Safety of long-term intranasal budesonide delivered via the mucosal atomization device for chronic rhinosinusitis

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Background: **Although short-term use (≤2 months) of atomized topical nasal steroids has been shown to be safe and effective, the long-term safety has yet to be demonstrated. The aim of this study was to determine the impact of long-term topical budesonide treatment via the mucosal atomization device (MAD) on the hypothalamic-pituitary-adrenal axis (HPAA) and intraocular pressure (IOP).**

Methods: **A cross-sectional study of patients with chronic rhinosinusitis (CRS), with or without nasal polyposis, managed with daily nasal budesonide via MAD was conducted at a tertiary rhinology center. Patients using systemic steroids within 3 months of assessment were excluded. HPAA impact was assessed using the cosyntropin stimulation test for adrenal function and a survey of relevant symptomatology. Patients also underwent tonometry to assess for elevated IOP potentially related to corticosteroid use.**

Results: **A total of 100 CRS patients were recruited with a mean budesonide treatment duration of 23.5 months (range, 6–37 months). Stimulated cortisol response was diminished in 3 patients (3%). No patients with adrenal suppression had relevant symptomatology. IOP was elevated in 6 patients (6%).**

Conclusion: **These findings suggest that there is a risk of adrenal suppression and raised IOP associated with the long-term use of topical nasal budesonide via MAD. Otolaryngologists should consider periodic surveillance for these adverse events in this patient cohort.** © 2017 ARS-AAOA, LLC.

Key Words:
budesonide; chronic rhinosinusitis; HPA axis; IOP; mucosal atomization device; postoperative care; safety

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Chronic rhinosinusitis (CRS) is a disease characterized by persistent inflammation of the nose and paranasal sinus mucosa. Although most patients failing maximal medical therapy will respond favorably to functional endoscopic sinus surgery (FESS),[1] a cohort of these patients will continue to suffer from refractory sinus disease and must be managed with long-term, high-dose topical intranasal corticosteroid therapy.

The benefits of nasal saline irrigation and standard topical corticosteroid sprays during the early postoperative healing period have been well established.[2,3] Budesonide-impregnated, high-volume nasal saline irrigation (INSI) is commonly prescribed to patients at our center during the acute period after FESS. However, beyond this period, many patients requiring ongoing daily treatment for sinonasal inflammation report that frequent irrigation causes headaches and discomfort, adversely impacting adherence to a daily budesonide-INSI treatment regimen. In addition, there is a subgroup of patients who do not settle on the diluted budesonide and require a more concentrated form of topical budesonide to keep the inflammation under control. Patients at our center who depend on long-term budesonide treatment find the low-volume, concentrated

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mucosal atomization device (MAD) preparation to be more tolerable.[4] The MAD has been shown to thoroughly distribute topical medication to the sinuses in cadaver models and effectively treat sinus disease in clinical studies.[5–7] Unfortunately, the same quality that is thought to make the MAD efficacious in the treatment of mucosal inflammation (ie, droplet distribution and retention)[8] may also increase the potential for systemic side effects.

Although the safety profile of standard topical nasal corticosteroid sprays (INCs) has been well established,[9,10] the off-label use of budesonide respules for topical treatment of sinonasal inflammation has occupied a gray area in the past.[2] A randomized, controlled trial from our center demonstrated short-term (≤60 days) safety of budesonide delivered via both the MAD and INSI.[4] Although all study participants satisfied the threshold for normal adrenal gland function, we also reported a disconcerting trend of diminishing cortisol response with serial testing over 60 days of treatment in the group administering budesonide via MAD. In light of these findings, we considered it pertinent to investigate the safety of topical budesonide via MAD in patients on long-term maintenance therapy for CRS. We sought to determine whether long-term treatment (>6 months) with intranasal budesonide via MAD was safe and well tolerated in patients with refractory CRS. Our objective was to measure the impact of long-term budesonide via MAD treatment on the hypothalamic-pituitary-adrenal axis (HPAA) and intraocular pressure (IOP).

Methods

This cross-sectional observational study was conducted at a tertiary rhinology center in Vancouver, BC, Canada. The investigation was conducted with approval from the University of British Columbia Clinical Research Ethics Board (H14-01608). Patients were consented for enrollment between September 2014 and February 2016. Those patients who were diagnosed with CRS with or without nasal polyposis based on the Canadian clinical practice guidelines for sinusitis,[11] received FESS in the past, and were actively being treated with daily intranasal budesonide via MAD for ≥6 months were invited to participate. Patients were excluded if they were <19 years of age; had used systemic steroids within 3 months of their recruitment visit; had a history of pituitary disease; or had a known hypersensitivity to cortisol, corticotropin, or cosyntropin.

Patients at our center are taught to load budesonide respules (Pulmicort, AstraZeneca Pharmaceuticals, Wilmington, DE) into a 3-mL luer-lock syringe affixed to a MAD tip (LMA MAD nasal). Budesonide respules are available in 0.25-, 0.5-, and 1.0-mg doses in 2 mL of normal saline (0.9% NaCl). Our patients are placed on the 0.5-mg/2-mL respules in most instances. Subjects are instructed to atomize medication equally to each side of the nose while assuming the lying-head-back position (Mygind position), as described elsewhere.[5] The proper administration technique is frequently reassessed at follow-up clinic visits. Patients concurrently using nasal saline irrigation are instructed to administer budesonide via MAD 30 minutes after irrigation to avoid washing out topical medication.

Upon recruitment, demographic and clinical variables were collected from medical charts, including history of sinus surgery, nasal polyposis status, asthma status, current medications, and other comorbidities. Subjects also completed a series of surveys that included the 22-item Sino-Nasal Outcomes Test (SNOT-22), and pointed questions related to clinical symptoms of adrenal suppression experienced during the course of their treatment (nausea, dizziness, vomiting, weakness, muscle aches, diarrhea). The SNOT-22 is a validated questionnaire used to subjectively assess sinonasal symptom severity.[12]

A standard (high-dose) adrenocorticotrophic hormone (ACTH) stimulation test (250 μg cosyntropin, deltoid intramuscular technique) was organized at the recruitment visit. Tests were preferentially performed in the morning between 8:00 and 10:00 AM when possible. Patients were instructed to refrain from administering budesonide on the morning of the test. Serum cortisol levels were reported at baseline, then 30 and 60 minutes after stimulation. Patients found to demonstrate insufficient response to the ACTH stimulation test were referred to an endocrinologist for a more thorough review of adrenal function. Criteria for secondary adrenal insufficiency were satisfied if either of the following conditions were met: (1) stimulated serum cortisol <496 nmol/L (16 μg/dL) at 60 minutes[13]; or (2) serum cortisol level diminished at baseline (<80 nmol/L)[14] and also demonstrating a depressed peak level (<700 nmol/L) after 60 minutes.[15]

IOP was measured in clinic using a handheld applanation tonometer (Tono-Pen AVIA electronic tonometer; Reichert Technologies, Depew, NY). Values between 10 and 21 mmHg were considered normal.[16] Patients found to have elevated IOP were referred to an ophthalmologist for follow-up assessment.

Statistical analysis

Descriptive analyses were conducted to compare the adrenal suppression group with the normal cortisol response group, along with other key associations. All continuous variables were skewed, so the nonparametric Mann-Whitney *U* rank sum test was used to test for differences between the 2 groups. Categorical variables were assessed using the chi-square test or Fisher's exact test when the number of cases per group was <5. Multivariate logistic regression analysis could not be conducted due to a lack of variation in the variables with $p < 0.2$ on univariate analysis. STATA version 12.1 (StataCorp, College Station, TX) was used for the analysis, with $p < 0.05$ considered statistically significant.

Results

A total of 390 patients were screened to participate in this study (Figure 1). Two hundred sixty-two of these patients

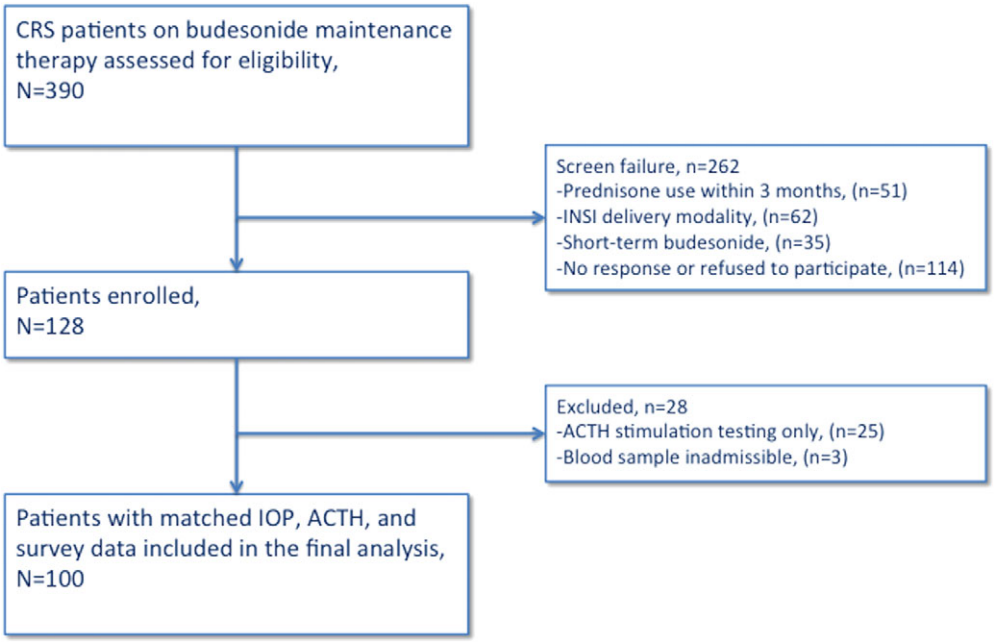

FIGURE 1. Patient study cohort. ACTH = adrenocorticotrophic hormone; CRS = chronic rhinosinusitis; INSI = impregnated nasal saline irrigation; IOP = intraocular pressure.

were excluded because they did not meet inclusion criteria or chose not to participate (n = 262). The remaining 128 subjects were enrolled into this study (n = 128). All enrolled patients completed the clinical survey series. Twenty-five patients underwent ACTH stimulation testing but did not have matched IOP measurements, so they were excluded from the final matched analysis. There were no cases of adrenal suppression in this excluded cohort (n = 25; average treatment duration, 23.9 months; average dose, 0.5 mg/day). Blood samples from 3 patients (n = 3) were deemed unreliable by the laboratory.

The final cohort consisted of 100 patients who underwent ACTH stimulation testing and IOP testing, and completed the clinical survey (Table 1). Within this cohort (n = 100), the mean budesonide exposure was 0.6 mg/day for 23.5 months. Three patients (3%) reported intermittent use of an additional nasal steroid spray (mometasone fuorate [Nasonex®, Merck, Kenilworth, NJ], fluticasone fuorate [Avamys®, GlaxoSmithKline, London, UK], and ciclesonide [Omnaris®, Sunovion, Marlborough, MA]). Thirty-two patients (32%) were actively using an inhaled corticosteroid for treatment of comorbid asthma. Seventeen patients (17%) were concurrently being treated with itraconazole for a fungal infection of the sinuses.

Three individuals from this cohort (3%) demonstrated adrenal insufficiency based on ACTH stimulation testing (budesonide treatment duration range, 10–23 months). These 3 patients were not found to have elevated IOP or manifest any clinical symptoms of adrenal suppression. Of these 3 patients, 1 was also being treated with inhaled budesonide (Pulmicort Turbuhaler®, AstraZeneca) for asthma. Patients on concurrent itraconazole treatment (n = 17) did not demonstrate adrenal insufficiency on the ACTH stimulation test. Table 1 provides a breakdown of the comparison between cases with adrenal suppression (n = 3) and those with normal adrenal function (n = 97). Receiver-operating characteristic (ROC) analysis was used to identify a threshold of 23.5 months for duration of budesonide use; however, this was not significant ($p = 0.082$). Multivariate analysis could not be attempted due to the lack of variation in the 3 abnormal cases in their duration of budesonide use and baseline cortisol.

Six individuals (6%) were found to have elevated IOP (>21 mmHg) in the absence of suppressed cortisol levels or clinical symptoms of adrenal suppression. Among these patients (age, 56–70 years), the mean duration of daily budesonide via MAD treatment was 23 months (range, 16–29 months). One patient was being treated concurrently with inhaled and intranasal corticosteroids. When treating IOP as a binary variable (elevated or normal), there did not appear to be any association between elevated IOP and concomitant use of inhaled corticosteroids for asthma ($p = 0.661$).

Patients who were discovered to have elevated IOP or adrenal suppression did not report any classic symptoms of adrenal suppression on the symptom survey.

Discussion

This study is the first to evaluate the long-term safety of intranasal budesonide administered via the MAD. Among our study population, there was a 3% incidence of adrenal suppression detected on ACTH stimulation testing and a 6% incidence of elevated IOP based on applanation

TABLE 1. Baseline and clinical characteristics for study cohort (n = 100) with matched ACTH and IOP data*

Variable	Normal	Suppressed	*p* value[a]
Number of patients	97	3	
Age (years)	62 (53-68)	55 (51-56)	0.179
Gender, male	49 (50.5)	2 (66.7)	1.000
Diagnosis			0.222
CRSwNP	10 (10.3)	1 (33.3)	
CRSsNP	39 (40.2)	0	
AFRS	48 (49.5)	2 (66.7)	
Extent of sinus surgery			
Complete, bilateral FESS	97 (100)	3 (100)	
Revision FESS	51 (52.6)	2 (66.7)	
Duration (months) of BUD use	26 (19-30)	23 (10-23)	0.225
Duration (months) of BUD use			0.082
<23.5	41 (42.3)	3 (100)	
≥23.5	56 (57.7)	0	
Concomitant medications			
Corticosteroids			1.000
Budesonide	94 (96.9)	3 (100)	
Budesonide + Nasonex	1 (1.0)	0	
Budesonide + Avamys	1 (1.0)	0	
Budesonide + Avamys + Omnaris	1 (1.0)	0	
Sporanox (itraconazole)	17 (17.5)	0	1.000
Inhaled steroids (asthma)	31 (31.9)	1 (33.3)	1.000
Investigations			
ACTH stimulation test			
Baseline (nmol/L)	293 (225-406)	35 (33-51)	0.005
Minute 60 (nmol/L)	848 (748-978)	504 (308-535)	0.004
Change from baseline to minute 60 (nmol/L)	540 (445-668)	453 (273-502)	0.010
IOP			
Left	15 (13-17)	16 (13-21)	0.632
Right	15 (14-18)	16 (13-21)	0.555

*Comparison between normal patients and those with suppressed adrenal gland function. Data expressed as median (IQR) or as number (% of group).
[a]$p < 0.05$ considered significant.
ACTH = adrenocorticotrophic hormone; AFRS = allergic fungal rhinosinusitis; BUD = budesonide; CRSsNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyposis; FESS = functional endoscopic sinus surgery; IOP = intraocular pressure; IQR = interquartile range.

tonometry. Interestingly, elevated IOP and adrenal suppression were not found concurrently in any of our patients.

Recent studies have evaluated the long-term safety of budesonide via INSI, with mixed results.[17,18] Topical budesonide via MAD is a higher concentration solution compared with the INSI preparation and is more likely to be retained in the sinonasal space[8]; given these properties, we expected a relatively higher risk of adrenal suppression within our study population. In their retrospective review, Smith et al found that long-term topical treatment with 2 mg budesonide via daily INSI was safe over an average duration of 38.2 months.[18] There were no cases of adrenal suppression on ACTH stimulation testing in their study population. Conversely, in a retrospective study by Soudry

et al, a 23% incidence of adrenal suppression on ACTH stimulation testing was found among a population of patients treated with a mean dose and duration of 0.75 mg budesonide via INSI daily for 22 months. There were no cases of elevated IOP found in their study population. Consistent with our findings, patients found to have adrenal suppression did not report having any relevant symptomatology in either of the aforementioned investigations. In this context, our findings suggest that the incidence of adverse events associated with budesonide delivered via MAD may be comparable to budesonide via INSI in the long term. In controlling for potential confounders, we were particularly mindful of drugs that may have impacted serum cortisol or budesonide metabolism. Most notably, itraconazole is a potent inhibitor of cytochrome isozymes (CYP3A4) and has been associated with a 4-fold increase in plasma concentrations of budesonide (and possible adrenal suppression) when given by inhalation among asthmatics.[15] However, patients in this study cohort who were treated with a combination of itraconazole and budesonide (17%) showed no suppression of adrenal function.

We found that 6% of our patient population presented with elevated IOP at the time of screening. Applanation tonometry is a sensitive screening tool to assess for early signs of corticosteroid-induced glaucoma. Persistent elevation of IOP can have severe consequences, such as optic disk cupping, visual field loss, and atrophy of the optic nerve.[9] This test can be performed fairly quickly as part of a regular clinic visit and may assist with appropriate referral of at-risk patients for more thorough testing by an ophthalmologist. The prevalence of elevated intraocular pressure in our sample population (6%) was slightly higher than the background prevalence of glaucoma for this age demographic (3.5%)[16]; thus, it would be reasonable to attribute part of this prevalence to corticosteroid exposure.

The design of a cross-sectional investigation is inherently limiting as it captures only a snapshot of these safety outcomes. In the absence of baseline measures of adrenal function and IOP it is difficult to ascertain the precise timeline for the development of adverse events. In an effort to rule out prior iatrogenic causes of adrenal suppression, patients exposed to prednisone within 3 months of the recruitment visit were excluded from this study. Although prednisone has a short half-life in the body (3.4-3.8 hours),[19] its impact on the HPAA is not as transient. Jamilloux et al demonstrated that only 53% of patients on long-term prednisone therapy for giant cell arteritis (GCA) who demonstrated adrenal suppression on ACTH stimulation testing had recovered function after 1 year.[20] Similarly, without a measure of baseline IOP, it is possible that cases in which IOP had increased significantly since beginning intranasal corticosteroid treatment, yet remained within the normal range, would have gone undetected.

Given that cases of elevated IOP in this study were distinct from those with depressed cortisol response to ACTH stimulation, the surveillance of patients on long-term intranasal steroid therapy should include both assessments. Implementing annual screening of these patients would be a cautious measure, with earlier testing in patients presenting with overt symptoms of adrenal suppression. In their retrospective study of budesonide via INSI safety, Soudry et al found that concomitant use of 2 forms of topical steroids (nasal and pulmonary) was associated with a greater risk for HPAA suppression.[17] Particular caution should be taken for patients on prednisone and topical corticosteroid therapy concurrently. Adrenal crisis is a severe, albeit rare, adverse event associated with corticosteroid use. However, the combination of oral, topical, or inhaled corticosteroids, along with the presence of physiologic stressors (eg, infection, surgery), could precipitate this severe outcome.[9,20] Discontinuing nasal corticosteroid treatment for patients with severe, recalcitrant sinus disease is usually not feasible, so we must pursue strategies to mitigate the risk of systemic sequelae.

Conclusion

This cross-sectional study has shown that a subgroup of recalcitrant CRS patients on long-term maintenance treatment with topical budesonide delivered via MAD demonstrated asymptomatic adrenal suppression (3%). A separate subgroup of these patients was found to have elevated IOP (6%). Although the cross-sectional design inherently limits our ability to ascribe these adverse events to topical budesonide exclusively, the stringent measures taken to control for potential confounders make this etiology plausible. These findings suggest that patients using the MAD to administer nasal budesonide may be at risk of developing these sequelae in the long term and should be monitored accordingly. Until specific screening guidelines can be established based on prospective research, a surveillance protocol for patients treated with long-term budesonide via MAD may include annual adrenal function and intraocular pressure testing.

References

1. Lanza DC, Kennedy DW. Current concepts in the surgical management of chronic and recurrent acute sinusitis. *J Allergy Clin Immunol*. 1992;90:505–510.
2. Rudmik L, Soler ZM, Orlandi RR, et al. Early postoperative care following endoscopic sinus surgery: an evidence-based review with recommendations. *Int Forum Allergy Rhinol*. 2011;1:417–430.
3. Jang DW, Lachanas VA, Segel J, Kountakis SE. Budesonide nasal irrigations in the postoperative management of chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2013;3:708–711.
4. Thamboo A, Manji J, Szeitz A, et al. The safety and efficacy of short-term budesonide delivered via mucosal atomization device for chronic rhinosinusitis without nasal polyposis. *Int Forum Allergy Rhinol*. 2014;4:397–402.
5. Habib AR, Thamboo A, Manji J, et al. The effect of head position on the distribution of topical nasal medication using the mucosal atomization device: a cadaver study. *Int Forum Allergy Rhinol*. 2013;3:958–962.
6. Neubauer PD, Schwam ZG, Manes RP. Comparison of intranasal fluticasone spray, budesonide atomizer, and budesonide respules in patients with chronic rhinosinusitis with polyposis after endoscopic sinus surgery. *Int Forum Allergy Rhinol*. 2016;6:233–237.
7. Kanowitz SJ, Batra PS, Citardi MJ. Topical budesonide via mucosal atomization device in refractory postoperative chronic rhinosinusitis. *Otolaryngol Head Neck Surg*. 2008;139:131–136.
8. Djupesland PG. Nasal drug delivery devices: characteristics and performance in a clinical perspective—a review. *Drug Delivery Transl Res*. 2013;3:42–62.

9. Liu D, Ahmet A, Ward Let al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol*. 2013;9:30.
10. Sastre J, Mosges R. Local and systemic safety of intranasal corticosteroids. *J Invest Allergol Clin Immunol*. 2012;22:1–12.
11. Desrosiers M, Evans GA, Keith PK, et al. Canadian clinical practice guidelines for acute and chronic rhinosinusitis. *J Otolaryngol Head Neck Surg*. 2011;40(suppl 2):S99–193.
12. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. *Clin Otolaryngol*. 2009;34:447–454.
13. Longui CA, Vottero A, Harris AG, Chrousos GP. Plasma cortisol responses after intramuscular corticotropin 1-24 in healthy men. *Metabol Clin Exp*. 1998;47:1419–1422.
14. Nieman LK. Dynamic evaluation of adrenal hypofunction. *J Endocrinol Invest*. 2003;26:74–82.
15. Jenkins D, Forsham PH, Laidlaw JC, Reddy WJ, Thorn GW. Use of ACTH in the diagnosis of adrenal cortical insufficiency. *Am J Med*. 1955;18:3–14.
16. Lee DA, Higginbotham EJ. Glaucoma and its treatment: a review. *Am J Health Syst Pharm*. 2005;62:691–699.
17. Soudry E, Wang J, Vaezeafshar R, Katznelson L, Hwang PH. Safety analysis of long-term budesonide nasal irrigations in patients with chronic rhinosinusitis post endoscopic sinus surgery. *Int Forum Allergy Rhinol*. 2016;6:568–572.
18. Smith KA, French G, Mechor B, Rudmik L. Safety of long-term high-volume sinonasal budesonide irrigations for chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2016;6:228–232.
19. Pickup ME. Clinical pharmacokinetics of prednisone and prednisolone. *Clin Pharmacokinet*. 1979;4:111–128.
20. Jamilloux Y, Liozon E, Pugnet G, et al. Recovery of adrenal function after long-term glucocorticoid therapy for giant cell arteritis: a cohort study. *PLoS One*. 2013;8:e68713.