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Prostaglandin analogues signal detection by data mining in the FDA Adverse Event Reporting System database

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ABSTRACT

Objective This study aims to identify safety signals of ophthalmic prostaglandin analogues through data mining the Food and Drug Administration Adverse Event Reporting System (FAERS) database.

Methods A data mining search by proportional reporting ratio, reporting OR, Bayesian confidence propagation neural network, information component 0.25 and χ^2 for safety signals detection was conducted to the FAERS database for the following ophthalmic medications: latanoprost, travoprost, tafluprost and bimatoprost.

Results 12 preferred terms were statistically associated: diabetes mellitus, n=2; hypoacusis, n=2; malignant mediastinal neoplasm, n=1; blood immunoglobulin E increased, n=1; cataract, n=1; blepharospasm, n=1; full blood count abnormal, n=1; skin exfoliation, n=1; chest discomfort, n=1; and dry mouth, n=1.

Limitation of the study The FAERS database's limitations, such as the undetermined causality of cases, under-reporting and the lack of restriction to only health professionals reporting this type of event, could modify the statistical outcomes. These limitations are particularly relevant in the context of ophthalmic drug analysis, as they can affect the accuracy and reliability of the data, potentially leading to biased or incomplete results.

Conclusions Our findings have revealed a potential relationship due to the biological plausibility among malignant mediastinal neoplasm, full blood count abnormal, blood immunoglobulin E increased, diabetes mellitus, blepharospasm, cataracts, chest discomfort and dry mouth; therefore, it is relevant to continue investigating the possible drug-event association, whether to refute the safety signal or identify a new risk.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Prostaglandin analogues can mimic the effects caused by endogenous prostaglandins, which modify multiple organs and tissues in the body and, therefore, could trigger unexpected side effects.

WHAT THIS STUDY ADDS

⇒ *Data mining* is a tool that allows the adequate analysis of prostaglandin analogues' drug side effects in a database to identify statistical associations that lead to the identification of new risks.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The identification of new risks could impact in the benefit–risk balance of these drugs and trigger activities focused on minimising them.

INTRODUCTION

The currently available pharmacological treatments for glaucoma include: alpha-adrenergic agonists, beta-adrenergic antagonists, prostaglandin analogues (PGAs), cholinergic and carbonic anhydrase inhibitors, with PGAs being the drug of choice due to their safety profile.[1]

Prostaglandins (PGs) are molecules derived from arachidonic acid, metabolised by cyclooxygenases; these include the following five types: prostaglandin E (PGE), prostaglandin F (PGF), prostaglandin I, prostaglandin D and thromboxane A.[2] Additionally, PGs induce the activation of broad different cell types, triggering diverse actions, that is, inflammation, modifications in the sleep cycle, membrane transport, synaptic modulation of the nervous system, cell cycle and blood flow regulation, among others.[3]

At present, all commercially available PGAs are prostaglandin F2α ($PGF_{2\alpha}$) prodrugs such as: latanoprost, travoprost and tafluprost. Alternately, bimatoprost is a synthetic analogue of an endogenous prostamide, binding to prostaglandin F receptors.[1 4] However, due to the relatively non-selective nature of $PGF_{2\alpha}$, the molecule can activate prostaglandin E receptors (EP), which could be responsible for unexpected adverse events (AEs).[4]

Commonly expected AEs for PGAs include: conjunctival hyperaemia, conjunctival allergy, blepharitis and corneal epithelial disorders, among others.[5–9] However, unexpected AEs (not mentioned in the safety information label) may occur and should be analysed as a safety signal. Once the drug-event association has been determined, they should be listed as a new risk.[10 11] Due to this, the determination

of safety signals from unexpected AEs must be analysed to identify new risks that could impact the risk-benefit balance of drugs.[11–14] Nowadays, there are tools that allow the detection of safety signals, for example, data mining, which pinpoint statistical associations between drugs with unexpected AEs in safety report databases.[15] Moreover, due to PGs exerting effects on different cell types around the body that PGs could activate due to their analogy, it is essential to identify the possible association that could cause the use of PGAs in ophthalmologic practice. This study aims to identify safety signals of ophthalmic PGAs by data mining the Food and Drug Administration's Adverse Event Reporting System (FAERS) database.

METHODS

Data standardisation

All the AEs within the FAERS database are grouped in System Organ Classes (SOCs) and Preferred Terms (PTs) levels of the Medical Dictionary for Regulatory Activities, which have five hierarchical levels: Lowest Level Terms, PTs, High Level Terms, High Level Group Terms and SOCs.[16]

Study design

A meticulous search was conducted in the FAERS database, focusing on the following ophthalmic drugs: latanoprost, travoprost, tafluprost and bimatoprost, with a cut-off date of Q4 2022. The FAERS data were then meticulously processed to eliminate duplicate data submitted by multiple individuals and institutions. This involved a careful selection process: If two or more reported CASEIDs (the number to identify a FAERS case) were the same, the last one FDA_DT (the date the FDA received the case) was selected. If CASEID and FDA_DT were equal, the highest PRIMARYID was selected (a unique number to identify a FAERS report). Finally, the following data were not analysed (selection criteria): less than 10 AEs in the database, AEs derived from quality problems, medication errors, lack of efficacy and expected AEs based on summary of product characteristics (SmPC) of Food and Drug Administration's New Drug Application (XALATAN latanoprost/ Pfizer Laboratories[5]; TRAVATAN Z travoprost solution/Novartis Pharmaceuticals[7]; ZIOPTAN tafluprost solution/Akorn[9]; LATISSE bimatoprost solution/Allegan)[8] (figure 1). Since FAERS is a voluntary reporting system with inconsistencies, only signals in all methods were used, reducing the type I error (decreasing the risk of false positives).

Methods for data mining

Reporting odds ratio

To calculate the OR for a specific adverse event associated with a particular drug, one must divide the ratio of the probability of these adverse events with the drug of interest by the ratio of the probability of the same adverse event occurring relative to all other adverse events. Formulation: (probability/1−probability).[17]

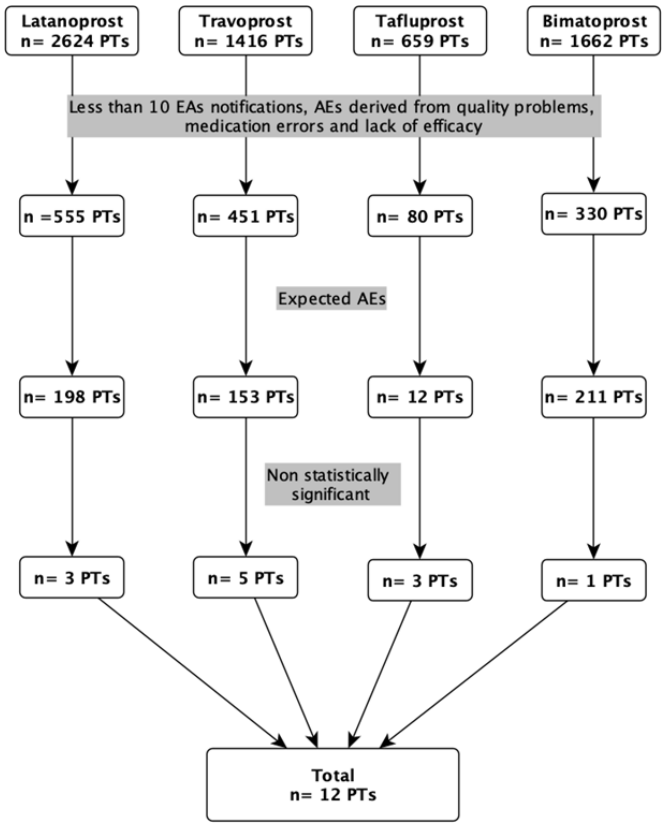

Figure 1 Study design. Adverse Events (AEs). Preferred Terms (PTs).

Proportional reporting ratio

The proportion of adverse events reported for a specific drug, relative to the proportion of adverse events reported for all other drugs within the database, represents the observed-to-expected ratio for that adverse event. The ratio provides a measure of the frequency of the adverse event associated with the drug in comparison to its expected frequency based on the broader database.[17]

Bayesian Confidence Propagation Neural Network

The quantitative method employed involves using log-based 2 to calculate the ratio of observed to expected adverse events. This approach incorporates a shrinkage adjustment to reduce the impact of sparse data by constraining the information component (IC) towards a null value of 0, thereby mitigating the risk of false positives.[18 19] This method is used at the Uppsala Monitoring Centre for signal detection purposes.[20]

Chi-square

The test evaluated the association between variables by comparing the observed frequency in each cell to the expected frequency, employing the χ^2 test with 1 df.[21]

In this manuscript, we have used all the aforementioned methods, as each demonstrates improvements in specific analyses. Consequently, it is challenging to designate a single algorithm as the superior approach for all types of associations.[17]

Disproportionality analysis for data mining

The following methods were performed: proportional reporting ratio (PRR)±CIs (95%), (Equation 1); reporting OR (ROR)±CI (95%), (Equation 2); Bayesian Confidence Propagation Neural Network (BCPNN)+information component 0.25 (IC025) (95%), (Equation 3); and χ^2 (statistical significance at a p value≤0.05) (Equation 4).

The criteria used to define a signal of disproportionate reporting were in accordance with 'Practical Aspects of Signal Detection in Pharmacovigilance', Council for International Organizations of Medical Sciences, 2010 (PRR and ROR: CI>2; IC025>0; χ^2>4).[17]

Equation 1: proportional reporting ratio

$$PRR = \left(\frac{A}{A+B}\right) / \left(\frac{C}{C+D}\right)$$

$$CI\ (\pm) = \left(e^{\left(\ln(PRR) \pm 1.96\right)}\right) \sqrt{\left(\frac{b}{a(a+b)}\right) + \left(\frac{d}{c(c+d)}\right)}$$

Equation 2: reporting OR

$$ROR = \frac{AD}{CB}$$

$$CI\ (\pm) = \left(e^{\left(\ln(ROR) \pm 1.96\right)}\right) \sqrt{\frac{1}{A} + \frac{1}{B} + \frac{1}{C} + \frac{1}{D}}$$

Equation 3: Bayesian Confidence Propagation Neural Network

$$BCPNN = \log^2\left((A)\left(\frac{(A+B+C+D)}{(A+B)(A+C)}\right)\right)$$

$$IC025 = \left(e^{\left(\ln(BCPNN) - 1.96\right)}\right) \sqrt{\frac{1}{A} + \frac{1}{B} + \frac{1}{C} + \frac{1}{D}}$$

Equation 4: χ^2 test

$$X^2 = \sum_{i=1}^{n}\left(\frac{(Oi - Ei)^2}{Ei}\right)$$

Notations for equations:

A=Interaction between reports for PGs and reports for AEs of interest.

B=Interaction between reports for PG and reports for all other AEs.

C=Interaction between reports for all other drugs and reports for AEs of interest.

D=Interaction between reports for all other drugs and reports for all other AEs.

RESULTS

A total of 26004135 AEs were displayed in the FAERS database. PGAs AEs were classified in 6361 different PTs, of which only 12 fulfilled the selection criteria (figure 1), (diabetes mellitus, n=2; hypoacusis, n=2; malignant mediastinal neoplasm, n=1; blood immunoglobulin E increased, n=1; cataract, n=1; blepharospasm, n=1; full blood count abnormal, n=1; skin exfoliation, n=1; chest discomfort, n=1; and dry mouth, n=1). These were distributed in 8 SOCs (eye disorders, n=2; ear and labyrinth disorders, n=2; investigations, n=2; metabolism and nutrition disorders, n=2; gastrointestinal disorders, n=1; skin and subcutaneous tissue disorders, n=1; general disorders and administration site conditions, n=1; neoplasms benign, malignant and unspecified, n=1). A total of 10 presented a p value<0.00001 (PRR: 3046.8–2.0, ROR: 3064.4–2.0, IC 10.3–1), one with 0.010844 and another with 0.017948 (online supplemental table 1).

Most subjects were women (ranged from 46% for skin exfoliation up to 100% for full blood count abnormal) between 65 and 85 years of age and the ophthalmic drug travoprost showed the highest incidence of serious AEs (all serious) (online supplemental table 2).

DISCUSSION

Statistical associations in data mining are the initial part of identifying a new risk since information from the literature, preclinical, clinical trials and post-marketing studies is required to issue the closure of safety signals.[11 22] Even if such an association is found, it must be determined whether the route and the dose are sufficient to be considered risks for a particular indication.[13] However, the first step in safety signal analysis is finding biological plausibility between the drug and the event, to explain potential mechanisms.

Our results show that the PT with the most statistical association of PRR, ROR and IC025 AE is a malignant mediastinal neoplasm belonging to the SOC neoplasms benign, malignant and unspecified (including cysts and polyps), of which various sources identify PGs as part of a significant role in the development of various types of cancer via increased tumour proliferation, survival and metastatic capacity, by PGA_2, PGE_1, PGE_2 and $PGF_{2\alpha}$ receptors.[23–27]

PGE_2, the most prevalent PG found in various human malignancies, promotes tumour growth and progression.[28–30] Its interaction with oncogenic signalling pathways, such as epidermal growth factor and its receptor, phosphoinositide 3-kinase, protein kinase Akt, b-catenin, mitogen-activated protein kinase and adenylyl cyclase activation, is a significant area of study.[28 29] These pathways are known to be related to the development and progression of cancer.[29 30] Furthermore, the changes in the tumour microenvironment mediated by immune cells responding to PGE_2 influence are also crucial in understanding cancer progression.[31]

Of particular concern is the abnormal or high expression of EP receptors, especially the EP_2 receptor.[28 29] These receptors, belonging to the G-protein coupled receptor family, have been linked to functions such as carcinogenesis and play a role in aberrant intracellular signal transmission that is commonly linked to tumour growth and metastasis.[29]

PGE_2 plays a significant role in cancer progression by suppressing innate and antigen-specific immunity. It reduces the activities of interleukins such as IL-2, IL-12, and IL-15, thereby suppressing the cytotoxic functions

and interferon production of natural killer cells.[30] This immune suppression by PGE_2 contributes to promoting cancer development and progression.

Contrasting the SOC 'Investigations' with literature reports, we have found the effects of PGs on blood cells and the immune system. For example, Carini *et al* found that PGF2α has a dual effect: it stimulates division in certain cell lines while inhibiting growth in others. that is, an increase in the division of circulating B lymphocytes[32] and a decrease in the number of neutrophils,[33] also, it has been mentioned the immune-suppressing effect of PGE_2 by inhibition of T-cell proliferation and the regulation of dendritic cell maturation[34]; which could result in a full blood count abnormal. Cianferoni mention that some inflammatory mediators, such as bradykinin or PGs can modulate the activation of mast cells and basophils, causing vasodilation and bronchoconstriction, resulting in anaphylaxis-type reactions.[35] Additionally, Gao *et al* described the increase in IgE release by EP_2 receptors, facilitating the activation of IL-4,[36] that could trigger a blood immunoglobulin E increased with the use of PGAs.

Several sources describe an association between PGs and fat metabolism, obesity and diabetes.[37–40] Furthermore, some authors showed the inhibition of glucose-stimulated insulin secretion (GSIS) by PGE_2,[40–43] however, in the research of Carboneau *et al,* this appears to be receptor-dependent as some PG receptors increase and others decrease ß-cell survival, producing the stimulation or inhibition of insulin secretion depending on the PG receptor activation.[39] On the other hand, Lee *et al*, found that a hyperglycaemia-induced PG production mechanism affects the neuronal activity in the medial part of the hypothalamus, probably by changing the activities in the ion channel, and it seems that PGs regulate GSIS from pancreatic beta cells in a similar way, which can respond to modifications in glucose metabolism.[44] This information could explain the increase in the recurrence of diabetes mellitus diagnosis with the use of PGAs in the FAERS database.

The SOC 'Eye Disorders' have also been contrasted with scientific literature. First, Matsuo *et al* the association of Müller's muscle and blepharospasm due to an increase in the contraction of the orbicularis oculi muscle is reported.[45] On the other hand, PGs and their analogues reveal contraction (Ca^{+2}) and relaxation (cAMP) on Müller's muscle.[46–48] therefore, blepharospasm could be explained by the stimulation of the PGs receptors located in the Müller's muscle.

On the other side, Andley *et al* mentioned in 1994 that the activation of PGE_2 could be involved in the posterior subcapsular cataract.[49] However, Goto *et al* showed that even though there is an increase in the synthesis of molecules involved in the formation of cataracts (PGE_2, IL-1α and IL-6) with latanoprost, the synthesis of these molecules is considerably higher with benzalkonium chloride,[50] which is the most widely used preservative in ophthalmic formulations. This risk is already labelled in the SmPC for travoprost, tafluprost and bimatoprost.[7–9]

Concerning SOC 'Gastrointestinal Disorders', various investigations mention PGs as molecules involved in decreased salivation related to calcium metabolism and inflammation, causing dry mouth.[51–53] This had already been published in 1986 by Yu, where rats were administered different prostanoids (PGE_1, PGE_2 and $PGF_{2\alpha}$). A decrease in the flow of submandibular saliva mediated by the decrease in the concentration and flow of calcium in nerve-evoked salivary secretion, decreased concentration of Na^+ and K^+ in nerve-evoked parotid saliva, as well as effects on parasympathetically-evoked submandibular saliva were described.[54]

Finally, the literature contrasting SOC 'General Disorders and Administration Site Conditions' showed an association between PGs and various chest discomfort events. Such as Stone *et al* who demonstrated that $PGF_{2\alpha}$ potentiates the effects of cough agents,[55] and various sources show that PGE_2 causes cough, retrosternal pain, increased sensation of dyspnoea during exercise, as well as the activation of intrapulmonary type C-fibres associated with bronchoconstriction, airway hypersecretion and bronchial vasodilatation.[56–59] Furthermore, given the involvement of PGs in pain and inflammation mechanisms, their potential to provoke allodynia (touch-evoked pain)[60 61] through the sensitisation of smooth muscles and visceral nociceptors,[62] could cause chest discomfort. These nociceptors are located in the heart, lung and gastrointestinal tract and are supplied by visceral afferents, which travel through the vagus nerve and cause visceral pain.[60] In some cases, the vasoconstriction and $PGF_{2\alpha}$ could be responsible for the cardiac effects.[62] Lai *et al,* demonstrate that $PGF_{2\alpha}$ may play an essential role in the hypertrophy of cardiac ventricular myocytes in vitro and in vivo (cardiac growth),[63] probably mediated by the expression of c-fos, atrial natriuretic factor and skeletal actin in cardiac myocyte in animal models. This hypertrophy increases oxygen demand, which could cause angina or ischaemia.[64] This, combined with chest discomfort, is also mentioned in the SmPC of latanoprost and travoprost.[5 7]

No information was found on the possible association of hypoacusis with PGs; on the contrary, many studies show a beneficial effect of PGs in sudden sensorineural hearing loss, alleviating vertigo, disequilibrium and improving hearing in Meniere's disease.[65–67]

Furthermore, insufficient information has been reported in the scientific literature about skin exfoliation and its possible association with PGs, although it was discovered as an identified risk in the SmPC of bimatoprost.[8] We only found information related to inflammation and ageing.[68 69]

LIMITATIONS OF THE STUDY

Although the FAERS database contains many cases with public access, it has several limitations that could influence the statistical outcomes. For instance, the database's voluntary reporting system can lead to under-reporting, and the lack of restriction to only health professionals

reporting AEs can introduce potential biases. Additionally, the undetermined causality of the AEs reported in the database can make it challenging to establish a clear link between the reported event and a specific product.

Despite the challenges in compensating for the limitations of the FAERS database and replacing it with pharmacovigilance studies, obtain crucial information, especially when dealing with large volumes of data. This is particularly true when the significance of the statistical tests performed is rigorously maintained, ensuring the reliability of the findings.

CONCLUSION

Of the 12 PTs analysed, 8 of them found information on the possible relationship due to the biological plausibility derived from information from previous research (malignant mediastinal neoplasm, full blood count abnormal, blood immunoglobulin E increased, diabetes mellitus, blepharospasm, cataracts, chest discomfort and dry mouth). Even though it was not possible to affirm that the events' information was or was not entirely related to PGAs, the evidence obtained is relevant to continue investigating the possible drug-event association, whether to refute the safety signal or identify a new risk with its consequent minimisation.

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Contributors HC-S assumed responsibility for the study design and planning, obtained the data from the Food and Drug Administration Adverse Event Reporting System database and curated it, analysed the data, performed the statistical analysis and wrote and edited the manuscript with input from all authors. MSR-L reviewed the data and provided input for writing improvement. OOM reviewed the data and provided medical and strategical guidance and oversight. LYR-H reviewed the data, provided input for writing improvement and supervised the research. HC-S was responsible for overseeing the content as the guarantor.

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Data availability statement Data are available upon reasonable request. The data presented in this article can be accessed from the Food and Drug Administration Adverse Event Reporting System webpage; however, the data is only available on request by the corresponding author.

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