Underreporting and Triggering Factors for Two Ophthalmic Drugs' ADR Notification; A Comparison between Spontaneous Reporting and Active Pharmacovigilance Databases

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Abstract: (1)Aims of the study: calculating the underreporting ratio for two different medications, a fixed combination of 0.5% timolol + 0.2% brimonidine + 2.0% dorzolamide (antiglaucoma) and a fixed combination of sodium hyaluronate 0.1% + chondroitin sulfate 0.18% (artificial tear) and characterizing the features influencing the reporting of adverse drug reactions (ADRs) in spontaneous reporting; (2) Methods: the underreporting ratio was calculated by comparing the adverse drug reactions reported in the spontaneous reporting database for every 10,000 defined daily doses marketed and the adverse drug reactions from an active surveillance study for every 10,000 defined daily doses used for different drugs (antiglaucoma and artificial tear). The factors related to the report in spontaneous reporting through statistical tests were also determined; (3) Results: The underreporting ratio of spontaneous reporting was 0.006029% for antiglaucoma and 0.003552% for artificial tear; additionally, statistically significant differences were found for severity, unexpected adverse drug reactions, and incidence of adverse drug reactions in females; (4) Conclusions: The underreporting ratio of ADRs related to ophthalmic medications indicates worry since the cornerstone of pharmacovigilance focuses on spontaneous reporting. Besides, since underreporting seems to be selective, the role of certain aspects like gender, seriousness, severity, and unexpected ADRs, must be considered in future research.

Keywords: Adverse Drug Reaction; Spontaneous reporting; Active surveillance; Underreporting; Antiglaucoma; Artificial tear

1. Introduction

Identifying adverse drug reactions (ADRs) is essential for pharmacovigilance activities; it determines the actions to be followed in order to prevent risks [1]. ADRs are identified during early preclinical stages and randomized controlled trials; however, it is challenging to detect rare ADRs, thus, post-marketing studies are crucial.[2, 3]. These considerations pose a challenge to detect rare ADRs and drug interactions; therefore, not all risks are identified by the time of initial marketing authorization[1, 4], and the implementation of strategies for the collection of post-marketing ADRs is consequently essential[2, 5, 6].

Spontaneous reporting is the most common form of post-marketing pharmacovigilance. It is characterized by no active actions to scrutinize ADRs apart from the encouragement of health professionals and patients to report them; therefore, such reports de-

pend entirely on their initiative and motivation[7]. Spontaneous reporting has some limitations like underreporting, variable quality of the reported data, and lack of information on drug exposure[4, 8].

One of the main reasons for underreporting in spontaneous reporting is that patients and health professionals do not believe it is necessary to register an already known or well-established ADR[9]. In addition, absence of time, different care priorities, uncertainty about the drug causing the ADR, difficulty in accessing notification formats, and a lack of understanding of the purpose of notification can also account for ADR underreporting[10]. Consequently, with spontaneous reporting, it is not likely to identify the true frequency of an ADR, nor does it allow an optimal appreciation of ADRs in new patients and/or populations[9].

Underreporting is a concern worldwide because it causes the frequency of ADRs to be underestimated, delaying the detection of safety issues and therefore making it difficult to undertake a timely action[5, 11]. Nevertheless, unlike spontaneous reporting, other tools such as active surveillance intentionally and continually search for the presence or absence of ADRs in a defined group of people; it thus allows the real incidence of ADRs to be known. Moreover, active pharmacovigilance provides data on the risk factors associated with a medication and allows a more efficient use of such product[12].

This research aimed to calculate the underreporting ratio in two different medications, a fixed combination of 0.5% timolol + 0.2% brimonidine + 2.0% dorzolamide (antiglaucoma) and a fixed combination of sodium hyaluronate 0.1% + chondroitin sulfate 0.18% (artificial tear) and characterize the features that influenced the reporting of ADRs in spontaneous reporting.

2. Materials and Methods

Study design

Two collection ADR reporting methods were compared (spontaneous reporting and active surveillance) by analyzing the data of two marketed products.

Spontaneous Reporting

The data for spontaneous reporting were collected from the ADRs referred to the Pharmacovigilance and Technovigilance Unit of Laboratorios Sophia S.A. de C.V over Jan 2017 to Jul 2022 in countries where artificial tear (México, Colombia, Bolivia, Uruguay, Costa Rica, Ecuador, El Salvador, Guatemala, Haití, Honduras, Nicaragua, Panamá, Perú and Venezuela) and antiglaucoma (México, El Salvador, Costa Rica, Guatemala, Nicaragua, Colombia, Panamá, Haití, Chile, República Dominicana, Bolivia, Ecuador and Honduras) are commercialized. Only spontaneous reports were included.

Active Surveillance Reporting

The data were gathered from two non-intervention active surveillance programs in Peru (antiglaucoma and artificial tear [all patients prescribed under the doctor's own decision, with signed informed consent joined the study]) and safety information collected through three follow-up calls after 30 and 60 days, respectively. During the initial contact call, the patients were questioned about personal data, drug prescription characteristics, clinical history, and identified ADRs. The second and third contact were aimed exclusively at identifying ADRs.

Categorization

In both databases, the patients were classified as children (0-12 years old [yo]), adolescents (>12-18 yo), adults (>18-60 yo), or elders (>60 yo). The ADRs were listed according to the Medical Dictionary for Regulatory Activities (MedDRA) in System Organ Class

(SOC) and Preferred Term (PT), while causalities were accomplished by WHO-UMC method[13]. Severity was evaluated using the ADR Severity Assessment Scale (Hartwig and Siegel modified) in Mild, Moderate or Severe[14, 15], and seriousness was assessed by the ADR's nature to generate permanent damage or to be considered life-threatening[16].

Calculating Defined Daily Dose indicators

The "Utilization in Defined Daily Dose (DDD)" for spontaneous reporting was calculated considering the marketed pieces of the product (Jan 2017 to Jul 2022), using the World Health Organization formula[17].

Utilization in DDD = (Number of packages) x (Number of DDDs in a package)

The "utilization in DDD" from the active surveillance study was calculated considering one DDD/day per patient during the study period (30 or 60 days), and this was multiplied by the number of patients admitted.

Utilization in DDD = (Days using DDDs) x (Number of patients in active surveillance program)

Finally, "ADRs per 10,000 DDDs" was calculated to visualize how many ADRs arose for every 10,000 DDDs.

$$ADRs\ per\ 10,000\ DDDs = \frac{ADRs}{Utilization\ in\ DDD} \times 10,000 \tag{1}$$

Underreporting ratio

The underreporting ratio was calculated using the formula mentioned below.

$$Underreporting\ ratio = \frac{ADRs\ per\ 10,000\ DDDs\ (spontaneous\ reporting)}{ADRs\ per\ 10,000\ DDDs\ (active\ surveillance)} \tag{2}$$

Factors related to reporting

Age group, gender, severity, seriousness, causality, and the different ADRs identified from both databases (spontaneous and active surveillance) and whether the ADRs appeared in the summary of each product's characteristics (SmPC)/monograph (label/unlabeled), were analyzed to determine which factors were involved in reporting rate.

Statistical Analysis

Qualitative variables were described as frequencies and percentages. Chi-square or Fisher´s exact tests (small samples) were performed for the inter-group analysis. In this study, the statistical significance was 2-sided set at a p-value ≤0.05. SPSS (version 21; SPSS, Inc., Chicago, IL, USA) was used for the statistical analysis.

3. Results

Spontaneous reporting from Jan 2017 to Jul 2022, were distributed 195,334,179 DDDs for antiglaucoma (75 ADRs notified) and 133,029,769 for artificial tear (26 ADRs notified), representing 0.003840 and 0.001955 ADRs for every 10,000 DDDs sold, respectively (Table 1). On the other hand, during the 60-day antiglaucoma (246 patients and 94 ADRs notified) and the 30-day artificial tear (212 patients and 35 ADRs notified) active surveillance studies, 63.69 and 55.03 ADRs per every 10,000 DDD were reported, respectively (Table 2). The

underreporting ratio of spontaneous reporting was calculated with the data described above, resulting in 0.006029% for antiglaucoma and 0.003552% for artificial tear. According to these calculations, artificial tear has a nearly twofold underreporting ratio compared to antiglaucoma.

Table 1. Defined Daily Dose of Spontaneous Notification

Drug	Time	ADRs	DDD	Use in DDD	ADRs Per 10,000 DDDs
Antiglaucoma	3 650 days	81	0.14 ml	276 120 000	0.002933507
Artificial tear	3 650 days	23	0.54 ml	193 952 556	0.001185857

ADRs, Adverse drug Reactions. DDD, Defined Daily Dose

Table 2. Defined Daily Dose of Active Surveillance

Drug	Time	Patients	ADRs	DDD	Use in DDD	ADRs Per 10,000 DDDs
Antiglaucoma	60 days	246	94	0.14 ml	14 760	63.68563686
Artificial tear	30 days	212	35	0.54 ml	6 360	55.03144654

ADRs, Adverse drug Reactions. DDD, Defined Daily Dose

The age groups included in the active surveillance study for antiglaucoma were children n=1; 0.41%, adults n=96; 39.02%, and elders n=149; 60.57%. Meanwhile, for the artificial tear study they were children n= 1; 0.47%, adolescents n= 2; 0.94%, adults n=110; 51.89%, and elders n=99; 46.70%. As expected, antiglaucoma was mostly prescribed to elder patients, whereas in artificial tear, mainly in the adult group was exposed. The information collected from active surveillance and spontaneous reporting showed that for the antiglaucoma study, the age group presenting ADRs most frequently was the elders. In contrast, the age group with most frequent ADR presentation for the artificial tear group were adults, congruently with the age groups where each of the medications were mostly prescribed. (Figure 1)
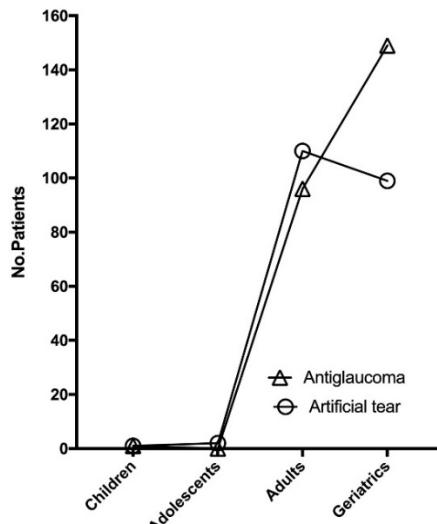
Figure 1. Age group of patients admitted to different active surveillance studies.

A statistically significant increase in severity was found for both spontaneous reporting databases (antiglaucoma and artificial tear) when they were contrasted with the active surveillance database [($X^2_{(2)}$ = 27.57, p < 0.0001) antiglaucoma], [(Fisher´s exact test, p = 0.0063) artificial tear]. A non-statistically significant trend was observed for the increase for ADR seriousness in spontaneous reporting compared to active surveillance for the antiglaucoma database (Fisher´s exact test, p = 0.1955. No serious adverse reactions were identified in the artificial tear study database (Table 3).

An increased number of ADRs was found in females compared to males in the active surveillance database; 19.2% in the antiglaucoma group and 14.2% more in the artificial tear group. In addition, when contrasting these results with the spontaneous reporting database, the increase in the presence of ADRs in females was superior to that of active surveillance, with a rise of 1.1-fold in the antiglaucoma group and 1.9-fold more in the artificial tear group (Table 3).

Table 3**.** Characteristics of patients´ ADRs from the databases

		Antiglaucoma		Artificial tear	
		AS, n (%)	SN, n (%)	AS, n (%)	SN, n (%)
Age group	Children	0 (0)	1 (1.2)	0 (0)	0 (0)
	Adolescents	0 (0)	0 (0)	0 (0)	0 (0)
	Adults	43 (45.7)	22 (27.2)	22 (62.9)	17 (73.9)
	Geriatrics	51 (54.3)	58 (71.6)	13 (37.1)	2 (8.7)
	Unknown	0 (0)	0 (0)	0 (0)	4 (17.4)
Gender	Male	38 (40.4)	28 (34.3)	15 (42.9)	9 (39.1)
	Female	56 (59.6)	53 (65.4)	20 (57.1)	14 (60.9)
Severity	Mild	94 (100)	67 (82.7)	35 (100)	16 (69.6)
	Moderate	0 (0)	13 (16.0)	0 (0)	3 (13.0)
	Severe	0 (0)	1 (1.2)	0 (0)	0 (0)
	Unknown	0 (0)	0 (0)	0 (0)	4 (17.4)
Seriousness	Not Serious	94 (100)	78 (96.3)	35 (100)	19 (82.6)
	Serious	0 (0)	3 (3.7)	0 (0)	0 (0)
	Unknown	0 (0)	0 (0)	0 (0)	4 (17.4)
Total	ADRs	94	81	35	23

AS, Active Surveillance. SN, Spontaneous Notification.

A total of 11 PTs were identified in the databases (active surveillance) compared to 33 PTs (spontaneous reporting) for the antiglaucoma group (Table 4), and 4 PT (active surveillance) compared to 15 PTs (spontaneous reporting) for the artificial tear group (Table 5).

Table 4**.** Most frequently reported ADRs in the antiglaucoma databases.

AS, Active Surveillance. SN, Spontaneous Notification.

Antiglaucoma			
PT	Labeled*	AS, n (%)	SN, n (%)
Eye irritation	Y	76 (80.9)	19 (23.5)
Vision blurred	Y	5 (5.3)	8 (9.9)
Eye pain	Y	1 (1.1)	5 (6.2)
Eye inflammation	Y	0 (0)	4 (4.9)
Eye pruritus	Y	3 (3.2)	3 (3.7)
Headache	N	1 (1.1)	3 (3.7)
Ocular hyperaemia	Y	1 (1.1)	3 (3.7)
Lacrimation increased	Y	0 (0)	3 (3.7)
Somnolence	Y	1 (1.1)	2 (2.5)
Blood pressure decreased	Y	1 (1.1)	2 (2.5)
Diffuse alopecia	N	0 (0)	2 (2.5)
Eyelid skin dryness	N	0 (0)	2 (2.5)
Cough	N	0 (0)	2 (2.5)
Dysgeusia	Y	2 (2.1)	1 (1.2)
Dry mouth	Y	1 (1.1)	1 (1.2)
Arthralgia	N	0 (0)	1 (1.2)
Eye allergy	Y	0 (0)	1 (1.2)
Asthenopia	N	0 (0)	1 (1.2)
Blepharitis	Y	0 (0)	1 (1.2)
Nasal congestion	Y	0 (0)	1 (1.2)
Neck pain	N	0 (0)	1 (1.2)
Musculoskeletal pain	N	0 (0)	1 (1.2)
Administration site oedema	Y	0 (0)	1 (1.2)
Drug ineffective	N	0 (0)	1 (1.2)
Eyelid oedema	Y	0 (0)	1 (1.2)
Rash maculo-papular	N	0 (0)	1 (1.2)
Periorbital swelling	N	0 (0)	1 (1.2)
Conjunctival hyperaemia	N	0 (0)	1 (1.2)
Hyperhidrosis	N	0 (0)	1 (1.2)
Throat irritation	N	0 (0)	1 (1.2)
Nausea	N	0 (0)	1 (1.2)
Nephrostomy	N	0 (0)	1 (1.2)
Nasal obstruction	N	0 (0)	1 (1.2)
Dry eye	N	0 (0)	1 (1.2)
Pruritus allergic	Y	0 (0)	1 (1.2)
Rhinorrhoea	Y	0 (0)	1 (1.2)
Nasopharyngitis	N	2 (2.1)	0 (0)

*Labeled according to SmPC/monograph

In the antiglaucoma database, the most frequent ADR was eye irritation, encompassing 80.9% of all active surveillance ADRs, as opposed to the spontaneous reporting database with a frequency of 25.3% of the total number of ADRs (Table 4). In the case of artificial tear treatment databases, the outcome was similar to those of antiglaucoma, where the most frequent ADR (burning sensation) showed a significantly higher incidence in the active surveillance database with 74.3% of the ADRs reported compared to 42.3% of the total ADRs notified in spontaneous reporting (Table 5).

Table 5**.** Most frequently reported ADRs in the artificial tear databases.

AS, Active Surveillance. SN, Spontaneous Notification.

Artificial tear			
PT	Labeled*	AS, n (%)	SN, n (%)
Burning sensation	Y	26 (74.3)	9 (39.1)
Ocular hyperaemia	N	0 (0)	2 (8.7)
Lacrimation increased	N	0 (0)	2 (8.7)
Vision blurred	Y	7 (20)	1 (4.3)
Ageusia	N	0 (0)	1 (4.3)
Visual impairment	N	0 (0)	1 (4.3)
Anosmia	N	0 (0)	1 (4.3)
Dry eye	N	0 (0)	1 (4.3)
Eye pruritus	N	0 (0)	1 (4.3)
Instillation site discharge	N	0 (0)	1 (4.3)
Eye discharge	N	0 (0)	1 (4.3)
Abnormal sensation in eye	N	0 (0)	1 (4.3)
Foreign body sensation in eyes	N	0 (0)	1 (4.3)
Ocular pain	N	1 (2.9)	0 (0)
Headache	N	1 (2.9)	0 (0)

*Labeled according to SmPC/monograph

The most frequent causality for active surveillance (both treatments) was "probable"; however, for this parameter, a marked difference is observed in the reports of active surveillance when compared to spontaneous reporting in both drug groups; antiglaucoma (86.17% vs 16.00%) and artificial tear (71.43% vs 42.30%) (Figure 2)
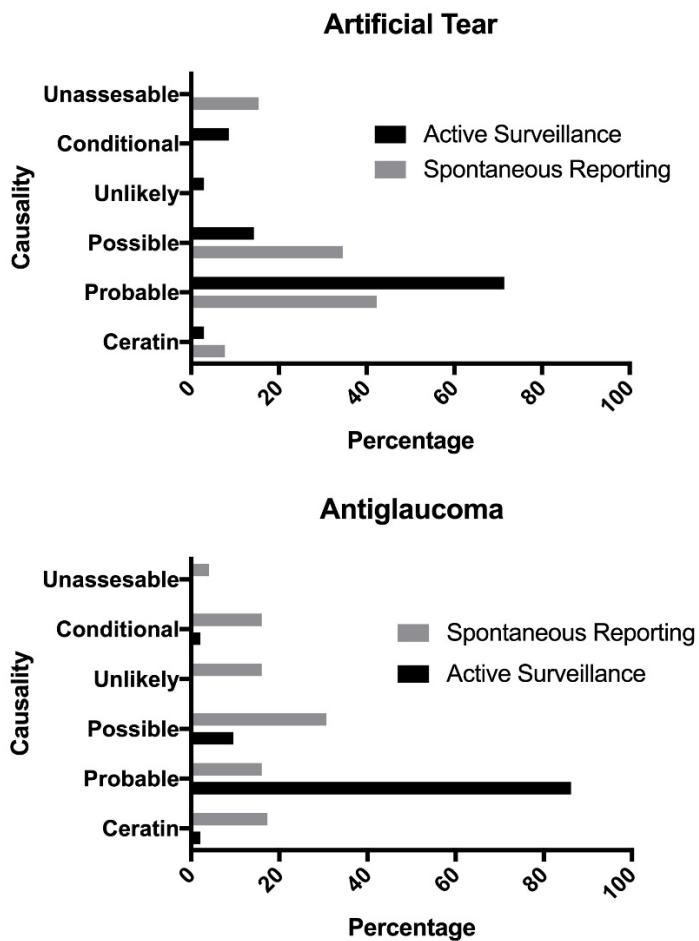
Figure 2. comparative of causalities between spontaneous reporting and active surveillance in the glaucoma and artificial tear databases

In addition, the spontaneous reporting databases show a statistically significant increase in ADRs not included in the SmPC/monograph (unlabeled). For antiglaucoma's spontaneous reporting 56 ADRs were labeled, while 19 were unlabeled; and for this same group's active surveillance 91 labeled, and 3 unlabeled ($X^2_{(1)}$ = 18.06, p < 0.0001) (Table 4). For artificial tear, spontaneous reporting included 13 labeled, and 13 unlabeled, while active surveillance included 33 labeled, and 2 unlabeled ($X^2_{(1)}$ = 15.29, p < 0.0001) (Table 5).

The lack of information on causality, severity, age group, gender and seriousness in four reports from artificial tear; as well as causality, severity, and age group in six reports from antiglaucoma in the spontaneous reporting database is worth mentioning. (Table 3 and Figure 2).

4. Discussion

The outcomes of the research show significant rates of underreporting (0.006029% for antiglaucoma and 0.003552% for artificial tear); this indicates a worrying result since the pillar of pharmacovigilance focuses on spontaneous reporting[18]; also, underreporting limits obtaining sufficient data to generate risk minimization activities, representing a significant threat to the population[19]; for this reason, there is a need to encourage reports in pharmacovigilance, especially in ophthalmic due there is evidence that the notification

in ophthalmology is less than other medical specialties[20, 21]. Additionally, underreporting seems to be selective for some factors like seriousness, severity, gender and unexpected ADRs.

As previously mentioned, several authors describe that one of the problems of spontaneous reporting is derived from the fact that patients only notify ADRs when they are severe or serious, leaving aside the notifications of less severe and serious events[22–24]. This agrees with what is observed when comparing the spontaneous reporting databases concerning active surveillance, where a statistically significant difference was observed in the presence of severe ADRs in the spontaneous reporting database and with the evidence of a tendency for seriousness, with a higher number of notifications of serious/severe ADRs. Furthermore, the difference for the underreporting ratio which was nearly twofold for artificial tear could be due to this effect. Since the severity/seriousness of adverse reactions in the artificial tear database is lower than for antiglaucoma (table 3).

Similar to what was found in this research, an increase of ADRs in females have already been reported. The literature divides this event into two main aspects, those related to gender (more informed on health issues, concern about your health, a propensity to report symptoms, increased interest in reporting) [25, 26], and those related to sex (metabolic, pharmacokinetic, pharmacodynamic, and hormonal factors) [27, 28]. It is possible that factors related to sex could be influencing the increase in ADRs in the active surveillance database. In contrast, factors associated with gender could not be influencing this type of study because the active surveillance responsibility for collecting ADRs rests on the sponsor (monitoring by the study period). Nevertheless, an increase is observed in the spontaneous reporting when compared to the active surveillance database. In this case, the factors related to gender are not inconsequential. This could explain the observed increase in the spontaneous reporting database; added to this, the relationship of gender in ophthalmic medication-related ADRs has already been reported in a previous article, finding a statistically significant difference between males and females in a drug safety surveillance study in a dexamethasone/ciprofloxacin ophthalmic solution[29].

A statistically significant difference was found between unexpected and expected ADRs in the spontaneous reporting database; this agrees with what has been previously reported in the literature. It is mentioned that patients tend to notify ADRs only when they are unexpected[22, 24].

The low number of ADRs in the spontaneous reporting database for antiglaucoma ("eye irritation" 25.3% incidence in spontaneous reporting vs 80.9% in active surveillance) and in the artificial tear database ("burning sensation" 42.3% (spontaneous reporting) vs 74.3% (active surveillance), (Table 4 and 5) highlights the low incidence of spontaneously reported ADRs due to lack of seriousness (not serious), low severity (mild), frequency and expectedness.

Finally, four ADRs for artificial tear and six reports for antiglaucoma lack data in the spontaneous reporting database; this problem has already been documented in the literature[4, 8], where spontaneous reports usually lack information due to the impossibility to follow-up.

The study's main limitations were the low number of ADRs analyzed and the relatively small sample size of active surveillance studies; as well as the use of DDD as a mechanism to determine the rate of underreporting due to the possibility that not all distributed doses were actually administered or not all patients maintained a posology as described by the DDD formula.

5. Conclusions

The underreporting ratio of ADRs related to ophthalmic medications indicates worry since the cornerstone of pharmacovigilance focuses on spontaneous reporting. Besides, since underreporting seems to be selective, the role of certain aspects like gender, seriousness, severity, and unexpected ADRs, must be considered in future research.

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Data Availability Statement: The data underlying this article will be shared on reasonable request to the corresponding author.

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