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Type IV hypersensitivity to timolol

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Introduction

Glaucoma is the leading cause of irreversible blindness in the world. Currently, glaucoma affects more than 60 million people and it is expected to reach 76 million by 2020.[1]

There are two kinds of chronic glaucoma:

1. Open-angle glaucoma
2. Closed-angle glaucoma [2]

Glaucoma is characterized as an optic neuropathy determined by structural changes and functional deficiencies. Primary glaucoma (open-angle) is the most prevalent in the general population (40-80 years 3-4%), and it constitutes the leading cause of irreversible vision loss in industrialized countries.[3]

Current pharmacological treatments seek to obtain optimal local tolerance, using preservative-free formulations in simple presentations or combinations, both in single-dose and multi-dose.

Contact dermatitis is caused by an ample inflammation which arises from the release of pro-inflammatory cytokines from keratinocytes, usually in response to chemical stimuli. Mainly, this causes alteration of the skin barrier, cellular changes at the epidermal level, and release of cytokines.[4]

Allergic contact dermatitis caused by eye medication is mainly attributed to active ingredients. But other excipient ingredients should also be analyzed in addition to the products on an "as is" basis.[5]

There is an entity called the Ocular Pharmacological Intolerance Syndrome (SIFO, in Spanish), which is an intolerance to the drop-based treatment for glaucoma which causes: conjunctival hyperemia, itching, sensation of foreign body presence, light sensitivity, lacrimation, and blepharitis. Exceptionally, these symptoms could also be present: superficial keratitis, deposits on the cornea, palpebral swelling, and blurred vision. SIFO in some of its degrees can also be caused by other topical drugs such as dyes, anesthetics, antibiotics, anti-inflammatories, antivirals, etc.

This paper presents a case of allergic contact dermatitis in a patient sensitized to timolol present in the ophthalmic preparations the patient used as a treatment for glaucoma.

Clinical Case

The patient is a 37-year-old male who was diagnosed 2 years ago with bilateral primary open angle glaucoma (POAG), with prescription of dorzolamide and a topical ß-adrenergic blocker (timolol) in drops, twice a day. In August of 2019, the patient seeked medical help for conjunctival hyperemia, itching, and inflammation of the eyelids of both eyes followed by erythematous dermatitis, which improved once the treatment was suspended. These symptoms repeated when the drug was used.

The patient was known to be hypertensive and received treatment with enalapril 10 mg and Aspirin 125 mg. The patient was not known to be asthmatic or allergic to drugs, nor was he known to be diabetic.

Thinking of a hypersensitivity reaction, a provocation test with timolol was performed and there was no immediate

reaction. Then, provocation tests were performed, first with enalapril and later with aspirin. Both were negative for an immediate hypersensitivity reaction. Given the clinical situation of the patient and the risk of being without treatment, the patient was suggested to consult his ophthalmologist to look for another alternative treatment. While waiting for a response, the patient received the patch test with all the prescribed active ingredients of the drug used, through drops; The results were negative in the reading at 48 hours. At 96 hours the patient was called, who for work reasons could not attend the clinic, clarifying however that there had been no changes. After 7 days he was screened at the clinic, and no changes were found. In some cases where different beta-blockers for ophthalmic use are tested, and which have caused dermatitis in the eyelid area, negative results can be observed in the patch test. This occurs because the skin of the eyelids has greater penetrability than the skin of the back, where skin patches are usually applied.[6,7] This would explain why the epicutaneous tests were negative for this patient, and the conjunctival provocation tests were positive.

Subsequently, provocation tests were performed using the provocation technique with increasing dilutions of 1/1000, 1/100, 1/10 and concentrated. As first dose tears were used as placebo, checking every 15 minutes the pulse of the patient as well as the pressure, the presence of pruritus, irritation, erythema, chemosis and epiphora. The patient remained in the hospital from 2 pm to 8 pm and the provocation was negative. The patient returned after 24 hours, and the provocation was once again negative. At 48 hours the reactions were positive (timolol maleate 0, 5%), with irritation, tearing, chemosis, and erythema in both eyelids.

Discussion

There are numerous substances contained in ophthalmic preparations responsible for producing true allergic contact reactions. The most important group responsible for this frequency is constituted by antimicrobial agents, and preservatives such as thimerosal, benzyl alcohol, benzalkonium chloride (BAC), ethylenediamine and parabens, among others.[8,9]

In recent years, there have been reports of contact dermatitis due to beta-blockers used in the treatment of glaucoma such as timolol [10], levobunolol [11], carteolol [12] or betaxolol [13]. In all cases, eczematous-like reactions on the eyelids, blepharoconjunctivitis, itching with inflammation and edema, conjunctival chemosis, and blurred vision manifested with different intensity.

Timolol is a non-selective beta-blocker commonly more preferred than other agents in terms of efficacy, adverse effects, and cost. Its topical application can produce a foreign body sensation, pruritus, conjunctivitis and in some instances contact dermatitis.[14]

Several authors have suggested the possible existence of cross reactions between the different beta-blockers [15,16], so that the replacement of the drug involved in sensitization by another one from the same family would not proceed.

Although there are many medications and ophthalmic products which can cause adverse effects at the ocular level, fortunately in most cases these adverse effects reverse once the medication is discontinued.

However, when these adverse effects are not detected early, some reactions can prolong causing irreversible eye damage.[17]

Bibliography

Patch test with timolol alone, timolol dorzolamide and excipients, enalapril and ASA

Negative patch test at 72 hours

Positive conjunctival provocative test at 48 hours