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Research Article

Corneal Calcium Deposits: Phosphate ROL in Eye Drops

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Abstract

Objective: To bring awareness to the ophthalmologist about the state of the discussion in relation to the issue regarding the phosphate content in the collyriums for ophthalmic use. In order to inform professionals so they could make an appropriate selection of the medicine to be prescribed.

Materials and Methods: Review of the composition of the eye drops market in the country and registry of the phosphate levels.

Data was retrieved from information provided by pharmaceutical companies and by Administración de Medicamentos, Alimentos y Tecnología Médica (ANMAT) [National Administration for Drugs, Food and Medical Technology] from the Argentine Republic.

Results: Through the analysis, it was seen that most collyrium which are marketed in our country have phosphate concentrations higher than the physiological lacrimal concentration (0.4 - 1.45 mmol/L).

Conclusion: In patients who present an alteration of the surface and/or ocular inflammation, the administration of drops with high levels of phosphate is implicated in the generation of calcium precipitation phenomena at the corneal level. The selection of eye drops which do not contain phosphates, or which contains them at physiological levels, might have a beneficial impact on the management of the patient.

Keywords: Eye Drops; Corneal Calcifications; ANMAT

Introduction

Corneal calcifications are classified into two types: band keratopathies and calcareous degeneration. Band keratopathy affects only the superficial layers of the cornea like the epithelium, the Bowman´s layer and the anterior stroma; localized at the interpalpebral zone of the cornea. Calcareous degeneration is a less frequent condition, which in addition affects the posterior corneal layers [1-3].

Histologically, the first change involves a basophilic stained of the basal epithelial membrane, followed by the disruption of the Bowman´s layer with calcium deposits and its eventual fragmentation. The calcium is deposited as hydroxyapatite salts and non-crystalline granules of calcium carbonate and phosphate salts, with a tendency to coalescer. These deposits are usually extra-cellular ones [1-3].

Many systemic and localized ocular conditions are associated with the development of these calcium degenerations (Table 1).

In the last couples of years, collyriums which contain phosphates have been identified as potential corneal calcium deposits generators, especially in eyes with chronic alterations of the ocular surface [7]. Phosphates are mainly used as buffer in ophthalmic collyriums, approximately in one third of them.

Sistemic risk factors	Local risk factors
Systemic hyperkalemia	Chronic epithelium defects
Treatment with calcium fixative	Ptisis bulbis
HIV	Long term glaucoma
Host versus draft disease	Interstitial keratitis
Sarcoidosis	Chronic ocular inflammation
Metastatic bone disease	Ocular surface alteration
Systemic erythematosus lupus	Dry eye
Gout	Intraocular silicone oil
	Use of a viscoelastic substance
	Host versus draft disease
	Treatment with phosphate containing drops

Table 1: Risk factors for the development of corneal calcium alterations.

This work is an actualization, and a review, about the current discussion of the role of phosphates and their influence in the development of corneal calcifications.

Methodology

Our work was based on performing a detailed analysis of the chemical formula of the collyriums with a market authorization provided by ANMAT in our country, whether antibiotics, antiviral, steroids, lubricants or anti-glaucoma collyriums.

Data was retrieved from information provided by pharmaceutical companies and from the information at the ANMAT website, www.anmat.gov.ar.

Afterwards, a list of those collyriums with phosphates and their concentration was made. They were also compared with the physiological levels of phosphate present in the tears (Table 2-4).

Trade name	Phamaceutical	Generic name	Concentration mmol/l
Dexametasona dorf	Dorf	Dexamethasone	39.6/94.99
Flarex	Alcon	Fluorometholone Acetate	Information not supplied
Gotabiotic	Poen	Tobramycin	9.51/2.5
Gotabiotic d	Poen	Dexamethasone naphazoline Tobramycin	42.2/25.6
Isoptomaxidex	Alcon	Dexamethasone	Information not supplied
Lopred biotic	Elea	Loteprednol tobramycin	49.3/2.94
Neoftalm dexa	Raymos	Tms polymyxin b Dexamethasone	Information not supplied
Neolag	Atlas	Tms polymyxin b Dexamethasone	0.41
Quinomed dx	Bausch&lomb	Moxifloxacin Dexamethasone	39.1/94.9
Sedesterol	Poen	Dexamethasone	2.79/52.85/9.33
Vigadexa	Alcon	Moxifloxacin Dexamethasone	1.0ng/ml
Zypred	Allergan	Gatifloxacin Prednisolone acetate	Information not supplied

Table 2: Antibiotics and steroids collyriums which contain phosphates in their different chemical forms. In alphabetical order according to their trade names.

Physiological phosphates ≤1.45 mmol/L.

Trade name	Pharmaceutical	Generic name	Concentration mmol/l
Brimopress t	Poen	Brimonidine Timolol	28.98
Dorlamida	Atlas	Dorzolamide	7.04 (approximate value)
Dorlamida t	Atlas	Dorzolamide timolol	28.98
Ganfort	Allergan	Bimatoprost timolol	Information not supplied
Glaucogesic	Atlas	Latanoprost	38,9208/33,82
Glaucogesic t	Atlas	Latanoprost timolol	33.82/33.8
Glaucostat	Raymos	Latanoprost	20.36
Glaucostat t	Raymos	Latanoprost timolol	33.82/33.8
Glaucotensil	Poen	Pilocarpine Timolol	13.47/53.42
Latanoprost dorf	Dorf	Latanoprost	33.7/26.9
Louten t	Poen	Latanoprost timolol	0.41
Lumigan	Allergan	Bimatoprsot	33.3/33.4
Ocuprostim	Bausch&lomb	Latanoporst timolol	47.41
Plostim	Alcon	Timolol	Information not supplied
Proflax 0.5	Sidus	Timolol	45.0337/84,9954
Timed	Bausch&lomb	Timolol	0.23
Timed d	Bausch&lomb	Dorzolamide timolol	46.3/20.36
Xalacom	Alcon	Latanoprost timolol	33.3/33.4
Xalatan	Alcon	Latanoprost	20.52/29.6
Zopirol	Elea	Timolol	35.23
Zopirol dm	Elea	Timolol dorzolamide	56.00/96.68

Table 3: Antiglaucoma collyriums which contain phosphates in its different chemical forms. In alphabetical order according to their trade names.

Physiological phosphates ≤1.45 mmol/L.

Trade name	Pharmaceutical	Generic name	Concentration mmol/l
Artelac	Bausch and lomb	Hydroxypropyl methylcellulose	Information not supplied
Dropstar	Poen	Sodium hyaluronate	0,0602
Hialudorf	Dorf	Sodium hyaluronate	5.4/56.38
Larmabak	Sidus	Sodium chloride 0.9%	Information not supplied
Latlas tears	Atlas	Hydroxypropyl methylcellulose	1.66
Liquifilm lagrimas	Allergan	Polyvinyl alcohol	4.29/9.86
Maxus	Bausch and lomb	Chondroitin sulfate	24.3/5.7

Table 4: Lubricant collyriums which contain phosphates in its different chemical forms. In alphabetic order according to their trade name.

Physiological phosphates ≤1.45 mmol/L.

It was difficult to obtain the phosphate concentration in products from some pharmaceutical companies (mainly multinational ones), even with data provided by ANMAT, due to the lack of concentration in some cases and dilution in others. This made it impossible to estimate the actual concentration.

Results

Collyriums with a phosphate containing formula used as buffer were grouped according to their therapeutic action: antibiotics, antiviral, steroids, anti-glaucoma and artificial tear. Results only show those collyriums which contain phosphate and are presented with their correspondent concentration (Table 2-4). Antiviral ointment do not contain phosphate in their composition.

For equal active ingredients and trade name, it was found that collyrium pharmaceutical forms do contain phosphates while the ointment ones do not.

National pharmaceutical companies provided complete data of their products, which allowed us to calculate the phosphate concentrations in their collyriums and to compare them with the lacrimal physiological concentration, 0.4 - 1.45 mmol/L.

Multinational pharmaceutical companies did not provide the data requested and the research done using the information available at ANMAT website did not allow us to know, in these cases, the actual phosphate concentration of the collyrium.

Discussion

Phosphates are physiologically present in the lacrimal film at a concentration of 0.4 - 1.45 mmol/L [5,6], in the corneal epithelium at a concentration of 3.5 mmol/kg (dry weight) and in the endothelium at a concentration of 4.03 mm/kg (dry weight). The pH at the interpalpebral area (the sector where calcium deposit begins) is higher than in the rest of the ocular surface.

Furthermore, phosphate are frequently used in collyriums. Commonly as part of the buffer system to control the pH and, occasionally, as part of the active ingredient mainly to Improve its solubility and penetration.

It is broadly known the phosphate ability to bind to the free calcium, to precipitate and to form calcium deposit at the tissue level.

Pharmaceutical collyriums composition often have Ph levels close to the values of the normal ocular surface; however, electrolyte values are not always close to the physiological levels. This imbalance could be implicated in the physiopathology of calcific band keratopathy.

This problem was initially reviewed by the German Federal Institute for Drugs and Medical Devices and then by the European Medicines Agency (EMA), in 2012 it issued a report which reviewed data supplied by the companies, the pharmaceuticals companies and from 117 case reports about corneal calcification related to phosphate containing collyrium in Europe.

In vitro and *in vivo* toxicology studies, in corneas from rabbits, showed that corneal ulcer treatment with eye drops which contain phosphate are associated with the development of corneal calcification, and this could be prevented if these were replaced by drops which contain citrate buffer [8].

EMA insists that this is not seen in eyes without previous pathology. This is true, as well as the fact that most of the corneal calcification reports by phosphate containing drops are in eyes with severe affection of the corneal surface, and these processes are the result of simultaneous factors and not just due to the medication received. For all of these reasons, EMA suggests that the benefits of using phosphate buffer in eyes drops outweigh the possible risks of developing calcification degeneration. They suggest continuing its use. On the other hand, EMA recommends an update of the information about the compounds and an actualization of the excipient guidelines of the European Union, with special attention to the problem of calcium deposits associated with ophthalmic products which contain phosphates. This information should be included in the product´s leaflet.

Finally, they recognize the possible calcium deposit generation in eyes with a severely damage corneal surface treated with phosphate containing eye drops. It is appropriate to remember that calcium degeneration is a multifactorial process, which is the result of several elements like calcium blood levels; corneal epithelium and Bowman´s layer damage, chronicity, intraocular inflammation, the state of the electrogenic sodium bicarbonate cotransporter at ocular level and topical medication, among others. Only some of these factors are modifiable or improvable and, if this is possible, it should be done in order to benefit our patients.

There is no doubt that if we could improve the topical medication to be used, this should be done and this is what authors like Norbert F. Schrage [7] showed when he suggested to change from drops with phosphate buffer to others with citrate buffer, these are

less harmful/damaging for the corneal epithelium. This change is happening slowly in the international ophthalmic field. Nonetheless, every ophthalmologist must have the freedom to be able to discern and to choose the collyrium that best suits the patient, according to the patient´s pathologic conditions.

In table 5 we summary those collyriums which do not contain phosphate in their composition, to facilitate the knowledge and information of the ophthalmologists.

Trade name	Pharmaceutical	Generic name
Alcon lagrimas	Alcon	Hydroxypropyl methylcellulose
Alcon lagrimas ii	alcon	Hydroxypropyl methylcellulose
Alrex	Bausch and lomb	Loteprednol
Arvo	Elea	Travoprost
Aucic	Poen	Sodium carboxymethylcellulose
Aucic 1,5%	Poen	Sodium carboxymethylcellulose
Azarga	Alcon	Brinzolamide timolol
Brimopress	Poen	Brimonidine
Cool tears	Raymos	Hydroxypropyl methylcellulose
Cosopt	Merck sharp and dohme	Dorzolamide timolol
Deltar	Elea	Prednisolone acetate Phenylephrine
Dorzoflax	Sidus	Dorzolamide timolol
Dropstar p	Poen	Sodium hyaluronate 0.2%
Duotrav	Alcon	Travoprost timolol
Efecoryl forte	Sidus	Prednisolone acetate Phenylephrine
Eritromicina elea	Elea	Erythromycin
Fotex	Elea	Tobramycin
Gatimicin	Elea	Gatifloxacin
Gatimicin d	Elea	Gatifloxacin dexametasone
Genteal	Novartis	Hydroxypropyl methylcellulose
Glaucotensil td	Poen	Dorzolamide timolol
Glaunot	Atlas	Travoprost
Glaunot t	Atlas	Travoprost timolol
Gotabiotic f	Poen	Tobramicine dexametasone
Hyalomb	Bausch and lomb	Hyaluronic acid
Lopred	Elea	Loteprednol
Lotemax	Bausch and lomb	Loteprednol
Lotesoft	Poen	Loteprednol

Lubrictin	Klonal	Chondroitin sulfate
Lusic	Poen	Polysorbate 80 1% - glycerin 1%
Muro	Bausch and lomb	Sodium chloride
Neoftalm	Raymos	Polymyxin b sulfate trimethoprim
Nevanac	Alcon	Nepafenac
Ocuprost	Bausch and lomb	Latanoprost
Oftaldrop	Denver farma	Prednisolone acetate Phenylephrine
Oftalook	Denver farma	Sodium chloride
Oftalook plus	Denver farma	Hydroxypropyl methylcellulose
Optilac	Raymos	Chondroitin sulfate aprotinin
Optive	Allergan	Sodium carboxymethylcellulose 0.5% glycerina 0,9%
Panoptic lagrimas	Bausch and lomb	Polyvinyl alcohol
Ph lagrimas col	Elea	Hydroxypropyl methylcellulose
Phylarm	Poen	Sodium chloride
Prednefrin forte	Allergan	Prednisolone acetate Phenylephrine
Press out t	Raymos	Dorzolamide timolol
Refresh liquigel	Allergan	Sodium carboxymethylcellulose
Refresh tears	Allergan	Sodium carboxymethylcellulose
Saflutan	Merck sharp and dohme	Tafluprost
Systane	Alcon	Propylene glycol
Systane ultra	Alcon	Polyethylene glycol propylene glycol
Systane balance	Alcon	Propylene glycol
Talof	Poen	Loteprednol
Tobradex	Alcon	Tobramicine dexametasone
Tobratlas dexa	Atlas	Tobramicine dexametasone
Travatan	Alcon	Travoprost
Vigamox	Alcon	Moxifloxacin
Viscotears	Novartis	Polyacrilyc acid
Zylet	Bausch and lomb	Tobramicine loteprednol
Zymaran	Allergan	Gatifloxacin

Table 5: Market collyriums which do not contain phosphates in their composition. In alphabetic order according to their trade name. Physiological phosphates ≤1.45 mmol/L.

It needs clarifying that corneal and/or ocular injury produce an increase in the lacrimal secretion and calcium; tissue degradation, inflammation and the epitheliopathy also produce this increase. These situations might lead to the use of eyes drops which most of them contain phosphates.

Conclusion

The administration of drops with high levels of phosphates is involved in the generation of calcium precipitation at the cornea level, in patients with alteration of the surface and ocular inflam-

mation. Hence, we believe it is a medical obligation to have knowledge about the composition of the medication we prescribe, including excipients, in order to make an even more accurate choice, since this is one of the few modifiable risk factors in this condition genesis.

Conflict of Interest

None of the authors have a financial interest, nor of property related to this material o any of the methods mentioned.

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