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Drug-related problems in ophthalmic practice: is product quality a contributing factor?

Problemas relacionados a medicamentos na prática oftalmológica: a qualidade do produto é um fator contribuinte?

Jaqueline Kalleian Eserian*; Márcia Lombardo
Centro de Medicamentos, Cosméticos e Saneantes, Instituto Adolfo Lutz, São Paulo, SP, Brasil.

***Corresponding author:** Jaqueline Kalleian Eserian. ORCID 0000-0002-4824-6339. Centro de Medicamentos, Cosméticos e Saneantes, Instituto Adolfo Lutz. Avenida Doutor Arnaldo, 355, Prédio BQ, 5º andar, CEP 01246-902, São Paulo, SP, Brazil. Phone: +551130682930.
email: jaqueline.eserian@ial.sp.gov.br

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ABSTRACT

Eye drops are the most common medication in ophthalmic practice, and ensuring product quality is vital to effective treatment and minimizing health risks. This cross-sectional study investigated whether reported drug-related problems in ophthalmic products were linked to quality deviations. Quality control tests were performed on products seized by the Post-marketing Surveillance Service – one containing travoprost and two containing tropicamide. Issues included irregular drop dispensing, adverse drug reaction, and therapeutic failure. For travoprost, tests assessed drip and drop size, while for tropicamide, tests focused on composition (identification, assay, and pH). Travoprost met drip (94.3 drops; specification: 80–110 drops) and drop size (27.1µL; specification: 20–70µL) standards. Tropicamide met identification (positive, positive; specification: positive), assay (101%, 101%; specification: 95–105%), and pH (5.0, 5.3; specification: 4.0–5.8) standards. The findings suggested that reported adverse events were unrelated to product quality, highlighting the need for further investigation into other contributing factors.

Keywords: Product Surveillance, Postmarketing; Tropicamide; Travoprost; Drug-Related Side Effects and Adverse Reactions; Quality control; Ophtalmic Solutions.

RESUMO

Os colírios são os medicamentos mais comuns na prática oftalmológica. Garantir a qualidade do produto é fundamental para um tratamento eficaz e para a minimização de riscos à saúde. Este estudo transversal investigou se os problemas relacionados a medicamentos relatados em produtos oftálmicos estavam associados a desvios de qualidade. Testes de controle de qualidade foram realizados em produtos apreendidos pelo Serviço de Vigilância Sanitária – um contendo travoprosta e dois contendo tropicamida. Os problemas incluíram dispensação irregular de gotas, reações adversas a medicamentos e falha terapêutica. Para a travoprosta, os testes avaliaram a quantidade de gotas e o tamanho das gotas, enquanto para a tropicamida, os testes focaram na composição (identificação, doseamento e pH). A travoprosta atendeu aos padrões de quantidade de gotas (94,3 gotas; especificação: 80–110 gotas) e tamanho de gotas (27,1µL; especificação: 20–70µL). A tropicamida atendeu aos padrões de identificação (positiva, positiva; especificação: positiva), doseamento (101%, 101%; especificação: 95–105%) e pH (5,0, 5,3; especificação: 4,0–5,8). Os resultados sugeriram que os eventos adversos relatados não

estavam relacionados à qualidade do produto, destacando a necessidade de uma investigação mais aprofundada sobre outros fatores contribuintes.

Palavras-chave: Vigilância de produtos comercializados; Tropicamida; Travoprosta; Efeitos colaterais e Reações Adversas Relacionados a Medicamentos; Controle de qualidade; Soluções Oftálmicas.

INTRODUCTION

Pharmacovigilance is a scientific discipline focused on the detection, assessment, understanding, and prevention of adverse effects and other potential drug-related problems. The field has expanded significantly, enhancing its scope and enabling the integration of multiple pharmaceutical sectors, including clinical development, clinical pharmacology, regulatory affairs, and manufacturing (BENINGER, 2018; WHO, 2025).

The primary functions of pharmacovigilance include: a. case management to standardize information in databases; b. signal management to establish associations between drugs and adverse events; and c. risk-benefit management to implement risk mitigation strategies and maintain a favorable safety profile for patients (BENINGER, 2018; ALOMAR et al., 2020).

Post-marketing surveillance generates real-world evidence on the safety of approved drugs, as it is conducted in a natural clinical setting. The methodologies employed for monitoring drugs following market authorization include spontaneous reporting, risk management plans, prospective safety studies, and patient registries (ALOMAR et al., 2020).

Spontaneous reporting remains the foundation of post-marketing surveillance, serving as a cost-effective system with broad population coverage. This passive approach relies on healthcare professionals, patients, and pharmaceutical companies to voluntarily report any drug-related problem to regulatory health authorities (BENINGER, 2018; ALOMAR et al., 2020).

Drug-related problems are defined as any undesirable outcomes linked to pharmacotherapy that either interfere with or have the potential to interfere with the expected treatment results (GUADAGNIN, SGNAOLIN, 2014; Ó, SIQUEIRA, 2021). These include adverse drug reactions, drug failure, drug overdose, under dosage, drug interactions, nonadherence, inappropriate treatment, inadequate monitoring, and drug quality deviations. The point at which quality deviations are identified during the pharmacotherapy process determines whether they lead to negative clinical outcomes. Any suspected quality deviations should be investigated and monitored due to their importance for the patient's clinical outcome. In fact, quality control of products conducted by the pharmaceutical companies could also be regarded as an effective strategy for preventing drug-related problems, with a primary focus on mitigating therapeutic failure and toxicity that may be associated with product quality (ESERIAN, 2022).

A significant portion of drug-related problems are preventable, frequently resulting from inadequate communication between patients and prescribing or dispensing professionals. Poor communication among healthcare providers, especially during transitions of care, also contributes to these issues (GUADAGNIN, SGNAOLIN, 2014; Ó, SIQUEIRA, 2021).

Eye drops are the predominant type of medication in ophthalmic clinical practice. These medications undergo strict quality control in the pharmaceutical industry to comply with good manufacturing practices. This control strategy includes evaluating the eye drop's composition, isotonicity, pH compatibility with tear fluid, and sterility, as well as processing effects and the quality of the primary packaging, which consists of the dropper bottle (PRISTA et al.,

1996; JUMELLE et al., 2020; USP, 2024a).

Prescription errors, inadequate monitoring, and patient-related medication use factors represent major challenges in pharmaceutical care and clinical pharmacy, including ophthalmic treatments. Pharmacist-led interventions can help reduce errors, optimize pharmacotherapy, prevent drug interactions, and support the management of adverse events (GUADAGNIN, SGNAOLIN, 2014; Ó, SIQUEIRA, 2021), ensuring safer and more effective use of ophthalmic medications.

Therefore, post-marketing studies are essential components of pharmacovigilance and medication safety, establishing a critical link between laboratory research and the real-world utilization of pharmaceutical products by patients. The aim of this study was to investigate whether drug-related problems with ophthalmic drugs, reported in three different scenarios, were associated with deviations in product quality.

METHODS

This is a cross-sectional study. The products were evaluated on a one-off basis, at a single point in time, and compared the occurrence of drug-related problems with the quality characteristics of the ophthalmic products. We investigated whether quality deviations were present in products seized by the local Post-marketing Surveillance Service of São Paulo between 2014 and 2024. Participants were not followed over time. The analyses were conducted immediately after sample collection.

The study followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for reporting observational studies (VON ELM et al., 2008).

Samples

The samples, containing either travoprost or tropicamide, were sourced from three distinct manufacturers (Manufacturers 1, 2, and 3). All eye drops were formulated as ophthalmic solutions and were within their shelf life at the time of analysis. Additionally, all collected samples originated from batches implicated in the reported drug-related problems.

- Travoprost 0.04mg/mL, 2.5mL dropper bottle, Manufacturer 1

Report: the product did not deliver the number of drops as indicated on the label and package insert. The reference value was 38 drops/mL (equivalent to 95 drops per bottle).

The patient reported delivering only 80 drops, 70 drops, 72 drops, and 82 drops from four bottles of different batches. The seized sample was the one reported to deliver 80 drops.

- Tropicamide 1%, 5mL dropper bottle, Manufacturer 2 (for Report A) and Manufacturer 3 (for Report B)

Report A: According to the surveillance service's report on the collected samples, patients experienced adverse drug reactions. However, the report did not specify the number of affected patients or the type of adverse reactions observed.

Report B: According to the surveillance service's report on the collected samples, patients experienced therapeutic failure, with difficulty in dilating their pupils and either delayed effects or no effect at all. The number of affected patients was not specified as well.

Conducted tests

The quality control tests conducted mirror those performed by the pharmaceutical industry. For travoprost, the focus was on drop dispensing tests, including drip and drop size assessments. Priority was given to composition tests, such as identification, assay, and pH measurements for tropicamide. Drop dispensing tests were also performed on the

Tropicamide Report B, as they could contribute to investigating therapeutic inefficacy. However, these tests were not deemed essential for evaluating the adverse reaction reported for the Tropicamide Report A.

a. Drip Test (Travoprost, Tropicamide Report B)

The drip test was conducted to determine the drop count per mL and the amount of drug per drop in liquids stored in dropper bottles. Ten bottles from the same batch were tested under controlled temperature condition. The drops' weight corresponding to 1 mL was measured using an analytical balance (AL 204, Mettler Toledo, Greifensee, Switzerland). For travoprost, the drop count per mL and per bottle was determined. After establishing the drop count per milliliter for tropicamide, the drug per drop was calculated based on Test d. "Identification and Assay of Tropicamide", described below.

The tropicamide content per drop should fall within 85% and 115% of the declared amount for each of the 10 bottles evaluated. For travoprost, results were expressed as the total number of drops per bottle for comparison with the report. The relative standard deviation should not exceed 6% (ANVISA, 2019).

b. Drop Size Determination (Travoprost, Tropicamide Report B)

For ophthalmic products dispensed via dropper, the drop size ranges from 20 to 70 µL. The test was conducted using the same procedure described in Test a. "Drip Test", measuring each drop's volume by its weight and the product's density (USP, 2024a).

c. pH Determination (Tropicamide Reports A and B)

The pH value measures hydrogen ion activity in a solution, which is crucial for the stability and physiological tolerance of ophthalmic products (PRISTA et al., 1996). The pH measurement was performed in duplicate using the direct method with a pH meter (Metrohm, Herisau, Switzerland). The pH of tropicamide should fall within the range of 4.0 and 5.8 (USP, 2024b).

d. Identification and Assay of Tropicamide (Tropicamide Reports A and B)

Tropicamide was analyzed using an HPLC-UV system (Waters, Milford, USA) equipped with a C18 column (15x4.6mm, 5µm) maintained at 30°C. The mobile phase consisted of potassium phosphate buffer (Vetec, Duque de Caxias, Brazil) and acetonitrile (Loba Chemie, Mumbai, India). The flow rate was set to 1.5 mL/min, with an injection volume of 100 µL, and detection was performed at 257 nm. The reference substance consisted of a secondary standard of tropicamide (a reference material validated against a primary standard, used for routine analysis) donated by the manufacturers.

The samples analyzed included a pool of 10 bottles from the same batch for Report A investigation and 4 bottles from the same batch for Report B investigation. Tropicamide was identified by comparing the retention time of the sample peak with that of the reference standard peak in the chromatograms. Quantification was carried out by comparing sample concentrations to the calibration curves derived from the reference standard, with concentrations of 30, 40, 50, 60 and 70 ppm. The acceptance criterion for the analysis was 95% to 105% of the declared amount of tropicamide on the label.

RESULT AND DISCUSSION

Table 1 presents the results of the tests conducted on travoprost eye drops. These tests are critical for determining the drop count per bottle and providing valuable information regarding the consistency and dosage of the travoprost formulation.

Table 1. Test results for travoprost eye drops.

TEST	SPECIFICATION	TRAVOPROST	
		RESULT	**CONCLUSION**
Drip Test (number of drops per bottle)	80 – 110 drops/bottle and RSD ≤ 6.0*	99; 95; 94; 95; 91; 91; 91; 95; 96; 96w (RSD: 2.7 %)	Passed
Drop Size Determination (µL)#	20 – 70 µL**	27.1 µL	Passed

RSD: Relative standard deviation. *ANVISA, 2019; **USP, 2024a; #Mean of 10 bottles from the same batch.

Table 2 presents the results of the tests conducted on tropicamide eye drops, including drop dispensing tests and composition analysis. These results are essential for assessing the quality and consistency of the eye drop formulations.

Table 2. Test results for tropicamide eye drops.

TEST	SPECIFICATION	TROPICAMIDE			
		REPORT A	REPORT B		
		RESULT	**CONCLUSION**	**RESULT**	**CONCLUSION**
Drip Test (% of declared amount)	85 - 115% and RSD ≤ 6.0*	-	-	98.5; 108.7; 108.0; 98.7; 108.5; 113.7; 106.0; 110.6; 105.7; 106.3 (RSD: 4.5 %)	Passed
Drop Size Determination (µL)#	20 – 70 µL**	-	-	30.6 µL	Passed
pH Determination	4.0 to 5.8***	5.3	Passed	5.0	Passed
Identification of Tropicamide	Positive****	Positive	Passed	Positive	Passed
Tropicamide Assay	95 – 105 %****	101 %	Passed	101 %	Passed

RSD: Relative standard deviation. *ANVISA, 2019; **USP, 2024a; ***USP, 2024b; ****Manufacturer's specification; - test not conducted; #Mean of 10 bottles from the same batch.

Figure 1 shows the chromatograms obtained for the identification and assay of tropicamide in samples from Tropicamide Report A and Tropicamide Report B.

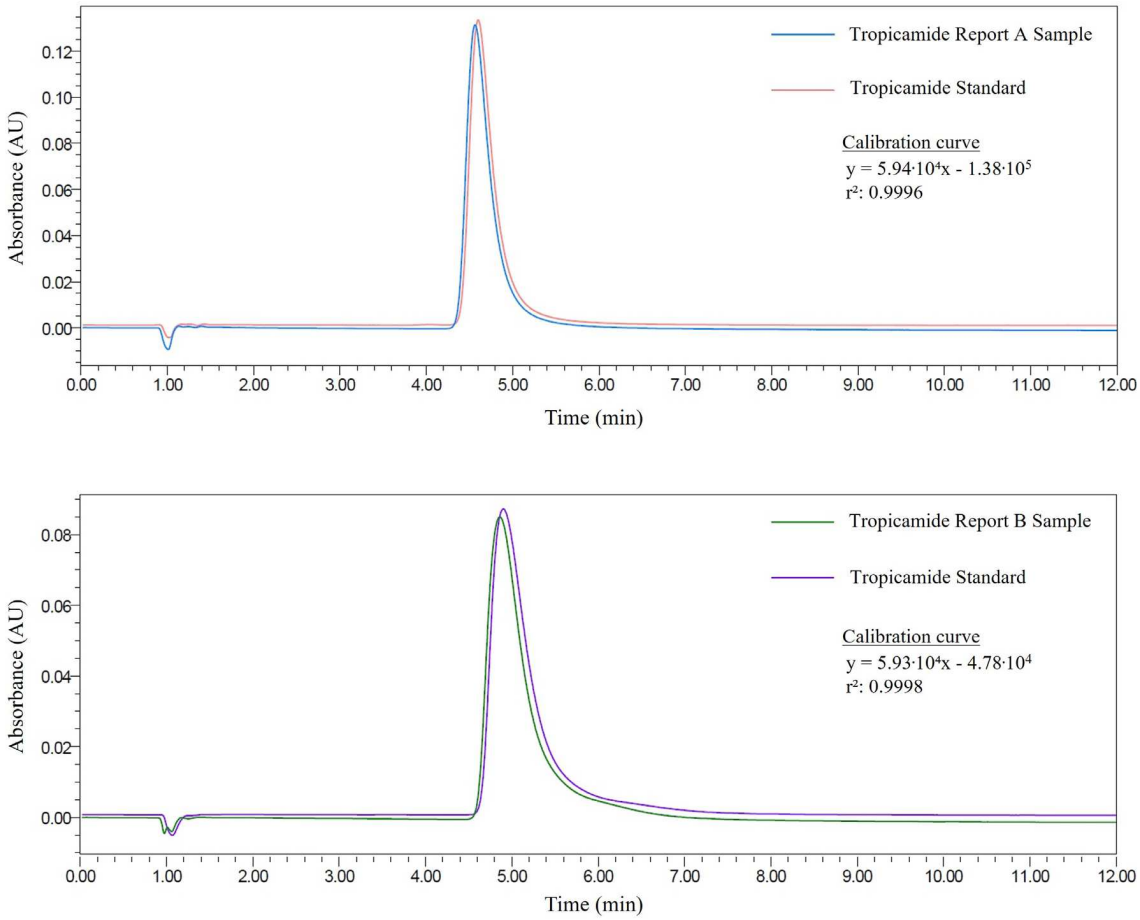

Figure 1. Chromatograms for identification and assay of tropicamide in samples from Tropicamide Report A and Tropicamide Report B, and calibration curves data.

Travoprost is a prostaglandin analogue used to lower elevated intraocular pressure, reducing the risk of glaucoma. It decreases pressure by about 30% with effects lasting over 24 hours, without long-term refractoriness (QUARANTA et al., 2015).

The drip test for travoprost eye drops showed an average of 94.3 drops per bottle, within the permitted range of 80–110 drops.

The issue of variability in eye drop volume has been extensively discussed in the literature, primarily concerning its economic implications due to waste and the need for standardization within the pharmaceutical industry. Menezes et al. (1994) reported that the drop volume in commercially available eye drops in Brazil was twice the recommended size. Likewise, Galvão-Neto (2004) identified inconsistencies in the number of drops dispensed from different bottles of the same product, as well as variations in the average number of drops among different formulations of prostaglandin analogs used for glaucoma treatment.

Moore, Beck, and Kryscio (2017) conducted a

comprehensive evaluation of commonly prescribed glaucoma eye drops, analyzing various bottle designs and tilt positions under standardized laboratory conditions. Their study revealed substantial variability in both the number of drops dispensed and the total available volume per bottle, depending on the tilt angle and manufacturer.

Factors like bottle shape, dropper design, tilt angle, filter membranes, solution viscosity, and surface tension affect eye drop administration. Excessive compression can cause multiple drops per instillation. Thus, quality and standardization of droppers are essential for consistent dosing (KASHIWAGI, 2019). Additionally, proper instillation technique prevents medication waste, reduces costs, avoids adverse events and contamination, and minimizes ocular injuries, enhancing treatment efficacy and safety (TATHAM et al., 2013; KASHIWAGI, 2019).

Tropicamide is an anticholinergic used to induce mydriasis and cycloplegia. It acts quickly and temporarily disrupts visual accommodation, making it useful for eye exams, surgery, and some inflammatory eye diseases (BELLMAN et al., 2022).

The tropicamide products met the requirements for identification, assay, and pH.

Patient adherence to ocular medications is crucial for treatment efficacy, requiring proper instillation at appropriate times. However, this can be a significant challenge, particularly for older adults and patients with physical limitations, as eye drop administration demands precise technique for successful delivery (DAVIES, WILLIAMS, MUIR, 2017).

Proper eye drop administration requires coordination, dexterity, and proprioception to ensure effective drug delivery. This process involves tilting the head back adequately, maintaining a stable grip on the bottle, and applying controlled pressure to dispense the drop accurately while avoiding contact with the ocular surface to prevent trauma or contamination. Inadequate administration can lead to poor treatment outcomes—missed doses may result in disease progression, while repeated attempts can cause excessive dosing, increasing the risk of systemic side effects and unnecessary treatment costs (DAVIES, WILLIAMS, MUIR, 2017; MOORE, BECK, KRYSCIO, 2017).

It is important to emphasize that variations in temperature or packaging damage during transportation, storage, distribution, and use should also be considered, as they may compromise product integrity and potentially impact its efficacy and safety (BENINGER, 2018).

The Vigimed panel, made available to the public by the Brazilian Health Regulatory Agency (Anvisa), provides information on suspected adverse events reported to the agency. While these data do not represent the results of formal causality assessments, they serve as an indicator for monitoring drug-related problems. Reports of adverse events associated with travoprost and tropicamide cover the period from January 2018 to April 2023, which is the full period available on the panel (ANVISA, 2023).

Ten adverse events related to tropicamide were reported (ANVISA, 2023), with the majority (40%) occurring in the state of São Paulo. Healthcare services accounted for 80% of the reports. The most frequently reported adverse events were general disorders and administration site conditions (30%), ocular disorders (20%), and injuries, poisoning, and procedural complications (20%).

For travoprost, six adverse events were reported (ANVISA, 2023), but the location of occurrence was not specified. Pharmaceutical companies were responsible for 83% of the reports. The most frequently reported adverse events were ocular disorders (33%), psychiatric disorders (33%), and benign, malignant, and unspecified neoplasms (33%).

Reports of ineffective medication (two for tropicamide and one for travoprost), medication administration errors (one for tropicamide), and incorrect route of administration (one for travoprost) were also observed (ANVISA, 2023).

This study had some limitations, and consequently, certain elements of STROBE were not fully addressed. A key limitation was the absence of specific information in the report accompanying the seized products, including patients' medical records, a comprehensive description of adverse events, medication dosage and administration details, the exact number of affected patients, and follow-up data. Additionally, while compliance with specifications is essential for ensuring pharmaceutical quality, it is not the only factor that should be considered when evaluating reported problems.

This investigation was initiated due to concerns that the reported events could be associated with quality deviations. However, following the completion of the tests, the results indicated that all products met the acceptance criteria, thereby ruling out this issue within the scope of the conducted tests.

CONCLUSION

All seized products met the testing requirements, and no evidence was found linking the reported issues to product quality based on the conducted tests. Factors related to medication use may have contributed to the reported adverse events and warrant further investigation.

Effective patient education and pharmacist counseling are crucial for preventing drug-related problems and optimizing pharmacotherapy outcomes. Ongoing laboratory monitoring remains essential for detecting potential drug quality deviations and supporting regulatory investigations into other contributing factors.

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DISCLOSURE STATEMENT

No potential conflict of interest was reported by the authors.

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