Prevention and management of drug-induced ocular disorders

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Although health professionals and the public may be less aware of the risk of an ocular adverse drug reaction (ADR), either as a discrete event or part of a larger ADR, they form a significant proportion of ADRs in the Medicines and Healthcare products Regulatory Agency’s (MHRA’s) Yellow Card system. Between 1964 and 2004, 4.3 per cent of the suspected ADRs reported to the scheme referred directly to disorders of the eye (personal communications, MHRA).

The eye’s complexity, specialised tissues, diverse metabolisms and integration into the CNS allow drug toxicity to present in many forms. Varying individual characteristics of both systemically and topically applied drugs increase the number of possible adverse effects.

Ocular structures may exhibit the earliest sensitivities to drug toxicity; however, the aging process, underlyng disease processes (such as diabetes) or even the need for new spectacles can make the process of detecting an ADR difficult. An ability to take a good drug history and a high degree of suspicion and knowledge about the potential for ocular ADRs are essential.

Mechanisms for ocular ADRs

Drugs can cause a variety of problems in the functioning of the eye dependent on the area of the eye they act upon.

Normal eye function requires a well-lubricated cornea and regular blinking of the eyelids distributing tears and other secretions from the meibomian glands, lacrimal glands and conjunctival goblet cells. Interference with tear production can lead to ocular discomfort, bacterial infection of the conjunctiva and, in extreme cases, corneal ulceration, scarring and vascularisation.

Direct effects on the cornea do not generally cause discomfort or reduce vision, but a number of drugs can produce corneal deposits within the corneal epithelium. Occasionally associated with a halo effect around lights, they usually disappear on discontinuation of the drug.

The metabolically active lens of the eye incorporates new lens fibres throughout its life. The lens is also attached to smooth muscle (the ciliary body) innervated by the parasympathetic nervous system. This enables drugs to affect the lens in one of four ways: lens opacities, lens deposits, an effect
on the parasympathetic system or changes in lens hydration. The most serious effect on the lens is cataract formation.

Drugs can also contribute to glaucoma, a condition characterised by cupping of the optic disc and loss of field and usually accompanied by raised ocular pressure. Intraocular pressure is maintained by the continuous formation and removal of aqueous humour from the eye. Actively secreted by the ciliary epithelium 90 per cent of aqueous humour is drained via the trabecular meshwork and Schlemm’s canal system, the remainder being removed via the uveoscleral system. Impairment of aqueous humour drainage can cause open-angle glaucoma. Less commonly, precipitation of narrow-angle glaucoma can occur in susceptible patients.

The photochemically reactive retina supplies the electrical impulses to the optic nerve and the visual centres in the CNS. The photoreceptors, neural elements of the retina and optic nerves are incapable of regeneration so chemical damage to these structures is irreversible leading to permanent loss of vision.

### Principal ocular reactions and causative drugs (see Table 1)

#### Dry eye

One of the most serious ocular reactions is that of Stevens-Johnson syndrome. Over 200 drugs can cause this acute inflammatory vesiculobulbous reaction of the skin and mucous membranes. Ocular involvement occurs in 43-81 per cent of patients, with 35 per cent experiencing permanent visual damage.

The inflammation is self-limiting, but subsequent conjunctival scarring and damage to lacrimal ductules and goblet cells can lead to intractable dry eye syndrome, sometimes further complicated by trichiasis (in-turning of the eyelashes). Effects on the cornea can include opacities, vascularisation, keratinisation and thinning.

A large number of drugs have been associated with Stevens-Johnson syndrome including penicillins, NSAIDs, tetracyclines, sulphonamides, carbamazepine and lamotrigine.

Anticholinergic drugs (anti-spasmodics and TCAs) can cause reversible reductions in tear production, potentially leading to ocular irritation, burning and itching.

Isotretinoin can also cause patient complaints of dry eye, blepharoconjunctivitis and corneal opacities. In some cases contact lens wearers may find they have to discontinue contact lens use or use additional preservative-free lubricating eye drops. Use for longer than a few weeks may rarely lead to reduced night vision performance in some patients, which can be permanent.

Despite the severe ocuromucocutaneous reactions that led to the withdrawal of practolol in the 1970s, oral beta-blockers are generally well tolerated, although blurred vision, dry eyes and reduced tear secretion have been reported. Topical beta-blockers can cause local stinging, burning, pain, itching, erythema, allergic reactions and dry eyes.

The use of bisphosphonates, such as alendronic acid and risedronate (Actonel), has been associated with dry and sore eyes, iritis, conjunctivitis and optic neuritis. Onset time ranges from days to a number of years, and in most patients appears to be reversible.

Bisphosphonates have also been linked to cases of scleritis.

#### Corneal and lens deposits

Deposits in the corneal epithelium have been associated with the use of amiodarone, chloroquine, gold therapy, chlorpromazine, hydroxychloroquine (Plaquenil), indometacin and tamoxifen. Topical adrenaline use has also been linked to black and brown deposits in the cornea.

Symptoms from corneal deposits are relatively rare. Occasionally the deposits can lead to a halo effect around lights. Rarer deposits in the corneal stroma, associated with gold therapy, chlorpromazine and indometacin, can occasionally affect

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**Table 1. Principal ocular reactions and causative agents**

<table>
<thead>
<tr>
<th>Ocular reaction</th>
<th>Causative drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry eye</td>
<td>anticholinergics (TCAs and antispasmodics), bisphosphonates, isotretinoin</td>
</tr>
<tr>
<td>Corneal and lens deposits</td>
<td>amiodarone, chloroquine, chlorpromazine, gold, hydroxychloroquine, indometacin, tamoxifen</td>
</tr>
<tr>
<td>Cataracts</td>
<td>antimitotics, glucocorticoids, isotretinoin, phenytoin</td>
</tr>
<tr>
<td>Eye accommodation</td>
<td>benztropine, phenothiazines, TCAs</td>
</tr>
<tr>
<td>Raised intraocular pressure and glaucoma</td>
<td>anticholinergic agents, corticosteroids</td>
</tr>
<tr>
<td>Retinal and nerve damage</td>
<td>ethambutol, isoniazid, tamoxifen, vigabatrin</td>
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Serious ADRs

vision. Discontinuation of the suspect drug usually results in the disappearance of deposits.

Gold therapy, amiodarone and chlorpromazine have also been linked with deposits in the lens of the eye. Again these deposits rarely affect vision and do not appear to be linked to cataract formation.

Cataracts

Cataracts are the most serious toxic effect that can occur on the lens, since they are irreversible and can necessitate removal (see Figure 1). Glucocorticosteroids are the most important cause of cataracts and can occur after oral, topical or parenteral administration. Evidence for a risk associated with inhaled steroids is less reliable. Early detection and removal of the steroid can prevent cataracts progressing, and sometimes regression may be seen.

Other implicated drugs include antimitotics such as busulfan and nitrogen mustards. Both isotretinoin and phenytoin have also been associated with cataracts.

Accommodation of the eye

Anticholinergic drugs such as benzatropine (Cogentin), the phe-nothiazines and TCAs can reduce accommodation of the eye. Cholinergic agents will also cause reduction leading to myopia and blurring distant vision. Myopia can also be induced by increases in lens hydration, leading to changes in the curvature of the lens; this reversible myopia can be caused by oral contraceptives, prochlorperazine, sulphonamides and tetracyclines.

Raised intraocular pressure and glaucoma

Topically administered corticosteroids can reduce the outflow of aqueous fluid through the trabecular network, with up to 30 per cent of patients developing raised pressures after several weeks’ treatment. Less frequently, systemic corticosteroids may also raise intraocular pressure. The glaucoma may be asymptomatic until irreversible loss of visual field occurs. Withdrawal or reduction in dosage of the steroid will usually reduce the intraocular pressure.

Anticholinergic agents can dilate the pupil precipitating angle closure in susceptible patients with a shallow anterior angle. Care should be taken in those who may have a predisposition for angle closure, such as the longsighted. The use of TCAs in patients with the more common open-angle glaucoma is not a risk and those with diagnosed angle-closure glaucoma will already have received an iridotomy. Although SSRIs have lower anticholinergic activity compared to TCAs, there are reports of angle closure.

Pilocarpine, although used to treat glaucoma, can induce acute angle-closure due to anterior movement of the lens-iris diaphragm.

<table>
<thead>
<tr>
<th>Drug</th>
<th>BNF advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>corneal microdeposits – advise patient may be dazzled by headlights at night</td>
</tr>
<tr>
<td>Anticholinergic bronchodilators (ipratropium/tiotropium)</td>
<td>risk of acute angle-closure glaucoma – protect patient’s eyes from nebulised drug or drug powder</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>only use if other drugs for chronic inflammatory conditions fail – ocular examinations according to locally agreed protocols</td>
</tr>
<tr>
<td>Corticosteroid (topical and systemic)</td>
<td>specific warning about risks of steroid glaucoma and steroid cataracts</td>
</tr>
<tr>
<td>Desferrioxamine</td>
<td>risk of lens opacity and retinopathy – pretreatment eye examinations and three-monthly checks</td>
</tr>
<tr>
<td>Didanosine</td>
<td>retinal and optic nerve changes (especially in children) – dilated retinal examinations recommended</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>test visual acuity before starting – advise patients to stop treatment immediately if vision deteriorates – use with caution in children less than 5 years old</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>pretreatment screening and treatment monitoring annually – advise patient to stop treatment if visual deterioration</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>visual disturbances – expert referral and possible withdrawal</td>
</tr>
<tr>
<td>Topical miotics</td>
<td>counsel patient on blurred vision and effect on skilled performance (particularly at night)</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>ophthalmological testing recommended – risk of visual disorders</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>visual field defects (for up to several years after initiation of treatment) – pretreatment screening and regular testing – advise patient to report new visual symptoms</td>
</tr>
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Table 2. A selection of drugs with monitoring or patient advice from the BNF.
Serious ADRs

The reversible visual effects of digoxin, thought to be a direct toxic effect on the photoreceptors, have been well described since the 18th century, and include shimmering effect on the photoreceptors, have been well described since the 18th century, and include shimmering or halo effects or even, on occasion, temporary blindness.

Antimalarial drugs in doses used to treat systemic lupus erythematosus and rheumatoid arthritis are toxic to the retina. The risk is related to the total dose, with few cases occurring in patients receiving less than 300g. The toxicity is experienced as a loss of visual acuity, with blind spots in the visual field. Colour recognition may also be affected. Once damage is established recovery of vision is unlikely.

Although high-dose tamoxifen (up to 1800mg) has been associated with cataracts and retinopathy, standard doses (20mg) are considered to have a lower propensity to cause eye damage, have less severe effects and are reversible in nature. Clinically insignificant reversible corneal deposits similar to those of chloroquine and amiodarone have also been reported. Although evidence for monitoring ocular toxicity of tamoxifen is limited, some have advocated annual eye examinations.

Ethambutol and isoniazid have both been associated with neuritis in some cases leading to optic atrophy and a permanent loss of vision. Cessation usually leads to a recovery.

Vigabatrin (Sabril) is associated with visual field defects. Although approximately a third of patients may be affected, many cases are asymptomatic as central visual acuity may be unchanged. The effects can be largely irreversible following discontinuation of the drug. Onset can be within weeks of treatment, but may occur several years later.

Cases of loss of vision related to COX-2 inhibitors have been reported. The possible mechanism is an effect on the retinal blood flow, which appears reversible.

Prevention and management of eye conditions

In many cases withdrawal of the drug resolves the eye condition. If treatment is to continue, use of palliative therapies such as eye lubricants may be indicated in minor, yet irritating, adverse effects such as dry eye.

In those drugs with a known propensity to affect the eye, appropriate monitoring and warnings to patients should be issued. For example, those taking long-term steroids should be advised to see an optometrist for assessment of visual acuity and measurement of intraocular pressure. The BNF contains a number of warnings and recommendations (see Table 2). An ongoing assessment of the risks and benefits of therapy should be undertaken when using those drugs with serious long-term risks to vision, eg chloroquine.

Adverse effects of topical glaucoma medicines, such as stinging, dry eye, itching and foreign body sensation may be reduced by the use of preservative-free preparations.

As always, the general advice related to good prescribing applies: prescribe drugs only when necessary and appropriate.

References


Further reading


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