Adverse Drug Reactions in Ophthalmology - are they a Myth?

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Abstract: Sometimes ocular (and systemic) therapeutics may cause ocular (and systemic) diseases, namely adverse drug reactions (ADRs). The Journal of Ocular Diseases and Therapeutics is therefore doubly adequate for discussion of the theme of ADRs in Ophthalmology.

Many terms are utilized as synonyms but the correct definition of ADR (according to the World Health Organization, WHO) is: "any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy".

Ophthalmology is one of the medical specialties in which there is a high difficulty in continuous diagnosis, assessment and treatment. Additionally, the specific and delicate anatomy and physiology of the eye may easily be disrupted by an ADR, with possible irreversible consequences. Ocular ADRs may be frequent (such as *cornea verticillata* caused by amiodarone) or specific. On the other hand, systemic ADRs may occur after ocular treatments (such as hypotension after instillation of a beta-blocker drop).

The timely detection and recognition of ADRs is therefore critical. Several methods exist for the detection of ADRs, but few are specific or apply to ADRs in Ophthalmology. Spontaneous reporting is a low-resource method for detection of ADRs but has flaws, namely under-detection and risk of bias. The literature can be confusing or incomplete, with several case reports and case series about ocular ADRs lacking a causality assessment (such as Naranjo's or WHO's).

In conclusion, ADRs in Ophthalmology are a heterogeneous group of ADRs that lack detection, assessment and systematization. Studies about ADRs should increase their quality for further clarification. Each ophthalmologist should know the specific ocular ADRs to systemic medication, the specific systemic ADRs to ocular medication, and to detect and treat them adequately for good clinical practice.

Keywords: Adverse drug reactions, Pharmacovigilance, Ophthalmology, Clinical practice, Therapeutics, Toxicology, Causality assessment, World Health Organization, Systemic drugs, Ocular Therapy.

INTRODUCTION

The Journal of Ocular Diseases and Therapeutics has an ambitious purpose of equipping professionals with skills to increase the detection of eye diseases and to improve the management of ocular therapeutics into good clinical practice.

These skills are invaluable in the world of adverse drug reactions (ADRs), where many confusions and myths persist.

This manuscript addresses ADRs in Ophthalmology, discusses some of the myths related to ADRs and attempts to clarify them, and provides recommendations to increase the quality in studies about ADRs and to improve recognition and management of ADRs in the clinical context.

ADRS IN OPHTHALMOLOGY

There are three basic types of ADRs in Ophthalmology:

1. Topical ADRs to a Topical Ocular Drug

These ADRs are usually easy to recognize, since the prescribing ophthalmologist is the one who detects these ADRs in the follow-up of the patient. They can be caused either by the drug administered or by its topical conservatives. One example is ocular hyperemia frequently caused by topical prostaglandins for the treatment of glaucoma [1].

2. Systemic ADRs to a Topical Ocular Drug

Topical ocular medications can be absorbed by the ophthalmic mucosa and nasal mucosa [2, 3] and reach levels in the blood enough to cause ADRs. The most common topically administered ocular drugs causing systemic side effects are the epinephrine-like compounds, which can rapidly lead to increased blood pressure and tachycardia [3]. Periocular injection of anesthetics combined with epinephrine can cause the same effects quite rapidly, leading to respiratory collapse and even death [3].

3. Topical/Ocular ADRs to a Systemic Drug

These ADRs may be difficult to diagnose, considering that in this case a general physician

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prescribes a drug, but a different physician usually is required for the diagnosis (an ophthalmologist). Other difficulty is the need of obtaining a complete medical history and registering the countless systemic medications prescribed for each patient.

The correlation of the symptoms and ocular signs of the patient with the suspect of an ADR caused by a particular drug is another difficulty, and confirming the causality of an ADR is by far even more difficult. With all these difficulties, it is not surprising that myths and confusion persist around ADRs, particularly in Ophthalmology.

MYTHS, ADRs AND OPHTHALMOLOGY

1. First Myth: Many Terms are Erroneously Applied as Synonyms of ADRs

To clarify this myth, we present definitions of different drug-related problems.

- An adverse event is [4]: "an injury related to medical management, in contrast to complications of disease". Medical management includes "all aspects of care, including diagnosis and treatment, failure to diagnose or treat, and the systems and equipment used to deliver care" [4].

- Drug-related problems are [5]: “a circumstance that involves a patient’s drug treatment that actually, or potentially, interferes with the achievement of an optimal outcome". They include ADRs.

- An adverse drug event is [6]: “An injury related to the use of a drug, although the causality of this relationship may not be proven”. These events include medication errors (namely the prescription of a wrong dose) and ADRs.

- A medication error is [7]: “Any error in the process of prescribing, dispensing or administering a drug, whether there are adverse consequences or not”.

- An adverse drug reaction (ADR) is: “any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy”, according to WHO’s definition [8] of 1972. This definition is the most widely used. Karch and Lasagna’s [9] have a definition for ADR which excludes therapeutic failures. An ADR according to Edwards and Aronson [10] is: “an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product”.

2. Second Myth: ADRs are not Important Nor Frequent

Some years ago, Lazarou and colleagues [11] estimated ADRs to be between the fourth and sixth more frequent causes of death. Although this study was criticized due to heterogeneity [12], it brought attention to the scientific community about the importance of ADRs. The mean frequency of ADRs that occur during hospitalization is estimated to be of 16.88% (95%CI: 13.56–20.21) [13] and the overall median of ADRs associated with hospital admissions is 5.3% (interquartile range 2.7–9.0%) [14].

ADRs are costly, representing US$1.56 billion in direct hospital costs per year (in the US) [15] and US$136.8 billion in indirect costs [16]. In fact, the cost of drug-related problems (including ADRs) is estimated to be higher than the total cost of cardiovascular or diabetes disease [5].

Consequently, ADRs are frequent, expensive and can be fatal, deserving to be studied in order to be detected and prevented.

3. Third Myth: ADRs in Ophthalmology are Not Specific

The theme of ADRs in Ophthalmology presents a challenge in assessment and systematization [17]. ADRs in Ophthalmology can be frequent and specific (and even irreversible), therefore healthcare team members (namely the ophthalmologist, physician, nurse, pharmacist, pharmacologist or other) should have skills for detection of an ADR to a drug in each patient.

The eye benefits of many barriers that limit access of drugs to intraocular structures, namely: tight junctions of the corneal epithelium and endothelium (which limit anterior access to the interior of the eye and belong to the blood-aqueous barrier), the vascular endothelium of the retina (non fenestrated and with tight junctions: inner blood-retinal barrier), tight junctions between the retinal pigment epithelium (with the Bruch's membrane: outer blood-retinal barrier) [2, 18].

Nevertheless, there is a plethora of possible ocular ADRs to ocular and systemic drugs. Fortunately, some systemic drugs tend to provoke specific ocular ADRs, enabling recognition of clinical patterns in specific drugs, namely: amiodarone which frequently provokes cornea verticillatta [19] and rarely provokes the potentially irreversible optic neuropathy [20], floppy iris syndrome caused by tamsulosine [21] and uveitis caused by rifabutin [22], among many others.

4. Fourth Myth: ADRs can Only be Identified by Spontaneous Reports

Many methods exist to aid Pharmacovigilance in the detection and verification of ADRs, but all have their methodological issues [23].

Spontaneous reporting (a health team member reports a presumable ADR) is the most utilized Pharmacovigilance method in Europe [24], however subnotification [25] is a problem. ***Administrative databases*** (which contain large amounts of information with clinical data that can be searched for the identification of an ADR) have been explored for ADR detection [26, 27] and present good detection rates with low resources, enabling nationwide perspectives [27].

Computerized methods are used for automatic alerts of ADRs with good results [28, 29].

Chart review (the revision of charts by an expert) is a reasonable methodology for ADR detection [30], however it is resource and time consuming, such as ***prospective monitoring*** and ***intensive monitoring*** [31] (both are monitoring methodologies performed by experts in a group of patients to detect ADRs) which are too costly to be performed regularly. Other methods exist, namely trials and pharmacogenetics studies.

ADRs that occur in the context of Ophthalmology can be detected through each of the methods above, however spontaneous reporting (and studies such as case reports and case series) are frequently utilized due to practical reasons [17]. It is important to increase the quality of these studies about ADRs to enable the scientific community to decide which conclusions can be drawn about each specific reported or presumable ADR.

INCREASING QUALITY IN STUDIES ABOUT ADRs

A few simple steps can be useful to increase quality in every study about ADRs.

First, I suggest the utilization of a definition of ADR (either WHO's definition of ADR [8], or other definition of ADR) which should have a reference in the study.

Second, a causality assessment (the assessment of the probability of a suspected ADR being a true ADR) is crucial and lacks in many ADR manuscripts. The most important and widely used causality assessments are Naranjo's [32] and WHO's [33], which apply to all ADRs, and are presented in this manuscript.

Third, if possible add further characterization of the ADR: present a classification of ADR according to Rawlins and Thomson's [34], evaluate the predictability of ADRs (using Hartwig's predictability scale, for example [35]), use Schumok and Thornton's preventability criteria [36], among others. Many technological breakthroughs in Ophthalmology allow us to provide an increased depth in the characterization of ocular ADRs with complementary testing and should be used [37].

Finally, many bibliographic or general reviews exist about ocular ADRs, but few attempt to be systematic. I

Table 1: Naranjo's Causality Assessment for ADRs [32]

Naranjo's causality assessment	Yes	No	Don't know
1. Are there previous conclusive reports of this reaction?	+1	0	0
2. Did the adverse event appear after the suspect drug was administered?	+2	-1	0
3. Did the adverse reaction improve when the drug was discontinued?	+1	0	0
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0
5. Are there alternate causes that on their own could have caused the reaction?	-1	+2	0
6. Did the reaction appear when a placebo was given?	-1	+1	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
8. Was the reaction more severe when the dose was increased or less severe when decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0
Total score*			

*****Interpretation of the Total Score: a) ≥9: *Highly probable* ADR; b) 5-8: *Probable* ADR; c) 1-4: *Possible* ADR: d) ≤ 0: *Doubtful* ADR.

Table 2: WHO's Causality Assessment for ADRs [33]

WHO's causality assessment	
1. Certain ADR	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
2. Probable ADR	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition. A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
3. Possible ADR	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear
4. Unlikely ADR	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
5. Conditional / unclassified ADR	A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.
6. Inaccessible / unclassifiable	A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

and my co-authors have identified ocular ADRs to systemic drugs that have recent original studies but are currently lacking a specific systematic review, including ocular ADRs from the following drugs: statins (we are performing a systematic review in collaboration with the Cochrane -Eyes and Vision Group), antituberculous agents, angiotensin-converting enzyme inhibitors and cidofovir. These may represent opportunities for a specific systematic review.

CONCLUSION

Confusion and myths about ADRs persist. Future studies about ADRs should: present a definition of ADR, describe a methodology for ADR detection, present standard assessments (causality assessment of Naranjo or WHO, severity assessment, classification of ADR, among others) and should increase their methodological quality.

Although spontaneous reporting is the most widely used method for detecting ADRs, other methods exist for that purpose. All methods have their methodological issues and probably should be used in conjunction to increase ADR detection.

In Ophthalmology, the theme of ADRs deserves clarification and assessment. Ocular ADRs may be frequent, specific, serious or even cause irreversible blindness. Therefore, the detection of ADRs is very important.

Methods of ADR detection should be explored and adapted to the specificity of ocular ADRs.

Additionally, each health care member (ophthalmologist, physician, nurse, pharmacist, pharmacologist or other) should know the specific ocular ADRs to systemic medication, the specific systemic ADRs to ocular medication, and should detect and treat ADRs in Ophthalmology adequately for good clinical practice.

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