

Lack of Ocular Side Effects After 2 Years of Topical Steroids for Allergic Rhinitis

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ABSTRACT

Purpose: The aim of this study was to investigate ocular side effects in children with allergic rhinitis taking chronic intermittent nasal corticosteroids.

Methods: The study group included 150 children who had used intermittent intranasal budesonide for more than 2 years for allergic rhinitis. Ninety patients who were newly diagnosed as having allergic rhinitis without any treatment comprised the control group. Central corneal thickness, Schirmer test results, visual acuity, intraocular pressure, cataract formation, keratometry, and tear break-up time were compared in the two groups.

Results: The ages of the 150 study patients (85 boys) were between 8 and 15 years. The average age ($\pm$ standard error of the mean [SEM]) was 11.7 ± 0.7 years and the mean ($\pm$ SEM) steroid dosage used was 93.3 ± 7.0

μg daily with 42.2 ± 3.2 g total steroid use during treatment. The ages of the 90 control patients (54 boys) were between 7 and 15 years. There was no statistically significant difference between the study and control groups according to ocular findings ($P > .05$). Eye functions including cataract formation, corneal ectasia, ocular hypertension or glaucoma, and dry eye were not observed in any of the patients in the study group and were not correlated with total steroid dosage ($r = 0.125$, $P = .447$).

Conclusion: A 2-year treatment of children with allergic rhinitis prescribed intermittent intranasal budesonide at an average daily dose of approximately 100 μg is not associated with ocular side effects such as cataract, glaucoma, corneal ectasia, and abnormal tear function.

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INTRODUCTION

Allergic rhinitis is a chronic inflammatory disease of the upper airways characterized by sneezing, itching, nasal congestion, and rhinorrhea.^{1,2} Current guidelines recommend intranasal corticosteroids (INS) as first-line treatment for moderate-to-severe persistent allergic rhinitis. INS provide effective treatment of nasal symptoms and congestion because of potent anti-inflammatory activity.^{3,4} The efficacy of currently available INS in allergic rhinitis is well documented and the low rate of side ef-

fects, despite extensive use of INS for many years, is indicative of the well-established safety of these drugs.^{5,6} Currently available INS, including beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, mometasone furoate, and triamcinolone acetonide, differ from each other in terms of their systemic absorption, volume of distribution, half-life, and the extent of systemic bioavailability.⁷⁻⁹ The systemic bioavailability of an inhaled corticosteroid is determined by the amount of drug delivered and subsequently absorbed by the lungs

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and the amount of drug absorbed from the gastrointestinal tract. In contrast, for INS, there is a high degree of deposition in the nasal cavity, followed by mucociliary clearance to the throat and eventually to the gastrointestinal tract. Absorption from the mucosal surface can contribute up to 50% systemic bioavailability of the INS.⁴ Although the systemic absorption of inhaled and nasal steroids has been established,^{10,11} the clinically relevant ocular side effects are poorly defined. The low frequency of side effects observed after long-term use of INS is suggestive of the well-established safety of INS; however, there should be careful monitoring of local and systemic side effects of INS, especially in patients undergoing long-term or life-time treatment, such as treatment of perennial allergic rhinitis.¹²

Although systemic, topical, and periocular corticosteroid administration methods have long been associated with ocular side effects, there has been little evidence to suggest that INS can cause ocular and systemic side effects. There are not enough data to draw a definitive conclusion on the effects of INS on eyes in children with perennial allergic rhinitis. A recent position statement review by the Joint Task Force for the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology on the safety of INS stated that the effects of INS on eyes and bones are inconclusive because of lack of sufficient data.¹² We report the results of possible effects of cross-sectional, chronically intermittent use of intranasal budesonide on some ocular functions in children with perennial allergic rhinitis. Our study asks whether children with perennial allergic rhinitis using nasal steroids are at an increased risk of developing ocular malfunctions; if so, how large is the risk compared with subjects not using these drugs; and whether the risk varies according to the dose or duration of the use of INS.

PATIENTS AND METHODS

Study Design

We conducted a case-control and cross-sectional study among children diagnosed as having mild-to-moderate perennial allergic rhinitis with or without bronchial asthma for the years 2007 to 2010 from outpatient pediatric allergy clinics at the Vakıf Gureba Training and Research Hospital, in Istanbul, Turkey. The diagnosis and severity of perennial allergic rhinitis were defined according to Allergic

Rhinitis and its Impact on Asthma (ARIA)¹³ guidelines. Informed consent was given by the families of the patients.

Participants

All children who had received intranasal budesonide (INB) intermittently for more than 2 years were included in the current study investigating the occurrence of some ocular side effects. This group of patients qualified as having perennial allergic rhinitis if they had at least two rhinitis symptoms requiring treatment at least 6 months of the year for the previous 2 years and had a positive skin-prick test response to at least one clinically significant perennial allergen (eg, house dust mites, molds, cockroaches, cockroach excrete, or animal dander).

The children had been seen at our outpatient pediatric allergy clinic at least every 3 to 4 months for 3 to 5 years at the time of the current study. Between clinic visits, changes in INB or other allergic rhinitis medications were always made under the supervision of the clinic so that transient changes in treatment during periods of increased allergic rhinitis symptoms were recorded. These records made it possible to accurately calculate the average dose of exogenous corticosteroid during the previous 2 years and the accumulated dose of budesonide. Compliance with the nasal steroids was checked at each visit by asking the child and family about their compliance and by checking medication level in the bottle. These measures allowed an assessment of compliance.

We identified all prescriptions for INB that had been filled in the past 2 years and studied the risk of current extra exposure to INB. To investigate the exposure to INB according to dose, we calculated the average daily dose of INB by dividing the total quantity (in micrograms) by the days of supply for that prescription. Participants had not received specific immunotherapy and none of them had asthma requiring chronic use of inhaled or systemic steroids. None of the children with perennial allergic rhinitis had nasal structural abnormalities. Budesonide was the only type of nasal steroid used by the study group patients. We included 90 children who were newly diagnosed as having perennial allergic rhinitis according to the ARIA guidelines¹³ to the control group to obtain a sufficient number of patients for comparison. None of these newly diagnosed children had ever received oral, inhaled, or nasal corticosteroids for more than 2 weeks.

Following a complete ophthalmologic examination, budesonide 0.05 mg two times daily was initiated in the control group. Age, height, weight, the presence of bronchial asthma, daily and total budesonide dosage, duration of treatment, time of diagnosis, family history of atopy, antihistamine use, and skin test results were recorded for all study group participants. To avoid the confounding influence of some covariates, the following exclusion criteria were used: more than 14 days of treatment with systemic corticosteroids ever (both groups); topical corticosteroids ever applied to 25% of the body surface (both groups); presence of metabolic disease, such as diabetes mellitus, or systemic disease, such as renal; cardiac hypertension; current exposure to ophthalmic corticosteroids (both groups); and family history posterior subcapsular cataracts. Patients with a systemic illness other than bronchial asthma or optical refraction between +4.00 and -5.00 diopters were also excluded. All patients were also questioned about the occurrence of any incidents (trauma) in the past that might cause malfunctions of the eye.

Outcome Measures

The primary end point for the study was to examine whether the INB spray contributed to some ocular side effects in children with perennial allergic rhinitis.

Visual acuity was measured by the Snellen visual acuity chart then transformed into logarithm of the minimum angle of resolution equivalents.

Intraocular pressure (IOP) was measured with an auto noncontact tonometer (Nidek NT-2000; Nidek; Aichi, Japan). Cataract formation was evaluated after pharmacologic pupillary dilatation with 1% cyclopentolate and 1% tropicamide by slit-lamp biomicroscopy. Refraction, topography, and keratometry were measured with an autokerato refractometer (Topcon KR 8100P; Topcon, Tokyo, Japan). Central corneal thickness was measured with an ultrasonic pachymeter (Nidek UP 1000; Nidek) after administration of topical anesthetic drops. Central corneal dioptric power of greater than 47.20 diopters, combined with steepening of the inferior cornea compared with the superior cornea of greater than 1.20 diopters, was determined as keratoconus.

Tear amount and functions were evaluated by use of a Schirmer I test and tear break-up time test, respectively. In the Schirmer test, a 35 × 5 mm filter paper strip was used to measure the amount of

tearing over a period of 5 minutes and was placed at the junction of the middle and lateral thirds of the lower eyelid under ambient light. The patient was instructed to look forward and to blink normally during the course of the test. A wetting value of more than 10 mm in 5 minutes was accepted as normal. Patients with dry eyes should have wetting values of less than 5 mm in 5 minutes.

In the tear break-up time test, sodium fluorescein dye was instilled into the eye and the tear film was observed under the slit lamp while the patient avoided blinking until tiny dry spots developed. If the first break in the tear film was observed within 5 seconds, it was interpreted as probable dry eye symptoms. If the duration was between 5 and 10 seconds, it was interpreted as possible dry eye symptoms, and if the duration was greater than 10 seconds, the test was interpreted as normal. All of the ophthalmologists were blinded to the patient group.

Ethical and Statistical Analysis

The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice and was approved by the local Ethics Committee. For statistical analyses, *t* tests were performed and *P* values of less than .05 (2-sided test) were considered statistically significant. Correlations between total steroid dose and visual acuity, IOP, central corneal thickness, Schirmer test results, and tear break-up time test results of the study group were analyzed with a Pearson correlation test.

RESULTS

The ages of the 150 study patients (85 boys and 65 girls) were between 8 and 15 years. Twenty-six patients had findings of asthma. The average ($\pm$ standard error of the mean [SEM]) follow-up time was 49.97 $\pm$ 11.26 months (range: 25 to 76 months). The average ($\pm$ SEM) age was 11.7 $\pm$ 0.7 years, height was 144.0 $\pm$ 1.93 cm, and weight was 39.4 $\pm$ 1.83 kg. The budesonide dose used was 93.3 $\pm$ 7.0 μ g daily with 42.2 $\pm$ 3.2 g total steroid use during treatment. The average IgE titer was 507.4 $\pm$ 41 kU/L (normal = 0 to 52 kU/L). All but 2 patients had positive skin test results for allergy (Table 1).

The ages of the 90 control patients (56 boys and 36 girls) were between 7 and 15 years. Eighteen patients had findings of asthma. The average ($\pm$ SEM) age was 10.4 $\pm$ 0.8 years, height was 138.1 $\pm$ 1.9 cm, and weight was 33.3 $\pm$ 1.37 kg. The average IgE con-

Characteristic	Study Group	Control Group	P
No. of patients	150	90	
Age, mean (range) (y)	11.7 ± 0.7 (8–15)	10.4 ± 0.8 (7–15)	.002
Female	43%	39%	
Height (cm) ^a	144.0 ± 1.93	138.1 ± 1.9	.033
Weight (kg) ^a	39.4 ± 1.83	33.3 ± 1.37	.016

^aValues are given as mean ± standard error of the mean.

centration was 476.6 ± 51.5 kU/L. All patients had positive skin test results. The differences between study and control group ages, heights, and weights were statistically significant because the study group had been observed for at least 2 years and this is a cross-sectional study (Table 1).

The right and left eyes of the groups were evaluated separately. On completion of the study, there

was no clinical significance between any of the parameters of the two groups. The results are summarized in Table 2.

There was no correlation between total budesonide doses and visual acuities, IOPs, central corneal thicknesses, Schirmer test results, or tear break-up time test results of the study group (Table 3).

The only clinical finding was papillary conjunctivitis in 7 patients in the study group and 3 patients in the control group. Cataract formation, corneal ectasia, ocular hypertension, and dry eye were not observed in any of the patients.

DISCUSSION

Although large studies have reported no substantial risk of intranasal steroids on the eye functions in patients with allergic rhinitis, there are no new data in the literature for the past 10 years. Our results corroborate those reported in previously published studies of smaller groups of less well-characterized children, adolescents, and adult patients treated for shorter periods of time with INS.^{14–16} Topical nasal

Parameter	Study Group	Control Group	P
Visual acuity (LogMAR)			
OD	0.02 ± 0.004	0.005 ± 0.004	.182
OS	0.01 ± 0.003	0.007 ± 0.006	.547
Intraocular pressure (mm Hg)			
OD	16.6 ± 0.4	15.5 ± 0.3	.177
OS	17.4 ± 0.3	16.4 ± 0.4	.192
Central corneal thickness (μm)			
OD	541.2 ± 14.2	555.1 ± 7.5	.645
OS	595.4 ± 5.7	586.4 ± 5.3	.262
Schirmer I test (cm)			
OD	22.6 ± 1.1	20.4 ± 1.2	.377
OS	21.4 ± 1.26	19.9 ± 1.4	.399
Tear break-up time (sec)			
OD	12.0 ± 1.1	11.4 ± 0.7	.566
OS	13.3 ± 1.01	12.3 ± 0.74	.869
Corneal topography	No ectasy	No ectasy	
Skin-prick test positivity to at least 1 allergen, (no. of patients)	150	90	.61
IgE (kU/L)	507.4 ± 41	476.6 ± 51.5	.53

LogMAR = logarithm of the minimum angle of resolution; OD = right eye; OS = left eye.
^aResults are expressed as mean ± standard error of the mean.

TABLE 3
Correlations Between Total Steroid Dose and Test Results of the Study Group

Eye	Total Steroid Dosage	VA (LogMAR)		CCT		IOP		Schirmer Test		TBUT	
		OD	OS	OD	OS	OD	OS	OD	OS	OD	OS
Pearson correlation	0.125	0.07	0.037	0.177	0.022	0.083	0.119	0.185	0.162	-0.2	0.011
P	.447	.699	.837	.324	.905	.669	.54	.294	.36	.257	.95

VA = visual acuity; LogMAR = logarithm of the minimum angle of resolution; CCT = central corneal thickness; IOP = intraocular pressure; TBUT = tear break-up time; OD = right eye; OS = left eye.

steroids have demonstrated efficacy and are considered first-line empiric therapy in the treatment of allergic and nonallergic rhinitis.^{17,18} The increase in nasal steroid spray use for allergic rhinitis was the impetus for this study. Although intranasal steroids are considered to have few systemic side effects, Knutsson et al.¹⁹ reported suppressed serum cortisol levels and down-regulated peripheral lymphocyte glucocorticoid receptor mRNA in healthy subjects after 2 weeks of twice-daily intranasal budesonide or fluticasone, suggesting systemic absorption does occur. The INS do vary in their systemic bioavailability, with budesonide well absorbed through the nasal mucosa into the systemic circulation and mometasone furoate with almost undetectable levels systemically at prescribed doses.²⁰ In our clinical study, we did not find that children with perennial allergic retinitis who used budesonide spray intermittently for two years experienced any clinically or statistically significant side effects.

First described by Black et al.²¹ in 1960, the association between systemic corticosteroid therapy and the development of posterior subcapsular cataract has been well established. However, the cataractogenic effect of inhaled steroids or INS is controversial. The current study shows that intermittent use of intranasal budesonide over 2 years did not result in any cataract formation in the pediatric age group. This result is in agreement with most of the previous studies done in the pediatric population.^{22,23}

Although most of the studies with pediatric patients revealed no association between nasal steroids and cataract formation,²⁴⁻²⁶ others reported steroid-induced cataracts in the adult and pediatric population.²⁷⁻²⁹ Kewley²⁷ was the first to report the association between inhaled steroids and cataract formation. Cumming et al.²⁸ found a strong association between the use of inhaled corticosteroids and posterior subcapsular or nuclear cataract formation.

In a retrospective observational cohort study, Jick et al.²⁹ found that inhaled steroid use led to a marginally increased risk of cataract formation in the adult population (relative risk = 1.3; 95% confidence interval 1.1 to 1.5). The cataracts that complicate chronic corticosteroid therapy are typically of the posterior subcapsular cataract type and prevalence has been reported to be influenced by the daily and cumulative dose of corticosteroid and duration of treatment and probably also by patient age.³⁰

When designing the current study, we tried to avoid some of the problems of interpreting potential findings of opacities in the patients treated with budesonide. This was achieved by restricting the study to well-characterized patients who we knew had never received systemic corticosteroids for more than 14 days and by including a control group of children with perennial allergic rhinitis who had never received exogenous corticosteroids. This is clinically more relevant than a comparison with healthy children because cataracts may occur at a higher frequency in patients with atopy in the anterior subcapsule, the posterior subcapsule, or throughout the lenses.³¹ In addition, the ophthalmologists were blinded with respect to the treatment given to minimize any possible bias.

Although the size of the previous studies was small and the lens of a child is more resistant to stress factors when compared with that of an adult, further studies are needed to assess the actual risk. Studying the effects of INS on cataract formation, Derby and Maier³² found that the incidence rate of cataract among the INS group was similar to the incidence rate among the unexposed group. However, Bielory et al.¹² and Bielory³³ studied INS for over-the-counter use and reported that the adverse effects of INS can be insidious and that these drugs should remain as prescription-only drugs.

It is well known that systemic and topical oph-

thalmic steroids can cause ocular hypertension or open-angle glaucoma. The effect of inhaled corticosteroids or INS has been studied in recent years, but the association is unclear.^{32,34} In our study, it was found that the IOP of the study group was not higher than that of the control group. This finding is in accordance with other studies in the literature. In a case-control study, Garbe et al.³⁴ reported that unless it was prescribed for 3 or more months, inhaled steroid or INS therapy was not associated with an increased risk of ocular hypertension or open-angle glaucoma. Bross-Soriano et al.¹⁶ compared three different INS with placebo in a comparative, double-blind, experimental, prospective, longitudinal study in which 360 patients were enrolled and reported that, although INS caused variations in the IOP, these variations were within normal limits. Spiliotopoulos et al.³⁵ studied the short-term effects of INS and found that they did not cause any significant IOP elevation.

Allergic rhinitis is mostly complicated by conjunctivitis, prompting the term rhinoconjunctivitis to describe the condition. Because the nature of allergic reactions is immunologic, they can be controlled by steroid therapy. It was shown that ocular symptoms in allergic rhinitis are reduced by INS therapy.³⁶ It is possible that the steroids can alter the tear functions. To the best of our knowledge, the influence of INS on the amount of tear secretion has not been previously studied in children with allergic rhinitis. In our study, comparing the function and amount of tear secretion did not lead to any statistically significant differences between the two groups, although the values of the Schirmer test in the study group were higher than those of the control group. Moreover, neither accumulated or current budesonide dose, nor duration of treatment correlated with the tear functions. This strongly suggests that xerophthalmia is unlikely to be a problem in children receiving long-term INS in doses used in the current study.

The association of atopy and corneal ectasia, especially keratoconus, was shown in some studies.^{37,38} It was found that 35% of patients with keratoconus also had atopy.³⁷ Because itching is a symptom of allergic rhinoconjunctivitis, continuous eye rubbing may induce a corneal ectasia. Also, it is known that steroids have negative effects on formation of collagen, which is the main protein of the cornea. In our study, the diagnosis of a corneal ectasia could not be

made in either of the groups on corneal topographic maps. There has been no report in the literature studied associating INS and changes in corneal architecture. It is possible that further studies made on this subject may reveal the real effect of INS therapy on corneal ectasia. To determine the possible ocular side effects of INS use, the study group was intentionally older than the control group in the current study.

A 2-year observation may not be sufficient time for some side effects to occur. However, there were enough data for safety concern for up to 2 years continuously for intranasal³⁹ or 3 to 6 years intermittently for inhaled budesonide treatment.²² A 24-month study revealed no significant adverse ocular effects with doses between 256 and 400 µg/day in children with allergic rhinitis.³⁹ Another study showed that 3 to 6 years of treatment with inhaled budesonide at an average daily dose of approximately 500 µg is not associated with increased occurrence of ocular side effects.²²

CONCLUSION

Two years of treatment of children with perennial allergic rhinitis with intranasal budesonide at an average daily dose of approximately 100 µg is not associated with increased occurrence of cataracts, glaucoma, xerophthalmia, and keratoconus. We cannot rule out later occurrence of side effects. Because there were no ocular side effects determined by the parameters used in the current study, chronic intermittent use of nasal budesonide in the pediatric age group, especially in children with perennial allergic rhinitis, seems clinically safe for the ocular structures studied.

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