaluable in reducing the risk for deterioration in vision and blindness. The effect of topical nasal steroids on IOP has been investigated in multiple studies with mixed results. Some studies have shown no association with IOP elevation,^{5-9,31} while others show increased risk, particularly in patients with glaucoma or using nasal steroids for longer than 3 months.^{11,32,33}

The effect of budesonide nasal irrigations on IOP has been studied as well. Sieberling et al.³¹ found that up to 6 months treatment with 0.5 mg budesonide nasal irrigations

daily is not associated with elevated IOP. Rotenberg et al.¹⁶ found no effect on IOP following 12 months' use of 1 mg budesonide irrigations daily. In our study group IOP levels remained within normal limits even with up to 66 months use of budesonide nasal irrigations.

Study limitations

Although our study reflects a fairly robust cohort size and mean follow-up time of almost 2 years, it reports a single institution's experience and has the inherent limitations associated with a retrospective case series. Prospective studies on larger cohorts with pretreatment baseline cortisol testing are needed to further corroborate these findings.

Conclusion

A cross sectional analysis of the safety profile of long-term use of budesonide nasal irrigations revealed that in nearly one-quarter of patients, a subclinical HPA suppression existed with stimulated cortisol levels below 18 µg/dL. In contrast, we did not find an increased risk for IOP elevation in our patient cohort. Statistical analysis revealed that concomitant use of 2 additional forms of topical steroids (nasal and pulmonary) was associated with a higher risk for HPA suppression. Male gender had a nearly significant higher risk for HPA suppression. Although no patients presented with clinically overt adrenal insufficiency, these findings should alert rhinologists to the potential risk of subclinical adrenal insufficiency associated with long-term use of budesonide nasal irrigations, particularly in patients receiving other forms of corticosteroid therapy. Laboratory monitoring for HPA suppression may be warranted given the lack of symptoms reported in patients with objective evidence of HPA suppression. In our experience, patients with asymptomatic HPA suppression may continue to use budesonide irrigations successfully under the supervision of an endocrinologist. ④

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