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General

Drugs and the retina

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The retina is relatively protected from systemic drug administration because of the blood–retinal barrier, a highly selective mechanism adapted to providing a regulated homeostatic environment for this highly specialised tissue. However, a number of drugs have been associated with retinal toxicity. Vigabatrin, as an adjunctive therapy for the management of partial epilepsy, is associated with visual field defects in ~ 40% of patients. Hydroxychloroquine, used in the treatment of rheumatoid arthritis and systemic lupus erythematosus, is also associated with a retinopathy. In view of this, ophthalmological screening and monitoring is recommended during prescription of both of these drugs. In these cases, the retina is the site for an adverse drug reaction and the dose of therapy may be important in determining the likelihood of retinal toxicity. However, in the case of cytomegalovirus retinitis, the retina is the intended site for pharmacological action. The treatment of this condition with the antiviral agents ganciclovir, valganciclovir, foscarnet and cidofovir, can also be associated with significant systemic toxicity.

Keywords: adverse drug reaction (ADR), hydroxychloroquine, monitoring, retinopathy, vigabatrin

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1. Introduction

The eye is an isolated unit but with a potentially high degree of sensitivity to toxic substances. The variety of the different types of reaction observed in response to injurious substances reflects the unique anatomical, physiological and biochemical features of this organ. Ocular side effects from the systemic administration of drugs are well-recognised and more than 30 drugs have been associated with retinal toxicity [1]. However, like the brain and the blood–brain barrier (BBB), as a specialised tissue, the retina is in a unique situation. Access of systemically administered drugs to the retina is restricted by the blood–retinal barrier (BRB) that, like the BBB, hinders the free exchange of substances between the blood and retina. This is through an epithelial layer sealed by tight junctions, with a transcellular mechanism of facilitated-diffusion and transporters for molecules such as glucose, amino acids and drugs.

When considering the retina in the context of drug safety, it is important to examine not only those drugs where the retina is the unwelcome and unexpected target for drugs with a systemic indication but also the systemic safety of drugs where the retina is the intended site of pharmacological action. This review will focus on these two broad areas, concentrating on the relationship between drugs and the retina specifically and therefore excluding the optic nerve. Adverse drug reactions (ADRs) for the eye as a whole are covered elsewhere [2].

2. The anatomy and physiology of the retina

The retina is the innermost of the three coats of the eye and is responsible for converting the image of the external environment into neural impulses that can be transmitted to the brain. The retina is underlined by the retinal pigment epithelium (RPE), which is a simple epithelial layer that acts as a selective semipermeable

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barrier. The retina is highly metabolically active with the highest oxygen consumption, relative to weight, of any human tissue. The anatomy of the retina is illustrated in Figure 1. A summary of the key retinal cell populations is given in Table 1.

The RPE is composed of a continuous monolayer of simple cuboidal cells located between the capillaries of the choroid and the neurosensory retina. In a normal eye, RPE cells are hexagonally shaped and packed together like cobblestones with a mottled brown colour due to the presence of melanin [3]. RPE cells have developed a complex structural and functional polarity that allows them to perform their highly specialised roles, with the RPE cell membrane having distinct apical, basal and lateral surfaces. The apical surface of the cells is covered with microvilli. The basal surface is convoluted into numerous basal infoldings, resulting in a high surface area suitable for transport properties. The lateral surfaces of adjacent RPE cells are joined by four types of junction: tight junctions, adherent junctions, desmosomes and gap junctions [4]. This highly selective BRB provided by the RPE serves to maintain a regulated homeostatic environment for this highly specialised tissue. Systemic drug administration does not guarantee high intraocular drug levels, at least in part because of the integrity of this barrier.

As light travels through the pupil it is focused onto the macula – the part of the retina responsible for central sharp vision and colour discrimination. The macula is also the area affected by age-related macular degeneration and central swelling in diabetic disease. There are multiple layers within the neurosensory retina itself and the inner surface is made up of ganglion cells that transmit impulses from the deeper retinal layers to the brain by way of the optic nerve. Light must travel through the ganglion cell layer and pass through the middle layers to reach the photoreceptor cells that ultimately transform light into recognisable signals for the brain. Light must, therefore, travel through the thickness of the retina before striking and activating the rods and cones (photoreceptor cells). Any disruption of the intervening layers would thus compromise vision. Disruptions could include exudates, haemorrhages and ischaemia of the various retinal layers from diseased vessels, such as those occurring in diabetes.

Melanin is found in the pigmented epithelial layer of the retina. There are many examples of drugs, otherwise structurally and pharmacologically unrelated, that bind to the melanin found within this layer of the retina, including numerous drugs acting on the CNS such as sympathomimetic amines, antimalarial drugs and antibiotics. β-agonists and antagonists also bind to retinal melanin. However, binding of drugs to retinal melanin is not necessarily predictive of retinal toxicity [5]. The critical factors are the acid/base status and the lipophilicity of the molecule. It appears that drug-related toxic effects on the retina described in humans and animals are unrelated to melanin binding: melanin binding and retinal toxicity are two separate entities, the latter being related to the intrinsic toxicity of the compound rather than its ability to bind. Melanin binding has also been found to be protective against the ocular toxicity of some drugs [5]. However, photosensitising agents such as the phenothiazines may become bound to melanin within the retina, absorb visible and ultraviolet radiation and, as a result, generate damaging free radicals.

3. Retinal toxicity of systemically administered drugs

3.1 Vigabatrin

Vigabatrin is given in combination with other anticonvulsant drugs in the treatment of partial epilepsy, with or without secondary generalisation. Its use is restricted to patients in whom all other combinations are inadequate or are not tolerated. It is also particularly useful as monotherapy in children with infantile spasms (West's syndrome).

3.1.1 Incidence

Vigabatrin is associated with visual field defects, which occur in ~ 40% of patients [6-9]. A report using multifocal electroretinography showed the prevalence of field defects to be as high as 59%, indicating that previous studies may have underestimated the prevalence of the defect [10]. Indeed, the incidence of asymptotic visual field loss may be more common than previously believed, with a figure of 67% recorded in one study [11]. The occurrence of this ADR originally emerged following the publication of a variety of anecdotal reports regarding patients who developed severely constricted visual fields bilaterally after the commencement of vigabatrin therapy [12-16].

3.1.2 Mechanism

The mechanism of the retinal damage with vigabatrin is unclear, although the visual field defects appear to be the result of peripheral retinal atrophy rather than optic nerve damage. A recent study in rats showed that vigabatrin preferentially accumulates in the retina and the authors suggested that its toxic effects may be mediated via the GABA-C receptor, which is highly expressed in the retina, although experimental evidence for this is currently lacking [17].

3.1.3 Clinical features

The evidence suggests that the onset of symptoms varies from 1 month to several years after starting vigabatrin. In most cases, visual field defects have persisted despite discontinuation of vigabatrin, although fortunately there is rarely any further deterioration [18,19]. Of the risk factors investigated, males appear to be at higher risk of developing retinal toxicity [20], whilst cumulative doses of > 1500 g have been found to correlate with the severity of the visual field defects [21]. In one study, the prevalence of visual field defects increased significantly with increasing total vigabatrin dose, from 4% in patients who had been exposed to < 1 kg of vigabatrin, to 75% in patients with a cumulative dose of 3 – 5 kg of vigabatrin [22]. Patients may complain of

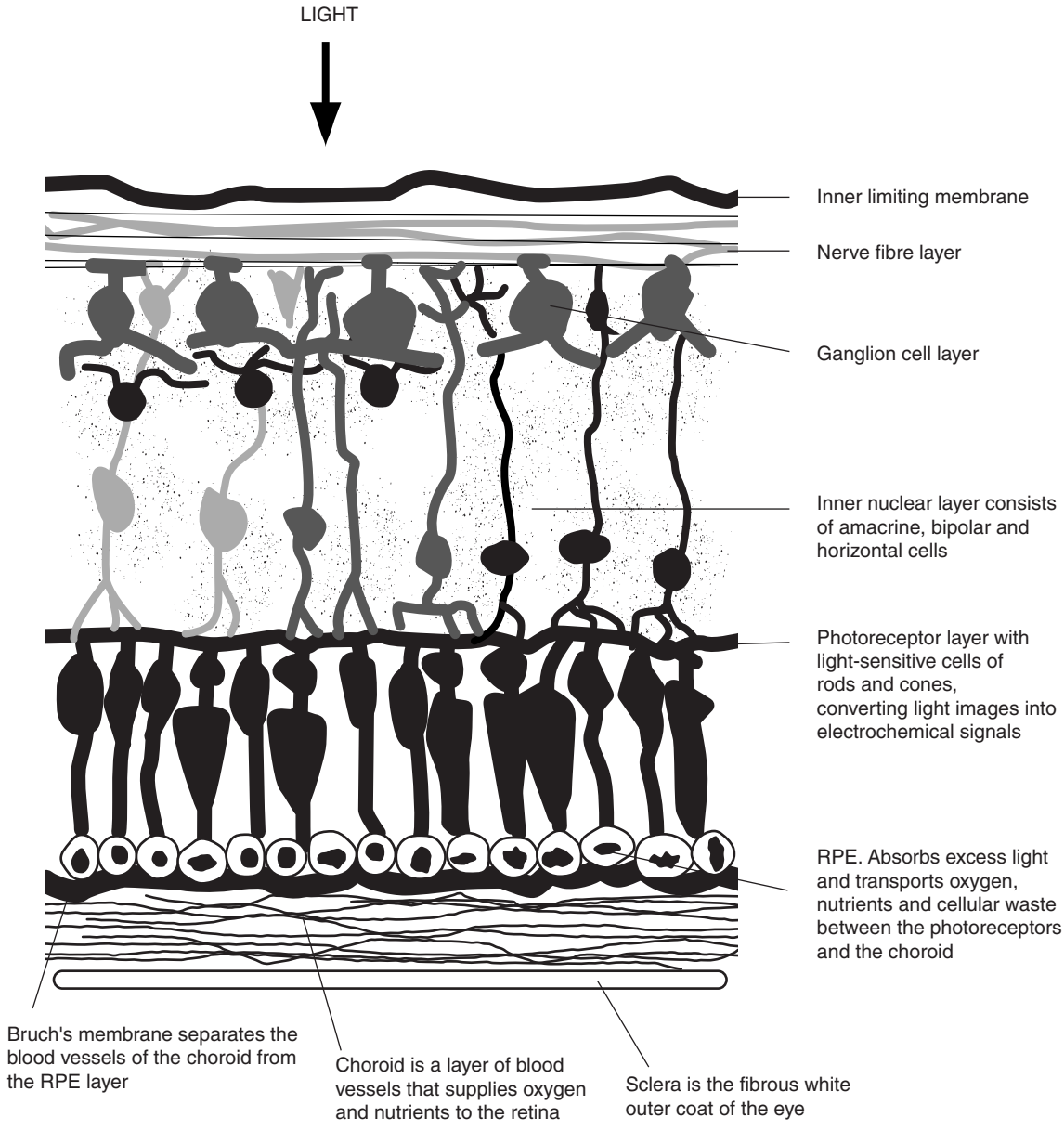

Figure 1. Schematic representation of the different cell layers within the retina, and their functions.
RPE: Retinal pigment epithelium.

symptoms but, in many cases, the patients are asymptomatic, their defects being detected upon visual field testing. The typical picture is of bilateral concentric visual field constriction (with some temporal sparing) or of binasal visual field loss. If visual field defects are present, the ophthalmologist may be able to detect a loss in retinal nerve fibres using red-free ophthalmoscopy. The retina does not appear to be normal and there may be significant loss of supero- and infero-temporal nerve fibres with an accumulation of yellow dots in the macular region [23]. Studies using electroretinograms (ERGs) have shown that vigabatrin affects the inner rather than the outer retina. Most of the ERG studies have reported a reduction in *b* wave amplitude, which may indicate effects on Müller cells, the principal glial cells in the retina, which remove neurotransmitters from the extracellular space after their release from synaptic terminals [24-26].

Tiagabine is also used in the adjunctive treatment for partial seizures, with or without secondary generalisation. Unlike vigabatrin, tiagabine treatment is associated with normal electroretinography and visual fields, with ophthalmological function similar to controls [27].

Table 1. The key retinal cell populations.

Retinal cell	Characteristics
Rods (photoreceptors)	More light-sensitive than cones. Particularly important for night vision. Can detect a single photon of light of suitable wavelength. Have poor point resolution and are not present in the fovea. Rods respond only to one narrow band of light frequency, and rod-only retinas are entirely colour blind. Rods contain one pigment type and are not responsible for colour vision.
Cones (photoreceptors)	Operate at higher light intensities and are the main receptor of 'daylight' vision, since rods saturate at very low light levels and essentially cease to function. Responsible for colour, based on the existence of three subtypes of cones sensitive to three distinct light wavelengths. Cones have a much shorter outer segment than rods.
Bipolar cells	Have a dendritic process, a cell body and an axon. The cells are not myelinated, and their excitation produces an inhibitory generator potential. Synaptic input to bipolar cells is from receptor cells (the rods and cones) and also from another type of interneuron, the horizontal cells.
Ganglion cells	The ganglion cell layer is the innermost layer of the retina. They have relatively large cell bodies, and from these arise long myelinated axons that exit the eye and make up the optic nerve/tract synapsing in the lateral geniculate or optic tectum of the midbrain. Ganglion cells are inhibited by bipolar cells, which are themselves inhibited by rods/cones, which in turn are inhibited by light.
Horizontal cells	Horizontal cells synapse with rods/cones and the bipolar cells. They have axons, but apparently do not develop action potentials. Generally, the horizontals receive synaptic input from the light receptor cells.
Amacrine cells	Amacrine cells lack an axon. The cells receive their synaptic input from bipolar cells. Their many cell processes ramify throughout the layer between bipolar and ganglion cells, and these processes synapse onto other bipolar cells. They are apparently inhibitory and may act as a regulator of bipolar action.

3.1.4 Treatment monitoring

The UK Committee on Safety of Medicines (CSM) now considers that vigabatrin therapy should only be initiated and supervised by an appropriate specialist and only where all other combination therapies have failed [28]. Ophthalmological consultation and visual field assessment should be undertaken before starting vigabatrin treatment and repeated at 6-monthly intervals during treatment for 3 years, after which it can be reduced to annual screening. Screening should be performed by either Humphrey or Goldmann perimetry. Patients should be counselled about the risk and should be warned to report any new visual symptoms that develop. Those patients with symptoms should be referred for an urgent ophthalmological opinion with a view to discontinuation of therapy. However, a clinical risk–benefit judgement needs to be made in each case, depending on seizure control and the degree of visual impairment. Patients who have had an excellent antiepileptic response to vigabatrin and demonstrated only mild visual changes may be able to continue therapy safely with close visual monitoring [29]. Vigabatrin should not be used in those patients with pre-existing visual field defects and the dose should not exceed 3 g daily [28,30].

The use of vigabatrin in children is further complicated by the fact that conventional perimetry may be unsuitable, if not impossible, for patients with a developmental age of < 9 years. The risk of developing visual field defects has to be weighed against the potential benefit of seizure control. For example, the potential benefits of vigabatrin therapy in the management of infantile spasms, a therapeutically challenging condition, are felt by some to outweigh the risks [30,31]. The use of electroretinography and field-specific visual evoked potentials may be helpful in the assessment of the paediatric population [32].

3.2 Chloroquine and hydroxychloroquine

The antimalarials chloroquine and hydroxychloroquine are used to treat rheumatoid arthritis (RA) of moderate inflammatory activity. They are also effective for mild systemic lupus erythematosus, particularly where there are predominant cutaneous and joint manifestations. Retinopathy is a potentially serious ocular adverse event associated with the use of chloroquine and hydroxychloroquine.

3.2.1 Incidence

Experience of the use of chloroquine and hydroxychloroquine in the treatment of rheumatological conditions indicates that the incidence of retinal toxicity is dose-related. Although the total cumulative dose, duration of treatment and the age of the patient may affect the incidence of retinal toxicity, it is believed that the daily dose is the most important factor. To avoid excessive dosage in obese patients, the dose of both chloroquine and hydroxychloroquine should be calculated on the basis of lean body weight, with a small risk of retinal damage with daily doses of < 6.5 mg chloroquine/kg of lean bodyweight [33-35]; it is not possible to advise on a safe maximum dose. It appears that retinopathy is rarely associated with the dose levels of chloroquine recommended for the prophylaxis of malaria [36,37].

3.2.2 Mechanism

The mechanism of retinal toxicity is unclear. However, impairment of metabolism of the RPE leading to degeneration of

photoreceptors has been suggested as an underlying mechanism of toxicity. The differential rates of toxicity of chloroquine (1 – 2%) compared with hydroxychloroquine (0.1%) may be due to the fact that the former is more lysosomotropic than the latter [38]. There may also be a genetic predisposition to the retinal toxicity, with mutations having been identified in the *ABCA4* gene, although this needs to be confirmed in a larger group of patients with and without toxicity [39].

3.2.3 Clinical features

Central vision is reduced with the retinopathy associated with chloroquine and hydroxychloroquine therapy. The earliest sign is a paracentral scotoma, which may be followed later by pigmentary mottling at the macula and, subsequently, by bull's eye maculopathy and widespread retinal pigment epithelial atrophy. Early preclinical signs of retinopathy may be detectable by electroretinography [40]. Whilst corneal deposits associated with the use of these drugs are completely reversible upon withdrawal of treatment, the outcome for retinopathy upon discontinuation is unpredictable, being either irreversible or even progressive, with a permanent reduction in central vision [41-43]. The earlier any changes are detected, the more likely it is that any damage to the retina will be reversible. Furthermore, delayed onset retinopathy has also been reported in patients many years after the cessation of treatment [44].

3.2.4 Treatment monitoring

The goal of monitoring hydroxychloroquine therapy is to detect early reversible retinal toxicity. Various screening tests have been suggested for the monitoring of patients on hydroxychloroquine, including the use of Amsler charts (the most commonly used to date), the assessment of visual acuity, colour vision, visual fields to red and white targets, fundoscopy and also by electro-oculography and electroretinography [45]. All of these have problems of nonspecificity and interpretation and there is no gold standard for the detection of retinopathy at an early stage. The use of fundoscopy and Amsler charts is considered to be unreliable in daily rheumatological and dermatological practice [46].

In the UK, the Royal College of Ophthalmologists has issued guidelines on the ophthalmological monitoring required with the use of hydroxychloroquine [47]. Baseline assessment before treatment with hydroxychloroquine is commenced (at a dosage not exceeding 6.5 mg/kg lean body weight) and should consist of questioning the patient about visual impairment not corrected by glasses and recording near visual acuity. An assessment of renal and liver function should also be made. Thereafter, patients should be monitored annually with enquiries about visual symptomatology (difficulty seeing entire words or faces, intolerance to glare, decreased night vision or loss of peripheral vision), rechecking of acuity and assessment for blurred vision. Patients should be referred to an ophthalmologist if problems are detected either before or during treatment. Those taking long-term hydroxychloroquine should be subject to occasional ophthalmological review after 5 years' continuous treatment. No such guidelines exist for ophthalmological monitoring during long-term chloroquine therapy, although it would seem logical to use a similar approach, even in the absence of evidence to support it. Ocular toxicity is unlikely with a chloroquine dose not exceeding 4.0 mg/kg lean body weight.

The American College of Rheumatology (ACR) advocates a different approach – a baseline eye evaluation is not routinely recommended in patients younger than 40 years of age and with no family history of eye disease, and a monitoring routine is only advised after 6 months of response to therapy [48]. In the ACR guidelines, patients with abnormal renal function or those who have received hydroxychloroquine for > 10 years require more frequent ophthalmological evaluation. Otherwise, in the absence of risk factors, it is recommended that an ophthalmological examination and central field testing be performed every 6 – 12 months (using an Amsler test or a modified Amsler test used to screen and augment formal ophthalmological testing).

There is controversy, however, as to whether such screening is actually necessary, and in clinical practice there is no consensus as to the appropriate approach to screening since no method is considered to be ideal. Furthermore, it has been shown that nationally set guidelines for the monitoring of ocular toxicity of hydroxychloroquine are not consistently followed by rheumatologists with regard to baseline assessment, referral to ophthalmology and frequency of monitoring [49,50]. It has also been argued that the incidence of sight-threatening retinopathy with hydroxychloroquine at the recommended dose of 400 mg/day is extremely small and at a level that, in other areas of medicine, would preclude the initiation of a screening programme [51]. For example, a cohort of 73 patients on hydroxychloroquine for RA for > 18 months were assessed with a battery of tests for evidence of retinal toxicity [52]. No retinal toxicity causing visual loss was found in these patients, leading the investigators to conclude that routine screening of patients for hydroxychloroquine retinal toxicity was not necessary. It is also unclear as to whether or not a comprehensive screening programme would stand up to the usual need to demonstrate a positive cost–benefit ratio. Thus, there is a need for further research in this area and to reach a consensus as to the need for and frequency of screening, which is both clinically- and cost-effective.

3.3 Phenothiazines

Phenothiazines, neuroleptic antipsychotics used largely but not exclusively in the management of schizophrenia, are associated with the development of a degenerative retinopathy with histopathological, symptomatological and electrophysiological features similar to those of primary retinitis pigmentosa [53,54]. These drugs all act as competitive antagonists of dopamine (DA) receptors in the CNS.

3.3.1 Incidence

Cases of neuroleptic-induced retinopathies have been described with phenothiazine derivatives such as

chlorpromazine, trifluoperazine, fluphenazine and, predominantly, thioridazine [55-58]. The prevalence of retinal toxicity with these agents is unclear, as most data are based on reports in individual patients. Thioridazine is now restricted for use as a second-line treatment for schizophrenia in adults and should only be prescribed under specialist supervision – a requirement deemed necessary in view of the potential for thioridazine to cause QT interval prolongation and serious ventricular arrhythmias, rather than because of any retinal toxicity.

3.3.2 Mechanism

It appears that the retinal toxicity associated with phenothiazine use is both dependent on the dose level and the duration of treatment, with significant importance being placed on the role of drug absorption by the RPE [59]. Furthermore, the molecular structure of the drug is believed to play an important part in determining its risk of leading to retinal toxicity – phenothiazine derivatives with piperidine side chains (such as thioridazine) having a higher risk of inducing retinal toxicity than other phenothiazine derivatives, with relatively few cases reported for those with aliphatic side chains such as chlorpromazine [60]. The classification of the phenothiazines based on the molecular structure is given in Table 2. It has also been suggested that blockade of the DA D2 and D4 receptors may lead to changes in the synthesis of melatonin and thereby alter the susceptibility of photoreceptors to being damaged by light [61]. This may explain the differential effects of the different antipsychotics based on their differential affinities for the DA receptor subtypes.

3.3.3 Clinical features

As well as an association with pigmentation in the cornea, lens and conjunctiva, phenothiazines may induce a pigmentary retinopathy, with reduced visual acuity, brownish discoloration of vision and impaired night vision. The retinopathy may present either acutely, with a sudden loss of vision associated with retinal oedema and hyperaemia of the optic disc, or more chronically, with a fine pigment scatter appearing in the central area of the fundus, a feature that extends peripherally but spares the macula. Chronic para- and pericentral scotomas may be found. Although pigmentary disturbances may progress after withdrawal of phenothiazines, they are not always paralleled by deterioration in visual function. Nonetheless, some cases have led to a progressive chorioretinopathy [62].

One patient, who had received fortnightly injections of fluphenazine, a phenothiazine derivative in a depot preparation, for 10 years, developed bilateral maculopathy following unprotected exposure to a welding arc for < 2 mins [63]. It was postulated that accumulation of phenothiazine in the retinal epithelium sensitised the patient to photic damage.

3.3.4 Treatment monitoring

No guidelines exist for the ophthalmological screening of retinal adverse effects during phenothiazine treatment. However, it appears that the critical ocular toxic dose of thioridazine is reported to be 800 mg/day and, in the UK, manufacturers recommend that a daily dose of 600 mg should not usually be exceeded.

3.4 Sildenafil

Sildenafil is a phosphodiesterase (PDE)-5 inhibitor licensed for the treatment of erectile dysfunction.

3.4.1 Incidence

In a systematic review and meta-analysis of the clinical trial data, visual disturbances were reported in 3% of patients receiving sildenafil, compared to 0.8% of patients receiving placebo – a statistically significant difference [64].

3.4.2 Mechanism

The mechanism for the effects of a single dose of 100 mg sildenafil has been studied in healthy volunteers with ERG measurements showing significant changes that correlated well with plasma sildenafil concentrations, peaking at 1 h after administration and showing complete recovery at the 6-h measurements [65]. The reason for ocular interest is that sildenafil, as an inhibitor of PDE-5, probably also affects PDE-6, which is found in the retina. PDE-6 is involved in light excitation of visual cells to generate an electrical impulse. It is thought that this inhibition of PDE-6 activity in rod photoreceptors is the most likely mechanism of sildenafil-associated retinal dysfunction but it is not yet clear whether this is evidence of retinal toxicity or whether repeated dosing with sildenafil could cause prolonged or further retinal dysfunction [65,66]. It is not yet known whether more elderly patients will demonstrate the same pharmacokinetic–pharmacodynamic relationship seen with the ERG measurements in the young healthy volunteers. There has also been a report of a case of anterior ischaemic optic neuropathy (AION), possibly attributable to an acute episode of hypotension associated with sildenafil use [67]. Sildenafil causes a mild lowering of blood pressure but this effect may be more profound in patients using other hypotensive medications such as nitrates, which are absolutely contraindicated in these circumstances.

3.4.3 Clinical features

Patients taking sildenafil have reported a bluish tinge or haze to vision and some increased light sensitivity, a phenomenon that appears to be dose-related. The incidence of errors in colour discrimination increases to between 20 and 50% when a dose of 100 mg sildenafil is exceeded [68]. Visual symptoms usually peak after 1 – 2 h following ingestion of sildenafil and resolve ~ 3 – 4 h later. These effects are not apparently associated with the other PDE-5 inhibitors, tadalafil and vardenafil [66].

Sildenafil is contraindicated in the presence of hereditary degenerative retinal disorders such as retinitis pigmentosa.

3.4.4 Treatment monitoring

No guidelines exist for ophthalmological screening of retinal adverse effects during sildenafil treatment. The pharmacology of sildenafil is reassuring in this regard.

3.5 Other drugs with retinal toxicity

A number of other drugs are associated with varying degrees of retinal toxicity, ranging from those reported as single cases to those documented in series. Some of these are included in Table 3.

4. The retina as an intended site for pharmacological action

The most significant issue in drug safety with respect to the retina as a target tissue for systemic drug administration is in the management of retinitis caused by cytomegalovirus (CMV). CMVs are members of the herpes virus group and can cause infection in the immunocompromised, especially transplant recipients and patients with AIDS. CMV infection is a major cause of morbidity and mortality in these patients. CMV retinitis is generally treated intravenously with ganciclovir or foscarnet [76], in view of the fact that systemic administration reduces extraretinal and bilateral infections. In patients with AIDS, the initial induction treatment is usually followed by lifelong maintenance therapy – ganciclovir and foscarnet both suppress, rather than eliminate, the virus [77]. However, maintenance therapy may be discontinued in patients who have received highly active antiretroviral therapy (HAART) with a resultant sufficient increase in their $CD4^+$ count [78-80]. Valganciclovir, the oral pro-drug of ganciclovir, may be used for either induction or maintenance treatment as an alternative to intravenous administration. Cidofovir is another alternative for the treatment of CMV retinitis and allows intermittent administration [81]. However, long-term treatment with any of these agents may be limited by significant systemic toxicity.

4.1 Ganciclovir and valganciclovir

Ganciclovir is a nucleoside guanosine analogue that incorporates ganciclovir triphosphate (the active moiety) into DNA during elongation, thereby inhibiting viral replication. The most common adverse effects of intravenous ganciclovir are haematological, particularly neutropenia and thrombocytopenia. Anaemia can also occur but is less frequent [82]. Neutropenia, affecting up to 40% of patients receiving intravenous ganciclovir – generally in the first or second week of treatment – is usually reversible. However, this may be prolonged or irreversible leading to potentially fatal infections, and patients with AIDS may be at greater risk of neutropenia than other immunosuppressed patients. Thrombocytopenia occurs in ~ 20% of patients administered intravenous ganciclovir and those patients with iatrogenic immunosuppression (rather than HIV disease) appear to be at more risk of developing this particular toxicity.

Other adverse effects occurring with intravenous ganciclovir include fever, rash and abnormal liver function tests (LFTs). As a result of the high pH, irritation or phlebitis may also occur at the site of injection. The most frequent adverse effects associated with ganciclovir administered orally include neutropenia, thrombocytopenia and anaemia, as well as fever, asthenia, headache, gastrointestinal disturbances, rash, pruritus, abnormal LFTs, pain and infection. Local adverse effects have been associated with the insertion of ocular implants containing ganciclovir.

Valganciclovir is an ester pro-drug of ganciclovir, developed in an attempt to increase the bioavailability of the parent compound potentially achieving a level of exposure similar to that of intravenous ganciclovir [83]. The toxicities are therefore that of the parent compound.

4.2 Foscarnet sodium

Foscarnet sodium is excreted unchanged in the urine. The most serious common adverse effect of foscarnet is nephrotoxicity, with clinically significant increases in serum creatinine concentrations occurring in approximately a third of patients. The incidence of nephrotoxicity tends to increase with increasing dose and duration of therapy [84,85]. Tubulo-interstitial lesions and deposition of crystals in the glomerular capillary lumen have been implicated in the pathophysiology of foscarnet nephrotoxicity [86]. The risk of developing nephrotoxicity can be minimised by ensuring adequate hydration, the use of intermittent dosing schedules and adjusting the dose according to serum creatinine concentrations [87]. Nephrogenic diabetes insipidus associated with foscarnet sodium has been reported [88,89].

4.3 Cidofovir

Dose-related nephrotoxicity is the most severe adverse effect of cidofovir. Severe proteinuria has also been reported in 13% of patients and there have been instances of acute renal failure occurring after only one or two doses (some of these resulting in fatalities). The drug is directly toxic to renal tubular cells and uptake into the cells is mediated via the human organic anion transporter (hOAT)-1 [90]. The incidence and severity of this toxicity can be reduced by ensuring adequate hydration and by concurrent administration of probenecid. Low plasma bicarbonate concentrations and metabolic acidosis, sometimes associated with proximal tubule injury and a renal wasting syndrome (including Fanconi's syndrome) or with liver dysfunction and pancreatitis, have also been reported [91]. Reversible neutropenia and nephrogenic diabetes insipidus occurring without premonitory laboratory abnormalities have also been described [92].

Specific ocular adverse effects associated with intravenous administration of cidofovir include iritis, uveitis and ocular hypotony [93,94]. Cidofovir administered via the intravitreal route has a different profile of adverse effects to that seen with systemic administration. Intravitreal administration of cidofovir may reduce the risk of developing immune recovery uveitis in patients with AIDS, compared to the intravenous administration of cidofovir or the use of an alternative treatment regimen [95].

Table 3. Miscellaneous drugs associated with retinal toxicity.

Drug	Indication	Mechanism/comments	Ref.
Aminoglycosides (intravitreal)	Bacterial end-ophthalmitis	Risk of retinal toxicity from intravitreal gentamicin. Reports that amikacin in doses of 0.2 – 0.4 mg can also cause toxicity. Relatively small dilution errors can cause retinal toxicity because of the low therapeutic index of aminoglycosides. Use of ceftazidime instead of amikacin or gentamicin has been recommended.	[69,70]
Desferrioxamine	Iron overload	Associated with retinal toxicity and visual disturbances, albeit at very high concentrations.	[71]
Digoxin	Heart failure, supraventricular arrhythmias	Inhibition of Na^+/K^+ adenosine triphosphatase influences normal uptake of extracellular potassium by retinal neurons producing abnormal, prolonged cone-mediated ERG responses.	[72]
Ethambutol	Tuberculosis	Causes dysfunction of the RPE.	[73]
Minoxidil	Severe hypertension	Bilateral retinitis (and optic neuritis) reported in a patient during treatment with minoxidil for hypertension following a renal transplant.	[74]
Tamoxifen	Adjuvant therapy in breast cancer, anovulatory infertility	Retinopathy associated with high-dose tamoxifen treatment. Low-dose tamoxifen may induce retinal toxicity in a small proportion of patients. Impossible to conclude that the retinal opacities observed with this drug are really caused by tamoxifen, as differentiation from age-related macular degeneration is difficult.	[75]

RPE: Retinal pigment epithelium.

5. Conclusion and expert opinion

Although many drugs have been associated with retinal toxicity, the retina is not a common target for drug action in general clinical practice, and through the BRB, it is relatively well-protected against systemic drug administration. As in all clinical management decision-making processes, the benefits of treatment need to be balanced against the risks. Unfortunately, it is not generally possible to identify those patients at risk from retinal toxicity, and toxicity cannot necessarily be anticipated either from the chemical structure of the compound or from the expected pharmacology. Furthermore, retinal toxicity may be subclinical, with many patients remaining asymptomatic, despite being affected by therapy. Perimetry and accurate testing of retinal function can be problematic and decisions may need to be made following serial, rather than single, assessments. Electroretinography may be helpful in the evaluation of certain patients, for example, children. With one or two exceptions, the mechanisms of toxicity are poorly understood. Furthermore, animal models are frequently not good for predicting retinal toxicity in man.

Ophthalmological screening and monitoring for retinal disease is only evidence-based and indicated during the prescription of a small minority of drugs, notably, vigabatrin and hydroxychloroquine. However, the prescribing physician needs to be alert to these significant, disabling toxicities in order to act appropriately, especially when an alternative agent may be available. Any suspicion that a drug is causing retinal toxicity in a patient should be reported to the regulatory agencies via the spontaneous ADR reporting schemes and also to the manufacturer. Furthermore, an awareness of the toxicities associated with the use of drugs in the management of a primary retinal pathology, such as CMV retinitis, leads to a level of vigilance and haematological and biochemical monitoring, required for these compounds.

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