REVIEW ARTICLE

Drugs 2007; 67 (1): 75-93
0012-6667/07/0001-0075/$49.95/0

Ocular Adverse Effects Associated with Systemic Medications

Recognition and Management

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Abstract

This article reviews several retrospective case series and reported adverse events regarding common ocular adverse effects related to systemic therapy. It is not intended as a comprehensive summary of these well described adverse drug reactions, nor is it intended to cover the complete spectrum of all ocular adverse effects of systemic therapy. Many systemic drugs may produce ocular toxicity, including bisphosphonates, topiramate, vigabatrin, isotretinoin and other retinoids, amiodarone, ethambutol, chloroquine and hydroxychloroquine, tamoxifen, quetiapine, cyclo-oxygenase (COX)-2 inhibitors, erectile dysfunction agents and some herbal medications. For this review, the certainty of the adverse effect

profile of each medication was evaluated according to the WHO Causality Assessment Guide.

A certain relationship has been established for pamidronate and alendronate as causes of scleritis, uveitis, conjunctivitis and blurred vision. Topiramate has been established as adversely causing symptoms consistent with acute angle-closure glaucoma, typically bilateral. Vigabatrin has been shown to cause bilateral irreversible visual field defects attributed to underlying medication-induced retinal pathology. Isotretinoin should be considered in the differential diagnosis of any patient with pseudotumour cerebri. Patients taking amiodarone and hydroxychloroquine should be monitored and screened regularly for development of optic neuropathy and maculopathy, respectively. Sildenafil has been reported to cause several changes in visual perception and is a possible, not yet certain, cause of anterior ischaemic optic neuropathy. Patients taking tamoxifen should also be monitored for development of dose-dependent maculopathy and decreased colour vision. COX-2 inhibitors should be included in the differential diagnosis of reversible conjunctivitis. Several herbal medications including canthaxanthine, chamomile, datura, *Echinacea purpurea*, *Ginkgo biloba* and liquorice have also been associated with several ocular adverse effects.

It is the role of all healthcare professionals to detect, treat and educate the public about adverse reactions to medications as they are an important health problem.

The term 'side effect' usually refers to an undesired or negative effect of medication that is extraneous to the intended therapy. When the effect is negative, the term 'adverse effect' is used. Drug-induced ocular adverse effects are the second most frequent reason for claims against ophthalmologists.[1,2] This may not be surprising given that prescribing medications is the most common therapeutic service provided by physicians. According to the National Center for Health Statistics, new or continued medications are ordered or provided at 41% of visits to an ophthalmologist's office. Because serious injury can occur, drug-related adverse effects can be costly to defend, indemnify or settle.[2]

The rich blood supply and relatively small mass of the eye make it particularly susceptible to drug-induced adverse reactions. Adverse ocular reactions to drugs are diverse. Drug molecules present in the system may become selectively deposited in specific ocular tissues such as the cornea, lens and retina, causing varied symptoms of drug toxicity. Fortunately, most adverse reactions induced by systemic medications are reversible if detected early. However, if undetected, toxic effects may progress and cause irreversible ocular damage often with an associated reduction in visual function.[3,4]

For ophthalmic drugs to be effective, they must reach ocular tissue in relatively high concentrations. There are several different administration routes for ophthalmic drugs, including the topical, oral, parenteral, periocular, intracameral (intraocular administration into the anterior segment) and intravitreal routes. Topical application is the most common route of administration because it is simple, less invasive and does not involve the passage of drugs through the blood-aqueous barrier. However, some disorders require systemic drug administration to achieve adequate therapeutic levels of the drug in and around the ocular tissues.

Certain factors increase the probability of an adverse ocular reaction. One such factor is use of a medication over long periods of time, for example, in cases of arthritic and cardiovascular diseases. In some patients, it may be difficult to establish whether ocular pathology is caused by the condition being treated or by a drug used to treat the condition.

Patient age is also a significant factor in the prevalence of ocular drug reactions. Older patients are more likely to have used medications for protracted periods. Also, the metabolism and excretion of a drug can be affected by decreased efficiency of the kidney and liver secondary to the patient's age, or by conditions adversely affecting these organs.[3,4]

Some drug responses cannot be predicted from the drug's pharmacological mode of action. A genetic basis may underlie many of these unpredictable responses, as observed in the rapid rise in intraocular pressure reported with topical corticosteroids.[5]

The prevalence of adverse reactions is closely associated with drug dosage. Most reported ocular reactions occur when the dose is beyond the therapeutic range. It is essential that clinicians try to establish whether the ocular problem coincided with the start of drug therapy or with a change in drug dosage. A useful marker is seen when the onset of the reaction coincides with commencement of the medication, but reactions can occur at any time during or after a course of medication, and can continue for years after cessation.

We performed a MEDLINE literature search using the following keywords: 'ocular', 'visual', 'eye', 'side effects', 'adverse effects', 'medication' and 'treatment'. Some of the medication adverse effects obtained through this search are summarised below; these were selected at the authors' discretion, taking into account some of the more recent published medication adverse effects, and are not presented in any particular order. This brief review is not intended as a comprehensive summary of these well described adverse drug reactions, nor is it intended to cover the complete spectrum of all ocular adverse effects of systemic therapy. Interested readers are encouraged to refer to textbooks cited within the references.

1. Categorising Adverse Drug-Related Events

The WHO Causality Assessment Guide of Suspected Adverse Reactions was used to classify the reported adverse drug-related events into the following categories: certain, probable/likely, possible, unlikely, conditional/unclassified and unassessable/unclassifiable.[6] The 'certain' category includes plausible time relationship to drug administration

Table I. WHO definitions: causality assessment of suspected adverse reactions (reproduced from Brick,[2] with permission)

Certain
A clinical event, including a 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
Probable/Likely
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
Possible
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
Unlikely
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
Conditional/Unclassified
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
Unassessable/Unclassifiable
A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified

Table II. Classification of adverse ocular effects associated with medication usage

Medication	Certain	Probable	Possible
Pamidronate	Blurred vision Pain Photophobia Ocular irritation Nonspecific conjunctivitis Anterior uveitis (rare posterior) Anterior scleritis (rare posterior) Episcleritis	Periocular, lid, and/or orbital oedema	Diplopia Visual hallucinations Yellow vision Retrobulbar neuritis Cranial nerve palsy
Alendronate	Blurred vision Pain Conjunctivitis Uveitis Scleritis	Diplopia	Glaucoma
Risedronate	No effects	Conjunctivitis Pain Scleritis Uveitis Blurred vision	Diplopia Papilloedema Episcleritis
Etidronate	Blurred vision	Conjunctivitis	Diplopia
Topiramate	Acute glaucoma (mainly bilateral) Anterior chamber shallowing Increased ocular pressure Mydriasis Suprachoroidal effusions	Blepharospasm Oculogyric crisis Retinal bleeds Uveitis	Scleritis Teratogenic effects, including ocular malformations
Isotretinoin	Abnormal meibomian gland secretion Blepharoconjunctivitis Corneal opacities Decreased dark adaptation Decreased tolerance for contact lens wear Decreased vision Increased tear osmolarity Keratitis Meibomian gland atrophy Myopia Ocular sicca Ocular discomfort Photophobia Pseudotumour cerebri Teratogenic ocular abnormalities	Decreased colour vision Permanent loss of dark adaptation	Corneal ulcers Diplopia Eyelid oedema Optic neuritis Idiopathic intracranial hypertension with optic disc oedema Permanent sicca-like syndrome Subconjunctival haemorrhage
Amiodarone	Aggravated sicca (drug in tears) Blepharoconjunctivitis Bright lights Coloured haloes around lights Corneal microdeposits Glare Hazy vision Photosensitivity Periocular skin pigmentation Thyroid eye disease Visual sensations	Anterior subcapsular lens opacities Corneal ulceration Loss of eyelashes or eyebrows Non-arteritic ischaemic optic neuropathy Pseudotumour cerebri	Autoimmune reaction (dry mouth, dry eyes, peripheral neuropathy and pneumonitis)

Continued next page

Table II. Contd

Medication	Certain	Probable	Possible
Sildenafil	Changes in colour perception coloured tinge decreased colour vision dark colours appear darker Blurred vision central haze transitory decreased vision Changes in light perception increased perception of brightness flashing lights, especially when blinking ERG changes Conjunctival hyperaemia Ocular pain Photophobia	No effects	Mydriasis (emotional effect?) Retinal vascular accidents (secondary to exertion?) Subconjunctival haemorrhage Anterior ischaemic optic neuropathy
Tamoxifen	Corneal opacities Retinal opacities, degeneration, pigmentary changes, haemorrhage Loss of visual acuity	No effects	No effects
COX-2 inhibitors	Conjunctivitis Blurred vision	No effects	No effects
Nicotinic acid	No effects	Cystoid macular oedema	Decreased vision, dry eyes, discoloration of the eyelids, eyelid oedema, Proptosis Loss of eyebrows and eyelashes, and superficial punctate keratitis
Canthaxanthine	Crystalline retinopathy	No effects	No effects
Chamomile	Allergic conjunctivitis	No effects	No effects
Datura	Mydriasis	No effects	No effects
Echinacea purpurea	No effects	Conjunctivitis	No effects
Ginkgo biloba	No effects	No effects	Spontaneous hyphema Retinal haemorrhage
Liquorice	No effects	No effects	Vasospasm, visual loss associated with migraine-like symptoms
Vitamin A	Intracranial hypertension (when taken in large doses)	No effects	No effects

COX = cyclo-oxygenase; **ERG** = electroretinogram.

and inability to explain the adverse effect by concurrent disease or other drugs or chemicals. Dechallenge data are necessary and rechallenge should be positive. 'Probable' is the same as 'certain' without positive rechallenge data. 'Possible' is an adverse event in a reasonable time sequence to administration of the drug, but could also be explained by concurrent disease or other drugs or chemicals. Positive dechallenge data are lacking or unclear in this category (table I).

2. Medications and Adverse Effects

2.1 Bisphosphonates

Bisphosphonates inhibit bone resorption by binding to hydroxyapatite crystals and inhibiting their dissolution.[7] Different bisphosphonates vary greatly in their efficacy and their adverse-effect profiles depending on the structure of the individual drug. These medications are associated with ocular adverse effects that are mainly inflammatory, i.e. conjunctivitis, uveitis and episcleritis.[8,9] Recent studies

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