Acta Clin Croat 2003; 42:41-45 Professional Paper

INHALED CORTICOSTEROIDS AND THE RISK OF GLAUCOMA AND INTRAOCULAR HYPERTENSION

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SUMMARY – The aim of this study was to examine whether any correlation exists between longterm use of high doses of inhaled corticosteroids and the occurrence of intraocular hypertension or open angle glaucoma. The study included 30 patients with bronchial asthma, treated with longterm high doses of inhaled corticosteroids, and a control group of 30 age-matched healthy subjects. Apart from family history, the clinical examination included ophthalmologic examination, measurement of intraocular pressure, automated perimetry and photography of the optic nerve head. At least two of the following parameters were required for the diagnosis of glaucoma: intraocular pressure level, visual field defects, and characteristic appearance of the optic nerve head. The level of intraocular pressure (without therapy from 22 to 30 mm Hg, daily pressure curve) was a criterion for the diagnosis of intraocular hypertension. In glaucoma free subjects, all parameters were within the normal limits. The study pointed to a correlation between longterm use of high doses of inhaled corticosteroids and the occurrence of intraocular hypertension in patients with a positive family history of glaucoma.

Key words: *Anti-inflammatory agents – steroidal, adverse effects; Glaucoma, therapy; Intraocular pressure, drug effects*

Introduction

Open angle glaucoma is a chronic progressive optic neuropathy characterized by intraocular pressure (IOP) exceeding 21 mm Hg without treatment (daily pressure curve), characteristic appearance of the optic nerve head (cup/disc ratio), visual field defects, and open angle determined by gonioscopy. Intraocular hypertension is characterized by a daily pressure curve between 21 and 30 mm Hg without therapy, while the appearance of the visual field and optic nerve head is normal[1]. It has long been known that in some persons oral or topic ophthalmic corticosteroids can lead to elevated IOP or the occurrence of open angle glaucoma. Armaly[2] and Becker[3] have postulated a genetic basis of elevated IOP after the application of corticosteroids. Numerous authors have investigated the possibility of hereditary predisposition. With the developments in molecular biology and genetics, the understanding of the genetic basis of glaucoma has rapidly advanced and 8 chromosomal loci have been reported for congenital glaucoma and 6 for primary open angle glaucoma[4]. Mutations in the trabecular meshwork induced glucocorticoid response (myocilin/TIGR) gene were found to account for most cases of autosomal dominant juvenile glaucoma and to play a role in adult primary open angle glaucoma. The increased risk of glaucoma in family members of patients with primary open angle glaucoma has long been recognized, and several studies have screened relatives of patients with primary open angle glaucoma for manifestation of the disease[5,6].

The pathogenesis of increased resistance of the ocular fluid outflow, which causes elevated IOP is still unknown[7]. The possible mechanism of elevated IOP caused by corticosteroids has been reported by Clarck[8]. Corticos-

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Received January 3, 2003, accepted February 14, 2003

teroids enter the cells of the trabecular meshwork of the anterior ocular chamber and activate steroid receptors, causing the trabecular meshwork genes to change, which leads to change in the extracellular material. Accumulation of abnormal extracellular material in the endothelial cells of Schlemm's canal can increase the resistance of the ocular fluid outflow, leading to elevated IOP[7].

Corticosteroids are the most effective anti-inflammatory drugs in the treatment of asthma with very well known mechanisms of effect. They can be administered parenterally, orally and in the form of inhalation. Longterm use of high doses of inhaled corticosteroids is used in the management of severe asthma. It is known that inhalation of beclomethasone in a dose exceeding 1000 mg *per* day can result in systemic absorption[8], and lead to systemic side effects (Cushing's syndrome, retarded growth in children, and osteoporosis).

It is generally known that inhaled corticosteroids do not have the same ocular side effects as topical ophthalmic and oral corticosteroids. On the other hand, some studies indicate that the use of inhaled corticosteroids is a possible risk factor for ocular hypertension and glaucoma[10-12].

Therefore, the aim of the study was to examine whether correlation exists between longterm use of high doses of inhaled corticosteroids and the occurrence of intraocular hypertension or open angle glaucoma.

Subjects and Methods

Study subjects were recruited from the Glaucoma Department, University Department of Ophthalmology, Sestre milosrdnice University Hospital, and Department of Allergic Diseases and Asthma, Jordanovac University Hospital of Pulmonary Diseases from Zagreb, Croatia. An informed consent was obtained from all subjects. Study subjects included patients with asthma on longterm therapy with high doses of inhaled corticosteroids, i.e. Becotide (beclomethasone), ≥800 mg *per* day, and Flixotide (fluticasone), 1000 mg/day, for three months or longer. Patient evaluation including interview and ophthalmic examination were performed at the beginning of therapy with inhaled corticosteroids and at 4 to 6 months of therapy. The study was carried out over a 4-year period. On interview, the patients were asked the following questions: "Have you ever used Becotide or Flixotide, the puffers used for asthma"?; "Have you ever taken steroid tablets or injections for asthma, arthritis or another condition?"; "How many puffs of Becotide or Flixotide do you use *per* day?". The patients were also asked whether they had ever used eyedrops and if so, about the currently used eyedrops.

Family history of glaucoma was obtained by asking the patients whether they had any first-degree relatives with glaucoma.

Clinical examination included refraction, applanation tonometry, ophthalmoscopy, visual field testing, and optic nerve head photography. Visual field testing was done by a standard full-threshold automated static perimetry (dG2 program on an Octopus Visual Field analyzer). Slit-lamp examination and gonioscopy were performed. IOP measurements were taken twice and averaged. Stereoscopic photographs of the optic nerve head were taken. Open angle glaucoma was diagnosed if the patient met two or three of the following criteria: 1) IOP 22 mm Hg in either eye; 2) visual field defects in either eye that were compatible with the characteristics of glaucoma as defined in the study of Katz *et al.*[13]; 3) optic nerve head configuration compatible with glaucoma in either eye as determined by two independent examiners. All three parameters had to be normal for a subject to be considered unaffected at the time of the study. Intraocular hypertension was diagnosed if the subject had IOP exceeding 22 mm Hg in either eye.

The control group consisted of age-matched subjects without bronchial asthma, who had never been treated with corticosteroid therapy in any form. Subjects with a previously diagnosed intraocular hypertension and glaucoma were excluded from the study.

Results

Thirty asthmatic patients treated with high doses of inhaled corticosteroids for more than 3 months were examined at the University Department of Ophthalmology. There were 17 women and 13 men, M/F ratio 0.7, age range 19-62 years, mean age 40.5 years. The control group consisted of 30 patients aged 20-65 years, mean age 42.5 years. All patients with asthma were current users of inhaled corticosteroids.

Among 30 asthmatic patients, elevated IOP was detected in four (three men and one woman), and glaucoma

Table 1. Distribution of subjects according to diagnosis

Diagnosis	Participants	%
Normal	26	86.6
Intraocular hypertension	4	13.4
Glaucoma status	0	0
Total	30	100

Table 2. Abnormal parameters (+) leading to diagnosis

Elevated intraocular pressure	Abnormal visual field	Abnormal optic disc	Number of of patients	Disease status
+	–	–	4	Intraocular hypertension
+	+	+	0	Glaucoma
–	+	–	0	Glaucoma
+	–	+	0	Glaucoma
–	+	+	0	Glaucoma
–	–	–	26	Normal
–	–	–	30	Control group

in none of them (Table 1). Patients with elevated IOP had normal appearance of the visual nerve and normal visual field (Table 2).

None of the control group subjects had elevated IOP or other parameters required for the diagnosis of glaucoma (Table 2). All four patients with elevated IOP had a positive family history of glaucoma.

Differences in the level of IOP, separately for the right and left eye, and average for both eyes, were not statistically significant either at the beginning or at the end of inhaled corticosteroid therapy (Table 3). The values of IOP for the right and left eye are expressed as mean ± standard deviation. Differences between the pretherapeutic and post-therapeutic IOP values were tested by Student's test for dependent samples. Pretherapeutically, all values of IOP were within the normal limits. Post-therapeutically, i.e. on the subsequent measurement, an increase in the values of IOP above the normal limit, i.e. intraocular hypertension, was recorded in four (13.3%) patients.

Table 3. Pretherapeutic and post-therapeutic values of intraocular pressure (mean ± SD)

Intraocular pressure	At the beginning of therapy	At the end of therapy	p
TOD	17.0±3.2	17.3±3.3	0.155
TOS	17.2±3.1	17.4±3.3	0.654
TO (D+S)	17.1±3.1	17.3±3.2	0.184

TOD = lat. tonus oculi dextri
TOS = lat. tonus oculi sinistri
TO (D+S) = tonus oculi dextri et sinistri

Discussion

Bronchial asthma is a chronic inflammatory disease of the respiratory pathways[14]. Inhaled corticosteroids are the basic anti-inflammatory agents for asthma, and their use has led to revolutionary changes in the treatment of chronic asthma, although all the mechanisms of their effects have not yet been fully clarified.

The optimal method of treating asthma is direct inhalation of the needed drugs into the respiratory pathways. Such a method of corticosteroid use has less systemic side effects than oral and parenteral routes of administration. It is currently recommended for the treatment of bronchial asthma to start the treatment with high doses of inhaled corticosteroids earlier than previously recommended, which is also associated with a higher incidence of systemic side effects (Cushing's syndrome, retarded growth in children, and osteoporosis)[15]. The most common ocular side effects are cataract (posterior, subcapsular and nuclear), intraocular hypertension, and glaucoma[16]. It has been reported in the literature that these conditions may be the result of systemic resorption of corticosteroids and also of poor inhalation techniques, which can lead to direct penetration of corticosteroids into the eye, which possibly occurred in our patients. Population studies carried out so far have indicated a correlation between the use of inhaled corticosteroids and an increased risk of intraocular hypertension and open angle glaucoma[10,12,16], which was also confirmed in our study.

One drawback of the present study was the small number of subjects and lack of insight into the actual values of IOP and glaucoma in the subjects' families. This was so because our knowledge was based on the information supplied by the subjects themselves. In our study, a correla-

tion was found between the use of inhaled corticosteroids and the occurrence of elevated IOP in subjects with a positive family history of glaucoma, which was also found in other population studies[10,12,16]. The results of such studies suggest that high doses of inhaled corticosteroids should be used with caution in individuals with a positive family history of glaucoma. In our study, no newly detected case of glaucoma was recorded. In the subjects with recorded intraocular hypertension, ophthalmologic control is required for life because of the increased risk of the development of glaucoma. In the future, patient testing for mutations in the myocilin or other glaucoma genes may become available, as they are found to be implicated, before initiating corticosteroid treatment.

Conclusion

The results of this study indicate that the use of inhaled corticosteroids can be associated with an increased risk of the occurrence of intraocular hypertension in subjects with a positive family history of glaucoma. However, no case of glaucoma was recoreded in the study subjects. Continuous ophthalmologic control is required in patients with intraocular hypertension and a positive family history, for possible progression of the disease.

Ophthalmologic control is also required in patients on longterm therapy with high doses of inhaled corticosteroids, with normal ocular finding and a positive family history of glaucoma.

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Sažetak

INHALACIJSKI KORTIKOSTEROIDI I RIZIK OD GLA UKOMA I INTRAOK ULARNE HIPER TENZIJE

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Cilj ovoga rada bio je ispitati postoji li veza između dugotrajne upotrebe visokih doza inhalacijskih kortikosteroida i pojave intraokularne hipertenzije ili glaukoma otvorenog k uta. Ispitivanjem je obuhvaćeno 30 bolesnika s bronhalnom astmom koji su bili na dugotrajnoj terapiji visokim dozama inhalacijskih kortikosteroida, a kontrolnu sk upinu je činilo 30 dobno prispodobivih zdravih ispitanika. Uz detaljnu obiteljsk u anamnezu, kliničko ispitivanje obuhvatilo je oftalmološki pregled, mjerenje intraokularnog tlaka, automatiziranu perimetriju i fotografiju glave vidnoga živca. Za dijagnozu glaukoma potrebna su najmanje dva od slijedećih parametara: visina intraok ularnog tlaka, ispadi u vidnom polju, te znakovit izgled glave vidnoga živca. Kriterij za dijagnozu intraokularne hipertenzije je visina intraok ularnog tlaka (bez terapije od 22 do 30 mm Hg, dnevna krivulja tlaka). Ispitanici bez glaukoma su imali sve parametre u granicama normale. Istraživanje je pokazalo povezanost između dugotrajne upotrebe visokih doza inhalacijskih kortikosteroida i pojave intraok ularne hipertenzije u bolesnika s pozitivnom obiteljskom anamnezom za glaukom.

Ključne riječi: *Protuupalni lijekovi – steroidni, neželjeni učinci; Glaukom, terapija; Očni tlak, učinci lijekova*