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CASE REPORT

Ethambutol-Induced Optic Neuritis in Patients with End Stage Renal Disease on Hemodialysis: Two Case Reports and Literature Review

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ABSTRACT

Ethambutol, a synthetic bacteriostatic agent, is a first line agent against *Mycobacterium tuberculosis*. Although optic neuritis is the most serious adverse effect of ethambutol, most cases in the literature are reversible. Renal failure prolongs the half-life of ethambutol and increases the risk of ethambutol-induced optic neuritis. We present two patients with end stage renal disease (ESRD), who were on maintenance dialysis and suffering ethambutol-induced optic neuritis. The first woman had been suffering ESRD on hemodialysis for 2 years. After tuberculosis was diagnosed, she was prescribed three-combined anti-tuberculosis medications, including ethambutol 800 mg/day. Bilateral blurred vision suddenly occurred 4 months after the start of treatment, and she became totally blind despite discontinuing ethambutol. The second woman had been on hemodialysis for 5 months. Tuberculosis was diagnosed by lung biopsy. After 3 weeks of three-combined anti-tuberculosis medications including ethambutol (1200 mg/day), reduced visual acuity and color vision defects occurred. One year after the discontinuation of ethambutol, visual acuity remained little improved. Physicians should be aware of ethambutol-induced optic neuritis and ethambutol should be used cautiously in patients with renal failure.

Key Words: Ethambutol; Optic neuritis; Chronic renal failure.

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INTRODUCTION

Tuberculosis has been found to occur more frequently in patients with chronic renal failure whether they are on maintenance dialysis or not. Ethambutol is a synthetic bacteriostatic agent against *Mycobacterium tuberculosis*. Optic neuritis is the most serious adverse effect of ethambutol, and most cases in the literature are reversible.[1,2] Renal failure prolongs the elimination half-life of ethambutol and increases the risk of ethambutol-induced optic neuritis. We present two patients with end stage renal disease on maintenance dialysis that were suffering from irreversible ethambutol-induced optic neuritis due to inadequate dosage and review the literature relevant to ethambutol-induced optic neuritis (Table 1).

CASE REPORT

Case 1

A 27-year-old female patient had received chronic maintenance hemodialysis for 2 years. She experienced malaise for a number of weeks. The patient had developed end stage renal disease due to chronic glomerulonephritis, but had no history of other significant systemic illnesses and in particular had not suffered from any eye problems. A chest X-ray revealed a cavitation over the right upper lung, and *Mycobacterium tuberculosis* was found in the her sputum. She received anti-tuberculosis treatment including isoniazid 300 mg/day, rifampicin 450 mg/day, ethambutol 800 mg/day and pyridoxine 50 mg/day (her dry weight was 50 kg), along with vitamin B complex, folic acid, calcium carbonate and erythropoietin.

After 4 months, the woman started experiencing blurring of vision and visited an ophthalmologist for help, where severe optic atrophy was found. The patient immediately discontinued ethambutol, but no specific medications were given for the optic atrophy due to its advanced stage. Vision acuity progressively deteriorated, and the patient was totally blind after 3 months. Isoniazid 300 mg/day, rifampicin 450 mg/day and pyridoxine 50 mg/day were continuously used as treatment for pulmonary tuberculosis, and the patient received a successful cadaveric renal transplantation later. However, her blindness had become the major problem in the patient's life.

Case 2

A 50-year-old female patient had been on chronic hemodialysis for 2 months, having developed end stage renal disease due to chronic glomerulonephritis. The patient had no history of other significant systemic illnesses, and in particular had not suffered any eye problems. Intermittent fever of up to 38°C occurred, particularly at night. Initial study found no focus of infection, nor any evidence of malignancy. After three months, a nodular lesion was found over the left upper lung by chest X-ray. Acid-fast stain of sputum was negative. The woman received an open biopsy for the lesion, and the pathology report showed caseating necrosis suggesting tuberculoma. The patient was put on isoniazid 300 mg/day, rifampicin 450 mg/day, ethambutol 1200 mg/day, pyrazinamide 750 mg/day and pyridoxine 50 mg/day (her dry weight was 54 kg).

She started experiencing blurred vision and color vision defects after 3 weeks of therapy. Severe numbness of extremities also occurred. Ophthalmologic examination revealed central scotoma and optic atrophy. Initial visual acuities were hand motion at 0.5 meter OD and hand motion at 0.7 meter OS, while the result of color vision testing to Ishihara plates was 1/13 OU. Given the evidence of ethambutol-induced

Table 1. Patients' characteristics with ethambutol-induced optic neuritis.

	Case 1	Case 2
Age	27 years	50 years
Sex	Female	Female
Dialysis duration	2 years	2 months
Eye problems history	No	No
Diabetes history	No	No
Location of tuberculosis	Lung	Lung
Dry weight	50 kg	54 kg
Ethambutol dosage	800 mg/day	1200 mg/day
Onset of optic neuritis	4 months	3 weeks
Outcome of optic neuritis	Irreversible	Irreversible

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ocular toxicity and peripheral neuropathy owing to isoniazid, anti-tuberculosis medications were changed to rifampicin 450 mg/day and pyrazinamide 750 mg/day. She returned every month for an eye examination to monitor any improvement in acuity, but no significant change in her vision was noted. One year after discontinuation of ethambutol, permanent color vision defect persisted and visual acuity was only slightly improved.

DISCUSSION

Host resistance to *Mycobacterium tuberculosis* is mediated by cellular immunity, and since this is impaired in patients with chronic renal failure, the incidence of tuberculosis in such patients is increased regardless of whether or not they are on maintenance dialysis.[3–6] Because of their impaired ability to excrete toxic substances, patients with chronic renal failure are vulnerable to various drugs and toxins.

Ethambutol (EMB), one of the first line agents against *Mycobacterium tuberculosis*, is a synthetic bacteriostatic agent, although recent evidence suggests that it displays bactericidal activity at higher doses. EMB was introduced in 1961 by Lederle Laboratories, initially being synthesized in racemic form (equal parts dextro- and levo-isomers), and was subsequently found to be associated with a high incidence of side effects. Further studies found that the dextrorotary forms were less harmful than the racemate, with the slower and less complete excretion of the more toxic levo-isomers causing the adverse effects of the racemic compound. The use of the racemic compound has now been abandoned, and only the dextro-isomer is termed EMB.[7]

The antimycobacterial effects of EMB appear to be related to its chelating properties. EMB disrupts bacterial metabolism by interfering with essential metal-containing enzyme systems, causing arrest in multiplication and cell death.[8] From numerous controlled clinical trials treating patients with severe smear-positive pulmonary tuberculosis, EMB exhibits the smallest sterilizing activity among five first-line agents against *Mycobacterium tuberculosis*. The efficacy of EMB in preventing the emergence of drug resistance exceeds only that of pyrazinamide.[9] EMB makes a smaller, but still significant contribution to preventing drug-resistant failures, but is effectively devoid of sterilizing activity. From this perspective, the use of EMB treating tuberculosis should be carefully evaluated in patients with high risk of EMB-induced optic neuritis.

Approximately 75 to 80% of an orally administered dose of ethambutol is absorbed from the gastrointestinal tract, and around 80% of the absorbed portion is excreted unchanged in the urine. Two metabolites of ethambutol have been isolated: a dicarboxylic acid derivative and an aldehyde intermediate that represents the initial product of ethambutol oxidation, both of which are ineffective against tuberculosis. Both metabolites are presumed to be metabolized by the liver. The half-life of ethambutol is around 4 hours in patients with normal renal function.[10] Only a single report concerning the elimination of ethambutol in patients with impaired renal function exists in which an analytical method of proven specificity has been used.[11] The results of this study clearly indicate that renal failure reduces total body clearance, renal clearance, and fraction of absorbed ethambutol excreted in urine, and prolongs half-life of EMB compared with a group of normal volunteers. In complete renal failure, the half-life of EMB can be increased to around 20 hours. Dosage adjustment is mandatory for EMB in patients with compromised renal function to optimize therapy and avoid undesirable side effects.

Ethambutol has many side effects, including hypersensitivity, hyperuricemia, peripheral neuropathy, acute interstitial nephritis and optic neuritis. Retrobulbar optic neuritis, which takes two forms, is the most serious toxic effect of EMB. The more common form is generally reversible and is related to treatment dose and duration. The central fibers of the optic nerve are most commonly affected, causing blurred vision, decreased visual acuity, central scotoma, and frequently, a loss of the ability to distinguish green and red. The rarer form of ocular toxicity, generally seen with higher doses, results in peripheral visual field defects.[10,11] Visual acuity and color vision are unaffected, although peripheral constriction of the visual field is found on examination. Because the neuritis is retrobulbar in both forms, the fundus appears normal on ophthalmoscopic examination.

The pathophysiology of EMB ocular toxicity remains largely unknown, but may be related to chelating activity. EMB is known to reduce the zinc content in serum, and an apparent inverse correlation even exists between serum zinc concentrations and EMB optic neuropathy. Consequently, it has been proposed that EMB may cause selective optic atrophy by lowering concentrations of zinc. However, a recent study by Young et al.[12] reveals that the addition of zinc to the retinal cell culture fails to attenuate either the vacuolar changes or the neuronal loss induced by EMB, but instead significantly aggravated both. In contradistinction, chelation of intracellular zinc with the

cell-permeant zinc chelate *N*, *N*, *N*′, *N*′-tetrakis ethylenediamine markedly reduced both the vacuolar changes and neuronal loss. Hence EMB toxicity is not simply the depletion of zinc through chelation but instead is somehow related to an EMB/zinc combination.

Most cases involving ocular toxicity of EMB are thought to be dose-related, with the incidence being as high as 6% with a 25 mg/kg dose and up to 15% for doses above 35 mg/kg.[2] The incidence of such toxicity at 15 mg/kg is thought to be negligible, although Roberts reports a 1.6% incidence of ocular toxicity at 15 mg/kg in his review of the ophthalmological side effects of EMB. Meanwhile, Poussos and Tsolkas found a 2% incidence of ocular toxicity among 250 patients receiving 15 mg/kg EMB daily for 4–8 months.[7] The maximum recommended dose (conventional dosage) for healthy people is 25 mg/kg/day, and this dose is generally only given for first two months of the therapy, after which it is reduced to 15 mg/kg/day. Because the risk of ocular toxicity is increased in patients with renal failure, the maximum recommended dose is 15 mg/kg/day, and the dosage of EMB should be adjusted according to residual renal function. Meanwhile, the recommended dose for ESRD patients is 15 mg/kg QOD. Symptoms of ocular toxicity usually occur after 2 months of EMB therapy, and usually reverse after the therapy is discontinued.[1] However, the literature has reported three cases of rapid onset of ocular toxicity (within three days of EMB therapy), which probably involve an idiosyncratic mechanism.[7,13,14] Although often reversible when the drug is discontinued early, many reports exist of permanent blindness following EMB treatment at the standard dosage.[1,7,13]

Owing to the similarities between the toxic optic neuropathy of EMB and nutritional (tobacco/alcohol) amblyopia, parenteral hydroxocobalamin therapy (vitamin B12) has been studied as a possible treatment for restoring vision loss. In one series, halting the drug and administering vitamin B12 treated 9 cases of EMB ocular toxicity. This measure brought about cure in 61% of the eyes involved.[15] In another report,[16] two patients with EMB-induced optic neuritis were treated with high and protracted doses of hydroxocobalamin (40 mg/iv/day for 5 months followed by 20 mg/iv/day for 3 months), and only a mild residual color vision defect was found after such treatment. Supplemental zinc therapy has been suggested as a treatment, and acts to offset any deficiencies that are present. However, this treatment has not been demonstrated to restore lost visual function, and is not useful if optic atrophy is advanced. In fact, according to Young et al.,[12] the addition of zinc may be more toxic than EMB alone. Neither of the above therapies has been substantiated and both require further investigation.

Many risk factors have been recognized that increase the chance of vision loss after EMB treatment. These factors include: 1) The cumulative effects of isoniazid and ethambutol are more damaging than for either used alone; 2) Impaired ability to excrete the drug will increase the risk of side effects; 3) Neuropathy is more frequent in geriatric patients; 4) Patients with plasma zinc levels of below 0.7 mg/L will display a higher incidence of neuropathy; 5) More common when the dosage of EMB exceeds 15 mg/kg and with prolonged treatment; 6) Patients had history of alcohol abuse, compromised optic nerve head, vascular disease.[17] The overall risk of toxicity with EMB can be minimized if dosing is controlled and the patient is carefully monitored. The most comprehensive guidelines are given by the Joint Tuberculosis Committee.[2] The guidelines are followings: 1) Determine pretreatment renal function. 2) Recommended dose and duration should not be exceeded. 3) Record any history of eye disease. 4) Pretreatment record of Snellen visual acuity should be made. Avoid ethambutol in patients with significantly reduced vision who may not notice further deterioration of vision. 5) The patient should be told that ethambutol may affect their vision, and the drug should be stopped immediately if vision becomes impaired. To guard against noncompliance, explain the small risk of this happening. 6) Ensure that the patient has been informed about the risk of ocular toxicity associated with ethambutol. 7) Patient complaints of ocular disturbance during therapy should be referred for a detailed ocular examination, and ethambutol should be discontinued pending this examination. 8) Routine visual acuity testing during treatment is generally not helpful in screening for ocular toxicity. 9) Ethambutol is best avoided in children too young for objective eye testing and in patients with language or communication problems.

In conclusion, the incidence of toxic ocular effects with EMB is low under conventional dosages. However, the reaction may be unpredictable and catastrophic, and there is the possibility of irreversible damage. Because the risk of EMB-induced ocular toxicity is increased in patients with renal failure, the dosage of EMB must be adjusted according to residual renal function. Additionally, prolonged courses must be avoided in patients with renal failure, and, if possible, EMB should be replaced by other anti-TB medications. Practitioners must become more aware when administering EMB, and should stop treatment immediately when visual impairment is noted.

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