

Retinopathy induced by drugs and herbal medicines

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Abstract. – Retina is the part of the eye suffering most damage from drugs. It is made up of a thin nervous membrane that covers the eye-ball internally, within the thickness of which three types of cells are ordered. In this paper we describe the drugs that are responsible for retinal side effects.

Most commonly recognized drugs-induced retinopathy have a particular affinity for the retinal pigmented epithelium: antimalarials (quinine, hydroxychloroquine, mefloquine), phenothiazines, indomethacin, ethambutol, and desferrioxamine.

Attention is especially focused on drugs more recently suspected of adverse reactions in the retina: vigabatrin, gabapentin, sildenafil, tamoxifen, isotretinoin, interferon, and omeprazole.

Moreover, we referred some reports of retinopathy by herbal medicines and nutritional supplements (canthaxanthine, *Ginkgo biloba* L. and *Glycyrrhiza glabra* L.)

This review is based on data published in scientific journals indexed by the PubMed and Medline databases. The last search of the literature was conducted in April 2008.

Key Words:

Retina, Retinopathy, Drugs, Adverse reactions, Herbal medicines

Introduction

Adverse ocular events resulting from pharmacological therapy have low incidence. They are not serious in most cases, being reversible once a cure has been undertaken. Nevertheless, several drugs result in some degree of severe ophthalmologic toxicity¹.

The eye is protected by the haemato-ocular barrier, which is able to obstruct the passage of a great many drugs. However, this barrier is not al-

ways a good defence; drugs, in fact, in widespread use are able to get through this barrier and cause ocular damage.

Toxicity can result from the methods used to administer the drug. These can be topical as in eyewashes, ointments, or subconjunctival and retrobulbar injections, or arise out of systemic use.

The retina is the part of the eye suffering most damage from pharmaceutical drugs. It is a thin nervous membrane that covers the eye-ball internally, within the thickness of which three types of cells are ordered. These are photoreceptors (rods and cones), median cells (the most important being bipolar), and gangliar cells connected together by synaptic contacts. The peripheral structures of the retina are responsible for peripheral vision while the central area, called the macula, is the instrument of central vision and the seeing of colours.

Most drugs noted for being responsible for retinopathy are reported in this paper, and attention is especially focused on those more recently suspected of having serious and non-serious, expected and unexpected side effects in the retina.

This review is based on data published in scientific journals indexed by the PubMed and Medline databases. The last search of the literature was conducted in April 2008.

AIFA (Italian Drug Agency) received six reports of iatrogenic retinopathy during the period between the January 2001 and April 2008. Three of these reports regarded interferon alfa, one concerned grave reaction with vigabatrin, one interferon-ribavirin, and one involved omeprazole.

Retinopathy and Drugs

The drugs involved in retinal disorders can bring about visual damage, which is sometimes irreversible. The main lesions occur in the macu-

la and can include degeneration, oedema, alterations in the pigment, detachment, vascular disorders (e.g. hypertensive, diabetic, or other types of retinopathy), inflammation, haemorrhages, and deposits.

Undoubtedly the drugs responsible for iatrogenic retinopathy are those with a particular

affinity for the retinal pigmented epithelium (RPE), such as antimalarials (quinine, hydroxychloroquine, mefloquine), phenothiazines, indomethacin, ethambutol, and desferrioxamine.

Table I reports the drugs mainly responsible for causing visual damage with a particular affinity for the retina²⁻⁴.

Table I. The most noted drugs inducing damages to the retina.

Drug	Effect	Mechanism
QUININE	Retinopathy for dosage above 4 g/die	Toxic effects on internal nervous tissue of retina
SYNTHETIC ANTIMALARIALS chloroquine sulfate, hydroxychloroquine sulphate, mefloquine	Morphological changes with anomalies of visual field (central and peripheral); alterations of colour vision and changes of electroretinogram (ERG). Iatrogenic effect dose-related	Drug accumulation caused by bond with melanin; damage of photoreceptors, and decreased of cones and rods
PHENOTIAZINES chlorpromazine	Decreased vision, colour vision of objects, hemeralopia and peripheral retinal pigmentation	Metabolic alteration induced for accumulation in retinal pigmented epithelium
DEFERRIOXAMINE	Deficit of visual field and alteration of pigmentation, hemeralopia Effect dose and time related	Severe damage of retinal pigmented epithelium and sometimes irreversible
CARDIAC GLYCOSIDES digitoxin, digoxin	Dyschromatopsia, xanthopsia, cyanopsia and anomalies of ERG (incidence of 25%)	Alteration of photoreceptors, inhibition of Na/K ATPase
ANTIBIOTIC AND ANTIBACTERIAL AGENTS amikacin, ethambutol, cephalosporins, fluoroquinolons	Retinal toxicity specially if endocular usage	Some cause retinal failure
ANTICOAGULANTS COUMARINS	Intraocular haemorrhages	Increases of the prothrombine time
DIURETICS acetazolamide, hydrochlorothiazide	Retinal haemorrhages	Damage of photoreceptors
ANTICANCER DRUGS mitomycin, doxorubicin, daunorubicin, cisplatin	Retinal toxicity Retinal toxicity Decreased of visus, ERG alteration	Eventual damage of cones
ALLOPURINOL	Photosensitivity	Accumulation in retinal pigmented epithelium and production of toxic metabolite by photo-activation
NSAIDs indomethacin, ketoprofen, naproxen, oxyphenbutazone, piroxicam	Visual field loss, photosensitivity; alteration of electro-oculogram and granular aspect of fundus (temporary symptoms)	Alteration of photoreceptors
ANTIPILEPTICS valproic acid, phenytoin, hydantoin	Dyschromatopsia	Injure in retinal pigmented epithelium
ANTIDEPRESSANTS IMAO isocarboxazid	Color vision defect and visual hallucinations	Action on retinal monoamine oxidase

The Retina and Recent Reports of Adverse Reactions to Drugs

Antiepileptic Drugs

Vigabatrin

Visual disorders are common side effects of this new antiepileptic drugs, with many reports leading in recent years to the firm belief that vigabatrin induces retinopathy. Therapeutically vigabatrin is very effective since it selectively increases the level of GABA (gamma-aminobutyric acid) in the brain. However, irreversible visual alterations were observed in a study of chronic epileptic patients⁵. The patients complained of deterioration in sight, visual obfuscation, and restriction in the field of vision. The electroretinogram (ERG) revealed bilateral retinal alterations, a decrease in the response of the cones, and no response from the oscillatory potentials, probably due to an anomaly of the highly GABAergic amacrine cells. Some patients also showed retinal alterations in the ophthalmoscopic examination, with narrowing of the arteries, retinopathy "surface wrinkling", and macular reflex anomaly.

Signs of alterations in the field of vision, accompanied by electrophysiologic evidence, like as in adults, were also observed in patients of paediatric age, sufficient for treatment using this drug to be seriously considered⁶. The mechanism responsible of this retinal alterations is not known. Studies on animals have found that the accumulation of this molecule in the retina was 18.5 times greater than its cerebral concentration⁷. It can be hypothesized that vigabatrin irreversibly inhibits the GABA-transaminase with a consequent increase in the GABA that, connected to its receptors, induces toxicity. This action probably is caused by the influx of calcium ions.

Multicentric clinical studies are underway to improve definition of the ocular side effects of vigabatrin, especially the irreversibility of its toxic effect⁸⁻¹⁰.

Gabapentin

In clinical practice gabapentin is used by millions of patients as an antiepileptic and, up to the time of writing, a causal relationship between use of this drug and the appearance of serious toxic ocular effects has not been established. Nevertheless, recent studies report an association between assumption of gabapentin and restriction of the field of vision¹¹⁻¹².

Gastric secretion inhibitors

Omeprazole

Omeprazole, a proton pump inhibitor (PPI), blocks the production of acid by the stomach. It is used for the treatment of conditions such as ulcers, gastroesophageal reflux disease (GERD) and the Zollinger-Ellison syndrome.

Ocular side effects reported with <1% prevalence are: blurred vision, ocular irritation, dry eye syndrome, optic atrophy, anterior ischemic optic neuropathy, optic neuritis, diplopia.

Visual disturbance has been associated with the use of high dose parenteral omeprazole¹³. However, the strength of this association has been debated, and the higher number of reports of visual disturbance with omeprazole compared with the other proton pump inhibitors may simply reflect greater omeprazole usage¹⁴. The results from one large cohort study failed to show a major increased risk for ocular disorder associated with the use of omeprazole or other anti-ulcer drugs, as the pantoprazole, rabeprazole and esomeprazole^{15,16}.

Famotidine

Only one report is known for the famotidine; the findings in ERG and other tests suggest that the retinopathy derived from a direct toxic effect to the photoreceptors-RPE complex. Further studies needs to establish if this side effect occurred through the interference of the histamine H₂ receptors¹⁷.

Interferon

Patients with hepatitis C treated with interferon (IFN) risk the development of retinopathy from the first week of treatment¹⁸. The retinal damage is a side effect of interferon alfa. Visual acuity does not deteriorate in most patients. Nevertheless, it has been reported that serious irreversible loss of visual acuity and disorders in the field of vision are possible. Damage to the retina can be composed of the formation of soft exudates, retinal haemorrhages, and occlusion of the central retinal artery or vein. The frequency of symptomatic and asymptomatic ocular disorders to interferon alfa vary from 20 to 80% in the first 3 months of therapy¹⁹, with regression after only a few months in spite of persistent treatment. Similar effects have also been attributed to the more recently developed pegylated form of inter-

feron alfa, introduced to treat hepatitis C in association with ribavirin^{20,21}. The patients must be informed of these risks and undergo an examination of the retina before treatment begins.

Isotretinoin

Isotretinoin is pharmacologically and structurally correlated with vitamin A, which regulates the growth and differentiation of epithelial cells.

Indicated for the topical treatment of the moderate form *acne vulgaris*, it is also indicated, orally, for the serious forms of acne (nodular or conglobate acne i.e. acne running the risk of permanent scars) that are immune to appropriate cycles of standard therapy using systemic antibiotics and a topical therapy.

This drug is highly teratogeneous, and even if its administration is limited to only a few days, it can cause sexual anomalies.

The side effects include dryness of the conjunctiva (sometimes conjunctivitis), intolerance to contact lenses, photosensitivity, difficulty adapting to darkness, and deterioration in nocturnal vision²²⁻²⁴.

A dose of 1 mg/kg a day can alter adaptation to darkness and the ERG. Once the drug has been stopped, many months are required for the visual disorders to disappear.

Sildenafil

Some patients treated with sildenafil perceive colours to be darker than normal, and often with a halo around them. Furthermore, an increase in luminosity has been noted in some cases. These dose dependent disorders are normally verified one to two hours after administration of the drug, alter vision for approximately 5 hours, and are reversible²⁵. The incidence is 3% for a 50 mg dose, rising to 10% for assumption of 100 mg, and reaches 40-50% for 200 mg.

It is hypothesized that these ocular effects were due to the action of sildenafil on retinal phosphodiesterase, and were found in a 7-year study of the spontaneous reports in a sample of 27 million of patients²⁶. The visual disorders observed were transitory alterations of sensitivity to light and colours, paralysis of the cranial nerves and several cases of non-arthritic anterior optic ischemia characterised by blurred vision, defects in the field of vision, and optic disk oedema.

The American Academy of Ophthalmology guidelines underline the contraindications of sildenafil in patients with hereditary degenerative disorders ascertained in the retina, such as pigmentous retinitis.

Tamoxifen

Tamoxifen is an antioestrogen drug frequently used in treating breast cancer, both following a relapse and after surgery. Furthermore, it is used to treat several other pathological conditions including infertility.

It is the cause of yellowish-white opacity in the macular and paramacular area with or without oedema. Sight can be diminished and the field of vision restricted²⁷.

The mechanism through which this drug causes retinopathy is now subject to study. The hypothesis that is currently supported by the scientific community is based on the fact that the accumulation of tamoxifen in the retina causes oxidative stress with a consequent ocular damage. Tamoxifen in the retina is metabolised by cytochrome P450 and by myeloperoxidase; the resulting metabolite is then conjugated with tripeptide glutathione. This biotransformation reaction causes the depletion of the glutathione with consequent oxidative stress and organ toxicity²⁸.

Herbal Medicines and Nutritional Supplements

Canthaxanthine

Canthaxanthine is a carotenoid generally isolated from various mushrooms or flamingo feathers. It is used in cosmetics such as tanning lotions, or as a colorant in food, above all to colour foodstuffs of animal origin (salmonids, poultry). It seems that canthaxanthine can form deposits in the macula of the retina, which take time to be reabsorbed. Therefore, they can cause alterations in visual acuteness and increase dark adaptation time²⁹⁻³¹.

Gingko biloba L.

This is one of the highest selling herbal medicines, most of all sold in the form of dry extract (EGB761) obtained from leaves and standardised

in 5-7% total terpene lactones (ginkgoloids A, B, C, J, and M, and the bilobalids) and in 22-27% ginkoflavonoids.

It has been used in various disorders of venous and lymphatic insufficiency, capillary fragility, adjuvant in ischemic cerebral and cardiac events, in retinal circulation disorders, in disorders of the cerebral circulation of elderly patients with memory deficit, in asthma and in hearing disorders.

The research found two cases of haemorrhaging, one in the anterior chamber of the eye and one in the retina. In fact, the ginkgoloids, especially ginkgoloid B, inhibit piastrinic aggregation by inhibiting the PAF (platelet activating factor). Therefore, it is contraindicated in patients who assume anticoagulant or antiaggregant drugs such as aspirin^{31,32}.

***Glycyrrhiza glabra* L.**

Liquorice (*Glycyrrhiza glabra*) has long been used for medical purposes. Powdered liquorice root is an effective expectorant, anti-cough, anti-inflammatory and additionally may be useful for both mouth ulcers and peptic ulcers. Liquorice root is a source of glycyrrhizin, also called glycyrrizic acid, a triterpene glycoside, which is 50-60 times sweeter than sucrose. Glycyrrhizin is steroid-like; because of its steroid-like pharmacological activity, there are some side effects, such as sodium retention, with oedema, hypertension, and hypokaliemia.

Ocular migraine-like visual symptoms have been reported that occur without a headache³³. The vasospasm of the brain, retinal and/or optic nerve blood vessels plays a role in these visual symptoms. There is strong evidence that liquorice, through its glucocorticoid and norepinephrine effects, can cause vasospasm throughout the body³⁴.

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