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Ocular Adverse Effects Associated With Cyclooxygenase-2 Inhibitors

An important event in the treatment of inflammatory disease was the identification of selective inhibitors of cyclooxygenase-2 (COX-2).

Cyclooxygenase-1 (COX-1) inhibitors are responsible for many of the adverse effects of nonsteroidal anti-inflammatory drugs, such as gastrointestinal disturbances, while blockade of COX-2 mediates the anti-inflammatory activity with fewer adverse effects. Selective COX-2 inhibitors include rofecoxib (Vioxx; Merck & Co, West Point, Pa), celecoxib (Celebrex; Pfizer Inc, New York, NY), valdecoxib (Bextra; Pfizer Inc), and lumiracoxib (Prexige; Novartis Pharmaceuticals Corp, Basel, Switzerland). Nimesulide (Ainex; Schering-Plough, Santiago, Chile) (and other trade names), and etodolac (Lodine; Wyeth, Madison, NJ) also exhibit selective COX-2 inhibition and can be included in this class of medication which is used in the treatment of osteoarthritis, rheumatoid arthritis, acute pain, and dysmenorrhea. Nimesulide and lumiracoxib are not approved by the Food and Drug Administration and are not marketed in the United States and Merck removed Vioxx from the market worldwide in September 2004 because of a possible increased risk of heart attack and stroke.

From the literature, there are 8 case reports of visual disturbance from treatment with COX-2 inhibitors. These include orange spots in vision while taking celecoxib, temporary blindness from rofecoxib, a jellybean-like area of vision loss centrally from celecoxib, and 5 cases of blurred vision (4 cases related to celecoxib and 1 related to rofecoxib). The visual disturbances all resolved within 72 hours of discontinuing the drug (positive dechallenge), however no rechallenge data (that the adverse reaction reoccurred when restarting the drug) is available.

Recently, a large number of inquiries and case reports were submitted to the National Registry of Drug-Induced Ocular Side Effects (www.eyedrugregistry.com) associating COX-2 inhibitors and visual adverse effects, prompting an examination of this first large series of spontaneous reports of possible adverse visual effects secondary to COX-2 inhibitors. The possible etiologies of the adverse ocular reactions are explored.

Methods. A total of 1006 reports were collected at the National Registry of Drug-Induced Ocular Side Effects (Casey Eye Institute, Portland, Ore). Spontaneous case reports from the National Registry, the Food and Drug Administration, and the World Health Organization were analyzed. The main information in the report from ophthalmologists includes the type of COX-2 inhibitor, age, sex, dosage, duration of therapy, concomitant therapies, and type of ocular adverse effect. Special attention was paid to reports with positive dechallenge and positive rechallenge, given that this information is the most compelling for a cause-and-effect relationship with COX-2 inhibitors causing a visual adverse effect. Spontaneous reports originated from the countries where the medications are marketed. Blurred vision and conjunctivitis were the majority of these types of reports and, therefore, are the focus of the results.

Results. Celecoxib. There were 238 reported cases of blurred vision from celecoxib, with 67 positive dechallenge and 15 positive rechallenge reports. There were also 71 case reports of conjunctivitis due to celecoxib, with 12 positive dechallenge and 4 positive rechallenge reports. Average age was 58 years (range, 43-81 years) receiving standard doses (200 mg/d) with an average duration of therapy of 48 days. Three subjects also received diazepam in addition to celecoxib (1 conjunctivitis, 2 blurred vision).

Rofecoxib. A total of 258 reports of blurred vision from rofecoxib were collected, with 48 positive dechallenge and 21 positive rechallenge reports. There were 85 cases of conjunctivitis due to rofecoxib, with 18 positive dechallenge and 4 positive rechallenge reports. Average age was 62 years (range, 36-85 years) receiving standard doses (12.5-25 mg/d) with an average duration of therapy of 76 days. Two subjects with blurred vision were also taking levothyroxine and experienced visual hallucinations with positive dechallenge and positive rechallenge.

Valdecoxib. There were 14 case reports of blurred vision secondary to valdecoxib, with 3 positive dechallenge reports and 1 positive rechallenge report. There were also 14 case reports of conjunctivitis due to valdecoxib, with 1 positive dechallenge report and 1 positive rechallenge report. Average age was 60 years (range, 45-76 years) receiving standard doses (10 mg/d) with an average duration of therapy of 35 days.

Etozolac. Forty-eight case reports of blurred vision secondary to...
etodolac were received, with 11 positive dechallenge reports and 1 positive rechallenge report. Thirteen cases of conjunctivitis were reported, with 1 positive dechallenge report. Average age was 60 years (range, 22-91 years) receiving standard doses (200-400 mg/d) with an average duration of therapy of 19 days. From the rechallenge case, the patient was also taking aspirin with codeine.

Nimesulide. There were 11 cases of abnormal vision, with 4 positive dechallenge reports. Five reports of conjunctivitis were received, with 5 positive dechallenge reports. Average age was 52 years (range, 23-68 years) receiving standard doses (200-400 mg/d) with an average duration of therapy of 51 days.

Lumiracoxib. No ocular adverse effects have been reported related to this medication.

Conclusions. Conjunctivitis and blurred vision are the 2 main ocular adverse effects that appear to have a certain cause-and-effect relationship in some patients treated with COX-2 inhibitors, using World Health Organization criteria. This analysis is based on positive dechallenge and positive rechallenge data. Other ocular adverse effects were reported relatively infrequently and without complete follow-up and a clear relationship between COX-2 inhibitors and an adverse ocular reaction could not be deduced. In every instance, the ocular adverse effect resolved within 72 hours of discontinuation of the COX-2 inhibitor.

Spontaneous reporting databases collect information passively and have inherent limitations including incomplete data, duplicate reporting, lack of follow-up, and few data as to other diseases which could contribute to a clinical picture. After a drug is marketed, exposure to a medication goes from thousands in the clinical trial phase to millions in the marketing phase, and this is where postmarketing surveillance plays an important role. Incidence data cannot be garnered from passive databases such as the ones represented here; however, these databases can provide the earliest signals that a drug-induced adverse effect is occurring, especially if positive rechallenge reports are submitted. It appears that COX-2 inhibitors can cause blurred vision and conjunctivitis in some patients.

It is rare for clinicians to restart therapy if a drug-induced ocular adverse effect is suspected, as patients and physicians are reticent to undergo treatment with a drug they suspect is problematic. In spontaneous reporting databases, even a small number of positive rechallenge reports may be compelling evidence for a cause-and-effect relationship between a drug and an adverse reaction. World Health Organization classification of blurred vision and conjunctivitis due to therapy with some COX-2 inhibitors is certain given the very large number of positive rechallenge reports and the similarity of the ocular symptoms on rechallenge to what they were before the medication was first discontinued. This is especially true for celecoxib and rofecoxib, which have an unusually large number of positive rechallenge reports.

Coulter et al. propose a possible mechanism behind the blurred vision some patients experience when taking COX-2 inhibitors. Inhibition of synthesis of prostaglandins and other related compounds that control retinal blood flow could lead to visual changes. The vascular endothelium of retinal blood vessels produces compounds such as prostacyclin, thromboxane A2, and prostaglandin H2. Both COX-1 and COX-2 mediate synthesis of prostacyclin. Inhibition of either COX-1 or COX-2 may alter the cyclooxygenase pathway and in turn alter regulation of retinal blood flow with potential changes in vision. Other nonsteroidal anti-inflammatory medications have been reported to cause blurred vision, which is consistent with this theory.

In the case of selective COX-2 inhibitors, another mechanism may contribute to the blurred vision some patients experience. Four of the 6 COX-2 inhibitors are sulfonamides: celecoxib, rofecoxib, valdecoxib, and nimesulide. Sulfonamide medications are known to cause blurred vision through what is thought to be transient myopia. The mechanism is not fully understood but could include lenticular swelling, forward rotation of the lens-iris diaphragm, ciliary body swelling causing increased curvature of the lens surfaces, and spasm of the iris sphincter. The sulfonamide property of these COX-2 inhibitors could contribute to some cases of blurred vision. Curiously, the 2 non–sulfur-containing selective COX-2 inhibitors do not have the bulk of data to support a certain association with blurred vision, including a paucity of positive rechallenge reports.

Conjunctivitis also has a certain association with some COX-2 inhibitors. Again, there are a number of positive rechallenge reports for celecoxib and rofecoxib, giving strong evidence of a cause-and-effect relationship. This may not be unusual as many medications are secreted in tears. It is possible that these medications are secreted in tears as well, leading to a transient inflammation of the conjunctiva which resolves on discontinuation of the drug. Many examples of this exist—such as irritative conjunctivitis from oral diazepam or oral isotretinoin.

From the literature on this topic, there are mentions of visual field changes including unusual orange spots in vision, irregularly shaped visual field defects, and even a motor vehicle crash that occurred after a patient took celecoxib for 2 days. Curiously, it is possible that the blurred vision in the subjects listed here includes visual field changes and more severe visual disturbances, which could lead to loss of motor vehicle control, and which were categorized as blurred vision for lack of a better term.

Cyclooxygenase-2 inhibitors can cause blurred vision and conjunctivitis in some patients and clinicians should be aware of this association. Discontinuation of therapy leads to resolution without long-term sequela.

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Vitreopapillary Traction Confirmed by Optical Coherence Tomography

The interface between the vitreous and optic nerve head is difficult to evaluate clinically. While vitreomacular traction has been well described, less attention has focused on the clinical effects of persistent attachment of contracting vitreous to the optic nerve head, especially as an isolated phenomenon. Both vitreomacular and vitreopapillary traction occur as manifestations of anomalous posterior vitreous detachment. Evaluation of the posterior vitreous cortex has been recently enhanced by optical coherence tomography (OCT). We describe 2 patients referred for neuro-ophthalmic evaluation of papilledema in whom optic nerve head elevation was shown by OCT to be caused by vitreopapillary traction in the absence of diabetic vitreoretinopathy or central retinal vein occlusion.

Report of Cases. Case 1. An 87-year-old woman was referred for evaluation of apparent optic nerve head swelling in her right eye. She had undergone phacoemulsification with intraocular lens placement in her left eye 3 months prior to evaluation. She was pleased with the vision in the left eye and noted blurring with glare in the right eye.

Best-corrected Snellen visual acuity was 20/30 OD and 20/30 OS. The pupils were equally reactive, with no relative afferent pupillary defect. Color vision was normal, and visual fields (Humphrey 30-2; Allergan, Inc, Irvine, Calif) contained minimal, nonspecific changes. Slit-lamp examination showed a moderate nuclear sclerotic cataract in the right eye and a posterior chamber intraocular lens in the left eye. Funduscopic examination revealed a few macular drusen in each eye. The right optic disc margins were blurred 360°, with the margins appearing elevated (Figure 1A). The posterior vitreous cortex was visibly attached at the optic nerve head, but it was separated from the adjacent retina. The left optic disc was elevated superiorly. Magnetic resonance imaging and computed tomographic examination results of the head and orbit were unremarkable.

Optical coherence tomography demonstrated elevation of the borders of the right optic nerve with linear densities extending from the areas of maximal elevation of the nerve head into the vitreous cavity (Figure 2A). Optical coherence tomography of the left optic nerve showed relatively normal optic disc curvature with a small, curled pre-papillary membrane and a preretinal membrane elevating the temporal papillary retina slightly. Both maculas appeared normal on initial examination. Four months later, the patient underwent right cataract extraction. Two months after that, she developed vitreomacular traction with macular edema in the right eye as well as a partial separation of the vitreopapillary membrane in the left eye. When last seen (15 months after we first saw her), the vitreopapillary traction was still present, the macula was slightly thickened (Figure 1B and Figure 2B), and visual acuity was 20/30 OD and 20/30 OS.

Case 2. An 83-year-old woman was referred for evaluation of apparent optic nerve head edema in the right eye. She had undergone cataract extraction and Yag capsulotomy in both eyes 5 years prior to evaluation. Postoperatively, an optic disc hemorrhage was noted in the right eye; 10 months prior to referral, a disc hemorrhage was noted in the left eye. The patient had noted some blurring of vision in her right eye for the last few months.

Best-corrected Snellen visual acuity was 20/70 OD and 20/20 OS. There was a trace relative afferent pupillary defect in the right eye. Slit-lamp examination showed posterior chamber intraocular lenses in both eyes. Fundus examination revealed macular drusen and peripapillary atrophy in each eye. The right optic nerve head was elevated nasally with disc hemorrhages temporally (Figure 1C), and there was elevation of the posterior vitreous cortex temporally, visible as a straight edge anterior to the disc. Nasally, vitreous bands were seen adherent to the nerve head. There was also cystoid macular edema in the right eye. The left fundus appeared normal.

Optical coherence tomography of the right eye showed elevation of the nasal margin of the disc by a linear density as well as a less distinct density temporally (Figure 2C). The right macula was elevated and contained cystoid edema with linear densities extending from the macular surface into the vitreous cavity.