Optic Neuropathy Associated with Ethambutol in Koreans

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Ethambutol is a useful first line antituberculous drug, but can cause significant visual impairment. In order to determine the clinical manifestations of optic neuropathy associated with ethambutol, and the margin of drug safety in Koreans, we investigated ten men and four women, diagnosed between 1995 and 1997 at Seoul Municipal Boramae Hospital as suffering from ethambutol toxicity. After determining their history, including the period during which ethambutol had been administered, and its dose, a complete eye examination was performed, including measurement of best-corrected visual acuity, pupillary examination, color vision, fundus examination and a test of visual field. Ocular ethambutol toxicity was observed at a dose as low as 12.3 mg/kg. Abnormal ophthalmic findings include decreased visual acuity and abnormal visual field, especially in the central scotoma, and abnormal color perception. In conclusion, ethambutol at a low dose can cause optic neuropathy, and for the early detection of this, a color vision test is important.

**Key words:** ethambutol, optic neuropathy

INTRODUCTION

Ethambutol, first synthesized in 1960, is widely used as a tuberculostatic drug, though it is well known that visual processing deficiencies arise. Decreased visual acuity, central scotoma, and—as a first sign of intoxication—changes in red-green color vision, have been reported. Visual acuity usually recovers within 3 to 4 months of discontinuing the drug, but up to one year is sometimes required. On occasion, however, acquired deficiency can be permanent. Examination of visual acuity, visual field and color vision prior to and during the course of ethambutol therapy is therefore recommended.

The aim of this paper is to investigate the clinical manifestations of ethambutol toxicity and to evaluate its safety margin in Koreans.

**MATERIALS AND METHODS**

Fourteen patients, diagnosed between October 1995 and September 1997 at Seoul Municipal Boramae Hospital, Seoul, Korea, as suffering from ethambutol toxicity were included in this study. Ten were men and four were women, and their mean age was 55.4 ± 14.4 years. They showed decreased visual acuity, abnormal color perception and visual field test abnormalities, which had developed after antituberculosis medication. They had no history of closed head injury or ocular trauma.

On presentation, a complete eye examination was performed, including measurement of best-corrected visual acuity and pupillary examination. In a few patients, color vision was examined with Ishihara color plates and the 100-hue test. After pupillary dilation, the fundus was examined, and the visual field was tested. Three patients underwent...
electroretinography.

RESULTS

The results of this study are summarized in Table 1. The time from initial ethambutol medication to the onset of visual disturbance varied from one month to three years; the dose of ethambutol ranged from 12.3 to 20.5 mg/kg.

Initial visual acuity at first ophthalmic examination was worse than 0.1 in 14 eyes, and better than 0.5 in four. In almost all cases, visual impairment was bilateral. Visual field examination revealed central scotoma in five patients (35.7%), peripheral constriction in two (14.3%), and normal findings in five (35.7%). Since they could not recognize any isopter, visual field examination was not possible in patients 4 and 7. In every case, color perception was abnormal. During their first visit, the disc was seen on fundus examination to be pale in two patients (3 and 10) and normal in four (1, 6, 7, and 9). Patients 4, 7 and 8 underwent electroretinography and all findings were normal.

At least one month later, follow-up examination was done in nine patients. Three showed improved color perception and visual acuity of more than two lines, but in four, color perception and visual acuity had not improved. The mean age of patients showing improvement was 57.3 ± 18.2 years, whereas the mean age of the others was 50.0 ± 16.0.

In no patient was there chronic renal failure or end stage renal disease.

DISCUSSION

Ethambutol, a dextrorotatory isomer of 2,2'- (ethylene diimino)-di-l-butanol, is very effective as a tuberculostatic drug. It is rapidly absorbed and excreted; up to 80% is passed unchanged in the urine, and only a small fraction appears in the feces. In general, 15 to 25 mg/kg is the recommended dose, though due to its renal excretion, this must be adjusted according to creatinine clearance.

Early toxicologic studies demonstrated that within three months of first administering high-dose ethambutol, rhesus monkeys showed severe neurologic symptoms, including blindness and ataxia. Since Carr and Henkind first reported toxic ocular manifestation in 1962, there have been many reports of ethambutol-related optic neuropathy. In Korea, Kim et al. (1975) reported nine cases, and Cho and Chang (1975) reported four.

Though it is widely known that ethambutol causes optic neural tract disturbance, there are many conflicting theories about its mode of action and the mechanism involved. In an experimental rat model, Lessell found swelling of axonal processes and thinning of myelin sheaths, especially in the chiasm, and Tateishi reported similar findings in rats and dogs. After electrophysiologic study of the sciatic nerve, Borchard found loss of function in neural membrane and decreased calcium ion concentration, and believed that calcium ion to be associated with ethambutol toxicity. Although ethambutol is known to cause optic neuropathy, there is some evidence that the retina is also impaired. Kakisu et al. reported that the mean amplitude of an ERG decreased significantly. Kohler et al. noted that at the level of the cone-horizontal cell synapse, ethambutol alters the color-coding process in a dose-related fashion, but does not affect rod pathways in fish retina. In this study, however, ERG findings were normal.

Liebold classified ethambutol-induced retrobulbar neuritis as one of two types. Patients with central or axial toxic effects showed reduced visual acuity, impaired color vision, and a central scotoma, while those with periaxial toxic effects had a defect in peripheral isopters of their field, with little or no decrease in visual acuity, and normal color vision. In his study, at dosage levels of 30 mg/kg of body weight, two of 59 patients evidenced axial-type, drug-related optic neuropathy after several months, while none experienced the periaxial type. In a group of 59 patients who received more than 35 mg/kg, axial toxicity was found in seven, and periaxial toxicity in four. It is difficult to explain why central scotoma was more prevalent than in the cases reported by Kim, and to determine the true clinical manifestation, further study seems to be needed. In this study, five patients can be classified as axial type, and one as periaxial. The others had poor visual acuity and poor color perception, with
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Interval: duration of ethambutol medication.
Dose: dose of ethambutol per kg of body weight.
Visual acuity: HM, hand motion.
Color vision: U, unknown; NC, cannot read control plate.
patients 1, 6, 8: increased error score in Farnsworth-Munsell 100 Hue test in both eyes.
patient 13 (using H-R-R pseudoisochromatic color test): OD, normal; OS, mild RG defect.
Visual field: CCS, cecocentral scotoma; CS, central scotoma; NC, not checkable; PC, peripheral constriction; N, normal.
F/U: Follow-up period.
no central scotoma, so were hard to classify according to Liebold's criteria.

According to previous reports, the incidence of optic neuropathy is about 1% of treated patients,\textsuperscript{5,6} and this correlates with dosage;\textsuperscript{4,11} ethambutol may cause optic neuropathy if the daily dosage exceeds 15 mg/kg.\textsuperscript{22} In this study, this ranged from 12.3 to 20.5 mg/kg, the former being lower than that usually reported. These patients did not suffer decreased renal function, though within 3 months of initial ethambutol medication, visual disturbance developed. It might be very important to know that ocular toxicity can develop even at a dose as low as 12.3 mg/kg. Blood levels of copper and zinc, as another important factor in susceptibility to ocular ethambutol toxicity, might be significant in these patients,\textsuperscript{23,24} but in this study were not determined.

According to previous report, an interval of between 15 days and two years is required before optic neuropathy develops,\textsuperscript{3,8,10,15,16} with the highest incidence seen within 3 to 6 months of initial medication. In this study, the interval from initial ethambutol medication to the onset of visual disturbance varied from 1 month to 3 years; in six patients (43%) disturbance was noted after 3 months. Onset after three years medication is longer than previously reported; during this time, the patient had attended another hospital, and 20 days before his first visit to us, noticed decreased visual acuity. After ethambutol was withdrawn, visual acuity improved.

Though their visual acuity was better than 0.5, ethambutol toxicity was diagnosed in two patients because of abnormal color perception; this finding is compatible with that of previous reports stating that abnormal color perception is an early and sensitive finding of ethambutol toxicity.\textsuperscript{9,16}

Visual field examinations have reported mostly central scotoma.\textsuperscript{3,10} The study by Kim et al. however, showed peripheral constriction in five patients (55.6%), relative ring scotoma in three, (33.3%) and central scotoma in only one (11.1%).\textsuperscript{15} In this study, 14.3% of patients revealed peripheral constriction, while central scotoma was seen in 35.7%.

The ocular toxicity of ethambutol is usually thought to be reversible after rapid withdrawal of the drug. However, Tsai and Lee reported permanent visual impairment in five of ten patients, especially in those aged over 60,\textsuperscript{25} and asserted that there is no so-called “safe-dosage” for older patients. The mean age of the subgroup who showed improved visual function was slightly more than that of the subgroup who did not, but because of the small number of patients involved, this difference may be statistically insignificant. In our study, visual acuity and color perception improved in three patients but did not improve in four; the mean age of the three was somewhat greater than that of the others.

In summary, ocular ethambutol toxicity is observed at doses as low as 12.3 mg/kg, and any patient receiving medication for tuberculosis must be properly informed of potential side effects.
Routine ophthalmic observation, including tests of visual acuity, visual field, and color vision, is recommended for patients with significant risk factors that could increase the possibility of side effects, as well as for those on longer treatment courses. Possible ethambutol toxicity can thus be detected early.

REFERENCES