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Glaucoma Eye Drops Adverse Skin Reactions

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Abstract: The term “Glaucoma” is used to describe a number of diseases of the eye characterized by a particular form of optic nerve damage that is often associated with high intraocular pressure (IOP). The open-angle glaucoma is the most common form that is also referred to as chronic glaucoma. This is described as an optic neuropathy with multifactorial nature in which there is a loss of characteristics of the optic nerve fibers. Therapeutic options for the treatment of this disease are different, you can take advantage of eye drops, laser therapy and conventional surgery or more combined treatments. Medicated eye drops are the most common way to treat glaucoma. Although eye drops are widely used, adverse reactions are not frequently observed and described. In particular, the adverse skin reactions are not frequently described in the literature, but often seen in dermatologic clinic, we reported their skin reactions and possible alternative treatments described in literature and their patent applications.

Keywords: Beta-blockers, eye drop, glaucoma, high intraocular pressure, ocular disorders, skin reactions.

INTRODUCTION

Glaucoma is a common eye disease resulting in an optic nerve damage, due to a significant increase of intraocular pressure (IOP >21 mmHg). In most cases, it can even lead to the gradual loss of vision. More specifically, several ocular pathologies, such as myopia, thin cornea and exfoliation syndrome or fluctuating intraocular pressure, that can constitute the major risk factors for this impairment [1].

At present, approximately 70 to 90 million peoples in the world have glaucoma [2]. The major signs and symptoms of this disease are visual disturbance and constriction of visual field. Indeed, patients with this disease can find a lot of difficulties even in the most spontaneous activities of every-day life. In elderly people, glaucoma is very common and it leads to several problems like eyeball hyperemia and retinal detachment.

Untreated glaucoma is one of the main causes of gradual blindness; therefore elderly people should be frequently checked by an ophthalmologist.

There are two different types of glaucoma: open-angle glaucoma and narrow-angle glaucoma. The former is a progressive neurodegenerative process involving retinal ganglion cells and their axons, presenting a particular pattern of visual field and optic nerve head damage [3]. The latter is impairment where the peripheral chamber angle is generally narrow. Moreover, particular conditions, like hyperopic or phakic eye could elevate the intraocular pressure value, leading the patient to a “glaucoma attack” (IOP>50mmHg), with corneal clouding, hyperemia and irregularly deformed pupil [1].

The main drug classes for the medical treatment of glaucoma include: beta-blockers, miotics, sympathomimetic, topical carbonic anhydrase inhibitors, and prostaglandin F2α analogs. These medications can be taken separately or in combination. According to a research of the American Academy of Ophthalmology (AAO), patients prefer to use eye drops like prostaglandin analogs and beta blockers.

Our paper focuses on adverse skin reactions to eye drops containing beta-blockers, prostaglandins and sympathomimetic. Moreover, it contains a detailed review of the recent literature that provides an overview of the cutaneous side effects that are caused by the use of eye drops in glaucoma treatment.

CUTANEOUS SIDE EFFECTS OF EYE DROPS

The eye drops can have mild side effects that involve only the medicated eye, or they can be absorbed into the bloodstream and cause serious damage such as cardiorespiratory problems. Topical ocular medications may cause different adverse cutaneous side effects such as allergic reactions, skin discoloration (hyper and hypopigmentation), periorcular contact dermatitis, flushing of the skin, photosensi-
tivity and, Stevens Johnson syndrome [4]. We described cutaneous side effects due to main medication classes.

BETA-BLOCKERS

Topical beta-blockers are absorbed into the blood and, for this reason they can cause systemic damage, usually cardiac and respiratory. Although not very common, some authors reported dermatological side effects due to eye drops containing beta-blockers, specifically cases of allergic contact dermatitis and lichen planus [5-7].

PROSTAGLANDIN ANALOGS EYE DROPS

Prostaglandin analogs ophthalmic solution can cause periocular skin pigmentation and hyperpigmentation of the iris and the eyelashes as well as an increase in the length and number [8, 9]. The increased ocular and periocular pigmentation is related to the melanogenic effects of prostaglandins; in fact these are one of the most potent stimulants of melanogenesis and melanocitary growth [10, 11].

SYMPATHOMIMETIC

Sympathomimetic acts on the aqueous humor, reducing the production and increasing the flow out from the eye. Atropine, apraclonidine, dorzolamide and brimonidine belong to this category.

In the literature, cases of contact dermatitis caused by topical atropine, apraclonidine and dorzolamide have been reported with an incidence ranging from 21-48%; conversely the dermatological adverse effects of brimonidine have rarely been noticed [12]. However, Sodhi et al. presented the case of three patients affected by open-angle glaucoma. The use of topical brimonidine can cause periorbital contact dermatitis and lichen planus of nail [13].

CARBONIC ANHYDRASE INHIBITORS

Carbonic anhydrase inhibitors are small chemical compounds that inhibit the production of aqueous humor by inhibiting the action of the enzyme carbonic anhydrase. Sulfonamides belong to this class; they are drugs that are even used topically and may cause systemic damage. The literature reports the following adverse skin reactions related to these drugs: Stevens Johnson syndrome, toxic epidermal necrolysis, allergic contact dermatitis and lichenoid eruption [14-17].

MIOTICS

The chronic glaucoma can also be treated with miotics. Their function is to increase the outflow of aqueous humor from the eye. Pilocarpine, carbachol and demecarium belong to this class of drug. This medication presents several common side effects such as pupillary constriction, ocular burning and limited night vision [18]. Miotics do not cause cutaneous side effects frequently, though the periocular allergic contact dermatitis has been associated with the use of this drug [19].

DIAGNOSIS OF SKIN REACTION

Skin tests with a suspected drug are used to establish the cause of cutaneous side effects. Patch tests are performed at least 6 weeks after the resolution of cutaneous adverse event, and after discontinuing the use of corticosteroids and immunosuppressive drugs for thirty days.

Skin tests include: Patch Tests, Prick tests and intradermal tests (IDT) [20]. Furthermore, in vitro tests are available to identify the drugs responsible for allergic reactions, in particular: radioallergosorbert tests (RASTs) [21] and histamine releasing tests (HRT) [22]. Back, arms and thighs are the anatomical sites used for the application of patch tests. Reading them is done after two days (D2), on the fourth day (D4) and possibly if they are negative on D4, a reading should be performed after seven days (D7) [23]. The results of patch tests are reported in accordance with the criteria established by the International Contact Dermatitis Research Group (ICDRG) [24], Table 1.

Skin prick tests are performed at the level of the volar forearm using the medication you want. They are used to verify the sensitization in IgE-mediated allergic disease. The reading of the skin prick test is performed after twenty min-

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utes and at D1. It is positive to the appearance of a skin reaction of diameter greater than 3mm. A negative control with saline and a positive control with histamine are made [20, 25]. If the results of the skin prick test is negative, it is possible to make the intradermal test (IDT).

IDT is performed on the extensor surface of the arm; a small volume (0.04ml) of the drug is injected into the dermis, forming a lesion with a diameter less than 6mm. The intradermal test is read at 30 minutes, to 6 hours, at D1. This is positive if a lesion with a diameter greater than 10mm is observed [20]. The HRT consist of the measurement of histamine released from mast cells of guinea pig in the presence of serum of the patient and of the suspected drug. The test result is expressed in percentage and corresponds to the difference between the number of degranulated cells in the presence and absence of the drug. The test is positive for values greater than 31% [22].

Allergen-specific IgE levels can be measured by radioallergosorbent tests (RASTs), but this test is possible only with certain drugs [21]. A safe way to prevent allergic reactions to drugs does not exist; however, it is advisable to take the least amount of drugs according to each patient and disease severity. Patient must inform the doctor about the allergies and reactions that have occurred prior to each new prescription. Medicines that have caused reactions in the past should not be taken and any cross-reactive medications. Once a reaction to a drug manifests, it is possible to have a more severe reaction to the reinstatement in future [26].

ALTERNATIVE TREATMENTS

Possible alternative treatments in patients with these kinds of reactions are described. First of all a surgery of the eye may be associated with a procedure of photo disruption. This includes in the application of surgical laser pulses to photo disrupt a portion of pathology area identified in a lens of an eye. This integrated surgical technique can use the same pulsed laser for photo-disrupting the target region (for example: glaucoma target region), to incise the capsule of the lens and the cornea [27] by using aqueous ophthalmic composition containing a beta blocker such as timolol, carte-ol or the like, and a sugar alcohol such as mannitol, sorbitol or the like, optionally together with boric acid. The composition of the invention can improve the corneal permeability of a drug, so that the dose of the drug can be lowered, for example by decreasing the frequency of application to the eyes. It is therefore expected that the risk of 80% of systemic side effects which may be induced by the application of the beta blocker to the eyes, including cardio toxicity or respiratory toxicity can be reduced [28]. Another method includes the steps of providing an ultrasonic device that emits ultrasonic energy, holding the ultrasonic instrument at a location external to the trabecular meshwork, transmitting the ultrasonic energy at a frequency to a desired location for a predetermined time, dislodging material built up in the trabecular meshwork, and generating heat that initiates biochemical changes in the eye. The oral appliance may have an electronic element and/or transducer capable of receiving input sounds and transform them in an electronic element and/or transducer capable of receiving input sounds and transform them and then transmit sound modified by a vibration transducer unit associated with one or more teeth. The oral appliance may be fabricated via three-dimensional digital scanning systems or via impression molding to create housing for an electronic element and/or transducer as well as to securely conform the appliance to the user's dentition [29]. Finally, another technique consists of introducing an implant into an anterior chamber of an eye.

The implant is inserted into the eye tissue in the vicinity of anterior chamber such that its proximal end resides in this ocular structure following implantation. The system is able to elute the drug as to leave active trail in the eye. Desirably, the release of the therapeutic agent from the implant is controlled. The controlled release of the therapeutic agent can be at a chosen rate and/or for a selected duration which can be episodic or periodic. The drug may be represented by an agent with anti-proliferative or anti-inflammatory activity or an agent to treat glaucoma or ocular hypertension [30]. Medications associated with ocular implants and their techniques are described in US20140012177.

CURRENT & FUTURE DEVELOPMENTS

At the end of the nineteenth century, glaucoma was cured only with pilocarpine. Since 1970, new drugs have been developed for the treatment of this disease. Initially, glaucoma is treated with drugs in the form of eye drops that lower the intraocular pressure. When medical therapy is not enough, laser treatment and/or surgery are needed. This therapeutic sequence is only possible if diagnosis is promptly made and glaucoma progresses slowly. Given the wide use of eye drops to treat glaucoma, which may also be associated, it is necessary to balance their risk-benefit ratio.

Most of the side effects of these drugs are burning, redness and dry eyes sensation. In some cases there may be systemic manifestations.

Although the cutaneous adverse reactions to eye drops are not very frequent when they occur they cause a significant reduction in patient’s life quality. On the basis of these considerations, we believe it important to identify the medication better tolerated by the patient by means of appropriate investigations, just as skin testing.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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