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Evaluation impact of long-term usage of inhaled Fluticasone propionate on ocular functions in children with asthma

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ABSTRACT

Objective: Although systemic, topical, and periocular corticosteroid administration have long been associated with ocular side effects, there has been little evidence to suggest that long-term inhaled corticosteroids can cause ocular side effects. The aim of this study was to evaluate the effects of long term treatment inhaled fluticasone propionate spray usage the recommended dose on some ocular functions in pediatric patients with asthma.
Methods: The study group consisted of 266 prepubertal children with asthma who had used inhaled fluticasone propionate spray at 3–6 years intermittently. One hundred and sixty children who were newly diagnosed with asthma without any treatment made up the control group. Schirmer test results, central corneal thickness, visual acuity, intraocular pressure, cataract formation, keratometry and tear break-up time compared between study and control groups.
Results: The ages of the 266 study patients (150 male) were between 7 and 11 years. The average age (±SEM) was 8.2 ± 1.7 years, and the mean (±SEM) a daily dose of 323 μg (range 250–450 μg) inhaled fluticasone propionate spray, with 865.2 ± 215 g total steroid use during treatment. 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 ($t = 0.150$, $p = 0.384$).
Conclusion: Our findings suggest that long-term intermittent treatment for 3–6 years with inhaled fluticasone propionate spray, as much as average 320 μg daily, in children with asthma seems to be safe for some eye functions.

1. Introduction

Asthma is the most common chronic childhood disease and shown an apparent increase in recent years [1]. Guidelines from the National asthma education and Prevention Program and the global Initiative for Asthma recommend that adults and children with asthma receive daily inhaled corticosteroids (ICSs) as first-line treatment [2,3]. The systemic bioavailability of an inhaled corticosteroids is determined by the amount of drug delivered and subsequently absorbed by the lungs and the amount of drug absorbed from the gastrointestinal tract [4]. In contrast to intranasal steroids, ICSs, there is a high degree of deposition in the oropharynx, nasal cavity, followed by mucociliary clearance to the throat and, eventually, to the gastrointestinal tract, and absorption from the mucosal surface can contribute up to 50% systemic bioavailability of the ICS [5]. The low frequency of side effect observed after long-term use of ICS is suggestive of the well-established safety of ICS, however, there should be careful monitoring of local and systemic side effect of ICS, especially in patients undergoing long-term or life-time treatment, such as treatment in children with asthma [6]. Although the systemic absorption of inhaled steroids has been established [7,8], the clinically relevant ocular side effect are poorly defined. In recent years, increasing concern has been expressed over possible systemic adverse effects of ICSs, following a trend to prescribe higher doses of these drugs [9–12]. Although systemic, topical, and periocular corticosteroid administration methods have long been associated with ocular side effects, there has been little evidence to suggest that ICS can cause ocular side effects. There are not enough data to draw a definitive conclusion possible side effects of long-term use of ICS on eyes in children with asthma. We report the results of possible effects of cross-sectional, long-term intermittent use

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of inhaled fluticasone propionate (FP) on some ocular functions in children with asthma. The following questions will be addressed by our study: are children with asthma using inhaled steroids at an increased risk of developing ocular malfunctions and if so, how large is the risk compared with subjects not using these drugs? Does the risk vary according to the dose or duration of use ICS?

2. Patients and methods

2.1. Study design

We conducted a cross-sectional study among the children diagnosed with mild-to-moderate asthma, with or without allergic rhinitis, for the years 2007–2010, from out-patient pediatric allergy clinics at the Vakif Gureba Training and Research Hospital, Istanbul, Turkey. The diagnosis and severity of asthma were defined according to American Thoracic Society (ATS) [13] guidelines.

2.2. Participants

Subjects who had received inhaled FP intermittently with a documented diagnosis for asthma for ≥3 years, as defined ATS, were included in the present study investigating the occurrence of some ocular side effects. The children had been seen at our out-patient pediatric allergy clinic at least every three-four month for 3–6 years at the time of the present study. The following recordings were always made at each visit; number of hospital admission, due to acute asthma during the previous 3 months, age, height, weight, use of concurrent medicine, dose of inhaled fluticasone propionate (FP) (Flixotide inhaler® or Flixotide Diskus®, GlaxoSmithKline, UK) and inhalation device. Eligible subjects also must have had a documented history of reversibility of ≥12% in FEV_1 or of ≥15% in peak expiratory flow with in 15–30 min after inhaling salbutamol with dynamic spirometry (Vitalograph; G.W. Berg-Co, UK). All participating children have got spirometric results. Between clinic visits, changes in FP or other allergic medications were always made under the supervision of the clinic so that transient changes in treatment during periods of increased asthma symptoms were recorded. Furthermore, adjustments of the dose inhaled FP were made based upon the assessment of clinical control of the disease in order to treat the child with the minimal effective dose. These recording made it possible to accurately calculate the average dose of exogenous corticosteroid during the previous 3–6 years and the accumulated dose of FP. Compliance with the asthma medication was checked at each visit by asking the child and family about their compliance and by checking inhalation skills and medication level. Finally, the child was given an inhaler at the clinic whenever the inhaler strength was changed. In such situations, the child was asked to return to clinic for another visit 2–3 months later and to bring the inhaler at that visit. These measures allowed an assessment of compliance by measuring the number of doses taken (weighing canister (pressurized metered dose inhaler; Flixotide inhaler® 50 μg, or 125 μg, pMDI, GlaxoSmithKline, UK)) or counting the number of doses left (Flixotide Diskus® 100 μg or 250 μg, GlaxoSmithKline, UK) in relation to the prescribed dose. We identified all prescriptions for FP that had been filled by cases at the last 3 years before and studied the risk of current extra exposure to FP. To investigate the exposure to FP according to dose, we calculate the average daily dose of FP by dividing the total quantity (in μg) by the days of supply for that prescription. Participants had not received specific immunotherapy. All of the study group patients had been using only one-type of inhaled steroid, FP. We have included newly diagnosed children with mild to moderate asthma to the control group in order to obtain a sufficient number of patients for comparison. None of these newly diagnosed children had ever received oral, inhaled or nasal corticosteroids for >2 months. Age, height, weight, the presence of allergic rhinitis symptoms, daily and total FP dosage, duration of treatment, time of diagnosis, family history of atopy, antihistamine use, and skin test results were recorded for all study and control group participants. To avoid the confounding influence of some covariates, the following exclusion criteria were used in the present study; >1 month treatment with systemic corticosteroids ever (both groups of children), topical corticosteroids ever applied to 25% of the body surface (both groups), presence of metabolic disease, such as diabetes or systemic disease, such as renal, cardiac hypertension, current exposure to ophthalmic corticosteroids (both groups), and family history posterior subcapsular cataracts (PSC). Patients with a systemic illness other than allergic disease or optical refraction between +4.00 and −5.00 diopters were, also excluded. All patients were questioned about the occurrence of any incidents (trauma) in the past that might cause malfunctions on the eye.

2.3. Outcome measures

Primary end point for the study was to examine whether the ICS spray contributed to some ocular side effects in children with PAR.

2.3.1. Visual acuity (VA)

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

2.3.2. Intraocular pressure (IOP)

IOP was measured with a auto noncontact tonometer (Nidek® NT-2000, 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 a autokerato refractometer (Topcon® KR 8100P, Japan). Central corneal thickness was measured with a ultrasonic pachymeter (Nidek UP 1000, Japan) after administration of topical anesthetic drops. Central corneal dioptric power of >47.20 dioptry, combined with steepening of the inferior cornea compared with the superior cornea of >1.20 dioptry, was determined as keratoconus.

2.3.3. Tear functions

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 mm × 5 mm filter paper strip was used to measure the amount of tearing over a period of 5 min and was placed at the junction of the middle and lateral thirds of the lower eye lid under ambient light. The patient was instructed to look forward and to blink normally during the course of the test. More than 10 mm wetting of the filter paper in 5 min was accepted as normal. Patients with dry eyes should have wetting values of less than 5 mm in 5 min.

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 s, it was interpreted as probable dry eye symptoms. If the duration was between 5 and 10 s, it was interpreted as possible dry eye symptoms, and if the duration was greater than 10 s, the test was interpreted as normal. All ophthalmologic examination were performed blind by 2 experienced ophthalmologist.

2.4. Ethical approval

The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice and was approved

Table 1
Patients characteristics of the study and control groups children with asthma.

	Study group	Control group	*P* value
No. of patients	266	160	
Age, mean, years	8.2 ± 1.7	8.4 ± 0.6	.450
Male (%)	150 (63)	97 (64)	.650
Height, mean, cm	130.0 ± 3.6	132.4 ± 2.7	.330
Weight, mean, kg	32.4 ± 1.2	32.8 ± 1.4	.160
Skin prick test positivity to at least 1 allergen, no. patients	250	145	
IgE (kU/L)	447.4 ± 81	466.6 ± 61.5	.234
Symptoms duration, mean, years	5.5 ± 0.7	3.2± 0.4	

Values are given as mean ± standard error of the mean.

by the local Ethics Committee. Written informed consent was obtained from each patient's parents or legal guardian and from the patient.

2.5. Statistical analysis

SPSS program (v11.5, SPSS Inc., Chicago, IL, USA) was used for all statistical analysis. Signal intensities are given in arbitrary units with mean, standard deviation (SD), or standard error of the mean (SEM). General characteristics were analyzed by independent sample *t*-test or Mann–Whitney test depending on the data, and category-wise data by Pearson chi-square. Correlations between total steroid dose and visual acuity, intraocular pressure, central corneal thickness, Schirmer I test results, and tear break-up time test results of the study group were made by using linear regression analysis. A *P*-value of less than 0.05 or OR with a 95% confidence interval (CI) that did not include 1.00 was considered statistically significant.

3. Results

The ages of the 266 study patients (150 male) were between 7 and 11 years. Seventy-six patients had findings of allergic rhinitis. The average (±SEM) follow-up time was 60.57 ± 10.26 months (range 45–70 months). The average (±SEM) age was 8.2 ± 1.7 years, height was 130.0 ± 3.6 cm, weight was 32.4 ± 1.2 kg. In the study group, inhaled FP dose used was 323 μg (range 250–450) μg daily, with 855.4 g (range 720–1300 g) total steroid use during treatment, and the mean treatment duration was 4.2 years (range: 3–6 years). The average IgE titer was 447.4 ± 81 kU/L (normal 0–52 kU/L). All but 16 patients had positive skin test results for allergy (Table 1).

The ages of the 160 control patients (97 male) were between 6 and 11 years. Fifty patients had findings of allergic rhinitis. The average (±SEM) age was 8.4 ± 0.6 years, height was 132.4 ± 2.7 cm, and weight was 32.8 ± 1.4 kg. The average IgE concentration was 466.6 ± 61.5 kU/L. All but 15 patients had positive skin test results. The differences between study and control group ages, heights, and weights were not statistically significant (Table 1).

The right and left eyes of the groups were evaluated separately. Upon completion of the study, there were no statistically significant differences between any of the parameters of the 2 groups. Three children in the FP group were diagnosed with corneal ectasia (both of eyes). However, Fisher's exact test did not find any increased risk of corneal ectasia in the FP group when compared with the control group. IOP values obtained were in the same range (12–13 mm Hg) as those previously reported for healthy control children in our study (12.9–13.3). No increase in mean IOP were noted in the two groups despite the large differences in the total cumulative doses of FP. Cataract formation, and dry eye were not observed in any of the patients. The results are summarized in Table 2. The only clinical finding was papillary conjunctivitis that was noted in 12 patients in the study group and 5 patient in the control group. We cannot exclude that this finding represent a signal of an adverse event impossible to verify with the number of patients included in the study.

Table 2
Ocular parameters of study and control groups.

Parameter	Study group	Control group	*P* value
Visual acuity (logMAR)			
OD	0.05 ± 0.004	0.004 ± 0.004	.169
OS	0.03 ± 0.003	0.006 ± 0.006	.458
Intraocular pressure, mm Hg			
OD	12.9 ± 0.5	12.7 ± 0.7	.190
OS	13.3 ± 0.5	12.6 ± 0.4	.143
Central corneal thickness, μm			
OD	587.2 ± 14.2	560.1 ± 5.5	.375
OS	569.4 ± 7.7	576.4 ± 7.3	.438
Schirmer I test, cm			
OD	20.5 ± 0.9	18.4 ± 1.2	.266
OS	20.2 ± 1.2	19.3 ± 1.1	.364
Tear break-up time, s			
OD	10.0 ± 1.5	9.4 ± 0.7	.530
OS	11.3 ± 1.01	10.3 ± 0.8	.890
Corneal topography			
Ectasia (number)	3	No ectasia	.370

MAR, minimum angle resolution; OD, right eye; OS, left eye.
Results are expressed as mean ± SEM.

Table 3
Estimates of total steroid dose and variables associated with some ocular functions children with asthma through linear regression (*N* = 260).

	t	95% CI
Visual acuity	0.19	0.77–3.88
Central corneal thickness	0.83	0.67–1.60
IOP	−1.69	0.91–3.51
TBUT	0.78	0.55–3.72
Schirmer test	−1.26	0.94–2.70

IOP, intraocular pressure; TBUT, tear break-up time; CI, confidence interval.

Furthermore, there was no correlation between total FP doses and visual acuities, intraocular pressures, central corneal thicknesses, Schirmer I test results, or tear break-up time test results of the study group (Table 3).

4. Discussion

The assessment of possible systemic side effect of long-term corticosteroids treatment is a central issue in pediatrics, as corticosteroids are being prescribed to more patients with asthma and for longer periods of time than ever before [9,10]. Oral and topical corticosteroids are known to have a potential to cause some ocular malfunctions [14–16], but ICS have generally been considered to be free this side effects [17]. In children with asthma treated with ICS, a few cases of posterior subcapsular opacity and nuclear cataracts have been reported [18,19]. Regarding an increased intraocular pressure (IOP) and tear-functions associated with long-term use of FP in children with asthma, studies are limited and controlled studies are warranted [20]. Our results are in agreement with most

of the previously published studies of smaller groups of less well-characterized children treated for shorter periods of time with ICS [21,22]. We did not find in our clinical study that a clinically and statistically significant ocular side effects with intermittent 3–5 years FP spray usage in children with asthma.

Since first described by Black et al. [23], in 1960, the association between systemic corticosteroid therapy and the development of posterior subcapsular cataract is well established. However, the cataractogenic effect of ICS is controversial. Kewley [24], was the first to report the association between inhaled steroids and cataract formation. Uboweja [25], found a strong association between the use of inhaled corticosteroids and posterior subcapsular or nuclear cataract formation. In children, analysis of data from the CAMP study demonstrated the presence of one PSC among 311 children who received inhaled budesonide, and this finding was reported as questionable [19]. Cataract formation could not be directly attributed to ICS use in this cases because the child also received oral and intranasal corticosteroids during the study. The cataracts that complicate chronic systemic corticosteroids therapy are typically of the PSC type, although nuclear lesions may be seen as well [26]

It is well known that systemic and topical ophthalmic steroids can cause ocular hypertension or open-angle glaucoma. The effect of inhaled corticosteroids has been studied in recent years, but the association is unclear [7,27]. The mechanism of steroid-induced increase of IOP is multifactorial, with a major effect on reduction of aqueous outflow. Target cells for glucocorticoids were identified in the trabecular meshwork of human glaucomatous and nonglaucomatous eyes, suggesting that steroid-specific receptors might play a role in steroid-induced increase in IOP [28,29]. An increased risk for ocular hypertension or open-angle glaucoma was reported in study involving patients aged ≥66 years prescribed high doses of ICSs for ≥3 months (OR = 1.44; 95% CI = 1.01–2.06) [30]. In children, Pelkonen et al., demonstrated that inhaled budesonide as much as 800 μg/d for a short period and long term (18 months) use of 400–200 μg/d did not cause increases in IOP in children with asthma [17].

Studies using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%), primarily due to incomplete absorption and pre-systemic metabolism in the gut and liver, the systemic availability of FP will equal lung deposition [30,31]. In contrast, the majority of the fluticasone propionate delivered to the is systemically absorbed. FP is said not to be metabolized locally in the lung. The drug is cleared rapidly by liver metabolism, with a total blood clearance equivalent to hepatic blood flow. Therefore, the fraction of drug inhaled contributes substantially to the systemic availability [32]. The systemic bioavailability of fluticasone propionate inhalation aerosol in healthy volunteers averaged about 30% of the dose delivered from the actuator. Peak plasma concentrations after an 880-mcg inhaled dose ranged from 0.1 to 1.0 ng/ml [33]. The total clearance of FP is high (average, 1093 mL/min), with renal clearance accounting for less than 0.002% of the total. The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of FP, which is formed through the cytochrome P450 3A4 pathway. This metabolite had approximately 2000 times less affinity than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligibility pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man [34]. Lower bioavailability and extensively metabolism of FP than other corticosteroids, may explain partly the lack of ocular side effects in our study.

We conclude that 3–5 years intermittent treatment of children with inhaled FP at an average daily dose of about 320 μg is not associated with increased occurrence of cataracts, glaucoma, xerophthalmia and keratoconus in children with asthma. Our study period is relatively short and there may be side effects of FP but the effect are weak and the usage duration is too short time to show any side effects. 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 inhaled fluticasone propionate, especially in children with asthma, seems clinically safe for the ocular structures studied.

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