Brief Communication

Adverse Drug Reactions in an Ophthalmic Set up

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Definition of adverse drug reaction (ADR)

The World Health Organization defines ADR as "A response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease or for modification of physiological function". The definition of an ADR is often confused with that of an adverse drug event (ADE). An ADR is a type of ADE whose cause can be directly attributed to a drug and its physiologic properties. A main distinction between ADRs and ADEs is that ADRs occur despite appropriate prescribing and dosing, whereas ADEs may also be associated with inappropriate use of the drug or medication error or other confounders that occur during drug therapy but are not necessarily caused by the pharmacology of the drug itself. A causal relationship is suspected for an ADR but is not required for an ADE.

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Article History
Received: 10th November 2021
Revision: 20th November 2021
Accepted: 10th December 2021
Published: 17th January 2022

Types of adverse drug reaction

Type A (Augmented) reactions result from an exaggeration of a drug's normal pharmacological actions when given at the usual therapeutic dose and are normally dose-dependent. Examples include respiratory depression with opioids or bleeding with warfarin.

Type B (bizarre) reactions are uncommon and unpredictable reaction that are not expected from the known pharmacological actions of the drug. They are independent of dose, suggesting that individual patient host factors are important. Examples include anaphylaxis with penicillin or skin rashes with antibiotics.

Type C (chronic) reactions due to cumulative long time exposure to the drug. Example includes analgesics interstitial nephritis.

Type D (delayed) reactions become apparent some time after the use of a medicine. An example is leucopoenia, which can occur up to six weeks after a dose of lomustine.

Type E (end-of-use) reactions are associated with the withdrawal of a medicine. An example is insomnia, anxiety and perceptual disturbances following the withdrawal of benzodiazepines.

How to cite this article: Jaichandran VV. Adverse drug reactions in an Ophthalmic set up. Indian J Ophthal Anaesth 2022;2(1):39-45

ADR in an Ophthalmic set-up

The most important ADR is Type B reaction which can be life threatening at times. In an ophthalmic set-up such type of reactions can be encountered in outpatient clinics, operation theatre (OT) and while performing fundus fluorescein angiogram.[1]

Authors have reported two cases of allergic reaction to topical azithromycin eye drops.[2] Patient developed epiphora, eyelid edema, chemosis, conjunctival injection, hyperemia, intensive papillary reaction, and rhinitis within 30 min of instillation.2 Both the patients immediately showed dramatic improvement after cessation of the topical medication and administration of anti-allergic therapy.

In the OT, allergic reaction to local anesthetic agents used in ophthalmic surgeries is rare. Literature review shows only four documented cases with allergic reaction to lignocaine. The first patient developed a reaction after sub-conjunctival anesthesia, the second and third patient developed after peribulbar anesthetic injection, and the fourth one developed after local infiltration for blepharoplasty.[3-6] The first three cases developed reaction several hours after the administration of anaesthetic, but the fourth case developed reaction immediately after the injection. The signs and symptoms were mostly localized in and around eye with proptosis, swelling of the upper and lower eye lid, conjunctival redness and extraocular movement restriction. In most of the cases with early detection and prompt treatment with IV antihistamines and steroids symptoms resolved completely. Deshmukh et al reported optic atrophy, a potentially blinding adverse drug reaction to peribulbar lignocaine anaesthesia.[5]

Additives in local anesthetic solutions such as antioxidants or preservatives (metabisulphite or parabens) and other adjuvants used especially injection hyaluronidase may also be responsible for adverse reactions. Peribulbar and subtenon use of hyaluronidase injection have been reported to cause both vision and life threatening reactions.[7,8] Ocular signs and symptoms include periorbital edema and erythema (unilateral or bilateral), conjunctival chemosis, proptosis, restriction of eye movements (ranging from mild to total ophthalmoplegia), puffiness of face/ear lobe, Figure 1.

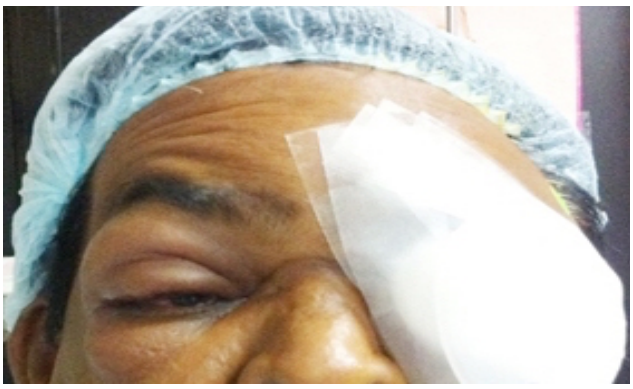

Figure 1. Contralateral periorbital swelling.

The cornea and anterior chamber remain clear although loss of vision occurred in some cases as a result of compression of the optic nerve or increase in IOP. Systemic reactions include nausea, vomiting, sweating, generalized rash, itching, tachycardia, dyspnea, angioedema of the larynx, swallowing difficulties, incontinence and anaphylactic shock. Most of the patients had undergone an earlier procedure that included hyaluronidase use, which suggests that these reactions may be a result of sensitization to the animal-derived product. It can be either due to Type I IgE mediated reaction or delayed Type IV cell mediated reaction.

The differential diagnosis includes retrobulbar haemorrhage and orbital cellulitis. Complete normal blood count with absence of fever, pain etc, history of positive exposure to hyaluronidase, positive intradermal test, serum IgE antibodies level specific to hyaluronidase, CT scan to look for any increased orbital fat haziness and /or enlargement of extraocular muscles are some of the investigations that can be done to confirm the diagnosis, Figure 2.

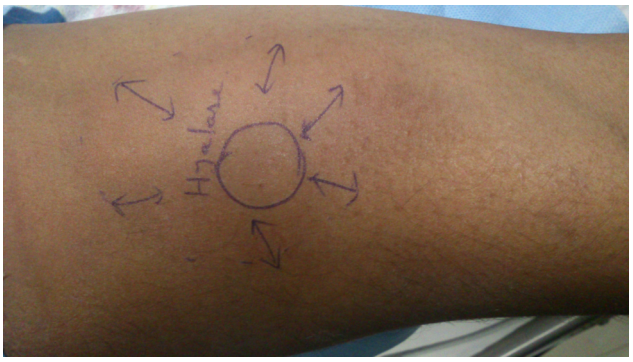

Figure 2. Positive intradermal skin test to Injection hyaluronidase.

Treatment for anaphylaxis includes epinephrine 0.3-0.5mg intramuscular, preferably in the mid-outer thigh, maintenance of airway, IV H1 antihistamine (chlorpheniramine 25-50 mg), IV steroids (Dexamethasone 8mg) and IV fluids.

To prevent such type of adverse reactions, we, at our institution, have started adopting preoperative intradermal skin test with 0.3ml of lignocaine HCL and Hyaluronidase mixture. Intradermal skin test is done for patients with history of allergy to food, insect bite, medications, bronchial asthma, allergic rhinitis, allergic skin disorders etc.

Previous authors have also reported that postoperative periorbital inflammation following use of excessive dose of hyaluronidase (50-250 IU/ml).[9,10]

This type of augmented (Type A) adverse drug reaction can be prevented by using hyaluronidase within the permissible limit of 15 IU/ml.[10]

The burden of ADR

It is clear that ADR adversely affect patient's quality of life and can also cause patients to lose confidence in the healthcare system. There is a significant impact through increase costs of patient care and the potential to lengthen hospital stay. ADR may also mimic disease, resulting in unnecessary investigations and delays in treatment. At times, ADR are serious enough to result in readmission to hospital or even referral to higher care center. It is well recognized that ADRs place a significant burden on the health service. Studies performed in an attempt to quantify this have shown adverse drug reactions account for 1 in 16 hospital admissions.[11]

Prevention of ADR

Once an ADR is suspected or diagnosed; it is important to report it as an incident to the hospital safety/drug committee so that trends can be monitored. The goal of evaluating ADRs is to increase patient safety by preventing harm. Each patient harmed by an ADR should be treated and evaluated as an individual case. Reporting leads to increased awareness and detection of ADRs and can prevent their occurrence in both inpatient and outpatient settings, which in turn can help to prevent hospital admissions or readmissions.

Following reporting of an ADR, a thorough evaluation should be done by a committee comprising of multidisciplinary team members. Begin by evaluating the nature of the event. A complete review of the patient's medical history, medication lists followed, classification of the severity of the reaction must be done.

After the reaction is evaluated, the cause of the reaction should be established, if possible. Simple tools such as the Naranjo ADR probability tool can be used to assist in determining causality.[12] By answering 10 questions about the ADR and assigning a numeric score to each answer, the ADR probability classification can be determined, see Table 1.[12]

Table 1. Naranjo ADR Probability Scale.

Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse event appear when the drug was re-administered?	+2	-1	0	
5. Are there alternative causes(other than the drug) that, on their own, could have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations know to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have 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: 9 – Highly Probable; 5–8 – Probable; 1-4 Possible; 0 - Doubtful

One should make sure the ADR is not caused by a medication error. This could influence whether a treatment is continued or discontinued. If the reaction can be attributed to a drug, a suggestion is to update the patient's allergy profile with the name of the drug and a brief description of the reaction.

Regular educational programs must be carried out. This can help remind health care professionals or the stakeholders involved about the importance of identifying and reporting ADRs. Another way of alerting health care practitioners is through publishing as case reports in the medical literature.

Conclusion

ADR will never completely be eliminated, even with the most sophisticated pharmacovigilance systems in place. The duty of the health care practitioner is to minimize the occurrence of ADRs by working to prevent them. Prevention is made possible through knowledge gained by the reporting of ADRs and in published primary literature. Sharing this information with colleagues and patients will create an awareness of ADR potential and can save lives. By including an ADR on the differential when a patient present with new or worsening symptoms, the process of identifying, classifying, and determining the causality of a potential ADR can begin immediately, and future harm may be prevented.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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