

Effect of Antituberculosis Regimen Containing Ethambutol on Serum Magnesium Level in Pulmonary Tuberculosis Patients

Mohammad Abbasi Nazari^{a,b}, Farzad Kobarfard^{c,d}, Payam Tabarsi^e,
Maryam Azimi^a and Jamshid Salamzadeh^{a,d*}

^aDepartment of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University, M.C., Tehran, Iran. ^bResearch Center for Gastrointestinal and Liver Diseases (RCGLD), Shahid Beheshti University, M.C., Tehran, Iran. ^cDepartment of Medicinal Chemistry, School of Pharmacy, Shahid Beheshti University, M.C., Tehran, Iran. ^dPharmaceutical Sciences Research Center, Shahid Beheshti University, M.C., TB and Lung Disease Research Center (NRITLD), Masih Daneshvari Hospital, Tehran, Iran.

Abstract

Magnesium is an essential metal that has important roles in physiological function of the body organs. Ethambutol is an oral antitubercular agent with chelating effects owing to its chemical structure. The aim of present study is to determine whether ethambutol usage can alter serum magnesium concentration in patients with pulmonary tuberculosis. Sixty patients with diagnosis of pulmonary tuberculosis were enrolled in the study. Blood samples were obtained before treatment from patients. Ten days after starting anti tuberculosis therapy, second blood samples were obtained. The amounts of serum magnesium were determined in all samples by spectrophotometric method. Statistical analysis showed that serum magnesium concentrations at baseline (0.61 ± 0.08 mmol/l) and at day 10 (0.62 ± 0.11 mmol/l) were not different. It is possible that ethambutol does not affect magnesium concentration in tuberculosis patients, however further studies about the other cationic trace elements are recommended.

Keywords: Magnesium; Ethambutol; Pulmonary tuberculosis; Patient.

Introduction

Magnesium is the fourth most abundant cation in the body and is present in more than 300 enzymatic systems. Magnesium deficiency is now considered to contribute to many diseases. As a therapeutic agent, it is being tested in numerous large clinical trials. Magnesium deficiency has been shown to correlate with a number of chronic cardiovascular diseases, including hypertension,

diabetes mellitus, and hyperlipidemia (1-3). Nearly 50 medications have been implicated as inducing hypomagnesaemia (4, 5).

Several drugs have structures that suggest them as chelating agents and therefore might affect metal metabolism. Ethambutol has a chemical structure that can make chelating complex with cations (6). In one study, serum magnesium levels were evaluated in 40 cases of pulmonary tuberculosis. Of them 22 cases (55%) faced low serum magnesium levels (7). Because of the important role of magnesium in human body, present study was designed to evaluate

* Corresponding author:

E-mail: Jsalamzadeh@yahoo.com

changes in the serum magnesium concentration after a short term treatment of tuberculosis with a drug regimen containing ethambutol.

Experimental

Patients

Adult inpatients with newly diagnosed pulmonary tuberculosis admitted to Masih Daneshvari hospital (Tehran, Iran) were enrolled in the study. This hospital also operates as the National Research Institute of Tuberculosis and Lung Disease (NRITLD), well-known by the World Health Organization (WHO) for its leadership in respiratory and tuberculosis treatment in the Eastern Mediterranean countries. All patients had pulmonary tuberculosis based on clinical examinations and bacteriological tests. Patients signed an informed written consent. Exclusion criteria were malnutrition, usage of any supplements containing minerals and drugs with established effects on the serum level of magnesium (such as amphotericin, cisplatin and cyclosporine). Because of the variation in mineral content of different foods, nutrition regimens of all inpatients were similar by supervision of a clinical nutrition specialist. Before starting the antituberculosis regimen a blood sample (2 ml) were collected from the forearm of patients (baseline measurement). Then, blood samples were centrifuged at 5000 rpm and serum was separated. Patients began standard regimen of antituberculosis consisting of isoniazid (300 mg/d), rifampin (600 mg/d), ethambutol (1500 mg/d) and pyrazinamide (2000 mg/d). Drugs were administered in the morning (about 8.00 AM). After 10 days, second blood samples (2 ml) were obtained in the morning (between 11.00 to 12.00 AM). All serum samples were kept in -70°C until magnesium measurements were done.

Analytical procedures

Serum magnesium levels were determined using atomic absorption spectrophotometer (Perkin Elmer 1100 B) in flame mode.

Statistical analysis

Data were analyzed using SPSS version 13. All values are shown as mean \pm SD. Statistical

Table 1. Demographic data distribution of patients (n= 60).

Parameter		
Age (Mean \pm SD)		55.8 \pm 16.8 year
Sex	Female	26
	Male	34
Smoker	Yes	12
	No	48

analyses were performed by paired t test. $P < 0.05$ was considered as statistically significant level.

The proposal of the study was approved by the ethical committee of the Shahid Beheshti University, M.C..

Results

Clinical phase of the study was done from September 2006 to May 2007. During this time, sixty patients enrolled in the study. In Table 1 demographic data of patients are shown.

Mean concentration of magnesium in serum was measured at baseline and at day 10 after antituberculosis regimen containing ethambutol was administered. Results are presented in the Figure 1.

Data analysis using paired t test showed there is no significant difference between mean serum magnesium concentrations measured before (0.61 \pm 0.08 mmol/l) and after (0.62 \pm 0.11 mmol/l) ethambutol use ($P=0.72$).

Discussion

Magnesium (Mg) is an essential element. Approximately the total Mg in the body is present intracellularly in soft tissues and bones. Serum Mg determination represents only 1% of total body's Mg concentration. But alteration of serum magnesium can affect the physiological function of human (8). Drugs are cited among the causes of hypomagnesemia (5, 9). Some drugs such as amphotericin, cisplatin and cyclosporine are labeled as being potentially hypomagnesaemic based on well established data, while some regarded as such following anecdotal reports or inference from other member of the same drug family (4).

Several drugs have structures suggesting they

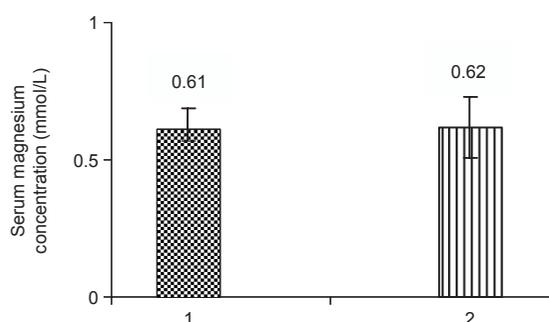


Figure 1. Mean serum concentration of magnesium at baseline and at 10th day of treatment.

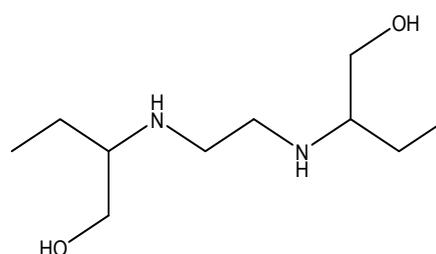


Figure 2. Chemical structure of ethambutol.

and/or their metabolites are chelating agents, and therefore might affect metal's metabolism (e.g. magnesium). Solecki et al. have shown effects of ethambutol on some trace metals in rats. They reported ethambutol caused a significant decrease in heart copper, kidney zinc, and plasma zinc, liver copper and liver zinc in rats (6). The chelating ability of ethambutol is probably related to the presence of two electron donating nitrogen atoms separated by two carbon atoms, the nitrogen can thus form stable saturated 5-membered rings by interacting with metals (10) (Figure 2). Although ethambutol is not used as a single agent in human, it seems that therapeutic regimens consisting of ethambutol may cause changes in magnesium concentration in serum. Some investigators evaluated serum concentration of magnesium in tuberculosis patients without targeting chelating effect of ethambutol on magnesium concentration. Podelsna has studied serum magnesium concentrations in cases of pulmonary tuberculosis but could not find any significant change (11). On the other hand, Jain et al who evaluated serum magnesium levels in 40 patients with tuberculosis, reported hypomagnesemia in 22 of 40 patients (%55) (7).

We designed a study to investigate alteration of magnesium during ethambutol usage in pulmonary tuberculosis patients. The study was conducted approaching to overcome interventional parameters that may affect serum magnesium concentrations in patients. Therefore, patients whom were fed with similar food in the hospital selected for the study. Also any patient that used to consume any minerals or any drugs

with established effects on magnesium levels was excluded from the study.

In conclusion our study showed no significant change between serum magnesium concentration before and after treatment. It seems that anti tuberculosis regimen consist of ethambutol could not change the serum concentration of magnesium. May be combination pharmacotherapy with several anti tuberculosis drugs or the little population of patients was a limiting factor for establishing the theory that ethambutol can not change magnesium level in the serum. There were some limitations in doing the study because of deletion of confounding parameters in the study. In future evaluation of study recommended in more patients. Since all of the patients in this study were on a multi drug antituberculosis therapy, the direct or indirect impact of the other drugs (isoniazid, rifampin and pyrazinamide) on serum levels of magnesium could be the subject for further investigations. Ethambutol may alter plasma concentration of the other elements in the body. This is because trace elements such as copper and zinc have less concentrations in plasma than the magnesium and ethambutol may be change amount of them in the plasma. So further studies about the other metals are recommended by the authors.

References

- (1) Fox C, Ramsoomair D and Carter C. Magnesium: its proven and potential clinical significance. *South Med. J.* (2001) 94: 1195-201
- (2) Huskisson E, Maggini S and Ruf M. The role of vitamins and minerals in energy metabolism and well-being. *J. Int. Med. Res.* (2007) 35: 277-89
- (3) Touyz RM. Magnesium in clinical medicine. *Front*

- Biosci.* (2004) 9: 1278-93
- (4) Atsmon J and Dolev E. Drug-induced hypomagnesaemia: scope and management. *Drug Saf.* (2005) 28: 763-88
- (5) Pelton R, LaValle J, Hawkins EB and Krinsky DL. *Drug Induced Nutrient Depletion*. 2nd ed. Lexi-comps Publisher, Hudson (2001) 286-288
- (6) Solecki TJ, Aviv A and Bogden JD. Effect of a chelating drug on balance and tissue distribution of four essential metals. *Toxicol.* (1984) 31: 207-216
- (7) Jain MK, Khanuo SK, Chande RD, Jain GC and Bisarya BN. Serum magnesium in pulmonary tuberculosis. *Ind. J. Tuberc.* (1976) 23: 177-181
- (8) Ahsan SK. Metabolism of magnesium in health and disease. *J. Indian. Med. Assoc.* (1997) 9: 507-10
- (9) Sanders GT, Huijgen HJ and Sanders R. Magnesium in disease: a review with special emphasis on the serum ionized magnesium. *Clin. Chem. Lab. Med.* (1999) 37: 1011-33
- (10) Bodgen JD. Blood zinc in health and disease. In: Nriagu, Jerome O. (ed.) *Zinc in the Environment*, Part 2. Willey, New York (1980) 137-169
- (11) Podelensa Z. Determination of serum magnesium level in patients with lung cancer, pneumonia and pulmonary tuberculosis. *Pol. Tyg. Lek.* (1972) 27: 1439-1441
-
- This article is available online at <http://www.ijpr-online.com>