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ORIGINAL ARTICLE

Determination of potential role of antioxidative status and circulating biochemical markers in the pathogenesis of ethambutol induced toxic optic neuropathy among diabetic and non-diabetic patients

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KEYWORDS

Toxic optic neuropathy;
Ethambutol;
Diabetes;
Vitamins;

Abstract The present study was designed to explore the antioxidative status and circulating biochemical markers having a potential role in the pathogenesis of ethambutol (EMB) induced toxic optic neuropathy (TON) among diabetic and non-diabetic patients.

Fifty patients under complete therapy of EMB for tuberculosis were included in the present study. Inclusion criteria for patients were to receive EMB everyday during treatment, a dose of

Abbreviations: TON, toxic optic neuropathy; EMB, ethambutol; Vit, vitamins; ROS, reactive oxygen species; SOD, superoxide dismutase; CAT, catalase; GSH, glutathione; MDA, malondialdehyde; ALT, alanine transaminase aspartate; ALP, alkaline phosphatase.

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Superoxide dismutase;
Catalase;
Glutathione

25 mg/kg for initial 2 months and 15 mg/kg during the rest of therapy period. We conducted color vision and visual acuity test for all patients.

Fifteen out of fifty EMB induced TON patients, were found to be diabetic. Color vision and visual acuity test results were evaluated for diabetic and non-diabetic as well as twenty age matched controls. The results demonstrated a significant pattern of circulating biochemical markers between the studied groups. Data regarding hematological (RBC, p value = 0.02; Hemoglobin, p value = 0.02), hepatic (total bilirubin, p value = 0.01), renal (urea, p value = 0.03; creatinine, p value = 0.007), lipid (total cholesterol, p value = 0.01; total triglycerides, p value = 0.03) and anti-oxidative (superoxide dismutase, p value = 0.005; glutathione, p value = 0.02; catalase, p value = 0.02) profile showed a highly significant difference among the studied groups specially patients with diabetes. Malondialdehyde (MDA) level had gone significantly up in diabetic TON patients (p value = 0.02), in comparison to other antioxidants and vitamins (Vit). Vit-A, E, B_1, B_{12} and Zinc seem to be playing a major role in the pathogenesis of TON, specially Vit-E and B_1 surpassed all the antioxidants as having highly significant inverse relationships with MDA (MDA vs Vit-E, $r = -0.676^{**}$ and MDA vs Vit-B_1, $r = -0.724^{**}$ respectively).

We conclude that during the ethambutol therapy the decreased levels of Vit-E and Vit-B_1 possibly play a role in the development of TON and may be used as therapeutic agents to lessen the deleterious effects of ethambutol.

1. Introduction

Ethambutol is a highly specific chemical drug (PubChem CID = 14052) (Fig. 1). It is specifically active against *Mycobacterium*, thus used for a treatment of tuberculosis and is considered to be very important drug. Like all other drugs EMB also has few adverse side effects such as visual acuity, reduction of visual fields, scotomas, and problem in discriminating between red and green color. About 2–6% patients of tuberculosis receiving EMB suffer from its serious side effect, toxic optic neuropathy, which is dose as well as duration dependent (Leibold, 1966; Kahana, 1987; Kho, 2004). Involvement of optic nerve is not common during treatment of less than 2 months and visual function can be improved by discontinuation of the drug while in some cases irreversibility has been observed (Schild and Fox, 1991; Alvarez and Krop, 1993; Cruz et al., 2010). Several studies indicated and confirmed toxic outcomes of EMB and a number of pathophysiological mechanisms have been explained like disruption of mitochondrial complex IV, glutamate excitotoxicity and Zinc-associated lysosomal membrane permeabilization.

The present study was designed to explore the antioxidative status and circulating biochemical markers having a potential role in the pathogenesis of EMB induced toxic optic neuropathy.

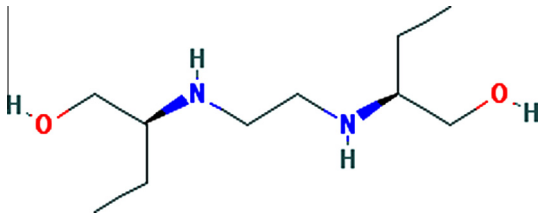

Figure 1 Structure of ethambutol (PubChem, CID 14052).

2. Materials and methods

A total of fifty patients taking complete therapy of EMB for tuberculosis were eligible for inclusion in the study at the Mayo Hospital, Lahore during March–September 2013. Informed consent form was taken before the start of the study. Detailed history, including clinical complications, smoking habits and tobacco chewing was collected in a detailed questionnaire. Clinical diagnosis of the patient was also being taken into consideration. Twenty controls, age matched healthy individuals, were included in the study. The study was approved by local ethics committee of the University of Lahore, Pakistan.

2.1. Biochemical assays

Hepatic profile [alanine transaminase (ALT), aspartate aminotransferase, and alkaline phosphatase (ALP)] was estimated by using the commercial Randox kits (Randox Laboratories, Northern Ireland, UK). Serum bilirubin levels were measured by the method of Jendrassik and Grof (1938). Hematological profile (Hemoglobin and RBC) was determined using cyanmeth reagent (Van-Kampen and Zijlstra, 1965). Blood urea was estimated by the kinetic method (Tiffany et al., 1972) and creatinine levels by the rate of change in absorbance using alkaline picrate (Larsen, 1972). Glutathione (GSH), catalase (CAT), superoxide dismutase (SOD) and MDA levels were estimated by the method of Ellman (Ellman, 1959), Aebi (Aebi, 1974), Kakkar (Kakkar et al., 1984) and Ohkawa (Ohkawa et al., 1979), respectively. Lipid profile (total cholesterol, low density lipoprotein, high density lipoprotein, and total triglycerides) was determined using Friedewald's formula (Friedewald et al., 1972).

2.2. Statistical analysis

Results have been expressed as mean ± standard deviation. The level of significance was determined by one way analysis