Medications and retinal toxicity

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Introduction

Several pharmaceuticals are associated with toxicity in the retina, the retinal pigment epithelium (RPE), and their blood supplies. It is important to be aware of these associations because prompt recognition and discontinuation of the agent may ameliorate its effect. Alternatively, some medications only cause problems when they are overdosed. In these patients, the ophthalmologist may make a vision-sparing or life-saving diagnosis.

Drugs causing pigmentary degeneration

Quinolines

The quinoline antimalarial chloroquine (Aralen) and its safer derivative hydroxychloroquine (HCQ; Plaquenil, Sanofi Winthrop Pharmaceuticals, New York, NY) cause a well-documented retinopathy—bull’s-eye maculopathy. Signs of visual dysfunction typically precede symptoms. Loss of the foveal light reflex (Fig. 1) may progress to macular pigment stippling and then to a bull’s-eye lesion (Fig. 2). Pigment mottling in the retinal periphery may advance to a tapetoretinal-like degeneration with vascular attenuation and optic disc atrophy (Fig. 3). An asymptomatic, verticillata-like change of the corneal epithelium may also occasionally be seen [1–4].

Perimetry often demonstrates a paracentral scotoma, which may be the first evidence of disease, particularly with the use of a red test object [5]. Similarly, a red Amsler grid may indicate abnormal results early [6], and color vision defects are frequent [7].

Chloroquine toxicity is more dependent on daily rather than cumulative dosage. Most cases occur in patients ingesting more than 250 mg/d for at least 1 year [8].

With prompt recognition of toxicity and discontinuation of chloroquine therapy, early maculopathy may resolve. In contrast, more advanced cases may progress even after the medication has been discontinued [9,10]. Retinopathy may not develop until years after the medication is discontinued [11,12], perhaps because of the exceptionally long clearance time of the drug [13].

Hydroxychloroquine toxicity is clinically identical to toxicity caused by chloroquine (Fig. 4), though it occurs less frequently. The reason for the relative safety of hydroxychloroquine is unknown. Retinopathy rarely occurs at or below the theoretically safe dosage of 6.5 mg/kg per day [14,15] and generally is not seen before 7 years of usage of the medication.

Because of the rarity of hydroxychloroquine toxicity, several authors have questioned the necessity of screening these patients [16–18]. Recently, a Task Force from the American Academy of Ophthalmology established new monitoring guidelines, and these guidelines were recently published [19]. It should be noted that obese patients and possibly those with renal and hepatic disease may be at increased risk for toxicity. Quinolines are stored in...
the intracellular compartment; thus, relatively more drug is taken up into leaner tissues than into body fat. Therefore, dosages calculated on actual body weight rather than lean (or ideal) body weight may cause overdoses [19,20].

Phenothiazines

The antipsychotic agent thioridazine (Mellaril, Sandoz Pharmaceuticals, East Hanover, NJ), a piperidine phenothiazine, causes decreased vision, dyschromatopsia (red or brown), and nyctalopia [21]. The first fundus change is mild stippling of the RPE or a salt-and-pepper pattern (Fig. 5), followed by circumscribed nummular areas of RPE and choriocapillaris atrophy in the macula and midperiphery (Fig. 6) [22]. This may progress to extensive complete atrophy, with alternating areas of hypopigmentation and pigment clumping, associated with vascular attenuation and optic atrophy (Fig. 7) [23].

As in the quinolines, the daily dose rather than the cumulative dose of thioridazine predicts future toxicity [24]. A daily dose of 800 mg or less is recommended, though long-term administration of low-dose medication may be toxic as well [25,26]. Prompt discontinuation of medication may result in spontaneous improvement [27]; however, even early retinopathy may progress. Progressive vision loss may ensue [22] because of the continued decline of previously damaged cells rather than a prolonged effect of medication [27].

Chlorpromazine (Thorazine, GlaxcoSmithKline, Research Triangle Park, NC) is a non-piperidine phenothiazine. Its toxic potential is uncertain [28,29], but several reports of pigmentary retinopathy have been described [30–32]. Some of these patients, however, had also previously ingested thioridazine [33].

Quinine

Quinine (Quinamm, Marion Merrell Dow, Inc., Kansas City, MO), a quinoline similar to chloroquine and hydroxychloroquine, is capable of causing a unique form of toxicity. When used at the recommended dosage (250–500 mg), it is a safe medication. Acute overdose (greater than 4.0 g) may cause headache, nausea, vomiting, tremor, hypotension, and loss of consciousness. On awakening, the patient may report total blindness, which may partially recover over time. Frequently, only a small central island of vision returns [34].
Acute features of toxicity include mild retinal edema, mild venous dilation, and normal-appearing arterioles. Over several weeks, the arterioles become attenuated and optic atrophy develops (Fig. 8). The end-stage fundus resembles that of a central retinal artery occlusion [34,35].

Deferoxamine

Deferoxamine (desferrioxamine, Desféral, Novartis, East Hanover, NJ) chelates iron and aluminum and is prescribed for patients receiving multiple blood transfusions. High-dose therapy may result in decreased vision, nyctalopia, and visual field loss [128]. The fundus may initially demonstrate a dull gray discoloration of the macula [36]. Over a period of several weeks, pigmentary changes occur in the macula and peripheral retina, with abnormal color vision, visual fields, electroretinography (ERG), electro-oculography (EOG), and dark adaptometry [37,38]. Retinal toxicity, occasionally with permanent abnormalities, may occur after a single dose of medication [38,39].

Other agents

Two drugs used in the management of patients with AIDS may cause retinal pigmentary retinopathy: clofazimine (Lamprene, Ciba Pharmaceuticals, Summit, NJ) [40–42], used in the management of atypical mycobacterial infections, and the reverse transcriptase inhibitor didanosine (Videx, Bristol-Myers Squibb, Princeton, NJ) [43,45].

Drugs causing crystalline deposits

Tamoxifen (AstraZeneca, Wilmington, DE)

The estrogen antagonist tamoxifen may cause crystalline retinopathy. Patients may have decreased vision and dyschromatopsia or they may be asymptomatic [46,47]. Retinopathy was more frequent when the medication was initially used at a higher dosage level (60 mg). When used at 20 mg/d, retinal crystals are infrequently seen. When they do occur, numerous white refractile deposits are noted in the paramacular retina (Fig. 9). Other associated features include cystoid macular edema (CME) and punctate retinal pigmentary changes. Because the crystals are often a benign finding, discontinuation of the medication in a patient with crystals in the absence of CME or vision loss may not be necessary [48].

Canthaxanthine

The carotenoid pigment canthaxanthine (Orobronze, Dewitte, Greenville, SC), used in the treatment of vitiligo and photosensitivity disorders, is also sold as an over-the-counter oral tanning agent. Patients present with an asymptomatic ring-shaped deposition of yellow-orange crystalline...
material in the macula (Fig. 10) [49]. The material is more prominent in eyes with preexisting retinal disease and with concurrent use of [beta]-carotene [50,51]. Abnormalities may be noted on perimetry, ERG, EOG, or dark adaptometry [52,53,130]. Long-term effects are not fully known, though it is generally recommended that the agent be discontinued, especially when used for sun tanning.

Methoxyflurane

After prolonged administration, the inhalational anesthetic methoxyflurane may occasionally be associated with irreversible renal failure partly caused by the deposition of calcium oxalate crystals in the kidney [54]. Similarly, numerous yellow-white punctate lesions are seen in the macular region and surrounding the arterioles [55,56].

Drugs causing no visible fundus changes

Cardiac glycosides

Xanthopsia caused by cardiac glycosides (including digitalis) was probably the first reported toxic retinopathy [57]. Other reported symptoms include blurred or “snowy” vision, photopsias, diplopia, or pain with eye movement [58]. Ocular symptoms generally occur in patients with systemic digitalis toxicity, though on occasion the digitalis level may be normal. Vision is variably affected, but color vision is usually diminished. Fundus examination, fluorescein angiography, and EOG results are typically normal, but ERG results may be abnormal. Vision and ERG findings return to normal when the medication is discontinued or the dose is lowered [59,60].

Sildenafil

Sildenafil (Viagra, Pfizer, Inc., New York, NY), a selective phosphodiesterase 5 (PDE-5) inhibitor, is used to treat male erectile dysfunction. Although sildenafil specifically inhibits the enzyme PDE-5 in the penile corpora cavernosa, it demonstrates some activity against the PDE-6 in the photoreceptors [61].

Transient dyschromatopsia may last minutes to hours after a therapeutic dose is ingested [62]. Objective changes are rare but include retinal hemorrhages, branch retinal vein occlusion, branch retinal
artery occlusion, anterior ischemic optic neuropathy, and acceleration of proliferative diabetic retinopathy [63–65]. Certain patients with retinal disease may be at relatively increased risk for complications, including those with ischemic retinopathies or retinitis pigmentosa [64]. In the absence of objective retinal findings, the long-term risk from dyschromatopsia is not fully known.

Drugs causing retinal edema

**Methanol**

Methanol is occasionally ingested by alcoholics or persons attempting suicide and results in decreased central or peripheral vision. Extensive retinal edema develops. Initially, the optic disc appears hyperemic or edematous; this generally progresses to optic atrophy. Methanol toxicity is associated with systemic acidosis, the degree of which correlates not only with visual disturbance [66–68], but also with the prognosis for life.

Drugs causing vasculopathies

**Aminoglycosides**

Intracameral aminoglycosides may cause significant toxicity when injected into the vitreous cavity or used in the irrigation fluid during cataract surgery [69–72]. Patients have severe central vision loss, intraretinal hemorrhage, retinal edema, cotton-wool spots, arteriolar attenuation, and venous beading (Fig. 11). This may progress to pigmentary retinopathy with optic atrophy and neovascular glaucoma. Toxicity is caused by occlusion of the retinal microcirculation. There is no effective treatment.

**Talc**

Magnesium silicate, or talc, is used as a vehicle in the manufacture of several oral medications, including methylphenidate (Ritalin, Novartis Pharmaceutical Corporation, East Hanover, NJ) and methadone. Persons who abuse these compounds by dissolving them in water and injecting them intravenously may develop talc retinopathy [73,74].

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Fig. 7. Photograph (A) showing total loss of the RPE in a patient on high-dose thioridazine, with the fluorescein angiogram (B) showing the residual large choroidal vessels that can now be visualized only because of total loss of the RPE.

Fig. 8. Photograph showing the end-stage results of quinine toxicity (2 months after ingestion) in a patient who attempted suicide by ingesting quinine. Note the distinct optic disc pallor and the retinal vascular attenuation. The vision was hand motions.

Fig. 9. Photograph revealing a paramacular ring of intraretinal crystals in a patient with metastatic breast carcinoma treated with tamoxifen. The patient was visually asymptomatic.
Talc particles embolize to the retinal arterioles, where they occlude the small vessels in the posterior pole. In advanced cases a syndrome develops that resembles other ischemic retinopathies (Fig. 12) [75–78].

**Hormone preparations**

Oral contraceptives have been associated with occlusion of retinal arteries, cilioretinal arteries, and retinal veins (Fig. 13) [79–83]. Similar compounds, prescribed for emergency contraception [84] or in the management of transsexual patients [85], may cause similar events. The synthetic estrogens and progesterones in these compounds induce a hypercoagulable state. Most oral contraceptives manufactured in the past 20 years contain lower concentrations of these agents and have a decreased incidence of complications [86,87].

**Interferon-[alpha]**

The antiangiogenic agents interferon (IFN)-[alpha]2a (Roche Pharmaceuticals, Nutley, NY) and IFN-[alpha]2b (Schering Corporation, Kenilworth, NJ) have antiviral and antineoplastic properties. They may cause retinal vasculopathy, with intraretinal hemorrhages and cotton-wool spots. Visual acuity is usually [88], but not invariably [89], unaffected. Coexisting systemic vascular disease predisposes to more severe retinopathy [53].

**Drugs causing maculopathy**

**Epinephrine**

In the aphakic eye, topical epinephrine may cause CME that is indistinguishable from typical Irvine-Gass edema [90]. Most, but not all, cases resolve with the discontinuation of the drug. The pro-drug dipivefrin (Propine) appears safer than epinephrine, but similar cases of CME may arise, even in phakic eyes [91].

**Latanoprost**

The synthetic prostaglandin analog latanoprost (Xalatan, Pharmacia & Upjohn, Peapack, NJ) may cause CME with or without iridocyclitis, probably through its effects on inflammatory mediators [92,93]. Less commonly reported posterior segment effects include vitreitis [94] and choroidal effusion [95]. The incidence of CME is increased by other conditions that cause macular edema, including vitreous loss during cataract surgery [96,97].

**Drugs causing other maculopathies**

**Niacin**

The lipid-lowering agent niacin may cause decreased vision, paracentral scotoma, or metamorphopsia [98]. Although examination reveals that it resembles typical CME, no vascular leakage is seen
on fluorescein angiography [99,100]. The clinical appearance, therefore, most likely represents intracellular fluid accumulation, as opposed to true edema (extracellular fluid) [101]. Discontinuation of the agent leads to resolution of the atypical CME.

**Drugs causing retinal folds**

*Sulfanilamide-like medications*

Several medications, with a structure similar to sulfanilamide, are associated with ciliary body swelling or choroidal effusion with subsequent anterior displacement of the lens-iris diaphragm. This leads to transient acute myopia, anterior chamber shallowing with angle closure, and retinal folds (Fig. 14a,b). Fluorescein angiography reveals no vascular leakage, and the folds are presumed to be due to vitreous traction on the macula during axial elongation of the eye. Drugs associated with this syndrome include sulfa antibiotics, acetazolamide (Diamox, Lederle Pharmaceuticals, Pearl River, NJ), hydrochlorothiazide, metronidazole, and others [102–105].

**Drugs causing uveitis**

*Rifabutin (Pharmacia & Upjohn, Peapack, NJ)*

Rifabutin, a semisynthetic antibiotic used in the management of atypical mycobacterial infections in patients with AIDS and other immunosuppressive conditions, has been associated with uveitis [106–108]. The inflammation is usually anterior but may include vitreitis and retinal vasculitis [109–111].

*Cidofovir (Gilead Sciences Inc., Forest City, GA)*

Cidofovir (HPMPC) is used in the prophylaxis and management of cytomegalovirus infection. Intravenous and intravitreal administration may induce severe iridocyclitis with hypotony and vision loss [44,112–115]. With the decreasing frequency of cytomegalovirus retinitis in the AIDS population, along with the above-noted concerns, this medication is infrequently used.

**Drugs causing multiple toxicities**

*Corticosteroid preparations*

Corticosteroids have little or no toxicity [116], but their vehicles may cause diffuse retinal necrosis if injected intravitreally. Two potentially toxic compounds are Celestone Soluspan and Depo-Medrol [117, 118]. In addition to their direct effects, corticosteroid compounds, when injected into the nasal cavity, have been associated with retinal and choroidal vascular occlusion [119]. Corticosteroids have also been implicated as a possible causative factor in select cases of central serous choroidopathy.
Cisplatin (Baxter Healthcare Corporation Anesthesia and Critical Care, New Providence, NJ) and carmustine (Guilford Pharmaceuticals, Baltimore, MD)

The alkylating agents cisplatin and carmustine (BCNU), when given as intracarotid infusions, may cause retinal toxicity. Vascular damage usually occurs. Patients receiving either agent may have irreversible vision loss from retinal vasculitis with arterial occlusions and optic disc edema [120–122,129]. Selective infusion of these drugs distal to the origin of the ophthalmic artery may prevent this toxicity [123], but not invariably [124,125]. These agents may also be associated with pigmentary retinopathy and occasionally with optic atrophy [121,126,127].

Summary

Approximately three dozen medications have been associated with retinal toxicity, and it is important to be aware of such associations. Several medications, such as acetazolamide and latanoprost, are commonly prescribed by the ophthalmologist. Most of the other medications are commonly administered by the patient’s primary physician. When assessing any patient for a retinal disturbance, it is imperative to question the patient regarding the use of systemic medications. This is especially important as more and more medications are brought to the market each year.

References


