PHARMACOVIGILANCE BULLETIN Information from BfArM and PEI

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BUNDESINSTITUT FÜR ARZNEIMITTEL UND MEDIZINPRODUKTE (BFARM, Federal Institute for Drugs and Medical Devices)

BfArM monitors the quality, effectiveness and harmlessness of drugs applied to humans. It controls clinical

testing, marketing authorization and registration of drugs as well as their safety following approval. Drugs and base material movements as well as the approval of clinical testing of pharmaceutical products and the gathering and assessment of application risks are among its areas of responsibility.

Paul-Ehrlich-Institute (PEI)

The Federal institute for vaccines and biomedical drugs monitors the quality, effectiveness and harmlessness of human and veterinary vaccines as well as of allergens and other biomedical drugs for humans. It is in charge of clinical tests, marketing authorizations, public batch control/monitoring and the assessment of biomedical drug safety.

OBJECTIVE

The quarterly pharmacovigilance bulletin provides information to federal agencies regarding current drug risk assessment aspects. The objective consists in improving the communication of potential drug risks while putting a spotlight on the significance on the monitoring prior and after marketing authorization (pharmacovigilance).

REPORTING OF SUSPICIOUS CASES

The reporting system for suspicious cases of side effects is one of

the most important early warning systems in the field of drug safety following approval. Reporting side effects in daily clinical practice is therefore

a crucial contribution for the safety of drugs. Both agencies explicitly encourage healthcare professionals to report any suspected drug side effects and/or vaccination complications following

approval. Additional information at www.bfarm.de and www.pei.de.

Phosphate buffer in ophthalmologic use -- Risk of corneal calcifications //

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Phosphate buffers are used in many ophthalmological preparations in order to adjust pH level. The use of phosphate buffer-containing eye medication in patients with severe corneal surface injuries can result in corneal calcifications due to calcium phosphate precipitation. Based on individual case reports, phosphate containing eye drops were subjected to a risk-benefit analysis in the European context during 2011/2012

BACKGROUND

In 2008, BfArM received two individual case reports in which patients developed corneal calcareous concretion following frequent use of phosphate buffer-containing eye drops.
Based on those cases, researches were conducted on phosphate buffer-containing eye drops approved in Germany, including their associated side effects and risk minimisation suggestions were simultaneously developed. The topic was then comprehensively discussed at the European level in order to achieve coordinated action in Europe. Manufacturers of relevant ophtalmological preparations in the EU were asked to take a survey in which they provided comprehensive drug information. A task force reuniting the Committee for Human Medical Products (CHMP) and the European Medicines Agency (EMA) assessed the data and published, in December 2012, a Q&A paper regarding its results and conclusions.

PATHOGENESIS OF CORNEAL CALCIFICATIONS

In case of advanced damage of the corneal epithelium, phosphate containing eye preparations may react with the calcium contained in the corneal stroma, causing the precipitation of calcium phosphate. The severity of the corneal epithelium damage seems decisive for calcification. System diseases, on the other hand, do not seem to play a role here.2 Other impacting factors, such as e.g. the pH level and the tonicity are being discussed.3 The role of phosphate concentration is unclear, since in case of both components (calcium and phosphate) being present, precipitation seems possible in principle. However, tear fluid also contains phosphate. Literature indicates the concentration at 1.45 mmol/ l.3,4 There are no known cases describing calcification at this physiological phosphate concentration level. A greater risk for higher phosphate concentrations therefore appears plausible.

PHOSPHATE BUFFER-CONTAINING EYE DROPS IN GERMANY AND THE EU

Phosphate buffers are widely used in ophtalmological preparations and are used in numerous eye - drops and eye gels for regulating pH levels. These buffers are indicated as excipients and must be listed in the drug product information (technical information and package leaflet) as ingredient, however not in their quantities.

Germany

In Germany, there are currently 569 approved eye drops collyrium, of which 478 eye drops, 50 eye ointments and 34 eye gels.5 213 of the 569 preparations contain phosphate buffers, of which 205 eye drops and 8 eye gels. The range of the preparations is wide. Especially in the group of anti-glaucomatous preparations, many are buffered with phosphate. Among those, especially Timolol preparations (and other beta blockers), as well as Prostaglandines analogs such as Latanoprost, Bimatoprost and Tafluprost (see Table 1).

Table 1:

Number of phosphate buffer-containing drugs according to active ingredients (indication of the five active ingredients with the most phosphate buffer-containing drugs)

Active ingredients	Number of phosphate buffer-containing drugs
Timolol	79
Latanoprost	53
Hypromellose	11
Sodium cromoglycate	11
Tetryzolin	11

The phosphate buffer content differs significantly depending on the drug and active ingredient. It is between 2.8 mmol/ l (carbomer preparation) and 153 mmol/ l (clonidine preparation). The table below summarises phosphate buffer concentration levels (minimum, maximum) in drugs approved in Germany (by active ingredients).

Table 2:

Minimum and maximum concentrations of phosphate buffer (mmol/l) of ophthalmological preparations summarised according to active ingredients

Source: Drugs information system AMIS, as of 2 /2013

Active ingredients	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
Dapiprazol hydrochloride	46.07	48.58
Dexamethasone	14.09	14.09
Dexamethasone-dihydrogen phosphate disodium	26.53	47.39
Dexpanthenol	17.39	17.39
Epinastine hydrochloride	50.00	50.00
Fluoresceine 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
Levocabastin 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
Timololmaleate	66.68	147.37
Tropicamide	134.47	134.47

EU

In the context of the topic being processed on EU-level (evaluation of data by CHMP task force), 655 eye drops were evaluated, 236 (36%) of which contained a phosphate buffer. The phosphate

buffer content varied greatly like for Germany. The data are based on company information and not on a centraldatabase, as is the case for Germany. It can be assumed that the data do not provide a complete summary of all eye drops available in the EU.

PHOSPHATE CONTAINING EYE DROPS AND CORNEAL CALCIFICATIONS -- CLINICAL AND PRE-CLINICAL DATA

Pre-clinical data

Two articles by Schrage et al. describe the formation of corneal calcifications following the application of phosphate containing solutions in an animal model: In 2001, the authors published a study on rabbits whose eyes were rinsed with an isotonic phosphate solution (Isogutt®) or a salt solution after an alkali burn. In the group treated with phosphate solution, corneal ulcerations and calcifications occurred early whereas the comparison group experienced similar ulcerations but without calcification.6 Another study showed that after mechanical removal of the epithelium and subsequent application of hyaluronic acid preparations with phosphate buffer, calcifications of the wound area occur. These did not occur when hyaluronic acid preparations with citrate buffers were used.7

Clinical data/ Litterature

A correlation between the use of phosphate-containing eye preparations and irreversible corneal calcifications in patients with pronounced corneal surface damage has been described in several publications:

Auw-Hädrich et al. studied a patient with chronic blepharitis and conjunctival overgrowth of the cornea (pannus) in 2008. Histologically, the pannus and the corneal epithelium showed calcium deposits. The authors suspected that these calcifications were favoured by phosphate-containing eye drops in combination with blepharitis.8

Bernauer et al. described in 2006 five patients with corneal calcifications who showed marked damage to the corneal surface (e.g. severe dry keratoconjunctivitis, complete erosion) and used very frequently tear substitutes containing hyaluronic acid. The calcifications occurred within a period of five days to two weeks after. All patients required corneal transplantation for visual rehabilitation.9

In a further study from 2007, the authors clarified the phosphate content of various antiglaucomatous agents and explained that the cause of calcification was due to the formation of hardly soluble crystals. Usually such calcium deposits in the cornea consisted of calcium phosphate hydroxylapatite Ca5(PO4)3OH.4

Huige et al. decribed in 1991 eight cases with stroma related calcium phosphate precipitates. These occurred in patients with epithelial defects who received a combined local therapy with a phosphate steroid (e.g. dexamethasone phosphate or prednisolone phosphate) and a beta-blocker preparation (Timolol). In most cases, calcifications developed within a few weeks (two to eight weeks).10

Other authors also observed corneal calcifications under therapy with phosphate-containing steroid preparations in patients with epithelial corneal damage: Rao et al. described in 1995 a patient with severe corneal pathology (severe dry keratoconjunctivitis, incipient corneal fusion) who developed two band-shaped corneal calcifications, over time, under treatment with phosphate steroid preparations (prednisolone phosphate, betamethasone phosphate) and other eye drops. The calcified areas occurred less than 72 hours after the therapy start.

Taravella et al. published five cases in 1994 in which calcium deposits developed very rapidly in the cornea after steroid phosphate preparations.2 They hypothesized that other buffer-containing eye drops used in parallel contributed to the calcification.

Lake et al. (2008) observed six patients with persistent epithelial defects, of different origins, over a period of 18 months. All patients received local therapy with preservative-free, phosphate containing eye drops and developed strong corneal calcifications within a period of seven days to five months.12

In a retrospective analysis, Kompa et al. studied in 2006 the relationship between the occurrence of corneal calcification after chemical burns and the use of phosphate buffer-containing local therapeutics.13 The authors analysed the data of 179 patients treated in Aachen between 1941 and 2000. Patients were only included if neither the substance leading to the burn nor the initially used rinsing solution contained phosphate (concerned 152 eyes). Of 63 eyes treated with phosphate buffer-containing eye drops, 49.2 percent (31 eyes) developed corneal calcifications, compared to 25.8 percent (23 eyes) of 89 eyes treated with phosphate buffer-free eye drops. The authors concluded that the use of phosphate-containing eye drops after burns doubles the risk of corneal calcification.

Schrage et al. had also carried out a retrospective analysis of chemical burns cases in 2005 (176 eyes of 98 patients). They came to the conclusion that a single rinse with phosphate containing solutions following chemical burns does not cause calcification, but that these are associated with the long-term use of phosphate-buffered eye drops after burns.14

Clinical data/Side effect reports

Germany

In the national database for adverse drug reactions of the BfArM, a total of 38 reports for ophthalmic drugs containing phosphate buffer are recorded under the term "Corneal disorders" (as of 2/2013). These reports concern various corneal reactions / diseases, for example corneal lesion, corneal oedema, keratitis, corneal deposits, xerophthalmia and keratopathy. In 8 of the 38 cases, corneal calcifications / corneal deposits are reported. In three of the eight cases, an assessment was not possible due to insufficient data.

The detailed evaluation of the 5 remaining cases (four spontaneous reports, one report from the literature), showed a possible correlation between corneal calcification / corneal deposit and the use of phosphate buffer-containing eye drops.

These five cases delivered the following information:

- in all cases predisposing corneal disorders / damage existed: Condition after photorefractive keratectomy, corneal ulcer, corneal erosion, keratoplasty in corneal thinning, conjunctival overgrowth of the cornea and blepharitis
- patient aged between 36 and 73, no paediatric patients
- therapy duration varied between two weeks up to several months
- the application frequency of eye drops varied from 15 minutes and twice daily.

Photos were sent to the BfArM for a patient who developed pronounced calcium concretion of the cornea (see figure).

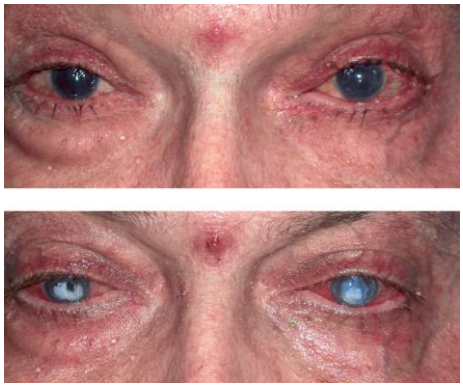

Figure:
State of the cornea before and after approx. 15-day of very frequent application of Artelac® eye drops (containing phosphate buffer) with formation of corneal calcium concretion on both sides
Source: Dr. med. Martin Dörner

EU

As mentioned above, manufacturers of concerned ophthalmic preparations in Europe were asked to compile information on their eye drops products. Among other, reports of adverse effects declared as corneal calcification for phosphate containing preparation were requested. The data analysis resulted in a total of 117 reports. These also include literature reports; some reports are duplicates.1 In the vast majority of cases reported by the companies, there was serious damage to the corneal surface.

Figure:
Corneal findings before and after approx. 14-day high-frequency application of Artelac® eye drops (containing phosphate buffer) with formation of corneal calcium plates on both sides
Source: Dr. med. Martin Dörner

CONCLUSIONS AND PROSPECT FOR THE FUTURE

Phosphate buffers are a buffer system frequently used in eye drops. Phosphate buffer-containing preparations are used millions of times without adverse reactions occurring. In patients with significant damage to the corneal surface (e.g. pronounced erosion, corneal ulcer), calcium phosphate crystals may however form in very rare cases and impress as calcium deposits in the cornea. These corneal calcifications are not without consequences for the patient, as a result of which keratoplasty may be required for visual rehabilitation. A critical phosphate threshold, at which precipitation occurs, is currently not known. It can be assumed that above the physiological phosphate concentration of the tear fluid (1.45 mmol/l) such crystal formations can occur. A correlation between the level of phosphate concentration and the frequency of application on one side and the occurrence of calcification on the other side is likely, but no clear data are available. The concentration of phosphate buffers is not indicated in the product information of the medicinal products. Pharmaceutical legislation requires that excipients - hence phosphate buffers - are listed in the product information, but their quantity.

In case of presence of phosphate in local ophthalmologic therapeutics the risk of corneal calcification should in principle persist. In addition to preparations containing phosphate buffer, this also applies to eye drops containing phosphate as a component of the excipient (e.g. prednisolone phosphate, betamethasone phosphate) as well as tear substitutes which are not sold as drugs but as medical devices.

The pathogenesis of the calcifications is not exactly clarified yet, a multifactorial condition is assumed. Apart from significant damage to the cornea and the presence of phosphate, no clear risk factors have yet been identified. Studies by Kompa et al. show that corneal calcifications after

chemical burns also occur without the use of phosphate-containing eye drops, but with a significantly lower probability.13 Based on the available data, it seems unlikely to us that phosphatic eye drops can also trigger calcifications in patients with intact corneas.

An evaluation of phosphate buffer-containing eye drops at European level has shown a clearly positive risk-benefit balance for these drugs. Phosphate buffers are assessed as safe buffer system in ophthalmology; it is not necessary to abandon these buffer systems. However, the very rare risk of corneal calcification in correspondingly predisposed patients should be taken into account by appropriate information in the product information.1 It was therefore recommended to supplement the so-called Excipients Guideline, which contains EU-wide information on excipients, accordingly. The revision of this guideline is expected to take some time. The substances have been included in the national list of excipients (so-called special list).

The EU-wide harmonised label is intended to inform about the possible risk without giving further recommendations for action. According to the author, however, phosphate-free preparations should be used for patients with massive corneal damage, provided such alternatives are available.

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