Ocular Ethambutol Toxicity

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Ethambutol is an antimicrobial agent used frequently to treat tuberculosis. The most commonly recognized toxic effect of ethambutol is optic neuropathy, which generally is considered uncommon and reversible in medical literature. We describe a 43-year-old man who developed signs and symptoms of bilateral optic neuropathy during treatment with ethambutol. This case and a review of the literature show the severe and unpredictable nature of ethambutol toxicity and its potential for irreversible vision loss despite careful ophthalmologic monitoring.


Ethambutol hydrochloride is a bacteriostatic antimicrobial agent used as a first-line defense against tuberculosis (TB). Initial TB regimens commonly include ethambutol in areas where the prevalence of isoniazid resistance is greater than 4%. The exact mechanism of action of ethambutol is unknown; however, it has been hypothesized that ethambutol acts as a chelating agent that disrupts 1 of several metal-containing enzyme systems in the nucleic acid structures of mycobacteria.1

Since its first use in the treatment of TB, the potential of optic neuropathy secondary to ethambutol has been well recognized.2,3 Early animal experiments showed that ethambutol causes lesions in the optic chiasm and optic nerves.4,5 Clinically, patients present with decreased visual acuity in the setting of a normal-appearing ocular examination. Visual fields typically show a cecocentral or bitemporal defect. Dyschromatopsia may be the earliest sign of toxicity, and blue-yellow color changes are the most common.6,7

Internal medicine literature frequently suggests that the toxic effects of ethambutol are readily reversible, albeit after some time; however, recent ophthalmologic experience does not support this belief. In fact, several recent studies8-11 show that patients who experience ethambutol toxicity often have severe and persistent visual defects despite the fact that they receive appropriate dosages and are monitored regularly for visual acuity and color vision and despite prompt discontinuation of ethambutol when symptoms are discovered.

REPORT OF A CASE
A 43-year-old man with a medical history remarkable for end-stage renal disease secondary to hypertension was hospitalized in May 2002 with shortness of breath. Chest radiography showed left-sided pleural effusion, and pleurocentesis revealed an exudative process. Pleural biopsy specimens showed extensive necrotic tissue with focal fibrosis, rare noncaseating granulomas, and acid-fast bacilli. Culture was positive for Mycobacterium tuberculosis. Isoniazid was initiated at a dosage of 300 mg orally and pyrazinamide at 2 g orally after hemodialysis sessions; also rifampin was initiated at 600 mg/d orally and vitamin B6 at 50 mg/d orally. One month later, elevation of alkaline phosphatase and bilirubin levels led to discontinuation of rifampin. Ethambutol was initiated at a dosage of 15 mg/kg per day. Three months later, the patient had lower extremity neuropathy, and 2 weeks after that he developed a rapidly progressive, severe decrease in vision. At this point, all TB medications were stopped.

The patient denied any history of ophthalmologic disorders but had a history of hepatitis C antibodies and hypertension. The patient stated that he drank alcohol rarely but had smoked a half pack of cigarettes per day for 25 years. He denied any exposure to toxic chemicals or heavy metals.

During the time he was treated with anti-TB medications, the patient had a dedicated home nurse and was monitored closely in the clinic. Follow-up included regular vision checks by Snellen chart and confrontation visual field testing. Visual acuity testing before initiation of treatment showed 20/20 vision in both eyes and normal color vision.

Ophthalmologic examination revealed a best corrected visual acuity of 20/200 with the right eye and counting fingers at 4 feet with the left eye. Intracocular pressure was normal. Pupils were reactive in both eyes with no relative afferent pupillary defect. The patient scored 0/15 in each eye on the Hardy-Rand-Rittler color vision test. An inferior temporal defect in each eye was noted on confrontation visual field testing. Automated visual field testing results revealed a central scotoma with inferior temporal quadrant defects in both eyes (Figure 1). Slit lamp examination results were normal. Funduscopic examination findings showed mild temporal pallor of both optic nerves.
Magnetic resonance images of the brain were normal. The patient’s visual symptoms remained unchanged throughout the next 6 months of follow-up.

**DISCUSSION**

Ethambutol toxicity is dose related. In 1 report of 18 patients treated with ethambutol at 60 to 100 mg/kg per day, 8 developed toxic optic neuropathy. Patients receiving 25 mg/kg per day have a 5% to 6% reported incidence of optic neuropathy, and the incidence of optic neuropathy with dosages of 15 mg/kg per day is reportedly less than 1%. Of note, most of these reports are from tertiary referral centers and may have a detection bias because severe cases tend to be referred. Therefore, the true incidence of optic neuropathy may be unknown. Current regimens recommend dosages of 15 mg/kg per day in patients who have not received previous anti-TB therapy. If patients received prior anti-TB therapy, initial treatment with 25 mg/kg per day for 60 days, followed by 15 mg/kg per day is recommended. Patients with renal disease should have their dose adjusted on the basis of their glomerular filtration rate.

Toxicity generally does not develop until after treatment for at least 1.5 months. In a series of 7 patients, the reported mean interval between onset of therapy and toxic effects was 3.4 months. In another series of 10 patients, the mean interval was 5 months. Manifestations of toxicity can occur as late as 12 months after initiation of therapy.

Ethambutol is cleared primarily by the kidneys via tubular secretion. The renal excretion of ethambutol approaches 7 mL/kg per minute. Because creatinine levels approximate those of glomerular filtration, they may be inaccurate for gauging the secretory capacity of renal tubules. Some investigators believe that patients with impaired renal function should not be treated with ethambutol because of the potential for toxicity and the difficulty in regulating appropriate serum drug levels.

According to medical literature, the cases described in this and other reports are exceptions to the rule. Many texts suggest that toxicity due to ethambutol is generally preventable with appropriate dosing, screening, and careful monitoring and that if toxicity occurs, it is usually reversible. The 2002 edition of *Mosby’s Drug Consult* reports, “Ethambutol HCl may produce decreases in visual acuity which appear to be due to optic neuritis. This effect may be related to dose and duration of treatment. This effect is generally reversible when administration of the drug is discontinued promptly.” Gorbach et al stated that “Ethambutol produces an optic neuritis that progresses to blindness if the drug is not withdrawn. Vision returns virtually to normal after the drug is withdrawn....”

In several recent series, patients experienced severe, irreversible vision loss from ethambutol toxicity. Vision loss occurred often despite frequent and regular monitoring. Kumar et al described a series of 7 patients treated with 25 mg/kg per day of ethambutol, along with isoniazid, rifampin, and vitamin B complex capsules. All these patients experienced sudden onset of decreased vision despite careful ophthalmologic follow-up and prompt discontinuation of ethambutol with initial visual dysfunction; 5 of the 7 patients presented with 20/200 vision or worse in at least 1 eye. Only 3 patients (43%) had a documented gain in visual acuity to better than 20/200 after a mean ± SD follow-up of 8.3±2.1 months. Tsai and Lee described 10 patients treated with presumably “safe” dosages of ethambutol,
ranging from 13 to 23 mg/kg per day. No patients had diabetes, hypertension, or other ocular disease, and all had normal renal function. All 10 presented with sudden decrease in vision, and ethambutol was discontinued promptly on diagnosis. Only 5 patients had any degree of visual improvement with a mean ± SD follow-up of 21.8±8.8 months. Among those with some improvement in visual acuity, none described complete recovery after the episode.

Smith described 3 patients in whom therapeutic levels of ethambutol were initiated; 2 had pulmonary TB and 1 presented with renal TB. All 3 patients developed sudden, severe vision loss; 2 remained legally blind after long-term follow-up, and 1 recovered to near-normal levels. DeVita et al described 2 patients with renal TB in whom therapeutic levels of ethambutol were initiated; both developed sudden, severe, irreversible vision loss. Sivakumaran et al also reported on a series of 4 patients with pulmonary TB who developed optic neuropathy; 3 improved on cessation of ethambutol, and 1 had permanent loss of visual acuity at 1-year follow-up. Our patient showed evidence of bilateral optic neuropathy 3 months after he started taking ethambutol. His vision has not changed despite cessation of the drug.

In summary, our review of the literature revealed several pertinent and enlightening facts. First, ethambutol toxicity occurs at the lowest recommended dosage levels. Second, toxicity occurs despite regular monitoring and close medical and ophthalmologic follow-up. Third, ethambutol toxicity can cause severe vision loss that is often permanent and irreversible. Unfortunately, patient education and immediate cessation of the drug do not appear to change the final visual outcome. Optic nerve toxicity with ethambutol use appears to be unpredictable, and the drug should be used cautiously.

REFERENCES