

Fundamental Aspects and Relevance of Components in Antihistamine Eye Drops

Herrero-Vanrell R^{1,2,3,4*}, Jáuregui Presa I^{5,6*}, Leceta Bilbao A⁷, Montero-Iruzubieta J⁸

¹Innovation, Therapy and Pharmaceutical Development in Ophthalmology (InnOftal) Research Group, UCM 920415

²Department of Pharmaceutics and Food Technology, Faculty of Pharmacy, Complutense University, Madrid, Spain

³San Carlos Clinical Hospital Health Research Institute (IdISSC), Madrid, Spain

⁴Instituto Universitario de Farmacia Industrial, Faculty of Pharmacy (UCM), Madrid, Spain

⁵Servicio de Alergia, Hospital Universitario Cruces, Barakaldo, Spain

⁶Biocruces Bizkaia Health Research Institute, Immunopathology Group, Barakaldo, Spain

⁷Medical Affairs Department, Faes Farma SA, Bizkaia, Spain

⁸Clínica CARTUJAVISION, Ophthalmological Center, Seville, Spain

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■ Abstract

Ocular allergy covers a series of immune-allergic inflammatory diseases of the ocular surface, with different degrees of involvement and severity. These pathologies are caused by a variety of IgE- and non-IgE-mediated immune mechanisms and may involve all parts of the external eye, including the conjunctiva, cornea, eyelids, tear film, and commensal flora. The most frequent is allergic conjunctivitis, a condition with different clinical forms that are classified according to the degree of involvement and the presence or absence of proliferative changes in the palpebral conjunctiva, associated atopic dermatitis, and mechanical stimuli by foreign bodies, including contact lenses. Treatment guidelines for allergic conjunctivitis propose a stepwise approach that includes medications for both ophthalmic and oral administration depending on symptom severity, allergic comorbidities, and degree of control. In the case of antihistamines, eye drops are the most prescribed ophthalmic formulations.

To avoid disrupting the delicate balance of the ocular surface, topical ophthalmic medications must be well tolerated. The primary aim of this article is to review the physicochemical characteristics and other features of excipients (preservative agents, buffers, pH adjusters, viscosity enhancers, wetting agents or cosolvents, antioxidants, tonicity adjusters, and osmo-protectants) and active compounds (ocular antihistamines) that must be considered when developing formulations for ophthalmic administration of antihistamines. We also provide a brief overview of antihistamine eye drops that could be of interest to professionals treating ocular allergy and encourage the use of preservative-free formulations when possible.

Key words: Antihistamine eye drops. Ocular allergy. Allergic conjunctivitis. Excipients, Preservatives. Ophthalmic drug administration. Ocular surface. Hyaluronate.

■ Resumen

El término alergia ocular engloba un conjunto de enfermedades inflamatorias de la superficie ocular de origen inmunoalérgico, con distintos niveles de afectación y gravedad. Están causadas por una variedad de mecanismos inmunes, mediados o no por IgE y pueden involucrar a todos los componentes de la superficie ocular, incluyendo conjuntiva, córnea, párpados, película lagrimal y flora comensal. De estos trastornos, el más común es la enfermedad alérgica conjuntival. En su clasificación se incluyen distintas formas clínicas según el nivel de afectación y la presencia o no de cambios proliferativos en la conjuntiva palpebral, asociación con dermatitis atópica, y estímulos mecánicos por cuerpo extraño, incluyendo lentes de contacto.

Las guías terapéuticas para el tratamiento de la conjuntivitis alérgica proponen un tratamiento escalonado, tanto en administración oftálmica como oral, en función de la gravedad de los síntomas, las comorbilidades alérgicas del paciente y el logro de un control adecuado. En general, cuando los síntomas oculares predominan o se presentan de forma aislada, se prefieren las formulaciones oftálmicas de antihistamínicos de administración tópica y, dentro de estas, los colirios.

Para mantener el equilibrio de la superficie ocular, las formulaciones tópicas oftálmicas deben mostrar una buena tolerancia. El objetivo principal de este artículo es revisar las características y otras propiedades de los excipientes (conservantes, tampones, agentes para ajustar el pH, viscosizantes, agentes humectantes o cosolventes, antioxidantes, isotonzantes y osmoprotectores) y sustancias activas (antihistamínicos oculares) que deben ser considerados cuando se formulan los preparados de administración tópica oftálmica de agentes antihistamínicos. Además, se realiza una breve revisión de los colirios de antihistamínicos con interés potencial en el tratamiento de la alergia ocular, destacando el empleo de los preparados formulados sin conservantes en aquellos casos en los que resulte posible.

Palabras clave: Colirios de antihistamínicos. Alergia ocular. Conjuntivitis alérgica. Excipientes. Conservantes. Administración oftálmica. Superficie ocular. Ácido hialurónico.

- **Key message**

Topical ophthalmic medications for the treatment of allergic conjunctivitis should be well tolerated so as not to disrupt the delicate balance of the ocular surface.

- **Mensaje clave**

Las formulaciones oftálmicas de administración tópica para el tratamiento de la conjuntivitis alérgica deben evitar alterar el equilibrio de la superficie ocular.

Introduction

Allergic diseases are a global public health problem. Their incidence is increasing, and they have a significant impact on patient quality of life. Additionally, if not adequately controlled, chronic allergies can generate a substantial socioeconomic burden in terms of lost labor productivity and use of health care resources [1].

The term ocular allergy covers a series of immune-allergic inflammatory diseases of the ocular surface, with different degrees of involvement and severity. These diseases are caused by a variety of IgE- and non-IgE-mediated immune mechanisms and may involve all parts of the external eye, including the conjunctiva, cornea, eyelids, tear film, and commensal flora [2].

The most frequent immune-allergic inflammatory disease is allergic conjunctivitis, a condition with several different clinical forms, which is classified according to the degree

of involvement and the presence or absence of proliferative changes in the palpebral conjunctiva, associated atopic dermatitis, and mechanical stimuli by foreign bodies, including contact lenses (Table 1) [3,4]. Allergic conjunctivitis affects up to 30% of the general population and is caused by an immediate (type I) IgE-mediated hypersensitivity mechanism. It is frequently associated with other allergic diseases, particularly rhinitis. Despite their high impact on patient quality of life, ocular symptoms in allergic conjunctivitis are often underdiagnosed and/or underreported [5].

Treatment guidelines for allergic conjunctivitis propose a stepwise approach that includes medications for both ophthalmic and oral administration, depending on symptom severity, allergic comorbidities, and achievement of (or failure to achieve) adequate control [5]. In the case of antihistamines, eye drops are the most prescribed formulations.

Topical ophthalmic medications should be well tolerated to avoid disrupting the delicate balance of the ocular surface. The

Table 1. Ocular Surface Diseases Caused by Hypersensitivity Mechanisms.^a

	Allergic conjunctivitis	Vernal keratoconjunctivitis	Atopic keratoconjunctivitis	Giant papillary conjunctivitis	Contact blepharoconjunctivitis
Presentation	– Onset in childhood	– Onset in childhood/adolescence	– Adolescents or adults	– Any age	– Any age
Natural history	– Both sexes – Intermittent or persistent – Bilateral	– Male predominance – Persistent with exacerbations – Bilateral	– Male predominance – Chronic with exacerbations – Bilateral	– Both sexes – Chronic – Resolution after removing antigen, eg, contact lenses, sutures, foreign body – Uni- or bilateral	– Both sexes – Chronic – Resolution after removing antigen, eg, eye drops, cosmetics – Bilateral
Hypersensitivity mechanism	Type I	Types I and IV	Types I and IV	Types I and IV	Type IV
Atopic Background	Yes	Possible	Yes	Possible	Possible
Eyelids	Edema	Edema Pseudoptosis	Eczema + meibomitis Blepharitis	-	Eczema, erythema, desquamation
Conjunctiva	Follicles and/or papillae	Giant papillae	Papillae ± fibrosis	Giant papillae	Hyperemia, follicles
Limbus	-	Thickened Trantas dots	Thickened Trantas dots	Hyperemia	-
Cornea	-	Punctate keratitis ± vernal plaque	Punctate keratitis Ulcer, opacities Neovascularization	Infrequent	-

^aAdapted from references [3] and [4].

primary aim of this article is to review the physicochemical characteristics and other special features of the excipients and compounds used in formulations for ophthalmic administration and their relevance in antihistamine eye drops.

Ophthalmic Administration of Medications

Ophthalmic administration may be topical, periocular, or intraocular, depending on the part of the eye that the active substances need to reach. Topical drug administration is the most convenient and patient-friendly approach, especially for the treatment of diseases affecting the ocular surface, such as allergic conjunctivitis.

Eye drops are the most widely used pharmaceutical formulations, because of their simplicity of use and ease of self-administration [6]. Eye drops must be sterile (guaranteed absence of microbial contamination), tolerable (compatible with the ocular surface, not causing additional damage to the eye), and durable (therapeutic drug concentrations must be maintained for as long as needed in the target tissues to provide efficacy) [7]. Recent research has focused on the development of optimized formulations and improved delivery devices to ensure effective drug levels at the target site while protecting the ocular surface.

Administration of topical ophthalmic drugs is associated with low bioavailability [8] for several reasons, mainly the short contact time of formulations with the ocular surface. This is a result of the anatomical and physiological characteristics of the site of administration and events triggered on the ocular surface after administration.

The ocular surface is protected by the eyelids and tears. The tear film, also known as the precorneal tear film, is a thin fluid layer with a thickness of 2.5-10 μm , that covers both the cornea and the conjunctiva [9,10]. It has an inner aqueous layer constituted by proteins and mucinous components that combine to form a gel. This inner layer is covered by an outer lipid layer that prevents water evaporation and improves the stability of the tear film itself [10].

When an ophthalmic formulation comes into contact with the eye surface, it first mixes with the tear fluid. As instillation of eye drops may result in increased reflex tear production, the concentration of the active substance is diluted. Additionally, about 90% of the total dose of the active substance (the usual volume of an eye drop is 50 μL) [6] is eliminated from the ocular surface in about 2 minutes, with only 1%-5% of the administered drug penetrating the cornea and reaching the interior of the eye [8]. For this reason, topical preparations (eg, ophthalmic antihistamines) are limited to the treatment of ocular surface diseases or other conditions in which the drug must reach the aqueous humor (eg, hypotensive formulations in glaucoma). As mentioned, the short contact time with the ocular surface of conventional formulations has led to various strategies to increase the permanence of eye drops on the corneal surface [11].

Tear osmolarity, which depends on the concentration of solutes, is close to 300 mOsm/L in healthy individuals. Normal pH varies between 7.3 and 7.7, and viscosity and surface tension values (Table 2) are adequate to help tears cover the ocular surface [12-15]. When developing ophthalmic topical

Table 2. Physicochemical Properties of Healthy Human Tears.^a

Property	Normal value/range
Osmolarity	300 mOsm/L
pH	7.2-7.8
Surface tension	43.6-46.6 mN/m
Viscosity	0.3 to 6 mPa·s

^aTaken from Reference [6].

formulations, it is crucial they are similar to the tear film so as to ensure optimal tolerance.

Overview of Topical Ophthalmic Preparations

The Spanish Royal Pharmacopoeia [16] defines ophthalmic formulations as sterile liquid, semisolid, or solid preparations intended to be applied to the eyeball and/or conjunctiva or to be introduced into the conjunctival sac.

The classification includes several types of formulations:

- Liquids (eye drops and suspensions)
- Solids to be dissolved or dispersed in an appropriate liquid vehicle at the time of administration (powders for eye drops and eye baths)
- Semisolids (ointments, creams, and gels)
- Ocular inserts and sterile polymeric systems, whether solid or semisolid, designed for insertion into the conjunctival sac.

Ophthalmic formulations are mostly supplied as eye drops, which are liquids containing 1 or more active ingredients and several excipients and designed to be instilled into the eye. Excipients are commonly used in eye drops for the following reasons:

- To confer optimal values of tonicity, viscosity, and pH
- To increase the solubility of the drug
- To stabilize the formulation
- To maintain the preparation sterile

In recent years, research on the treatment of dry eye disease (DED), a better understanding of the target area, and improvements in pharmaceutical technology have led to important progress in eye drop formulation and contributed to optimal ocular tolerance, while improving ocular surface conditions. In this sense, bioadhesive polymers are of great interest, as they increase the contact time of the formulation with the target tissue [6]. Some can also help to hydrate the ocular surface [17,18].

The appearance of artificial tears for the treatment of DED has also encouraged the removal of preservatives from many preparations and the development of new devices capable of maintaining sterility.

Formulation of Eye Drops: Excipients

Medicated eye drops contain 1 or more drugs in a liquid vehicle and excipients. Any component of a medication

other than the active substance and the packaging material is considered an excipient.

Excipients, or adjuvants, play a crucial role in the formulation of ophthalmic preparations and include preservative agents, buffers, pH adjusters, viscosity enhancers, wetting agents or cosolvents, antioxidants, and tonicity adjusters.

Artificial tears are mainly solutions that do not contain substances with pharmacological action and are, therefore, classed as medical devices and not medicinal products. The vehicles (sterile water) and excipients (eg, hyaluronic acid) used in these preparations have properties that prevent and relieve the symptoms of DED.

Vehicles

Purified, sterile water is the most widely used vehicle in eye drops. More rarely, natural, or semisynthetic oily vehicles are used [6].

Preservatives

Most eye drops in multidose packaging contain an antimicrobial preservative, except when the formulation itself includes an active ingredient with sufficient antimicrobial properties. Preservatives are included to prevent contamination of the formulation and maintain its sterility. Single-dose containers and new special multidose devices that guarantee sterility are also available in preservative-free formulations [19].

The nature of the preservatives used in ophthalmic formulations may differ (Table 3). Benzalkonium chloride (BAC) is the most common preservative in antiallergic eye drop formulations owing to its antimicrobial properties, stability, and long-shelf life. However, it has been associated with ocular allergies and toxicity in the medium and long terms [20]. The biocidal activity of BAC is attributed to its surfactant properties, which destabilize the bacterial membrane. Unfortunately, this action is not selective, and even at low concentrations (0.01%), BAC exerts a toxic effect on human cells [20]. In addition, it destabilizes the lipid layer of the precorneal tear film, causing water to evaporate, and eventually reduces the number of goblet cells, thus decreasing

Table 3. Preservatives Used in Ophthalmic Formulations.^a

Preservative	
Alcohols	Chlorobutanol and phenylethyl alcohol
Phenols	Chlorocresol
Quaternary ammonium compounds	Benzalkonium chloride, cetylpyridinium chloride, and polyquaternium-1
Organic mercurials	Thimerosal or merthiolate and phenylmercury salts
Antibiotics	Polymyxin sulfate
Guanidine	Chlorhexidine
Other	Stabilized oxychloro complexes, sodium perborate, EDTA, boric acid, mixtures with other components

^aTable based on reference [6].

moistening of the corneal epithelium, especially in patients with pre-existing DED [20].

Thanks to advances in the management of DED, we know that long-term use of formulations containing preservatives can destabilize the precorneal tear film and produce adverse effects in the conjunctiva, including conjunctival cell apoptosis, allergic conjunctivitis, and keratitis. If the ocular surface is already altered, as is the case with allergic eyes, the effect is even more pronounced [21]. Therefore, particularly in ocular allergy, the use of preservative-free topical ophthalmic medications is preferred, as these significantly improve tolerance and patient comfort while preventing precorneal film denaturation and potentially irreversible damage to the ocular surface.

Other preservative agents such as thiomersal or chlorhexidine may cause significant hypersensitivity reactions and are no longer used in antihistamine eye drops.

Tonicity-adjusting agents

Isotonic or slightly hypertonic preparations are better tolerated than hypotonic preparations [6]; therefore, most ophthalmic solutions are isotonic with tear fluid in order to reduce irritation of the ocular surface. However, several formulations of artificial tears are slightly hypotonic [22] to better dilute the high concentration of salts present in the tear film of DED patients. Tonicity of ophthalmic formulations is commonly adjusted with sodium or potassium chloride, although sugars such as trehalose and mannitol may also be used.

pH regulators

Most ophthalmic solutions are formulated with a pH between 6 and 8, which makes them more comfortable for administration. The different buffers that can be used to regulate pH are as follows:

- Acetic, boric, hydrochloric, and phosphoric acids or their potassium or sodium salts (eg, acetate, bicarbonate, borates, carbonate, citrate, phosphates)
- Sodium hydroxide

Phosphate buffers (eg, hydrated sodium phosphates), which are common in ophthalmic preparations, may play a role in the formation of corneal calcium deposits. As these can cause eye injury in patients with corneal surface disorders [23], their use has been limited to date.

Surfactants (emulsifiers)

Surfactants are included in topical ophthalmic formulations because they reduce surface tension, and this helps to extend the solution throughout the ocular surface. Depending on their nature, they may be ionic or nonionic.

Nonionic surfactants (eg, polyvinyl alcohol, polyvinylpyrrolidone [povidone], polysorbates 20 and 80, poloxamer 282, and tyloxapol) are better tolerated by the ocular surface and are therefore more frequent in ophthalmic formulations [24].

Viscosity enhancers

Viscosity enhancers are added to eye drops to increase the contact time of the formulation with the ocular surface. The

optimal viscosity of ophthalmic preparations is between 25 and 55 mPa·s [6]. Higher viscosity values entail a risk of tear canal obstruction, and excessively viscous preparations tend to leave a residue on the eyelids that can interfere with vision.

The compounds used to increase viscosity in eye drops include hyaluronic acid, dextran 70, gelatin, poloxamer 407, polyvinylpyrrolidone, cellulose derivatives (methylcellulose, hypromellose, and carmellose), and acrylic acid derivatives (carbopol).

Antioxidants

If the active substance is susceptible to oxidation, antioxidant agents may be used.

Osmo-protective excipients

The recent introduction of osmolytes and osmo-protectants in ophthalmic preparations has proven beneficial in patients with DED, as they protect corneal epithelial cells from ocular

Table 4. Antihistamine Eye Drops.^a

Chemical group	Active ingredient	Trademark	Concentration	Content	Stability	Preservative	Other excipients
Alkylamines	Pheniramine	Alergoftal (in combination)	5 mg/mL	10 cc	28 d	Benzalkonium chloride	Polyethylene glycol (macrogol) 8000, Polyvinylalcohol Disodium edetate (E385) NaOH and/or hydrochloric acid
Ethylenediamines	Antazoline	Optialerg (in combination)	5 mg/mL	10 cc	28 d		
Ethanolamines	Bepotastine	Traler	NOT MARKETED IN SPAIN (2022)				
	Alcaftadine	Lastacaft					
Piperidines	Bilastine	Bilaxten eye drops	6 mg/mL	5 cc	3 y (2 mo from opening)	NO	Sodium hyaluronate (1 mg/mL) Glycerol (E422) Sodium hydroxide (E524) Hydroxypropylbetadex
	Emedastine	Emadine	0.5 mg/mL	5 and 10 cc	30 mo (28 d from opening)	Benzalkonium chloride	Trometamol Hypromellose (E464) NaOH and/or hydrochloric acid
	Epinastine	Relestat	0.5 mg/mL	5 cc	2 y (28 d from opening)	Benzalkonium chloride	Disodium edetate (E385) Sodium acid phosphate dihydrate NaOH and/or hydrochloric acid
	Ketotifen	Multidose: Bentifen, Ketisal, Ketobril, Zaditen, Zalerg Single dose: Ketobril, Zaditen	0.25 mg/mL	5 cc	28 d from opening	Benzalkonium chloride	Glycerol (E422) NaOH (E524)
				8 cc (20 single doses)	3 mo	NO	
	Levocabastine	Bilina, Reactine	0.5 mg/mL	4 cc	2 y (28 d from opening)	Benzalkonium chloride	Propylene glycol, hypromellose (E464) Polysorbate 80 Hydrated sodium phosphates Disodium edetate (E385)
	Olopatadine	Opatanol	1 mg/mL	5 cc	3 y (28 d from opening)	Benzalkonium chloride	Hydrated sodium phosphates NaOH and/or hydrochloric acid
Phthalazinones	Azelastine	Multidose: Aflunon, Corifina	0.5 mg/mL	6 cc	3 y (28 d from opening)	Benzalkonium chloride	Disodium edetate (E385), hypromellose (E464), liquid sorbitol (E420), NaOH (E524)
		Multidose: Azelastina POS		10 cc	2 y (3 mo from opening)	NO	Disodium edetate (E385), hypromellose (E464), liquid sorbitol (E420), NaOH (E524)
		Single dose: Tebarat		5 cc (20 single doses)	3 mo from opening	NO	Disodium edetate (E385), hypromellose (E464), liquid sorbitol (E420), NaOH (E524), polyvinyl alcohol (E1203)

^aI. Jáuregui – Data according to CIMA SmPCs (<https://cima.aemps.es/cima/publico/home.html>).

surface damage caused by tear hyperosmolarity. These compounds include betaine, dextrose, ectoine, erythritol, glycerol, glycine, levocarnitine, sorbitol, and trehalose [24].

Ocular Antihistamines

Treatment of allergic conjunctivitis is based on a wide therapeutic arsenal, including antihistamines, membrane-stabilizing agents, vasoconstrictors, corticosteroids, and nonsteroidal anti-inflammatory drugs (NSAIDs).

Oral and/or topical ophthalmic antihistamines relieve the itching, erythema, tearing, and edema that characterize the immediate response to allergens. Ophthalmic formulations have a rapid onset of action after instillation (3 to 15 minutes), and in many cases can relieve nasal symptoms as well as ocular symptoms. In patients with allergic conjunctivitis, antihistamines have a more favorable risk-benefit ratio than all the other classes of drugs, including NSAIDs, vasoconstrictors, and corticosteroids [25].

Since the mid-20th century, around 50 H1-antihistamines have been marketed; of these, about a dozen are used in ophthalmic formulations (Table 4). They are classified according to their structure into 7 chemical groups and according to their sedative properties and length of time on the market, as sedating or first-generation drugs (those marketed before the 1980s) and nonsedating or second-generation compounds.

In terms of mechanism of action, antihistamines are not strictly histamine antagonists but rather inverse agonists that stabilize the H1 receptors in their inactive state [26]. In addition, most antihistamines have shown anti-inflammatory properties *in vitro*, since they inhibit histamine release by mast cells in a manner that is directly proportional to their concentration, thus impairing to some extent the development of the late phase of allergic reactions. The hypothetical mechanism by which antihistamines stabilize the function of mast cell membranes is based on the down-regulation of intracellular calcium [27-28]. The high concentrations needed to exert this anti-inflammatory effect are difficult to reach with oral doses but may be achieved by direct application of high concentrations to the ocular conjunctiva, as with ophthalmic formulations [28].

Thus, classifying ocular antihistamines as either only antihistamines or dual-effect agents is now considered somewhat artificial, since almost all antihistamines in eye drop formulations can also act to some extent as mast cell stabilizers (ie, as local anti-inflammatory drugs) and, as such, can be considered dual inhibitors [3,28].

First-Generation Antihistamines in Ophthalmic Formulations

The most widely prescribed first-generation topical antihistamines are antazoline and pheniramine. These are usually combined with topical vasoconstrictors to relieve the symptoms of acute conjunctivitis but are not considered suitable for the long-term treatment of conditions such as allergic conjunctivitis.

First-generation antihistamines characteristically show a lack of receptor specificity, resulting in nonselective

actions that can cause antiadrenergic, antiserotonergic, and anticholinergic effects, leading to dryness of the ocular surface and blurred vision due to impaired accommodation [28].

Another characteristic of classic, first-generation antihistamines is that, when taken orally, they act through active metabolites; therefore, they need extensive first-pass metabolism in the liver to become effective [28]. Ophthalmic and nasal formulations do not require this first-pass effect.

Moreover, the physicochemical properties of these drugs (lipophilicity, low molecular weight, polarity) and their lack of interaction with transport pumps such as P-glycoprotein [28] mean that they cross the blood-brain barrier (BBB) easily and penetrate the central nervous system (CNS) when used systemically. Thus, they saturate hypothalamic H1 receptors in a dose-dependent and quantifiable way, inducing sedation and psychomotor impairment. Comparative studies based on positron emission tomography (PET) have confirmed this effect for conventional, first-generation antihistamines (dexchlorpheniramine, hydroxyzine, and diphenhydramine) and for others classified as second-generation agents (ketotifen, cetirizine, mequitazine, and azelastine), even when used in eye drops [29].

Nonsedating or Second-Generation Antihistamines

Currently marketed nonsedating second-generation antihistamines in ophthalmic formulations include azelastine, bilastine, emedastine, epinastine, ketotifen, levocabastine, and olopatadine (along with alcaftadine and bepotastine, not marketed in Spain but available in other countries).

Most of these antihistamines are derivatives or analogues of conventional, first-generation sedating compounds, although they have a more selective action and a lower CNS penetration. This has been demonstrated by PET imaging for receptor occupancy. Bilastine and olopatadine are particularly interesting, since they have demonstrated zero occupancy when administered orally [29].

Although systemic exposure associated with ophthalmic formulations is very low, central receptor occupancy can occur with some antihistamines, even when used as eye drops. Some specific pharmacological characteristics, and the fact that nasal and/or ophthalmic administration are free from a first hepatic pass, enable permeability across the BBB for some molecules and subsequent brain H1 receptor occupancy. PET studies have shown that ketotifen, eg, when administered as an ophthalmic formulation and depending on the dose, has been shown to occupy more than 50% of brain H1 receptors [29]. This might result in an increased risk of sedation and psychomotor impairment.

Newer antihistamines, on the other hand, tend to have fewer drug-drug interactions than first-generation agents and are associated with fewer anticholinergic effects on the ocular surface and eye accommodation. However, some of them still maintain a certain affinity for muscarinic receptors, and their topical or systemic use can alter the tear film, causing DED as an adverse effect, along with barrier function changes in the conjunctival response to allergens and pollution, and

even an exacerbation of the late inflammatory response to allergens [21].

Preservatives in Marketed Antihistamine Eye Drops

As shown in Table 4, all antihistamines in ophthalmic formulations contain the preservative BAC, except for the new bilastine formulation [30], a multidose presentation of azelastine, and single-dose presentations of ketotifen and azelastine.

As discussed above, a formulation free from BAC or other preservatives not only significantly improves tolerance and patient comfort, but also prevents potentially irreversible precorneal film denaturation and damage to the eye.

Conclusions

- Within the available armamentarium of antihistamines in ophthalmic formulations, it is advisable to choose preparations that are better adapted to the precorneal tear film and do not require preservatives, especially BAC, in their composition. Similarly, given the possible adverse effect of corneal calcium deposits and their consequences, ophthalmic formulations should not contain phosphate buffers [23].
- The addition of sodium hyaluronate in an ophthalmic formulation helps hydrate the ocular surface, prevents tear film dysfunction, and protects the surface from the effects of allergic conjunctivitis, thus improving patient comfort and control.
- When selecting the active substance from the range of available antihistamines in ophthalmic formulations, it is advisable to choose nonsedating, long-acting antihistamines, with selective affinity for peripheral H1 receptors and no affinity for muscarinic receptors.
- The specific mechanism of action of almost all antihistamine eye drops also means that they act to some extent as mast cell stabilizers [3,28]. For this reason, the classification of ocular antihistamines as either antihistamines or dual-effect preparations is somewhat artificial, since all new molecules can act as local anti-inflammatory agents when used at the conjunctival concentrations reached in direct topical use.

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■ **Rocío Herrero Vanrell**
E-mail: rociohv@ucm.es

Ignacio Jáuregui Presa
E-mail: ignacio.jaureguipresa@osakidetza.eus