

English translation of A. Blumberg (BfArM) “Phosphatpuffer in Ophthalmika - Risiko für Hornhautkalkifizierungen” in Bulletin zur Arzneimittelsicherheit - Informationen aus BfArM und PEI 01_March 2013

Phosphate buffers in ophthalmology - Risk of corneal calcification

Phosphate buffers are used in many ophthalmological preparations for adjustment of the pH. The use of eye medication containing a phosphate buffer in patients with pronounced damage to the corneal surface can result in corneal calcification as a result of precipitation of calcium phosphate. On the basis of individual case reports, ophthalmological preparations containing phosphate were subjected to a benefit-risk assessment in Europe in 2011/2012.

BACKGROUND

In 2008, BfArM received two case reports of patients, who had developed calcified plaques in the cornea during frequent use of ophthalmological preparations containing phosphate buffer. On the basis of these cases, studies were conducted on phosphate buffer-containing eye drops licensed in Germany, and their related side effects, and proposals for risk minimisation were developed. This topic was subsequently discussed extensively on the European level so as to achieve a harmonised European approach. Manufacturers of relevant ophthalmological preparations in the EU were requested, by means of a questionnaire, to supply extensive information about their medicinal products. A work group of the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) evaluated the data and, in December 2012, published a Questions and Answers Paper with its results and conclusions.¹

PATHOGENESIS OF CORNEAL CALCIFICATION

Phosphate-containing ophthalmological preparations can, in cases of severe corneal epithelial damage, react with the calcium present within the corneal stroma, leading to the precipitation of calcium phosphate. The extent of corneal epithelial damage is a decisive factor for calcification. On the other hand, systemic disease does not appear to play any part.² Other factors, such as pH and tonicity have been discussed.³ The role of the phosphate concentration is unclear, since, in principal, precipitation is possible when both components (calcium and phosphate) are present. Tears, however, also contain phosphate. In the literature, the concentration is cited as being 1.45 mmol/l.^{3,4} There are no known reports describing calcification at this physiological concentration of phosphate. Thus, a higher risk at higher phosphate concentrations seems plausible.

PHOSPHATE BUFFER-CONTAINING OPHTHALMOLOGICAL PREPARATIONS IN GERMANY AND THE EU

Phosphate buffers are widely used in ophthalmological preparations, being used for pH adjustment in many eye drops and eye gels. These buffers are declared as excipients and must be listed by type, but with no indication of quantity, in the product information (SPC and PIL) for the medicinal product.

Germany

In Germany, 569 ophthalmological products may currently be marketed, including 478 eye drops, 50 eye ointments and 34 eye gels.⁵ Of these 569 preparations, 213 contain phosphate buffer, namely 205 eye drops and eight eye gels. The preparations comprise an extensive range of products. Many phosphate-buffered preparations are found in the group of anti-glaucoma agents, this applying particularly to timolol (and other beta blockers) preparations in this group, as well as to the prostaglandin analogues, latanoprost, bimatoprost and tafluprost (see Table 1).

Table 1: Number of medicinal products containing phosphate buffer by active substance

(Listing of the five active substances found in the greatest number of medicinal products containing phosphate buffer)

Active substance	Number of medicinal products containing phosphate buffer
Timolol	79
Latanoprost	53
Hypromellose	11
Sodium cromoglicate	11
Tetryzoline	11

The phosphate buffer content varies greatly according to medicinal product and active substance, being in the range 2.8 mmol/l (carbomer preparation) to 153 mmol/l (clonidine preparation). The following table presents an overview of phosphate buffer concentrations (minimum, maximum) by active substance in medicinal products licensed in Germany.

Table 2: Minimum and maximum concentrations of phosphate buffer (mmol/l) in ophthalmological preparations, summarised by active substance

Source: AMIS medicinal product information system, as of February 2013

Active substance	Phosphate buffer concentration (mmol/l)	
	Minimum	Maximum
Bimatoprost	10.00	10.00
Carbomer/Carbomer 940	2.79	2.79
Carteolol hydrochloride	5.35	5.35
Clonidine hydrochloride	129.94	153.49
Dapiprazole hydrochloride	46.07	48.58
Dexamethasone	14.09	14.09
Dexamethasone dihydrogenphosphate disodium	26.53	47.39
Dexpanthenol	17.39	17.39
Epinastine hydrochloride	50.00	50.00
Fluorescein sodium	29.29	29.29
Fluorometholone	12.16	20.06
Gentamicin sulphate	42.36	68.08
Hypromellose	19.37	19.37
Latanoprost	46.57	66.73
Levobunolol hydrochloride	19.98	20.01
Levocabastine hydrochloride	99.99	99.99
Sodium cromoglicate	20.37	43.56
Olopatadine hydrochloride	35.18	35.18
Povidone	67.87	67.87
Tafluprost	12.82	12.82
Tetryzoline hydrochloride	20.48	25.29
Timolol maleate	66.68	147.37
Tropicamide	134.47	134.47

EU

When the topic was considered at the EU level (evaluation of data by the CHMP work group), 655 eye drop preparations were evaluated, of which 236 (36%) contained phosphate buffer. The phosphate buffer content varied greatly, as already demonstrated for Germany. The data were based on company information and not on a central database, as was the case with the German data. It can thus be assumed that the data do not provide a complete overview of all the eye drops available in the EU.

PHOSPHATE-CONTAINING OPHTHALMOLOGICAL PREPARATIONS AND CORNEAL CALCIFICATION - CLINICAL AND PRECLINICAL DATA

Preclinical data

Two articles by Schräge et al. describe the development of corneal calcification following the use of phosphate-containing solutions in an animal model: In 2001, the authors published a study in rabbits, the eyes of which were subjected to alkali burn and then rinsed with either an isotonic phosphate solution (Isogutt®) or with saline. Corneal ulceration and calcification developed early in the group treated with phosphate solution, while the control group showed similar ulceration but no calcification.⁶ Another study demonstrated calcification of the wound region following mechanical removal of the epithelium from rabbit corneas and subsequent application of hyaluronic acid preparations with phosphate buffer. This did not occur when hyaluronic acid preparations with citrate buffer were used.⁷

Clinical data/Literature

A relationship between the use of phosphate-containing ophthalmological preparations and the occurrence of irreversible corneal calcification in patients with severe damage of the corneal surface has been described in several publications:

In 2008, Auw-Hädrich et al. reported a patient with chronic blepharitis and conjunctival hyperplasia of the cornea (pannus). On histological examination, calcium deposits were seen in the pannus and in the corneal epithelium. The authors suggested that the phosphate-containing eye drops combined with the blepharitis had favoured the development of this calcification.⁸

In 2006, Bernauer et al. described five patients with corneal calcification, who had severe damage of the corneal surface (e.g. severe keratoconjunctivitis sicca, complete erosion) and who were using artificial tears containing hyaluronic acid on a very frequent basis. The calcification appeared within a period of five days to two weeks. All patients required corneal transplants in order to restore vision.⁹

In a further paper, published in 2007, the authors reported their measurements of the phosphate content of various anti-glaucoma agents and cited the formation of poorly soluble crystals to be the cause of the calcification. Usually, these types of corneal calcium deposits consist of calcium phosphate hydroxyapatite $\text{Ca}_5(\text{PO}_4)_3\text{OH}$.⁴

In 1991, Huige et al. reported eight cases of stromal precipitation of calcium phosphate. These occurred in patients with epithelial damage, who had received local therapy with a phosphate-containing steroid preparation (e.g. dexamethasone phosphate or prednisolone phosphate) and beta-blocker preparations (timolol). In most cases, the calcification developed within a few (two to eight) weeks.¹⁰

Other authors have also observed corneal calcification during treatment with phosphate-containing steroid preparations in patients with corneal damage: In 1995, Rao et al. described a female patient with severe corneal problems (severe keratoconjunctivitis sicca, incipient corneal melt), who over time developed band-shaped corneal calcification on two occasions while under treatment with phosphate-containing steroid preparations (prednisolone phosphate, betamethasone phosphate) as

well as other ophthalmological preparations. The calcified area appeared within 72 hours following initiation of therapy.¹¹

In 1994, Taravella et al. published five cases, in which calcium deposits developed very rapidly within the cornea following the use of steroid phosphate preparations.² They put forward the hypothesis that other concomitantly applied ophthalmological preparations, which contained buffer, also influenced calcification.

Lake et al. (2008) observed six patients with persistent epithelial defects of diverse aetiologies over a period of 18 months. All patients received local therapy with preservative-free, phosphate-containing ophthalmological preparations and developed deep corneal calcification within a period ranging from seven days to five months.¹²

Kompa et al. (2006) performed a retrospective analysis to investigate the relationship between the occurrence of corneal calcification following chemical burns and the use of locally applied preparations containing phosphate buffer.¹³ The authors analysed data from 179 patients, who had been treated in Aachen between 1941 and 2000. Patients were only included if the substance causing the burn did not contain calcium and the initially used rinse did not contain phosphate (152 eyes affected). Of 63 eyes, which had been treated with ophthalmological preparations containing phosphate buffer, 49.2% (31 eyes) developed corneal calcification, compared to only 25.8% (23 eyes) of the 89 eyes treated with phosphate buffer-free eye drops. The authors came to the conclusion that the use of ophthalmological preparations containing phosphate subsequent to a chemical burn doubles the risk of corneal calcification.

Schräge et al. also conducted a retrospective analysis in 2005 of chemical burn cases (176 eyes in 98 patients). Their results showed that a single rinsing with phosphate-containing solutions after a chemical burn does not cause calcification, however the latter is associated with long-term use of eye drops containing phosphate buffer subsequent to chemical burns.¹⁴

Clinical data/Adverse effect reports

Germany

The BfArM national database of adverse drug reactions contains a total of 38 reports concerning ophthalmological preparations containing phosphate buffer, which are classified under “Corneal disorders” (as of February 2013). These reports relate to various corneal reactions and diseases, for example corneal lesions, corneal oedema, keratitis, corneal deposits, xerophthalmia and neuropathies. Corneal calcification/corneal deposits were reported in eight of the 38 cases. An assessment was not possible in three of these eight cases due to insufficient data.

In the remaining five cases (four spontaneous notifications, one report from the literature), assessment of the individual case reports showed a possible relationship between corneal calcification/corneal deposits and the use of ophthalmological preparations containing phosphate buffer.

In summary, the following information is provided by these five cases:

- in all cases, predisposing corneal disorders or damage were present: Status following photorefractive keratectomy, corneal ulcer, corneal erosion, keratoplasty in the context of corneal thinning, conjunctival hyperplasia of the cornea and blepharitis
- Patients aged between 36 and 73 years, no paediatric patients
- Duration of treatment varied from two weeks to several months
- The frequency at which the ophthalmological preparations were applied varied between every four hours and twice weekly.

In the case of one patient, who developed pronounced calcified plaques of the cornea, photographs were sent to BfArM (see Figure).

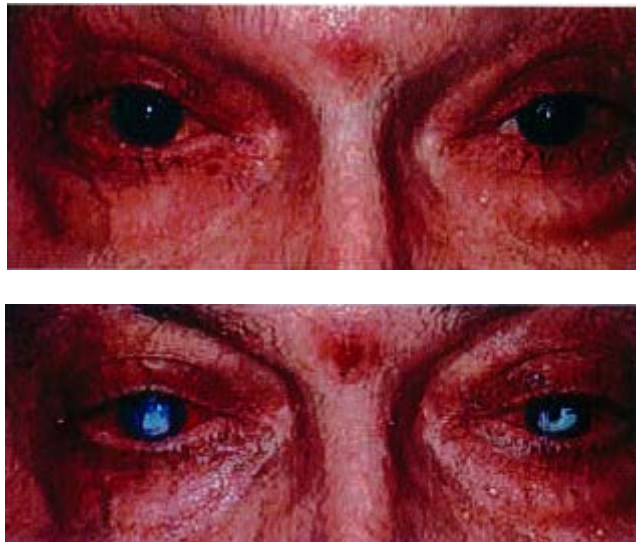


Figure: Corneal findings before and after approximately 14 days of frequent use of Artelac® eye drops (containing phosphate buffer) with development of corneal calcified plaques bilaterally

EU

As already mentioned, manufacturers of relevant ophthalmological preparations in Europe were requested to compile information on their products. During this process, they were also asked to provide adverse drug reaction notifications of corneal calcification relating to preparations containing phosphate buffer. Data from a total of 117 reports were evaluated. These also included reports from the literature, with some notifications being duplicates.¹ In the overwhelming majority of cases notified by the companies, severe damage of the corneal surface was present.

CONCLUSION AND PROSPECTS

Phosphate buffer is a frequently used buffer system in ophthalmological preparations. Preparations containing phosphate buffer are used by millions without any adverse reactions occurring. In patients with significant damage to the corneal surface (e.g. pronounced erosion, corneal ulcer), in very rare cases, calcium phosphate crystals may, however develop, which take the form of calcium deposits in the cornea. This corneal calcification is a serious event for patients, because it may make keratoplasty necessary in order to restore vision. It is not currently known whether there is a critical phosphate threshold at which precipitation occurs. It is expected that such crystal formation could occur when the physiological phosphate concentration of tears (1.45 mmol/l) is exceeded. There is a probable relationship between the level of the phosphate concentration as well as application frequency and the occurrence of calcification; unequivocal data are not, however, available. The concentration of the phosphate buffer is not stated in the product information for the medicinal product. According to legislative requirements for medicinal products, excipients, among which phosphate buffer is also included, must be listed by type but not by quantity in the product information.

When phosphate is present in a topical ophthalmological preparation, the risk of corneal calcification, as presented here, must in principle exist. This concerns not only preparations containing phosphate buffer, but also products, which contain phosphate as a component of the active substance (e.g. prednisolone phosphate, betamethasone phosphate)^{2,11} as well as artificial tears, which are marketed not as medicinal products, but as medical devices. The pathogenesis of the calcification has not been clarified in detail, but is assumed to be a multifactorial process. Apart from severe corneal damage and the presence of phosphate, no other unequivocal risk factors have so far been identified. The studies of Kompa et al. show that corneal calcification following chemical burns occurs even without the use of phosphate-containing ophthalmological preparations, although the probability is clearly much lower.¹³ On the basis of the available data, it appears unlikely that phosphate-containing ophthalmological preparations can also trigger calcification in patients with intact corneas.

An assessment of ophthalmological preparations containing phosphate buffer at the European level has demonstrated a clearly positive benefit-risk ratio for these medicinal products. Phosphate buffer can be assumed to be a safe buffer system in ophthalmology and the banning of these buffer systems is not required. The very rare risk of corneal calcification in patients with such a predisposition should, however, be taken into account by means of appropriate information in the product information.¹ It is therefore recommended that the so-called Excipients Guideline, which includes information on excipients applying to the whole of the EU, should be extended accordingly. The revision of this Guideline is expected to take some time. This information has been included into the national list of excipients (the so-called features list).

The EU-wide harmonised information should inform about the possible risk without giving any further recommendations. In the author's opinion, however, phosphate-free preparations should be used in patients with extensive corneal damage, whenever such alternatives are available.

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