Ophthalmology Update

Richmond Eye Associates, P.C.

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Ophthalmic Topics of Interest to the Medical Physician

Ophthalmic Side Effects of Drugs

This issue discusses examples of adverse side-effects of selected drugs on the eye and visual system.

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Ophthalmology Update:

Life Threatening Ophthalmic Conditions

- **"Routine" Uveitis**
- **Myasthenia Ptosis?**
- **"Blurred Vision"**
- **Gaze Evoked Amaurosis**

Statin Use and the Risk of Cataract

Statins are becoming one of the most frequently prescribed classes of medication in history, and there has been some controversy in the past as to whether or not their use leads to cataract development. Two recent studies help to determine this risk.

A 2001 study[1] published in the *Archives of Internal Medicine* used a case-control analysis of cataract and statins using the United Kingdom's General Practice Research Database. Out of 3 million patient records from 1994-1998, 7405 patients were identified with the first diagnosis of cataract between the ages of 40 to 79. Those with concomitant ocular disease or diabetes were excluded.

Subjects were matched randomly with four control subjects based on age, sex, practice, date of diagnosis, and number of years in the database before the date. The use of statins, fibrates, or other lipid lowering drugs was compared with non-use in all subjects.

Of the case population identified with the first diagnosis of cataract, 111 were also using statins, mostly Zocor and Pravachol. Long term use of statins (more than 30 prescriptions) was **not** found to be associated with an increased risk of cataract compared to the control groups.

However, in 5 cataract patients and 6 matched control subjects, there was a suggestion of a significant interaction between simultaneous statin and erythromycin use with the development of cataract. Even a single course of erythromycin doubled risk of cataract in people taking Zocor. Inhibitors of cytochrome P-450 are known to increase systemic availability of statins.

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Hormone Replacement Therapy and Dry Eye

Dry eye syndrome is an increasingly common problem especially in post-menopausal women. An analysis[1] of nearly forty thousand U.S. women participating in the Women's Health Study found the diagnosis of dry eye syndrome in 5.7% of women under age 50, and in 9.8% in those over 75. Thus, more than 3.2 million middle-aged and older American women have a clinical diagnosis of dry eye syndrome, or have severe symptoms from it.

Furthermore, recent research indicates that androgen deficiency as

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Hormone Replacement Therapy and Dry Eye (from page 1)

systemic Hormone Replacement Therapy (HRT) in postmenopausal women may lead to dry eye.

An epidemiological study[2] of over 25 thousand postmenopausal women found that those using estrogen HRT had a significantly higher prevalence of severe dry eye symptoms and clinically diagnosed dry eye syndrome compared to women who never used HRT. It is felt that estrogens may affect the meibomian glands, which are oil secreting glands that open at the margin of the eyelids. These glands produce an oil layer which helps to prevent tear evaporation from the eye. Estrogens appear to induce a significant decrease in the size, activity, and lipid production of sebaceous glands.

Conversely, androgens appear to positively influence the secretory processes of the lacrimal glands. Patients with Sjogren's syndrome are commonly women, and are generally found to be androgen deficient. While there is an inflammatory component to Sjogren's syndrome, systemic androgen administration was found to reduce dry eye signs and symptoms and increase tear flow volume in Sjogren's syndrome patients[3].

Dry eye syndrome is a significant ophthalmic disorder, leading to symptoms of ocular discomfort including burning, grittiness, a foreign body sensation, ocular redness, paradoxical tearing, sensitivity to light, pain, and blurred vision.

[1]American Journal of Ophthalmology 2003;136:318-326.
[2]Schaumberg DA, et al. JAMA 2001;286:2114-2119.
[3]Sullivan DA, et al. The Netherlands: Aeolus Press, 1997:95-152.

Viagra Update

Viagra (sildenafil) has been associated with at least three cases of visual loss due to ischemia of the optic nerve. Apparently, systemic arterial hypotension was induced with the drug sufficient to decrease the perfusion of small arteries supplying the optic nerve head, essentially causing a stroke of the optic nerve.

Retinal changes can also occur at the level of the photoreceptors, where Viagra inhibits PDE-6 (Viagra's normal target is PDE-5, leading to vascular smooth muscle relaxation). When PDE-6 in the retina is inhibited, visual changes occur, such as blue vision and increased light sensitivity. This normally resolves in about 4 hours, but patients with a genetic defect in PDE-6, such as with autosomal recessive retinitis pigmentosa, should not use the drug.

Viagra has also been found to cause dilation of retinal vessels in healthy patients, leading to increased perfusion of the retina. However, it is not known whether this is a beneficial or dangerous effect, and it is not known if the same effect would be seen in older patients with vascular disease.

Clinical Pearl: Safety of Glaucoma Drugs During Pregnancy

Glaucoma is often assumed to be a disease of the elderly, but there a significant number of glaucoma patients within childbearing age. African-American and Hispanic women may develop the most common type of glaucoma, open angle glaucoma, in their mid-30's. Other more uncommon types of glaucoma, such as pigmentary glaucoma, juvenile onset glaucoma, congenital glaucoma, inflammatory glaucoma, and glaucoma associated with anatomical abnormalities of the eye begin at an even earlier age. Thus, it is important for all medical practitioners to have an awareness of the risks associated with using glaucoma medications during pregnancy and during lactation.

Glaucoma medications are usually given in the form of eye drops, often only once per day. Nevertheless, there can be significant systemic absorption through the nasal mucosa after eye medications drain away from the eye via the nasolacrimal system. The following FDA rating system categorizes risk to the fetus:

Class A (Controlled studies show no risk to the fetus): No glaucoma medications fall into this category.

Class B (No evidence of risk in humans): Alphagan, Alphagan-P, and Propine fall into this category. In animal studies, there is no evidence of teratogenicity. Alphagan has been found excreted in rat breast milk, but there is no data in humans. Alphagan has caused bradycardia, hypotension, hypothermia, and apnea in neonates, so breastfed infants may be at risk.

Class C (Risk cannot be ruled out): All glaucoma medications except those in Class B and Class X fall into this category. Here, fetal loss has been demonstrated in animals given much higher doses than humans receive. With these drugs, potential benefits of the drug may outweigh risks.

Note that Xalatan and Travatan contain Prostaglandin F2 alpha, which has been used to terminate pregnancy. These drugs are generally contraindicated during pregnancy.

Timolol and acetazolamide (Diamox) have been approved by the American Academy of Pediatrics for use during lactation, but Beta blockers such as timolol can become concentrated in breast milk, and can lead to beta blockade in infants.

Class D (Definite evidence of fetal risk): No glaucoma medications fall into this category.

Class X (Contraindicated during pregnancy): Humorsol is the only glaucoma medication in this category.

Plaquenil Update

Plaquenil (hydroxychloroquine) is a commonly used drug to treat autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosis. The use of 4-aminoquinolone antimalarial drugs have been associated with an irreversible retinal toxicity, especially with chloroquine, and less so with hydroxychloroquine. A 2001 survey of U.S. rheumatologist's attitudes toward ophthalmic screening examinations for Plaquenil retinopathy revealed that 94% recommended at least annual examinations, because they were unwilling to accept any risk of visual damage.

However, Plaquenil retinopathy is very rare. Guidelines published in 2002 by the American Academy of Ophthalmology Task Force for screening for Plaquenil toxicity recommend a baseline eye examination followed by periodic eye examinations during the first 5 years of use. During these first 5 years, the follow-up intervals are based on the age of the patient, as if Plaquenil was not being used. After that period, annual examinations are recommended. If the patient has concomitant retinal, renal, or liver disease, annual Plaquenil eye examinations are recommended from the start.

A July 2003 prospective cohort study1 of 526 patients using hydroxychloroquine for at least 6 years further clarified the risk of retinal toxicity. The results of this study are summarized below:

- No patient with normal renal function and a maximum daily dose of 6.5 mg/kg developed retinal toxicity during 6 years of use.
- In patients treated for more than 6 years, two developed findings consistent with retinal toxicity, for an overall incidence of 0.5% of long term users.
- The two affected patients were asymptomatic, but had characteristic retinal "bull's eye" pigmentation, paracentral scotomas on visual field testing, abnormal findings on fluorescein angiography, and normal color vision and visual acuity. These findings did not resolve after the medication was discontinued, even after 7-9 years.
- The Authors of the study recommend a baseline eye examination at the onset of Plaquenil treatment followed by at least annual examinations after 6 years of treatment (assuming that the maximum daily dosage is 6.5 mg/kg, and that renal function is normal).

In general, at a dosage of 6.5 mg/kg, a patient can safely weigh 34 lbs. per 100 mg used per day. Thus, for 400 mg a day to be safely used, the patient should weigh at least 136 lbs. There have been cases of Plaquenil toxicity in lightweight patients taking disproportionately high dosages.

[1]Mavrikakis, et al. Ophthalmology 2003;110:1321-1326.

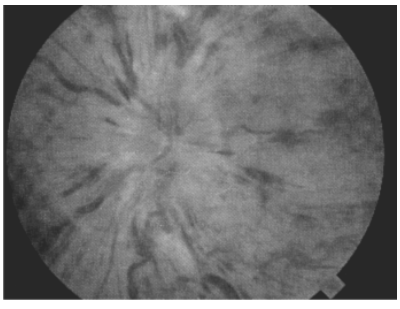
Ocular Complications of Cocaine Use

The abuse of cocaine is a significant health problem in the United States, with reportedly 10% of the population having tried cocaine and up to 5 million regular users. Cocaine use has been connected with numerous cases of ophthalmic pathology, including corneal ulcer, optic neuropathy, impaired color vision, nasolacrimal duct obstruction, orbital cellulitis, acute angle closure glaucoma, central retinal artery occlusion, and central retinal vein occlusion.

Case 1:

A 42 year old Hispanic male presented with a sudden decrease of vision in the left eye, starting 3 weeks earlier. The patient had no significant past medical, family, or social history, although he did finally admit to occasional inhalational use of cocaine. His most recent use was on the day prior to the loss of vision.

The examination showed a visual acuity of 20/60 in the affected left eye, and 20/20 in the right eye. Pupillary function was normal and symmetrical. The fundoscopic examination showed a normal right eye, but the left retina had dilated and tortuous vessels with retinal hemorrhages in all quadrants. (See photo on left.)



Systemic workup for occult vascular disease was negative, including no evidence of hypertension, collagen vascular disease, AIDS, or protein C, S, or antithrombin III deficiency. It was felt that the cocaine use was the most likely cause of the central retinal vein occlusion, due to a cocaine induced retinal venous vasoconstriction. clot formation. and subsequent vein occlusion.[1]

Case 2:

A 39 year old woman presented with an 8-month history of double vision and occasional tearing from the left eye. She wore a patch over the left eye to eliminate the double vision. She denied any history of trauma, pain, or any significant medical problems. She took an occasional "tranquilizer" for anxiety.

The examination showed a visual acuity of 20/20 on the right and 20/25 on the left, with normal pupillary function and visual field testing. The movement of the left eye was significantly abnormal, and was unable to turn the eye

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- Extensive patient information, including discussion of over 80 eye conditions and a section discussing risks and benefits of laser vision correction.
- Interactive Clinical Section concerning eye disease and physical findings
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Statin Use and Cataract (page 1)

These include erythromycin, clarithromycin, verapamil, cyclosporine, fluconazole, and ketoconazole, and these were all evaluated in the study.

In a 2003 study[2] from the *Journal of Lipid Research*, rats with a genetic defect in their cholesterol synthesis pathway developed cataracts after only two weeks of receiving simvastatin (Zocor). However, rats with a normal cholesterol pathway did not develop cataract. It is hypothesized that the elevated levels of statins found in the genetically abnormal rats as well as in humans taking simultaneous erythromycin lead to abnormalities in the cholesterol rich membrane that surrounds the lens, leading to cataract.

[1]Schlienger RG, et al. Arch Inter Med. 2001;161:2021-2026.
[2]Cenedella, RJ, et al. J Lipid Res 2003;44:198-211.

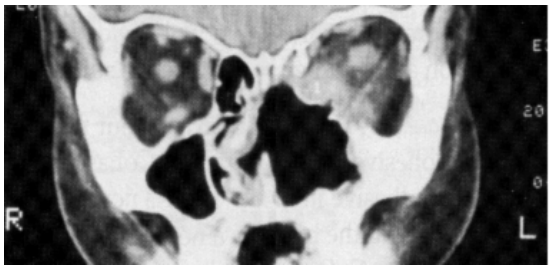
Cocaine Complications (page 3)

upward or outward. There was severe restriction of the eye to movement in these directions with direct testing of the eye. The eye was found to be sunken back into the orbit by 3 millimeters.

A facial CT scan (see image below) showed absence of the nasal septum, loss of the medial orbital wall, and severe thinning of the orbital floor. The left turbinate structures were also missing.

The differential diagnosis in this case could include Wegener's Granulomatosis, lymphoma, mucormycosis, neoplasm, and sarcoidosis. With further questioning, the patient admitted to an 8-year history of intranasal cocaine use, leading to destruction of the nasal cavity and scarring of the adjacent extraocular muscles to the orbital bone.[2]

[1]Mayo GL, et al. Ophthalmology Times 11/1/02:32-33.
[2]Yoder DM, et al. Ophthalmology Times 9/15/02:52-54.



CT Scan showing loss of nasal septum and L medial orbital wall, and thinning of orbital floor.