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OCCULAR ADVERSE EFFECTS OF SYSTEMIC MEDICATIONS: A REVIEW

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INTRODUCTION

Patient safety of is one of the most important issues in contemporary medicine. Drugs that are taken orally are systemically absorbed, with the potential to affect all parts of the body including the eye. Its rich blood supply and relatively small mass increase the susceptibility of the eye to drug-related adverse effects.[1]

Some ocular adverse effects may be reversed with medical or surgical intervention whereas other drugs may cause irreversible loss of vision.

The risk of visual loss can be reduced by a number of approaches, including monitoring for ocular toxicity, reducing the drug dose, or stopping the drug and looking for an alternative.

Information related to adverse drug effects caused by ocular medications and ocular adverse effects of systemically administered drugs has increased over the last several decades. Here we review the medical literature to determine the ocular toxicity of non-ocular drugs.[2]

Amiodarone: Is an anti-arrhythmic drug used in the treatment of ventricular tachycardia and fibrillation, and in restoration of sinus rhythm in atrial fibrillation. Ocular side effects have been noted, the most common being corneal microdeposits, which are found in 70–100% of patients. Other's are, which rarely cause visual impairment, include anterior subcapsular lens opacities, multiple chalazia, and dry eye syndrome.[3]

It leads to deposit on the basal epithelial layer of the cornea causing the formation of whorl-like corneal microdeposits called vortex keratopathy or corneal verticillata. It causes the appearance of a whorl in the cornea, which can have a little bit of blurred vision. Opacities in the anterior subcapsular lens may also form. 4 It can also cause ischemic optic neuropathy. It may be due to mechanical or biochemical hindering of axoplasmic flow due to the accumulation of intracytoplasmic lamellar inclusion bodies, a drug-induced lipidosis, articularly in large optic nerve axons.[5,6]

Anticoagulants and Antiplatelets: Have very few ocular side effects.While they generally do not cause hemorrhages on the surface of the eye (subconjunctival hemorrhages), they can prolong bleeding time make these hemorrhages worse than they normally would be. In some cases, this type of medication should be stopped before eye surgery (Possibly not cataract surgery), and they usually should be stopped before eyelid surgery. Also, a 2012 study found that the risks for early age-related macular degeneration (AMD) and wet late AMD are associated with frequent aspirin use, and the risk increases with greater aspirin consumption.[7,8]

Antipsychotics: In typical antipsychotics, phenothiazines bind to melanin granules and can cause a severe phototoxic retinopathy. Chlorpromazine, especially when used in high doses more than 2 grams daily, causes abnormal pigmentation in the eyelids, interpalpebral conjunctiva, cornea, and the lens.[9] Phenothiazines can cause the development of corneal epithelial changes that can eventually result in corneal oedema.[10] Antipsychotics like chlorpromazine and thioridazine are the mostly examined two drugs in this group which can form eye opacity after using high dose.[11,12] Of 61 patients who have used 800 mg of chlorpromazine for two years, 35 have faced the development of pigment accumulation.[13] In another study, 33% of 384 patients with long-term chlorpromazine use have shown deposits in the lens and cornea.[14]

Most frequently, retinal lesion occurring as a result of using thioridazine is retinitis pigmentosa. Pigment accumulation progresses from the periphery of the retina through the central area. By this way, peripheral vision loss, night blindness, central scotoma, and as a result total loss of sight develop.[15]

Clozapine: Is a tricyclic dibenzodiazepine derivative with weak D2 and D1 dopamine-receptor blocking activity. It is a relatively new atypical antipsychotic that is used in place of phenothiazines, particularly for refractory schizophrenia. It has been postulated that photosensitisation of tissue proteins occurs in areas with increased sun exposure after accumulation of the drug in these tissues. As clozapine also acts on dopamine receptors, the dopaminergic system of the retina may respond to accumulation of clozapine.[16] Altered dopaminergic regulation of melatonin is suspected to increase susceptibility of photoreceptors to damage by light.[17]

Tricyclic antidepressants: They are used to treat depression, some types of anxiety, and they can help control chronic pain. They can cause serious ocular side effects in the early periods of the treatment. The two most common side effects are mydriasis and cycloplegia. Cycloplegia is related to the paretic effect on ciliary muscle. Mydriasis and cyclopegia rise in result of TCAs' anticholinergic effect.[18] Anticholinergic and Anti H1 effects of TCAs increase dry eye. Dry eye may also manifest as photophobia, and rarely keratoconjunctivitis. Accommodation difficulty and near vision blurring is typically an anticholinergic effect of TCAs.[19]

SSRIs and SNRIs: The prescription of antidepressants has risen considerably in last decade with a preference for using newer antidepressants like Selective Serotonin Reuptake Inhibitors (SSRIs). Serotonin in tears modulates sensitization of corneal nociceptor. Increase in serotonin levels can decrease corneal nerve sensitivity, lacrimal reflexes and the tear film. Thus, SSRIs have much greater propensity for dry eye than SNRI.[20]

Paroxetine, SSRI's and SNRI's like venlafaxine, noradrenergic effects with sympathomimetic effects might cause active mydriasis and passive mydriasis due to serotonergic activity. Therefore, aqueous outflow is prevented and glaucoma attack develops with IOP increase.[21] In the literature survey, 11 articles have reported glaucoma in relation with SSRI. While 6 of these are related with paroxetine, 2 with citalopram, one with escitalopram, one with fluoxetine, and one with fluvoxamine.[22,23,24]

In the last few years, cases have been reported with maculopathy related to Sertraline, including bilateral bull's eye maculopathy and bilateral cystoid edema.[25,26]

Bisphosphonates: are used to inhibit bone resorption in postmenopausal women and in the management of hypercalcemia of malignancy. Cases of ocular inflammation in patients taking bisphosphonates have been reported since the early 1990s.[27] Ocular side effects that have been associated with bisphosphonate treatment include conjunctivitis, uveitis, episcleritis, scleritis, and keratitis.[28] Of those, scleritis and keratitis carry the greatest risk of long-term vision loss. Other rare conditions, such as optic neuritis and orbital or periorbital edema have occasionally been reported. Oftentimes more than 1 ocular side effect will present at the same time. Presentation can be unilateral or bilateral.[29]

Cyclosporin and Tacrolimus: These drugs are commonly used in patients who have undergone organ or bone marrow transplants, and they can cause posterior reversible encephalopathy syndrome. These patients will present with bilateral vision loss. Tacrolimus is known to cause optic neuropathy and proposed mechanisms includes direct neurotoxic effect causing axonal swelling or a vascular mechanism. Although optic neuropathy is most commonly seen bilaterally, a significant number of these cases initially present with unilateral or asymmetric symptoms.[30] Optic neuropathy from tacrolimus toxicity is very uncommon but, when present, can result in severe vision loss. Cyclosporin A given after bone marrow transplantation may have caused bilateral optic neuropathy. Microangiopathy of the optic nerve may be the pathogenetic mechanism.[31]

Corticosteroids: used to treat inflammatory conditions. They can accelerate cataract progression. Slowly progressive visual loss in both eyes, but may be asymmetric in two eyes. Classically, they cause posterior subcapsular cataracts developing in 25% of patients who use prednisone 15 mg/day for 1 year or more, or equivalent doses of other corticosteroids. Slowly progressive visual loss in both eyes, but may be asymmetric in two eyes.This may relate to corticosteroid-induced changes to gene transcription in the epithelial cells of the lens.[32]

Chloroquine prevents malaria, **Hydroxychloroquine** treats rheumatic illnesses. It is a known retinal toxin, and the effects are irreversible.[33] Most common ophthalmic side effect seen is damage to retinal pigment epithelium, causing irreversible vision loss. Pericentral scotomas on special visual fields and Fading of orange color of retina around fovea ("bull's eye maculopathy"), appearing well after visual symptoms begin. Patients who have been taking hydroxychloroquine for a period longer than 5 years or have been taking doses greater than 5 mg/kg/day are at an increased risk of maculopathy.[34]

Clofazimine: has shown activity against MDR TB. It can cause red-brown discoloration of conjunctiva, cornea and lacrimal fluid (tears).[35] 38-57% of patients may develop conjunctival discoloration which is dose related.[36] Resolution usually occurs when clofazimine is discontinued.

Digoxin: Digoxin, an Na+/K+ ATPase inhibitor, is widely used for the treatment of congestive heart failure. It is well known that digoxin can produce alterations in the visual system of patients, such as reduced visual acuity, photophobia, and blurred or yellow vision.[37]

It is known that the inner segment of the photoreceptors contains Na+/K+ ATPase, which plays an important role to maintain a dark current along the photoreceptors. Furthermore, it has been reported that digoxin, an Na+/K+ ATPase inhibitor, induced concentration-dependent reductions in the light response of isolated photoreceptors from amphibians.[38] Thus, it is speculated that the reversible visual disturbances in digoxin-treated patients are associated with inhibition of Na+/K+ ATPase in the inner segment of the photoreceptors. These changes are likely due to direct photoreceptor toxicity.[39]

Deferoxamine: Desferrioxamine mesylate is the commonest iron chelating agent used in the management of iron toxicity and can be administered subcutaneously or intravenously. The ocular toxicity is postulated to be due to the direct effect of desferrioxamine, chelation of ions (iron, copper, aluminum) on the retinal pigment epithelial with resultant dysfunction or due to defective vasoregulation.[40] Ocular side-effects include cataracts, retrobulbar optic neuritis, pigmentary retinopathy, bull's eye maculopathy and vitelliform maculopathy, which results in impaired visual acuity, visual field, night vision, color vision.[41] The pigmentary retinopathy is classically macular or peripheral but can rarely present in the paramacular, papillomacular or peripapillary pattern.

Ethambutol: Medication used to treat mycobacterial diseases, including tuberculosis. Most common ophthalmic side effect is bilateral optic neuropathy. Optic neuropathy develops in 2% to 5% treated with more than 15mg/kg/day, and in up to 25% treated with more than 25mg/kg/day characterised by decreased visual acuity, central scotomas, loss of red-green color vision, and eventually optic atrophy.[42] Optic neuritis due to ETB is generally considered to be reversible when the drug is discontinued promptly. Symptoms usually appear between four and twelve months after the onset of ethambutol, but rarely, they may also occur within a few days of initiation of therapy. Colour vision abnormality (dyschromatopsia) may be one of the first detectable signs of ocular toxicity owing to ethambutol.[43]

Rifampicin: It is a semi-synthetic compound first synthesized in 1965. The drug causes orange red discoloration of all body fluids including tears which doesn't need any modification of treatment. It can produce conjunctivitis and orange staining of contact lenses.[44]

Rifabutin: is used to treat Mycobacterium Avium Complex (MAC) disease in patients with HIV/AIDS on antiretrovirals who cannot tolerate rifampicin. Rifampicin decreases the therapeutic levels of non-nucleoside reverse transcriptase inhibitors and protease inhibitors.[45] Thus rifampicin is not given in patients with HIV. Rifabutin associated uveitis is well documented in patients with HIV infections and AIDS. Patient presents with eye pain and blurred vision.[46]

Minocycline: Antibiotic derived from tetracycline effective against wide variety of bacteria, used to treat refractory acne vulgaris. The most common ophthalmic side effect is papilledema (from increased intracranial pressure). Vision loss may be delayed because axonal damage in papilledema proceeds slowly and initially spares visual acuity. If papilledema detected early, vision loss is reversible and if detected late vision loss is permanent and disabling.[47]

Sildenafil, tadalafil: Phosphodiesterase inhibitor used to treat erectile dysfunction. A bluish discoloration of vision may occur starting within 1–2 hours of taking medication, presumed to be effect on retinal photoreceptors or their connections. The possible ophthalmic side effect is ischemic optic neuropathy. Sudden, persistent loss of vision occurring within 24 hours of medication use, associated with swollen optic disc and afferent pupil defect in ischemic optic neuropathy. Ischemic optic neuropathy causes irreversible and untreatable vision loss.[48] These drugs can also cause central serious retinopathy, which is a collection of fluid in the macula in the back of the eye, and they can cause subconjunctival hemorrhages.[49]

Tamsulosin: Selective alpha-1A antagonist used to treat symptoms in benign prostatic hypertrophy. Most common ophthalmic side effect seen is floppy iris syndrome in which iris becomes mobile during cataract surgery, a phenomenon called intraoperative floppy iris syndrome. This probably could be related to the blockade of alpha1 adrenergic receptors within the dilator muscle of the iris. This leads to a greater chance of postoperative blurred vision.[50]

Topiramate: used to treat seizures and migraine. It can cause secondary angle-closure glaucoma caused by edema of the ciliary body. Most cases present in the first few weeks of treatment although some cases are reported within hours of treatment. Visual field defects. Oculogyric crisis – a dystonic reaction characterised by prolonged involuntary upward deviation of the eyes.[51]

Tamoxifen: Tamoxifen is a commonly used estrogen receptor modulator used in the management of breast cancer. Currently, it is used to treat early and advanced stages of estrogen-receptor–positive breast cancer in pre- and postmenopausal women. Intraretinal crystalline deposits, corneal deposits, macular edema (swelling), and localized retinal pigmentary changes, along with decreased visual acuity (VA), have been linked with tamoxifen doses greater than 60 mg/m2 per day. The macular toxicity of tamoxifen may also predispose to macular hole formation. Upon eye examination, crystalline deposits are most commonly within the parafoveal area of the macula. Discontinuation of tamoxifen usually improves vision and edema but has no effect on the crystalline deposits.[52]

Vigabatrin: Anti-epileptic agent used mainly for refractory childhood seizure disorder called infantile spasms. Patients can develop opthalmic side effect as visual field constriction attributed to effect of excess neurotransmitter GABA on retinal photoreceptors and ganglion cells. Patients may not notice visual field loss until the central field is affected. Visual field constriction and optic disc pallor indicate advanced damage.[53]

Prostaglandin analogues: (PGAs) are recommended as first choice treatment for Primary open angle glaucoma. The occular side effects are conjunctival hyperaemia, increased pigmentation of periocular skin, longer and thicker eyelashes, and change in iris colour in some eyes (mostly in green-brown or grey-brown eyes). A few cases of recurrence of herpetic keratitis have been reported with the use of prostaglandins.[54]

Interferon-α: is used to treat various illnesses including chronic hepatitis B and C infection, renal cell carcinoma, leukemia, lymphoma, AIDS-related Kaposi's sarcoma, malignant melanoma, and hemangiomatosis. Interferon can lead to retinal damage anywhere from 2 weeks to 3 months after the medication is started. The retinopathy is typically characterized by cotton wool spots and retinal hemorrhages near the optic nerves. Retinal complications may or may not be dose-dependent, and usually resolve spontaneously or disappear when the drug is discontinued. Branch retinal artery and vein occlusion, central retinal vein occlusion, branch retinal artery occlusion, CME, and optic disc edema have all been associated with interferon therapy and can cause irreversible vision loss.[55]

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