ARCHIVOS DE LA SOCIEDAD ESPAÑOLA DE OFTALMOLOGÍA

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Original article

Determination of phosphate concentration in glaucoma eye drops commercially available in Spain☆

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ARTICLE INFO

Article history:
Received 10 November 2014
Accepted 16 February 2016
Available online 21 May 2016

Keywords:
Glaucoma medication
Absorption spectrophotometry
Phosphate
Eye drop
pH

ABSTRACT

Objectives: To identify and analyze the phosphate concentration in glaucoma eye drops available in Spain.

Material and methods: Glaucoma medications containing phosphates were identified according to the 2013 Vademecum and the website of the Spanish Agency for Medicines and Medical Devices. Phosphate concentration was determined in these eye drops using ultraviolet molecular absorption spectrophotometry, and pH was determined using scan image analysis algorithms of pH strips.

Results: A total of 37 phosphate containing glaucoma eye drops were identified. The mean phosphate concentration was 97.72 ± 75.52 mM. The group with higher concentration of active substance was timolol (204.85 ± 42.38 mM) followed by brimonidine/timolol (200.9 mM). No statistically significant difference was found between brand name (95.65 ± 71.11 mM) and generic eye drops (99.14 ± 80 mM, $p = 0.892$). Although no statistically significant difference was found between products containing preservatives (99.24 ± 76.78 mM) and those without preservatives (85.17 ± 72.86 mM) ($p = 0.730$), a lower phosphate concentration was observed in the preservative-free Timolol and Latanoprost. Single dose samples showed a lower phosphate concentration than multi-dose ones (102.04 ± 75.39 vs. 22.24 ± 2.98 mM, $p < 0.001$). The mean pH was 7.13 ± 0.63. No statistical correlation was found between phosphate concentration and pH (*r*: 0.07).

Conclusion: The phosphate concentration in glaucoma eye drops exceeded the tear film physiological level (1.45 mM). No difference was observed between brand names and generic eye drops. Lower phosphate concentration was observed in preservative-free single dose eye drops.

☆ Please cite this article as: Martínez-Soroa I, de Frutos-Lezaun M, Ostra Beldarrain M, Egía Zurutuza A, Irastorza Larburu MB, Bachiller Cacho MP. Determinación de la concentración de fosfatos en los colirios antiglaucomatosos comercializados en España. Arch Soc Esp Oftalmol. 2016;91:363–371.

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Determinación de la concentración de fosfatos en los colirios antiglaucomatosos comercializados en España

Palabras clave:
Antiglaucomatoso
Espectrofotometría de absorción
Fosfatos
Colirio
pH

RESUMEN

Objetivo: Identificar y determinar la concentración de fosfatos en colirios antiglaucomatosos comercializados en España.

Material y método: Se identificaron colirios antiglaucomatosos según Vademecum 2013 y página web de la Agencia Española del Medicamento y Productos Sanitarios. En los que contenían fosfatos según la ficha técnica se determinó la concentración de estos mediante espectrofotometría de absorción molecular basada en radiación ultravioleta y el pH mediante algoritmos de análisis de imagen por escáner a partir de tiras de papel.

Resultados: Se registraron 37 colirios antiglaucomatosos con fosfatos. La media de la concentración de fosfatos fue 97,72 ± 75,52 mM. El principio activo con mayor concentración fue timolol (204,85 ± 42,38 mM) seguido de brimonidina/timolol (200,9 mM). No se registraron diferencias estadísticamente significativas entre los colirios de referencia de especialidad (95,65 ± 71,11 mM) y los genéricos (99,14 ± 80 mM; p = 0,892). Tampoco se observaron diferencias entre aquellos con conservantes (99,24 ± 76,78 mM) y sin ellos (85,17 ± 72,86 mM; p = 0,730), aunque los principios de timolol y latanoprost presentaron menos fosfatos en su composición sin conservantes. Las unidosis presentaron menos fosfatos que las multidosis (102,04 ± 75,39 vs. 22,24 ± 2,98 mM; p < 0,001). El pH medio fue 7,13 ± 0,63. No se encontró correlación estadística entre la concentración de fosfatos y el pH (r: 0,07).

Conclusiones: La concentración de fosfatos en todos los colirios superaba la concentración fisiológica en la película lagrimal (1,45 mM). No se observaron diferencias en la cantidad de fosfatos entre los medicamentos genéricos y los de referencia de especialidad. Los antiglaucomatosos sin conservantes en unidosis presentaron menos fosfatos.

Introduction

All drugs, including topical ophthalmological medicaments, comprise a pharmacologically active substance and excipients in their chemical composition. The side effects associated to said active principle has been studied systematically[1] and, in the case of eyedrops, said studies included toxic effects associated to the use of preservatives.[2,3] Excipients comprise a range of chemical substances that provide the active principle with adequate characteristics regarding tone, tamponade, color, texture, viscosity and other qualities to facilitate its pharmacological effect. In turn, buffer systems can comprise acetic, boric or hydrochloric acid, potassium, sodium bicarbonate, borate, phosphate and citrate,[1] among others. To achieve said effect, phosphates are chemically formulated in the form of dodecadhydrate phosphate hydrogen disodium or dihydrate phosphate dihydrogen sodium. These phosphates are routinely used in eyedrops as tamponade systems for adjusting the pH of the formula to the neutral pH of the lacrimal tear. In recent years, corneal calcification cases have been reported related to the use of eyedrops with a high phosphate content in their chemical composition.[4–7] In 2012, due to the increasing amount of said cases, the European Medicines Agency issued a number of recommendations in an information bulletin[8] which admitted the appearance of calcium deposits in patients with previous corneal disease associated to the use of eyedrops comprising phosphate derivates among its excipients. According to said report, this complication was considered infrequent with an estimated risk below 1 for every 10,000 patients treated with phosphate-containing eyedrops. To date, 117 cases of this complication have been reported. According to said study, the benefits derived from the application of said eyedrops offsets the low risk of said complications and recommends the inclusion of a warning in the adverse effects of the medicament label.

According to the literature, the development of calcium deposits after the application of eyedrops has been observed in patients who previously exhibited a corneal condition, either keratoconjunctivitis sicca, epithelial defects or had suffered caustications.[4–7] Intracellular calcium is released as a consequence of epithelial or stromal defects. This constant, together with the increased presence of phosphates in the ocular surface due to the use of phosphate-containing eyedrops, produces the precipitation of calcium salts in the form of hydroxyapatite crystals ($Ca_5[PO_4]_3OH$).[5–7] This precipitation is facilitated particularly in the presence of inflammation on the ocular surface, as the alkaline pH of the lacrimal tear increases the insollubility of the hydroxyapatite. The majority of precipitations are located in the central area of the cornea, facilitated by increased evaporation and tendency to tear drying in this area.

Spanish law establishes the obligation of including all the excipients of the chemical formulation of a drug in its label but does not require the exact concentration of each one.[9] In addition, generic drugs identified as a generic pharmaceutical specialty (GPS) are not required to utilize the same excipients as the reference drug, although the therapeutic