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A drug safety surveillance study of a ciprofloxacin / dexamethasone ophthalmic fixed combination in Peruvian population

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Abstract: (1) Background: drugs provide a significant benefit; however, their use implies an intrinsic potential danger, with the possibility to cause unwanted effects. These effects are known as adverse drug reactions (ADRs). Post-marketing drug safety surveillance detects unknown risks that have not been identified in clinical trials and it is necessary to monitor marketed medications under real-life practice. Due to the scarce information about fixed combination of ciprofloxacin 0.3% / dexamethasone 0.1% (SDO), we performed a drug safety surveillance study. (2) Methods: A prospective non-controlled drug safety surveillance study was conducted in Peruvian population. A total of 236 patients prescribed SDO were included derivates from 12 sites. Patients' standardized information was collected through two phone calls, including demographics, medical history, prescribing patterns of SDO, concomitant medication, and ADRs in detail. The ADRs were classified by causality and severity, followed by outcome measures to identify new risk. (3) Results: 236 patients prescribed with SDO participated in the study and 220 were included. A total of 82 ADRs/220 patients were reported after the use of SDO, presenting a ratio 0.37 ADR/patient. The most frequent ADR with SDO administration was eye irritation (30%). The totality of the ADR was classified as non-serious, and the 97.5% (n=80) was classified as mild and 2.5% as moderate (n=2). No cases under the severe category were identified. (4) Conclusion: No new risks were found in the population where this study was conducted.

Keywords: Drug Safety Surveillance, Adverse Drug Reaction, Ophthalmic, Ciprofloxacin, Dexamethasone.

1. Introduction

Prescription drugs provide a significant benefit by treating, preventing or diagnosing diseases; however, their use implies an intrinsic potential danger, possibly causing unwanted effects. These effects are known as adverse drug reactions (ADRs).[1,2] The World Health Organization (WHO) defined ADRs as "A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or the modification of physiological function," and represent a significant cause of damage that impacts health and economy of patients, their families and society in general.[1,3]ADR monitoring enables the discovery of relevant safety information on an ongoing basis and therefore the identification of both benefits and risks of a specific marketed medication, thus allowing the reduction of the societal burden from adverse drug reactions[4,5] since ADRs can cause a reduction in patient's quality life and an important number of deaths annually, with a high economic cost.[4,6] Post-marketing drug safety surveillance is one of the pillars of

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pharmacovigilance in order to detect unknown risks that have not been identified in clinical trials, since at this stage the drug has been tested for a short period of time on a limited number of individuals. For these reasons, it is necessary to know the behavior of drugs in multiple populations, in uncontrolled environments, in vulnerable groups, during chronic use and when used in combination with other drugs; evaluation which is carried out through the monitoring of marketed medications under real life clinical practice.[4]

There are different combinations of antibiotic/steroid ophthalmic medications available for the treatment of ocular infections that have been used for several years.[7] The concomitant use of antibiotics and steroids gained relevance due to the negative effects produced by the severe inflammation caused by ocular infections.[8] The ophthalmic solution containing ciprofloxacin 0.3% / dexamethasone 0.1%, is a combination of a fluoroquinolone, an antibiotic that inhibits bacterial DNA synthesis through its action on topoisomerase II and topoisomerase IV, and a corticosteroid that suppresses inflammation by inhibiting the production of multiple inflammatory cytokines. [9,10] This ophthalmic fixed combination has demonstrated its aid in controlling post-surgery ocular inflammation, proving to be effective and safe; however it has been tested on a limited population.[11,12]

In this study we characterized the ADRs associated to the use of an ophthalmic fixed combination of ciprofloxacin 0.3% / dexamethasone 0.1% Sophixin DX Ofteno® (SDO) (Laboratorios Sophia, S.A. de C.V., México) in uncontrolled Peruvian population through drug safety surveillance.

2. Methods

A prospective non-controlled drug safety surveillance was conducted in Lima, Perú during February 2019 to April 2020 by 12 collaborating sites. The study's protocol and its corresponding informed consent form were reviewed and approved by an ethics committee (see Ethics approval section).

Patients were recruited from February 27, 2019 (first enrolled patient) to April 29, 2020 (last patient´s completion). Because this is a non-interventional study, patients who were prescribed SDO by an ophthalmologist (on his/her own initiative) were derived to a member of our team. Afterwards, they were informed about the enrollment process and invited to participate in the study. If the patient agreed to participate, the informed consent was signed.

Over a period of 14 days, a member of our team conducted telephonic interviews with the patients on two different dates, days 7 and 14 after the start of the drug´s administration. On day 7, the personal data were collected (age, gender, nationality, pregnancy or breastfeeding) as well as the characteristics of the drug and its prescription (dose, route of administration, expiration date, batch), data from the patient's medical history (reason for prescription, concomitant drugs used and their dose, route of administration, start application) and data from any ADR in case they appeared (onset date, description of intensity, ADR duration, need of treatment, re-challenge [if applicable], existence of a similar preceding ADR with the same drug, dechallenge [if applicable], response to dose modification [if applicable], existence of other cause different to drug application that may explain the ADR [if applicable]). During the call that took place on day 14, follow up and general experience with the drug´s use was inquired.

The data collected in each of the scheduled calls was registered in an Excel document (Microsoft Office® 365 ProPlus., Washington, Redmond, USA) by Laboratorios Sophia's Pharmacovigilance Unit and patients were classified according to their age as follows: children (0-12 years old [y/o]), adolescents,

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(>12-18 y/o), adults (>18-60 y/o), and geriatric (>60 y/o). If any of the patients reported any ADRs, these were classified and evaluated according to severity and causal relationship.

Severity was evaluated in accordance with the Modified Hartwig and Siegel Severity Assessment Scale (Mild, Moderate, Severe).[13,14] Subsequently, the causal relationship was assessed in accordance with the Naranjo algorithm as: indefinite, probable, possible, doubtful or un-assessable.[15] All ADR were listed in System Organ Class (SOC) and Preferred Term (PT) according to MedDRA v 22.0 (Medical Dictionary for Regulatory Activities).

Outcome Measures

Tolerability

TBD's tolerability was evaluated by measuring different parameters: drug interactions (searched in Micromedex® IBM Corporation 2020),[9,10] safety signals, ADR severity, seriousness and duration besides ADRs of different genders.

Bibliographic analysis of ADRs

An analysis was performed comparing the incidence of reported ADRs of this study with those found in two reference drug information databases (Micromedex® IBM Corporation 2020 and MedicinesComplete® "Martindale Drug reference" The Royal Pharmaceutical Society 2020). [9,10,16] The frequencies obtained in the databases for individual ophthalmic drugs (ciprofloxacin and dexamethasone) were contrasted with those found in the fixed combination of SDO. On the other hand, a search for interactions with patients who use one or more products concomitantly with SDO were searched in the Micromedex® database.

Statistical analysis

Quantitative variables were expressed as the mean ± SD, and qualitative variables were described as frequencies and percentages. A chi-square test was performed to compare proportions and Fisher's exact for small-sized samples. The Statistical significance was 2-sided set at a p-value <0.05. (GraphPad 7 Software, La Jolla, California, USA).

3. Results

This A total of 263 patients receiving a prescription for SDO signed the informed consent form. Nevertheless, it was not possible to contact 16.3% of the patients (n=43) on account of one of the following: unanswered call (60.5% /n=26) or wrong registered number (39.5% / n=17). A total of 220 patients were contacted; 122 women (children: n=1, adults: n=62, geriatric: n=59), none of them were pregnant; and 98 men (children: n=3, adolescent n=2, adults: n=47, geriatric: n=46) (Table 1).

The 66% (n=145) of patients under treatment with SDO used other simultaneous treatments like artificial tears (n=59; 27%) who were the products most commonly used with SDO followed by ophthalmic NSAIDs (n=20; 9%), antiglaucoma drugs (n=19; 9%), glucose-lowering medications (n=15; 7%), antihypertensive medications (n=13; 6%), monoclonal antibodies (n=7; 3%) and others (n=12; 5%); the remaining 34% of patients were not using any concomitant therapy. With those data a search of different bibliographic sources was conducted, and 21 possible systemic drug interactions with SDO (ciprofloxacin / dexamethasone) were identified: 2 patients used fluoxetine, 7 used oral glucose-lowering medications and 12 used NSAIDs.

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A total of 82 ADRs/220 patients were reported after the use of SDO, presenting a ratio of 0.37 ADR/patient; these ADRs were classified into 3 SOC and 9 PT groups, finding that the most frequent SOC group was eye disorders (93%) and the more frequent PT was eye irritation (75%). The most frequent causality was probable with 72% of cases, followed by possible with 15% (Table 2). The ADRs were classified according to severity as follows: 97.5% as mild (n=80) and 2.5% as moderate (n = 2). Also, 67% of the patients that presented any ADRs improved in one minute or less after the application of the product. No cases under the severe category were identified, in the same way no serious ADRs were identified.

Additionally, a comparative analysis was conducted to determine whether ADRs in different genders had a similar incidence: females 57 ADRs (n=122), males 25 ADRs (n=98), and we found a statistically significant increase of the incidence of ADRs in females in comparison to males ($X^2_{(1)} = 3.234$, p= 0.0012) (Table 3).

The bibliographic analysis showed differences between SDO against its individual active ingredients, showing that the most frequent ADR with SDO was eye irritation, presenting a statistically significant difference only for dexamethasone ($X^2_{(1)} = 27.5$, p= <0.0001), but not for ciprofloxacin ($X^2_{(1)} = 1.379$, p= 0.2402). Likewise, eye edema and eye pain were found not statistically significant ($F_{219,219}$= >0.9999) when comparing SDO with ciprofloxacin or dexamethasone. The incidence of the rest of reported ADRs was below expected (Table 4).

Table 1. Patient demographics

		Children	Adolescent	Adult	Geriatric
n		4	2	109	105
Age, years		3.8 ± 3.8	15 ± 2.8	41.4 ± 11.7	72 ± 7.5
Gender		Female (n=1) Male (n=3)	Female (n=0) Male (n=2)	Female (n=62) Male (n=47)	Female (n=59) Male (n=46)
Comorbidity		2	1	66	78
ADRs		0	0	51	31
ROP	Eye Infection	1	1	41	50
	Post- surgical	-	-	31	33
	Conjunctivitis	1	-	13	7
	Chalazion	2	-	11	4
	Other	-	1	13	11
Total (ROP)		4	2	109	105

ADR, Adverse Drug Reaction. ROP, Reason of prescription

Table 2. Causality and severity of ADRs.

SOC	PT	n	Causality	Severity

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Eye disorders	Eye irritation	66	Definite (n=5), Probable (n=54), Possible (n=6), Doubtful (n=1).	Mild (n = 66)
	Vision blurred	3	Probable (n=1), Doubtful (n=1)	Mild (n=2)
			Doubtful (n=1)	Moderate (n=1)
	Ocular hyperemia	3	Probable (n=2), Possible (n=1).	Mild (n=3)
	Eye pain	2	Possible (n=1),	Mild (n=1)
			Doubtful (n=1).	Moderate (n=1)
	Eyelid edema	1	Possible (n=1).	Mild (n=1)
	Foreign body sensation in eyes	1	Probable (n=1).	Mild (n=1)
Infections and infestations	Nasopharyngitis	1	Possible (n=1).	Mild (n=1)
Nervous system disorders	Somnolence	1	Doubtful (n=1).	Mild (n=1)
	Dysgeusia	4	Probable (n=2), Doubtful (n=2)	Mild (n=1)
	Total	**82**		

SOC, System Organ Class. PT, Preferred Term.

Table 3. ADR per gender

Gender	n	ADRs	ADR/patient	p value
Female	122	57	0.47	0.0012**
Male	98	25	0.26	

ADR, Drug Adverse Reaction. Pearson Chi-square test, **p<0.01

Table 4. Bibliographic comparison of fixed combination and individual treatment.

PT	SDO	D	p	C	p
Eye irritation	(n=66) 30.0%	10.0%[2]	<0.0001[a]	25.0%[2]	0.2402[a]
Vision blurred	(n=3) 1.4%	9.0%[1]	0.0030[a]	1.0%[2]	0.6529[a]
Ocular hyperemia	(n=3) 1.4%	5.0%[1]	0.0298[a]	10.0%[1]	<0.0001[a]
Vitreous opacities	-	-	-	16.6%[1]	-
Eyelid edema	(n=1) 0.5%	-	-	1.0%[1]	>0.9999[b]

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Foreign body sensation in eyes	(n=1) 0.5%	-	-	10.0%[1]	<0.0001 [b]
Dysgeusia	(n=4) 1.8%	10.0%[2]	0.0008 [a]	-	-
Nasopharyngitis	(n=1) 0.5%	4.0%[2]	0.0201 [b]	-	-
Uveitis	-	54.0%[1]	-	-	-
Macular edema	-	68.0%[1]	-	-	-
Conjunctivitis	-	6.0%[2]	-	-	-
Eye pain	(n=2) 1.0%	1.0%[2]	>0.9999 [b]	-	-
Inflammation	-	9.0%[1]	-	-	-
Dry eye	-	5.0%[1]	-	-	-
Iritis	-	15.0%[1]	-	-	-
Intraocular pressure increased	-	25.0%[1]	-	-	-
Conjunctival hyperemia	-	5.0%[1]	-	-	-
Somnolence	(n=1) 0.5%	-	-	-	-

D, dexamethasone. C, ciprofloxacin. ADR, Adverse Drug Reaction. SDO, ciprofloxacin 0.3% / dexamethasone 0.1 %. PT, Preferred Term.

Notes: Data from: 1, Micromedex.[9,10] 2, Martindale.[16] Statistic methods: a, Chi square test. b, Fisher exact test.

4. Discussion

Authors Several sources mention that the fixed antibiotic/steroid combination has been shown to be effective in different infectious, allergic and inflammatory pathologies;[7,17,18] however, there is limited information about the safety profile of the ophthalmic ciprofloxacin / dexamethasone combination. Nevertheless, we found that SDO is well tolerated by the patients, no patients presenting ADRs discontinued treatment, since the vast majority of these were mild, no serious and receded within a minute or less after instillation.

Interestingly, we found a statistically significant increase among the patients' gender, finding that females showed a higher (statistically significant) incidence (0.47 ADR/patient) as compared to males (0.26 ADR/patient). These results coincided with several sources which mention that females present ADRs more frequently than males since multiple factors like pharmacokinetic and pharmacodynamics, adipose tissue, gastrointestinal motility, enzymatic activities differences[19–22] could affect the incidence of ADRs in males and females; nevertheless, this incidence has not been reported before for ophthalmic medications.

Although there were 21 possible interactions none of the patients reported any symptoms, this could be since doses used in ophthalmic formulations are lower than those necessary to cause systemic effects. In addition, even though the presentation of systemic effects following topical instillation of ciprofloxacin and dexamethasone has been reported, this is but a rare instance. [23–26]

A bibliographic analysis comparing SDO´s ADRs to the expected ADRs of each of the individual active ingredient was performed.[9,10,16] The results showed that eye irritation, which was the most frequent ADR in patients using SDO, was statistically significantly higher than that reported with the use of dexamethasone individually; however, no significant differences were found in patients with ciprofloxacin individually for this ADR. Therefore, SDO being a fixed combination of both (ciprofloxacin / dexamethasone), this ADR could be attributable to ciprofloxacin. Additionally, the remaining reported ADRs are either similar to or lower than expected if active ingredients were used separately (Table 4), showing that SDO does not increase the incidence of ADRs compared to individual use.

The identification of safety signals is an important part of the benefit-risk assessment of drugs, for this reason an analysis of the ADRs collected on this study was performed, finding one unexpected ADR according to the available published references of the active ingredients of SDO,[9,10,27] with a SOC of Nervous system disorders and a PT of Somnolence with doubtful causality. Using the Bradford-Hill criteria (Strength of Association, Consistency, Specificity, Temporality, Biological Gradient Dose-Response, Plausibility, Coherence, Experiment, Analogy) there is not enough information to support that the application of SDO caused the ADR.[28]

Our study's limitations were that since the follow-up was done through phone calls, it was impossible to identify some adverse reactions that require a doctor's evaluations to be identified. Furthermore, the comparison between the identified ADRs for SDO and those reported for dexamethasone and ciprofloxacin individually was not carried out in the same population.

5. Conclusions

In our study, we found no increase in the incidence of ADRs related to SDO use compared to those reported in the literature for its active ingredients administered individually; also, no new risks or safety signals were observed in the population where this study was conducted; consequentially, a good tolerability safety profile was confirmed.

We identified an increase of ADR in females exposed to systemic drugs supported by the literature but limited, or no data on this regard was available for ophthalmic drugs specifically; nevertheless, more studies are needed to assess these results.

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Ethics approval: This study was approved by the "Comité Institucional de Bioética (CIB)", Vía libre, located in Lima, Perú (Approval Number 4206).

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Conflicts of Interest: C.S.H., R.H.L.Y., B.H.M., B.D.L.M. are employees of Laboratorios Sophia S.A. de C.V.

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