Linezolid-Associated Toxic Optic Neuropathy: A Report of 2 Cases

Elsie Lee,1 Susanne Burger,2,* Jian Shah,3 Christine Melton,4 Michael Mullen,9 Floyd Warren,7 and Robert Press1

1Division of Infectious Diseases, 2Gastroenterology, and 3Ophthalmology, New York University School of Medicine, and 4Division of Infectious Diseases, Cabrini Medical Center, New York, New York.

We describe 2 cases in which the prolonged use of linezolid to treat complicated methicillin-resistant Staphylococcus aureus infections was followed by acutely developed blurred vision and progressive loss of vision and color perception during the ensuing few weeks. Both patients received a diagnosis of toxic optic neuropathy, and linezolid therapy was stopped. The patients experienced an initial rapid partial improvement and a subsequent gradual, almost complete, recovery over many months.

Toxic optic neuropathy is characterized by bilateral and symmetrical acute vision loss, central or cecocentral scotomas, and impaired color vision. Early after onset, the optic nerves may appear to be normal, with later development of disc edema and hyperemia. Papillomacular bundle loss and optic atrophy also occur, with absence of disc vessels and optic disc pallor revealed by ophthalmologic examination. Impairment of color vision and visual acuity may become so severe that only hand movements are recognizable.

The causative agents of toxic optic neuropathies are extensive and include medications, such as chemotherapeutic agents, ethambutol, fluoroquinolones, isoniazid, quinine, streptomyacin, and sulfacetamides, and environmental toxins, such as ethylene glycol mercury and methyl alcohol. Nutritional deficiencies can also result in toxic optic neuropathies, with vitamin deficiencies—in particular, of the B complex vitamins and folic acid—being the most crucial. These nutritional factors are frequently exacerbated by excessive consumption of alcohol and by smoking, which results in classical tobacco-alcohol amblyopia. Both patients described below were nonsmokers and did not drink alcohol. In this report, we describe 2 cases of toxic optic neuropathy associated with the prolonged use of the antimicrobial agent linezolid (Zyvox; Pharmacia).

**Patient 1.** The first case of toxic optic neuropathy occurred in a 71-year-old woman with hypertension (controlled with enalapril therapy during the 6 months before presentation) and osteoarthritis (controlled with rofecoxib therapy during the 2 years before presentation) who had had recurrent methicillin-resistant *Staphylococcus aureus* (MRSA) infection in the right knee of a prosthetic joint since 1994. The infection required 3 surgical revisions and was treated with prolonged courses of intravenous vancomycin therapy. After her last revision in 1998, patient 1 was switched from intravenous vancomycin to oral linezolid therapy.

After receiving linezolid therapy for ∼10 months without myelosuppression and with no evidence of adverse side effects during monthly evaluations, patient 1 woke up one morning with acutely blurred vision. Her vision progressively worsened during the following 2 weeks. A formal ophthalmologic examination was done. Her best-corrected distance visual acuity was “count fingers” at 150 cm in both eyes, and her corrected near visual acuity was 20/200. The patient did not respond to tests for color vision in either eye, but she was able to identify the control plate, which suggests that she understood the concept of identifying a number outlined by dots and that the color vision deficit was real. A dilated fundus examination showed mild hypertensive retinopathy, and her optic nerves were pale temporally. The remainder of the examination, including that of the cranial nerves, was normal.

Patient 1 was referred elsewhere to undergo electroretinography, visually evoked potential testing (VEP), and visual field testing. The responses to any VEP pattern were extinguished in both eyes. She had bilateral visual field defects. The findings of a CT scan of her head and posterior fossa and an MRI of the brain with gadolinium contrast were normal. Results of serological tests for detection of *Borrelia burgdorferi*, as well as rapid plasma reagin (RPR), fluorescent treponemal antibody (FTA), and purified protein derivative (PPD) tests, were negative. After further consultation with both retina and neuroophthalmology specialists, the patient received a diagnosis of toxic optic neuropathy. Linezolid therapy was discontinued at this time, and intravenous vancomycin therapy was resumed. Two months after the discontinuation of linezolid, the vision of patient 1 improved to 20/30 in both eyes. A repeat dilated fundus examination revealed no interval changes. The bilateral...
visual field defects improved, and she regained some color vision in both eyes. Nine months after the discontinuation of linezolid, her visual acuity was 20/30 in the right eye and 20/25 in the left eye. She had normal color vision in both eyes and no visual field defects at the time of writing.

**Patient 2.** The second case occurred in a 45-year-old man with paraplegia secondary to a spinal cord ependymoma that was surgically removed in 1968 and subsequent spinal rod placement in 1987. Since 1999, he had recurrent hardware-associated *S. aureus* spinal infections requiring multiple surgeries and prolonged treatment with intravenous antibiotics. After receiving long-term intravenous vancomycin therapy for MRSA infection, vancomycin was replaced by chronic suppressive therapy with oral linezolid. Patient 2 had a good clinical response to linezolid therapy, with suppression of his symptoms. The patient was monitored monthly for myelosuppression, increasing WBC count, and inflammatory markers, of which he had none. He had no other evidence of adverse side effects.

Approximately 10 months after initiation of linezolid therapy, the patient had new-onset blurred vision and decreased night vision. During the following month, his vision progressively worsened, with loss of color perception. He described his visual field as covered with “bubbles, shadows, and glares.” An eye examination revealed that visual acuity was 20/60 bilaterally, with marginally swollen optic discs. He presented to the hospital 1 month later with progressive worsening of his visual symptoms. At presentation, his visual acuity was 20/80 bilaterally, and results of visual field testing revealed bilateral visual field defects. He counted fingers at ~300 cm with difficulty. The extraocular muscles were intact. The pupils were healthy, with no relative afferent defect. Findings of slit-lamp and ocular pressure examinations were normal. Fundoscopic analysis of the right eye showed generically pink optic disks, with some temporal pallor inferiorly. There was an unremarkable nerve fiber layer. In the left eye, there was a slight elevation superiorly and nasally and some obscuration. An intact retinal nerve fiber layer was seen, but there was some thinning inferotemporally in the macular bundle. Findings of the remainder of the examination were normal.

Linezolid therapy was discontinued. MRI and magnetic resonance angiography of the brain revealed only an ectatic basilar artery. Findings of CSF analysis were normal, as was intracranial pressure. The ophthalmology consultant’s diagnosis was probable toxic optic neuropathy. Patient 2 was given a short course of steroid therapy, which led to initial improvement of his visual acuity to 20/40 bilaterally. He subsequently had transient subjective worsening of his vision, and successive MRIs revealed questionable transient occipital changes of undetermined significance that resolved over a period of a few days.

Approximately 3 weeks after the discontinuation of linezolid treatment, his visual acuity improved to 20/30 in the right eye and to 20/40 in the left eye. Color vision returned, and there was improvement in the tangential visual field defects. After 6 months, he continued to have gradual subjective improvement in vision, but improvements had not returned to baseline levels at the time of writing.

**Discussion.** When making a diagnosis of an optic pathway disease, the possibility of an adverse drug effect should be considered [1]. In a review of 1000 reports of adverse drug reactions affecting the eye, more than one-third (393) were attributed to anti-infective agents [2]. In view of the implication of older antibacterials in the etiology of abnormal vision, we must be vigilant in monitoring vision problems in patients receiving new antibacterial and antifungal agents. This report reinforces that need, as do recent reports of vision problems associated with voriconazole therapy [3].

The occurrence of linezolid-associated optic neuropathy may be associated with the duration of linezolid therapy. Previous randomized clinical trials assessing the adverse effects associated with linezolid evaluated only up to 28 days of treatment [4]. Both patients in this report had been receiving linezolid therapy for ~10 months when visual symptoms developed.

The Australian Adverse Drug Reactions Bulletin has cited 4 reported cases of peripheral neuropathy associated with linezolid use [5]. In 1 of the 4 cases, optic neuropathy was noted in a patient who had been receiving linezolid for 6 months for an MRSA prosthetic hip infection [6]. Like our 2 patients, that patient had gradual visual improvement once linezolid therapy was discontinued; however, the peripheral neuropathy persisted. Neither of our patients reported new-onset peripheral neuropathy.

Pharmacia has issued the following statement in the Postmarketing Experience section of their package insert, which acknowledges the potential for this adverse effect: “Neuropathy (peripheral, optic) has been reported in patients treated with Zyvox. Although these reports have primarily been in patients treated for longer than the maximum recommended duration of 28 days, these events have also been reported in patients receiving shorter courses of therapy.... Because they are reported voluntarily from a population of unknown size estimates of frequency cannot be made and causal relationship cannot be precisely established” [4].

The exact mechanism of linezolid-associated toxic optic neuropathy has not yet been elucidated, although it may be similar to the mechanism proposed for nutritional deficiency–based optic neuropathy. The most important area of the retina is the macula, an area packed with photoreceptors whose axons form the most important bundle of fibers—the papillomacular bundle—entering the optic nerve. In episodes of nutritional deficiency–based optic neuropathies, injury to this papillomacular bundle occurs when proteins, which are crucial for efficient mitochondrial functioning, are absent because of the nutri-
tional deficiencies. Impairments in the mitochondria lead to axonal death, and damage to this fiber bundle leads to loss of vision [7]. Ethambutol is another drug that commonly is associated with toxic optic neuropathy, and its effect is dose and duration dependent. Loss of vision does not occur for at least 2 months after initiation of therapy, but symptoms generally appear between 4 and 12 months. Discontinuation of the medication usually results in visual improvement. It could be the case that linezolid and ethambutol have similar mitochondrial impairment properties that are dose and duration dependent.

On the basis of what is being learned about toxic optic neuropathies associated with linezolid, health care workers should take care to monitor patients who will be receiving linezolid therapy for ≥28 days. Performance of a baseline ophthalmologic examination before treatment is initiated should be considered, with regular monthly monitoring by an ophthalmologist. Patients should be educated on symptoms associated with vision loss and color loss and instructed to report them if they occur.

If patients receiving prolonged linezolid therapy do have symptoms of optic neuropathy, complete blood cell count, blood chemistry analysis, urinalysis (to test for other toxins), RPR and FTA testing, and measurement of the serum lead level (particularly if there is concurrent peripheral neuropathy) should be done. Serum B12 and RBC folate levels should also be measured. Other procedures that could be done include performance of direct or indirect vitamin assays and measurement of serum protein concentrations and antioxidant levels. Consultation with ophthalmology specialists should be ordered for performance of formal eye, visual field, and color vision evaluations [8].

References