The Relationship of Intranasal Steroids to Intraocular Pressure

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Intranasal corticosteroids have become a gold standard in therapy for allergic rhinoconjunctivitis. A direct relationship between topical and systemic corticosteroids and elevated intraocular pressure (IOP) has been recognized for more than 50 years. However, this steroid-induced response is highly variable. Glaucoma is an eye disease caused by an increase in IOP and results in optic nerve cell death and vision loss. Intranasal corticosteroids are absorbed systemically albeit in small measurable amounts. Some studies suggest a relationship between intranasal steroids and increased IOP. Large prospective studies to determine if there is a significant relationship between intranasal steroids and increased IOP are lacking. We review the current knowledge base regarding intranasal steroid usage and steroid-induced glaucoma.

Introduction

Rhinoconjunctivitis, allergic or nonallergic, is a common condition that plagues approximately 30% of adults and 40% of children in the United States on a yearly basis [1]. Allergic rhinoconjunctivitis (ARC) can frequently lead to significant impairment of quality of life. Symptoms such as fatigue, drowsiness (due to the disease or medications), and malaise can lead to impaired work and school performance, missed school or work days, and traffic accidents. It is important for the treating clinician to recognize, however, that more serious medical sequelae, such as sleep disruption, asthma exacerbations, otitis media, and rhinosinusitis, can be associated with rhinitis [2].

Antihistamines and decongestants have long been the cornerstone of therapies directed at relieving the signs and symptoms of allergic rhinitis patients. Over the past several decades, nasal corticosteroids have gained favor as a way of avoiding the common and undesirable side effects of drowsiness and cardiovascular complications that can be associated with nonsteroidal medications. The use of nasal corticosteroids is now a standard treatment of ARC in the United States. The favorable response to nasal corticosteroids is largely due to their prolonged local action and few side effects. Corticosteroids have the potential to cause a wide range of adverse effects. These potentially disturbing effects include glaucoma, cataracts, osteoporosis, adrenal suppression, and impaired growth. These and other systemic effects could, of course, only be possible if nasal steroids were absorbed systemically at concentrations high enough to show systemic activity.

It has long been believed that there are few, if any, systemic side effects related to nasal steroids and their usage to treat rhinoconjunctivitis [3]. According to a 1992 report from the US Pharmacopeia Convention, there is a documented rate of absorption of nasal steroid sprays in excess of 50% [4]. Despite this rather high absorption rate, it is believed that these medications are largely safe when used at the current recommended dosages [5].

Nasal steroids are designed to have a direct effect on the nasal mucosa. Due to the hypervascularity of the nasal mucosa, direct systemic absorption through an intravascular route is expected. Serum levels of corticosteroids have been measured after routine dosing of nasal steroid products. The serum levels of steroids after nasal administration have never been considered high enough to produce the same systemic side effects that oral or parenteral administration of steroids are known to produce.

The bioavailability of each of the two most commonly used intranasal steroids, mometasone and budesonide, is less than 1% [6]. It is also important to recognize that each spray carries a far less dosage of medication (50 μg and 32 μg, respectively) than even a small dose of the most commonly used oral corticosteroid in the United States, prednisone (which has a much larger bioavailability).

Glaucoma

Glaucoma represents a group of ocular diseases with a characteristic triad of intraocular pressure (IOP) elevation, optic nerve damage, and visual field loss. The increased

IOP in susceptible patients causes direct damage to the optic nerve involving the loss of retinal ganglion cells, where the nerve enters the back of the eye. The characteristic optic nerve damage (increased cupping) leads to progressive peripheral visual field loss that can eventually lead to irreversible blindness, if left untreated. Normal IOP is between 12 and 21 mm Hg.

Glaucoma is the second leading cause of decreased vision and the number one cause of irreversible blindness in the world today. It accounts for approximately 120,000 cases of blindness in the United States, which represents 9% to 12% of all US cases of blindness. It is also the leading cause of blindness among African Americans [7]. Approximately 4 million Americans have glaucoma [7].

Steroid-induced Glaucoma

Since the 1950s, there has been a well-known relationship between the administration of corticosteroids and increased IOP [8]. In 1953, Gordon et al. [9] reported a relationship between the administration of systemic cortisone and increased IOP in patients being treated for anterior uveitis. Over the years, the relationship between IOP increase and steroid usage has been extensively studied [1,9–13,14•,15].

In the 1960s, Armaly [10] reported that the general population could be divided into groups of low and moderate steroid responders or high steroid responders to topical steroid administration. He suggested that the steroid's effect on IOP was based on inheritance of certain recessive genes. Among these subset groups, IOP was seen to respond to steroid exposure along a continuum, from no effect to large increases in pressure. Armaly's theory was further supported by the hypothesis of Becker [16] who, in his investigations, independently showed the same breakdown of steroid responsiveness and proposed a similar genetic origin. The validity of this hypothesis of a genetic origin to steroid-responsive glaucoma is still debated, but the fact that patients show varying responses to steroid exposure is no longer questioned.

Around 35% of the general population will show a moderate increase of IOP into the 22 to 30 mm Hg range after administration of topical ophthalmic corticosteroids [17]. Furthermore, 5% to 6% of the general population and up to 90% of patients with primary open-angle glaucoma have a more significant rise in IOP that can lead to glaucomatous damage to the optic nerve and associated loss of vision [8]. These "high" responders can have increases of IOP of 15 mm Hg or more over 4 to 6 weeks of steroid exposure [13]. These statistics, however, are based on topical administration of ophthalmic corticosteroids. Individuals receiving systemic steroids are less prone to elevation in IOP [17]. The reversibility of steroid-induced IOP elevation also has been exhibited over time [1,8,12]. Generally, the IOP will return to normal within 2 to 4 weeks following discontinuation of the responsible steroid medication [8]. Longer duration of exposure results in longer recovery periods. There also have been instances in which the IOP did not return to normal, and further medical or surgical intervention was necessary to reduce the IOP elevation following exposure to steroids [8]. Overall, there is little debate over whether steroid medication can cause increases in IOP. Subsequently, many risk factors have been identified that predispose a patient to an increase in IOP with steroid usage. These risk factors include a diagnosis of primary open-angle glaucoma, presence of a first-degree relative with primary open-angle glaucoma, diabetes mellitus, high myopia (nearsightedness), and connective tissue disorders [8].

The theories proposed to explain the corticosteroid-induced pressure response include the following: increased synthesis of trabecular meshwork mucopolysaccharides (eg, hyaluronic acid); increased episcleral venous pressure from corticosteroid-induced vasoconstriction; increased aqueous humor osmolarity from altered electrolyte secretion by the ciliary processes; and a change in the actin organization in trabecular meshwork cells [18]. It is believed that a link between increased IOP and steroid usage is derived from the corticosteroids' effect on aqueous outflow facility as regulated by the trabecular meshwork. The trabecular meshwork is an intraocular structure found in the filtration angle of the eye, which allows the aqueous humor to percolate and escape from the eye into the venous system through a series of channels. The trabecular meshwork cells contain high concentrations of steroid receptors. It is believed that the increase in aqueous resistance at the site of the trabecular meshwork is responsible for the effect seen in these patients who experience a steroid-induced increase in IOP [11].

Three current theories explain how cellular regulation by steroid compounds can exert this effect. The first theory is that steroids induce a physical and mechanical change in the structure of the trabecular meshwork at the microscopic level. Studies have demonstrated a reversible reorganization of actin stress fibers in the presence of dexamethasone that reduced outflow by inhibiting both paracellular and transcellular levels of outflow [1,8,15,19]. These changes in microfilaments result in a more rigid structure within the components of the trabecular meshwork. This more rigid structure, in turn, results in an increased resistance to outflow [20•].

A second theory states that steroids stimulate the deposition of extracellular matrix proteins into the trabecular meshwork. These proteins, such as fibronectin, elastin, glycosaminoglycan, and laminin, lead to plaque formation within the juxtacanalicular trabecular meshwork of patients, thereby reducing outflow facility [20•]. The third theory depends on a decrease in the levels of tissue plaminogen activator, stromelysin, and metalloproteases in the trabecular meshwork. The decreased activity of these substances, combined with inhibition of the phagocytic properties

of the normal endothelial cells within the trabecular meshwork, result in a buildup of substance and debris that results in reduced outflow facility [20•,21]. Any of these theories alone or in combination can explain the potent effect that corticosteroid exposure can have on IOP. They all do, however, depend on the "direct" exposure of the cells within the trabecular meshwork to a steroid compound in sufficient levels to induce these changes in function at a cellular level. Direct exposure of the trabecular meshwork to steroid compounds through the use of topical ophthalmic steroids that are designed to directly penetrate the eye, enter the anterior chamber, and eventually, bathe the trabecular meshwork, is a basic "mechanism of action" concept. The use of systemic steroids (eg, oral or parenteral) that create measurable serum levels of steroids can also explain the potential intraocular levels of steroids through the ocular vascular system. The direct exposure of steroid compounds to the trabecular meshwork through the administration of nasal steroids has two theoretical mechanisms of action.

First, if the systemic absorption of a steroid through the nasal mucosa is high enough, then it should act as a systemically administered steroid. Second, the nasal mucosa is contiguous with the ocular mucosa (conjunctiva) by way of the nasolacrimal duct and canalicular system. A retrograde movement of actual nasal product through the lacrimal drainage system is highly unlikely because of the one-way valve system found within the system (eg, valve of Rosenmuller and the valve of Hasner). However, an axoplasmic-like retrograde phenomenon triggered by the nasal mucosal steroid receptors could potentially signal conjunctival steroid receptors to act similarly. However, this would not explain direct exposure of the trabecular meshwork cells to the steroid product. As stated earlier, it has been documented that up to 50% of a nasal steroid can be expected to make its way into systemic circulation when administered at recommended doses [4].

Currently, six nasal steroid formulations are available to prescribing physicians and patients in the United States. Each medication has its own potency and bioavailability. Less potent drugs and shorter courses of exposure result in a decreased risk of IOP increase or a milder increase in most individuals [20•]. Different routes of absorption will also lead to different systemic exposures; those absorbed from the oropharynx and nasal mucosa bypass first-pass metabolism in the liver, thereby delivering more active compound to end organs such as the eye. Whereas, if the steroid is absorbed via the gut, it will be exposed to the liver via the bloodstream prior to being delivered to the eye and thus, less active compound will reach the end organ.

Physicians treating patients for ARC with topical (intranasal) corticosteroids should be aware of the possible consequences of their treatment and the appropriate way to monitor patients for adverse events. It is of particular interest to practicing physicians whether or not intranasal steroids are absorbed systemically in doses large enough to increase IOP to levels that cause glaucomatous optic nerve damage.

Literature Review

A review of the current medical literature examining the link between nasal steroids and IOP reveals several relevant studies. The largest study that examined the relationship between nasal steroids and ocular hypertension/glaucoma was reported by Garbe et al. [11] in 1997. This study was conducted in Quebec and utilized Canada's provincial health insurance plan database. From this group of nearly 750,000 patients, 9793 patients were identified as having the new diagnosis of glaucoma or ocular hypertension, or were recently started on treatment for such conditions during the study period from 1988 to 1994. Each study patient was concurrently receiving either an inhaled or nasal steroid medication. An additional 38,325 control patients were randomly selected during this period who also had received nasal steroids and had documented examination by an ophthalmologist, without the diagnoses of glaucoma or ocular hypertension. The investigators found that there was no increased risk for new diagnosis of ocular hypertension or open-angle glaucoma in continuous users of nasal steroids (OR, 1.02; 95% CI, 0.59–1.77). They also found no increase in risk in patients with any prescribed use of nasal steroids, not necessarily continuous use (OR, 1.09; 95% CI, 0.87–1.37). It is important to note that this study contained several limitations. First, the true measurement and amount of change in IOP was not reported by the authors because their data were based on diagnosis codes of glaucoma/ocular hypertension and not by examination and documentation of the IOP by an ophthalmologist. Secondly, given the seasonal fluctuation in rhinoconjunctivitis and, therefore, the often short or sporadic prescribing pattern of nasal steroids, there was not a large enough group exposed to high-dose nasal steroids on a continuous basis to adequately investigate whether true increased risk existed in this group.

A smaller Turkish study with a similar outcome was published in 1998 [15]. This prospective study followed a group of patients during the immediate postoperative period following endoscopic sinus surgery, in which administration of nasal steroids was the mainstay of treatment. The patients received either budesonide or beclomethasone dipropionate as part of their normal postoperative care. This group's data showed no statistically significant increase in IOP in the treated patients. The investigators excluded patients that had previously been diagnosed with glaucoma or who had a family history of glaucoma. By eliminating this high-risk group, which should have been most likely to show an increase in IOP when exposed to steroids, the authors made the results of their study less expandable to the

general public—where both glaucoma and nonglaucoma patients coexist [15].

More recently, a study involving 54 patients examined the effects of short-term intranasal steroid use on IOP [14•]. These patients were receiving intranasal steroid treatment for ARC and had no documented ophthalmic disease, such as glaucoma. Small increases in IOP were observed in many of the participants (33.3%), ranging from 1 to 4mm Hg after initiation of nasal steroid. Over a mean follow-up of 31 days, however, the authors found no significant increase in IOP and concluded that short-term administration of intranasal steroids did not put the patients at risk for this complication [14•].

Despite the above evidence that demonstrates a lack of an IOP-rising effect from intranasal steroids, several reports support a different conclusion. In 1994, Opatowsky et al. [12] reported the cases of two patients in whom initiation of intranasal beclomethasone dipropionate resulted in increased IOP. In both cases, the patient had no personal or family history of glaucoma, and the rise in IOP was great enough to warrant initiation of antiglaucoma medication. With the discontinuation of the nasal steroid, IOP returned to a normal range (less than 24 mm Hg), and the IOP remained in the normal range even after discontinuation of the antiglaucoma medications.

A study by Bui et al. [1] identified 12 patients (24 eyes) currently using a nasal steroid, with an active diagnosis of either ocular hypertension or glaucoma. Of these patients, none reported use of any other systemic or topical steroid, nor did they receive any additional medical or surgical intervention for their IOP during the study period. The subjects agreed to discontinue the intranasal steroid and return for at least two follow-up visits. This study aimed to evaluate the change in IOP following discontinuation of the nasal steroid. A decrease in IOP upon discontinuing the nasal steroid would indicate a direct steroid-induced IOP elevation effect from the nasal steroid. Of the 24 eyes, 15 had not undergone any previous glaucoma surgery. In these 15 eyes, there was a decline in IOP of 1 to 6 mm Hg following discontinuation of steroid. In the nine previously operated eyes, less predictable responses in IOP occurred than the non-operated eyes. Ten of 12 patients experienced an average increase in IOP with nasal steroid administration. Of the 12 patients, three experienced visual field deterioration in at least one eye during the time they were receiving nasal steroids. The investigators found that discontinuation of the nasal steroids resulted in a clinically and statistically significant decrease in IOP in the studied patients. This study's weaknesses included that it did not examine the type of steroid, the dosage, or duration of exposure as it relates to changes in the IOP. In addition, it did not reintroduce the nasal steroid in order to establish that the steroid spray was the sole causative agent in the change in pressure. In the nine eyes that had previous glaucoma surgery, a surgical effect (eg, enhanced filtration) not associated with the use of nasal steroids could have had a direct effect on the IOP.

Discussion

Clearly, it appears that there is no consensus as to whether nasal steroids truly impact IOP. Several studies declare them safe for usage in patients, whereas there is also strong evidence supporting their effect in increasing IOP. The question also remains whether this impact, even if only a slight increase in IOP, is significant enough to warrant any change in treatment practices, especially in patients with no personal or family history of glaucoma.

Patients with a history of glaucoma or with a first-degree relative with glaucoma are much more likely to experience an increase in IOP associated with steroid use. Based on the current literature, in the general population of rhinoconjunctivitis patients, the risk of a steroid-induced IOP elevation is extremely low. The administration of intranasal steroids, certainly for the short-term and probably for the long-term, is safe for the treatment of rhinoconjunctivitis. Garbe et al. [11] found no increased risk of developing glaucoma or ocular hypertension in the intranasal steroid users compared with the general population. Bui et al. [1], on the contrary, demonstrated a significant decrease in IOP following discontinuation of intranasal steroids in patients with glaucoma or ocular hypertension. Patients who have glaucoma or a family history of glaucoma must be approached with caution when considering treatment with intraocular nasal steroids. There appears to be a demonstrable link between nasal steroid use and increased IOP in these susceptible patients. In these susceptible patients, this rise could be great enough to result in glaucomatous damage to the optic nerve and resultant loss of vision [1].

Change in IOP can be more problematic than the absolute measured IOP. It is also important to consider the rare patient who has a normal pre-steroid treatment IOP. A small increase in IOP may be enough to result in damage to a susceptible optic nerve. For example, consider a patient with a normal IOP of 12 mm Hg, which should not be detrimental to his/her optic nerve prior to steroid use. After initiating intranasal steroids, the patient has a 6 mm Hg–increase in IOP to 18 mm Hg. Although the IOP is still within the normal range, this represents a 50% increase in IOP. A patient with a pretreatment-compromised optic nerve may experience glaucomatous changes at a pressure in the upper teens that would not have been experienced in the lower teens. A single IOP screening after initiation of an intranasal steroid may not be enough, especially if pretreatment IOP was not known.

Increased IOP due to steroid exposure can occur at any time during that exposure [22]. Closer attention should be given to patients with risk factors for the development of glaucoma and associated steroid responsiveness.

Conclusions

The authors acknowledge the lack of large, prospective studies to examine the incidence of steroid-induced IOP elevation in rhinoconjunctivitis patients treated with

intranasal steroids. Such studies in large rhinitis centers would not be difficult to develop because handheld ocular tonometers are available. Intraocular pressure measurements are typically performed with these instruments by technicians and do not require physician supervision. It is clear that a certain amount of caution should be used when prescribing intranasal steroids to any patient with the risk factors for developing a steroid-induced IOP rise that were discussed above.

If IOP testing is not readily available in the office of an ear, nose, and throat doctor or allergist, then referral to an eye care practitioner (ie, ophthalmologist or optometrist) for a midtreatment IOP measurement would be prudent. Baseline IOP measurements prior to initiation of intranasal steroid therapy would be scientific but not practical. An IOP measurement approximately 1 month and 3 months after initiating treatment would give the treating physician a realistic indication of whether or not the patient is at risk of steroid-induced glaucoma.

Disclosure

No potential conflicts of interest relevant to this article were reported.

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