Are we pharmacovigilant enough in ophthalmic practice?

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No drug is absolutely safe. Pharmacovigilance is the science related to detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems. The ocular medications and devices can cause localized and systemic adverse effects. Not all adverse effects are known when a drug or device is launched in market because of limitations of clinical trials. Many adverse effects are recognized due to the spontaneous reporting of the vigilant doctors who observe and report such events encountered in their practice. Despite a large ophthalmic patient population base, India does not have robust adverse drug reaction (ADR) database because of lack of reporting culture. Government of India recently launched the Pharmacovigilance Programme of India (PvPI) to monitor ADRs and create awareness among the healthcare professionals about the importance of ADRs. Suspecting and reporting a possible drug reaction is very important in developing a safe and rational ophthalmic practice.

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There is no drug in the clinical practice without any adverse effects. Paracelsus, the Greek physician and philosopher (also known as the father of toxicology) had stated in the fifteenth century, that "All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy". That statement remains true even today and will continue to be so (till the medical science comes up with ultimate harmless 'utopian drugs').

As with other organs of the body, the eyes also go through the various predictable and sometimes unpredictable adverse reactions after the use of medications or devices for different conditions. All types of adverse drug reactions (ADRs) are of concern to an ophthalmologist. Pharmacovigilance or ADR monitoring is of utmost importance in this field of practice.

WHO defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems. The term now also encompasses the problems related to the use of herbals, traditional and complementary medicines (especially relevant to population in our country), blood products, biological, medical devices and vaccines.[1] It is an observational system of drug safety monitoring or surveillance. This is meant to generate hypotheses about possible adverse effects of drug treatment; and subsequently evaluating such hypothetical 'alerts', to establish their actual significant association with the drugs.[2] When applied to ocular therapeutics, pharmacovigilance covers the adverse effects in the eyes, impact of substandard ocular medicines and medication errors (in a review of medicolegal cases in ophthalmology, medication errors were found to be the third most frequent complaint).[3] Pharmacovigilance in ophthalmic practice will also include lack of drug efficacy reports, use of medicines for ophthalmic indications that are not approved and for which there is an inadequate scientific basis and adverse interactions of medicines with chemicals or other medicines.

Ocular adverse effects of drugs

The ocular medications and devices may cause localized adverse effects in the eyes. They may also cause systemic reactions and affect the developing fetus, if used during pregnancy, resulting in various abnormalities. Not uncommonly, drugs used to manage conditions unrelated to eyes can produce ocular adverse effects. Most of such manifestations can only be detected if the ophthalmologists have a keen eye for any drug involvement. Many of these clinical complications can be avoided or managed if one has a 'pharmacovigilant mindset'.

ADRs in eyes can be due to the use of various classes of drugs. These can range from mild reactions to significantly severe and serious ones. Adverse event is what a physician first reports as an abnormal observation suspected to be related to drug use. Once the causal association with the drug is confirmed the event is acknowledged as a reaction. There are many such examples of reported adverse events, which acting initially as 'signals' are later confirmed to have an association with drug usage. Following are the examples of a few of such inputs in the last decade which have contributed to a safer ophthalmic practice.

During the phacoemulsification surgery of an elderly patient, one may find a slightly miotic pupil with sluggish iris trying to protrude repeatedly through the phaco tunnel or in the side port. This could have been avoided by the surgeon, if anticipated to be caused by the α-1 adrenergic antagonists (most commonly tamsulosin). These drugs, used to treat benign hyperplasia of prostate, are known to bind to the postsynaptic nerve endings of the iris dilator muscles, leading

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to "intraoperative floppy iris syndrome".[4] Tamsulosin has also been suspected to be a precipitating factor for the lower lid entropion by its action on the α-1 receptors of the Muller's muscle.[5]

Topiramate, is an oral medication indicated for epilepsy, migraine and bipolar disorder. It has been seen to cause myopia and angle closure glaucoma. This possibly results due to uveal effusions and the ciliary body swelling which leads to forward rotation of the lens-iris diaphragm resulting in angle closure.[6] Corneal endothelial deposits are known adverse effects of some drugs. Rifabutin, which is used to prevent Mycobacterium avium complex disease in immunocompromised patients, can also cause uveitis and corneal endothelial deposits.[7]

Such complications need to be followed up after discontinuing the offending drug. The drug withdrawal generally results in complete resolution.

Panicky parents bringing a child with oculogyric crisis to an ophthalmologist may give the history of seemingly unrelated cold or allergic condition. But the antiallergic drug, cetrizine has been seen to cause oculogyric crisis in the pediatric age group. Recognizing this adverse effect could help avoid the trouble of going through detailed and exhaustive neurological examinations and investigations.[8] In some patients of sight threatening scleritis, the etiology could be traced to the previous use of bisphosphonates. These drugs are used in the treatment of osteoporosis, Paget's disease, hypercalcaemia associated with malignancy, multiple myeloma, etc. This class of drugs is known to cause serious ocular adverse effects such as uveitis, nonspecific conjunctivitis, episcleritis, and scleritis. These conditions will not resolve, regardless of the best of therapies, unless the biphosphonates are also discontinued.[9]

Drugs have long been implicated in the pathogenesis of glaucoma and cataract. Use of glucocorticoids is well known to be associated with increased intraocular pressure. Docetaxel and paclitaxel, the anticancer agents, are also associated with painless form of glaucoma.[10]

Prostaglandin analogues are fast becoming the first choice drugs to treat glaucoma even in the developing countries. Use of these drugs has been reported to cause cystoid macular edema. Though latanoprost has been reported in various studies to be the most commonly involved drug, a study has suggested the association of this problem with other prostaglandin analogs also, including bimatoprost and travoprost.[11]

Impairment of color vision and retinal dysfunction has been associated with the use of digoxin, a cardiac glycoside. This has been seen to occur even at therapeutic dose in the elderly hospitalized patients receiving maintenance therapy.[12]

PDE5-selective inhibitors such as sildenafil and tadalafil which are used to treat erectile dysfunction are suggested to cause several changes in visual perception. Nonarteritic ischemic optic neuropathy (NAION) is one of the possible complications of their use but the association is not yet certain and is debated to be coincidental.[13,14] Results of a randomized placebo-controlled study to evaluate the retinal effects of 6 months of daily use of tadalafil or sildenafil showed no abnormalities in electroretinography or visual function suggestive of any toxicity.[15]

Chronic use of linezolid, an antimicrobial effective against methicillin-resistant *Staphylococcus* and penicillin-resistant *Streptococcus*, has sometimes resulted in toxic optic neuropathy. Diagnosing the condition and discontinuation of the drug can result in significant recovery of vision.[16] Amiodarone, a commonly used drug for cardiac arrhythmias, is also associated with optic neuropathy. Regular ophthalmological examinations particularly during the initial months of the treatment can help improve the early detection of such optic neuropathy.[17] Ethambutol, an antitubercular drug, has an established association with optic neuropathy. In a study it was shown to cause a significant decrease in the retinal nerve fiber layer thickness in all the quadrants, with the greatest decrease noticed in the temporal quadrant.[18] High dose of tamoxifen, used for treatment of breast cancer and infertility, may result in peripheral crystalline retinopathy and perifoveal opacities.[19] Continuous intravenous infusion of deferoxamine (used in the patients of iron overload due to prolonged transfusions) has been reported to cause rapid development of irreversible diffuse pigmentary retinopathy with severe visual loss.[20] Interferon, used in treating chronic hepatitis, hematological malignancies, multiple sclerosis, etc., is known to cause retinopathy characterized by retinal hemorrhages, cotton wool spots and macular edema. The incidence of such retinopathy is low with pegylated interferon. These retinal complications are asymptomatic and resolve as the treatment continues.[21] Fludaribine, another drug used in the treatment of hematological malignancies, may result in severe vision loss due to retinal bipolar and ganglion cells damage. So vision loss in a patient one month after treatment with fludaribine should prompt a consideration of this toxicity.[22] Isotretinoin used in various dermatological and malignant conditions has been seen to produce persistent and clinically significant abnormalities in night vision. Hence patients with previous history of use of this drug need to be screened for night blindness if they are considering a job where night vision is critical.[23]

There are numerous other such examples which highlight the importance of an alert and vigilant physician in identifying and implicating a prescribed drug's role in the etiology of an ocular condition.

These adverse effects have come to our knowledge due to physicians and ophthalmologists who have observed and reported the events and thus have contributed to collecting and collating meaningful data for further validation and spread of significant information.

Is a drug or surgical device approved and marketed only after *everything* is known about it?

There can be many unexpected events or complications in the clinical practice which might not have been in the list of adverse reactions of a marketed product as known to an ophthalmologist even from the most authentic source possible. This is the limitation of the drug discovery process and is applicable to everything new that is coming in the market and is being prescribed, and this limitation demands the vigilant involvement of the prescriber for the product-related valuable experience as feedback.

A drug before being marketed undergoes the preclinical

(animal) and then clinical (humans) trials. It is obvious that clinical trials are important to know the drug effect on humans as we cannot directly extrapolate the results of preclinical animal studies due to individual species specific response variations. The different phases of human trials use a limited number of participants in a restricted environment with specific inclusion and exclusion criteria. The actual patient population finally using the product may be thousand times larger and diverse as compared to the trial volunteers. Thus significant side effects with low incidence rate may be missed during the trials due to the small number of participants, only to surface when used in large number of patients after marketing of the drug. Children, pregnant women, elderly population are generally not part of the routine trials and these special groups of population may be at risk for unique ADRs or for an increased frequency of ADRs compared with the general population.[24]

A patient with an eye problem may be of any age and sex, suffering from diseases of other systems at the same time and also using traditional medicines (especially in developing countries) which are likely to interact with the drugs we prescribe. Also, most of the drug development is still being done in the western countries and the efficacy and safety data are from trials on the Caucasian population which may respond differently from other populations.[25] So during practice there may be unexpected adverse reactions that we will be seeing for the first time and it becomes our duty to report those reactions and help in the evolution of scientific knowledge.

Many of the drug bans, new "black box" warnings and modified product labels are due to the simple efforts of practitioners who take the little extra initiative to inform about the abnormal reaction (whether established or suspected) and get it added to the regional or national data.

Under reporting of ADRs is one of the biggest challenges to be overcome. A number of methods have been used to identify the previously unknown harmful effects likely to be due to use of drugs. Premarketing clinical trials, postapproval spontaneous case reports, postmarketing cohort studies, computerized collections of data from organized medical care programs, meta-analysis, etc., are some of the methods used for detecting ADRs. More than any other detection method, serious ADRs have been identified by the spontaneous case reporting.[24]

The Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services under the aegis of Ministry of Health and Family Welfare, Government of India has recently launched the Pharmacovigilance Programme of India (PvPI) to monitor ADRs and create awareness among the healthcare professionals about the importance of ADRs. The program became operational in July 2010 and envisages setting up ADR-monitoring centers in medical colleges and private hospitals to help foster the reporting culture among healthcare professionals. There are plans to make a provision of online reporting of ADRs by healthcare professionals not covered under the program. The ADR reporting form and details of the program are available at the CDSCO website.[25]

Conclusions

We are in no way lagging behind the best of ophthalmologists the world over, but when it comes to quoting references in our research work, clinical talks and discussions, we rely on the data from countries which may even be smaller than one of our states. This is because we do not have our own national ADR data despite having one of the largest ophthalmic patient populations. Although the newly launched PvPI is in its initial phase, now that it has been rolled out, we can hope that in near future the reporting of ADRs will become popular. Noticing and suspecting a drug among other possible causes of a therapeutic complication must become a reflex in our clinical practice.

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