Iranian Journal of Pharmaceutical Sciences
Autumn 2007: 3(4): 191-196
www.ijps.ir

Original Article

Aminophylline Infusion Induced Excretion of Magnesium During Magnesium Loading Test in Critically Ill Patients

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Abstract

The aim of this study was to investigate the prevalence of Mg deficiency and effect of aminophylline infusion on urine magnesium concentration after magnesium loading test (MLT). To determine serum Mg, venous blood specimens were obtained just before the first MLT. Two MLTs were performed. The first one was done before starting aminophylline infusion and the 2nd one was done during aminophylline infusion. Urine samples were collected from the starting of Mg infusion in each phase. Although low serum Mg was present only in 2 patients, MLT showed Mg deficiency in 18 patients. MLT detected Mg deficiency in 13 out of 14 patients with normal serum Mg, in 2 out of 2 subjects with serum hypomagnesemia, and in 3 out of 5 cases with serum hypomagnesemia. There was no relationship between Mg retention, age and serum Mg concentrations. Aminophylline administration increased the 24-h urine Mg concentration by 29.3%.

Keywords: Aminophylline; Critically ill; Hypomagnesaemia; Magnesium Loading Test; Theophylline.
Received: September 13, 2007; *Accepted:* November 15, 2007

1. Introduction

Magnesium (Mg) is the fourth most abundant cation in the body and the second most prevalent intracellular cation. It serves as a cofactor for about 300 cellular enzymes [1, 2]. Magnesium is essential for virtually all hormonal reactions that occur in the body [3]. It plays an essential role in the function of the cell membrane sodium-potassium ATPase pump [4]. Hypomagnesemia may cause cardiac, neuromuscular and central nervous system dysfunction. It is also associated with imbalance of other electrolytes, such as K^+ and Ca^{2+} [5].

Since only 1% of total body Mg is in the extra cellular fluid, serum Mg concentration may not adequately reflect Mg status. Significant Mg deficiency may exist while plasma Mg level is normal. Thus normal serum Mg could constitute a serious underestimation of the severity of Mg deficit [6-8]. The simplest and possibly the most reliable test

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used in the assessment of functional magnesium deficiency is believed to be the magnesium loading test (MLT). MLT appears to be valid in critically ill patients. Surveys of serum Mg levels in hospitalized patients indicate a high incidence of hypomagnesaemia (presumably an underestimate of the true incidence of Mg deficiency), ranging from 11% to 47% in general patients [9-11] and 20% to 65% in patients admitted to intensive care units [11-13].

The main uses of aminophylline (ethylenediamine theophylline) in critically ill patients are bronchospasm treatment and weaning patients from the ventilator [14]. One of the electrolyte abnormalities associated with theophylline administration is hypomagnesaemia [15]. There is no report yet that has evaluated aminophylline effects on urine Mg concentration after MLT in the intensive care unit (ICU) patients. Due to the importance of Mg deficiency and widespread use of aminophylline in the ICU, we decided to evaluate Mg status and the interaction between aminophylline and Mg status. This study was conducted in the critically ill patients at Sina Hospital (Affiliated with Tehran University of Medical Sciences, Iran).

2. Materials and methods

This study was a quasi-experimental survey on 21 cases who were admitted for at least 72 h in the intensive care unit (ICU). The study was approved by the human ethics committee of Tehran University of Medical Sciences. The exclusion criteria were impaired renal function (serum creatinine>1.5 mg/dl) and known cases of renal failure, heart rate <60 beats/min., sever metabolic disturbances, furosemide infusion more than 1 mg/h, coagulopathy, myasthenia gravis or any other known neuromuscular diseases. At the beginning of the study and immediately after patient's admission to the ICU, blood specimens were collected for total serum Mg determination. Immediately after that the first MLT was done. Then 2 g/day Mg sulfate was administered to each patient to replace the 24-h basal excretion of Mg in the urine [16] until indication of aminophylline administration obviously occurred. Twenty four h after aminophylline loading dose was given and the infusion was started, patients' blood was taken for determining serum theophylline level and the 2nd MLT was performed. The MLT was performed as described earlier in detail [17]. $MgSO_4$ (30 mmole; 7.5 g) was administered as a continuous intravenous infusion for an 8 h period [16,18] . Mean arterial blood

Fig. 1. Patients serum magnesium status just before the first MLT

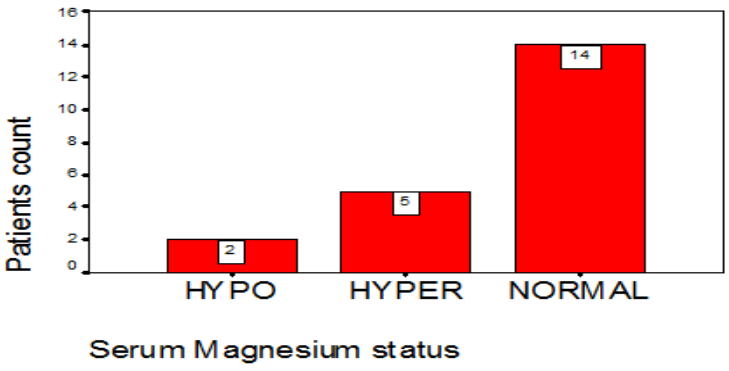

Figure 1. Patients' serum Mg status just before the first MLT.

Table 1: 24- h Patients urine magnesium content with and without aminophylline.

Urine magnesium (mg)	N	Mean	SD	Results
Without aminophylline	21	2302.4	1065.7	T= -5.5 Df= 20 p<0.0001
With aminophylline	21	2773.5	991.2	

pressure, electrocardiogram, pulse rate, respiratory rate and deep tendon reflexes were recorded to detect any sign of hypomagnesaemia. Urine samples were collected in plastic bottles acidified with 15 ml 10% HCl from the beginning of the infusion for 24 h [19]. The uptake of Mg was calculated from the Mg dose given intravenously and the amount excreted during the study time and was expressed in percent of the amount of Mg given [1, 17].

[(30 mmol Mg^{2+} infused - amount of Mg^{2+} excreted in urine) 100]/30 mmol Mg^{2+} infused

Venous blood specimens were obtained before defined as <50% Mg excretion over a 24 h period [20]. Serum theophylline concentration was determined by HPLC [21] and serum and urine Mg assay were done by Technicon RA-XT (USA). Statistical analysis was performed using Chi-square for categorical variables, and Pearson correlation coefficient was used to correlate data with normal distribution.

3. Results

Mean patients age was 50±21 years (10 male, 11 female). Magnesium uptake (retention) in patients ranged from 39 to 93% with a mean value of 68.4%±13.2. Based on MLT, 18 patients had definite Mg deficiency and only 3 patients had normal level. The Pearson correlation coefficient (r) showed no linear relationship between Mg retention, age (r=0.1, p=0.63) and serum Mg (r=0.01, p=0.94). There was no correlation between Mg uptake and sex (Chi2=14.3, p=0.575). Serum Mg concentrations (just before first MLT) were high in 5 patients, low in 2 patients, and normal in 14 patients (Figure1).

Mg deficiency (according to MLT) was greatly found in 13 patients whose serum Mg levels were normal, in all hypomagnesemic cases and in 3 hypermagnesemic ones (Figure 2).

The mean serum theophylline concentration and clearance were 5.9±2.6 mg/l and 1.64±0.93 l/h, respectively. Aminophylline administration increased 24 h urine magnesium concentration from 2302±1065 mg to 2773±9910 mg (by 29.3%; Table 1). No correlation was found between serum theophylline level and increase in urine Mg concentration (r=0.26, p=0.255).

4. Discussion

Mg deficiency may have clinical importance due to important functions of Mg in the body. However, Mg deficiency has not usually been considered in clinical practice due to the lack of relevant blood tests and because the symptoms are not often clear or specific. Serum Mg is generally agreed to be a poor indicator of tissue Mg. Many of the methods used to determine intracellular Mg concentration have been unreliable, difficult to replace and tedious. The MLT has been suggested to reflect Mg status of the patients [18].

This study shows the importance of MLT in determining the true Mg status in the ICU admitted patients. In agreement with previous studies [18], Mg deficiency was highly prevalent in critically ill patients. MLT was able to detect Mg deficiency in 18 out of 21 critically ill patients whereas serum Mg levels indicated deficiency only in 2 of those patients. Sina Hospital MLT appears to reflect the true Mg status of patients better, it should

be the test of choice when assessing Mg deficiency.

Mg deficiency seems to be more common in our study population than others. According to our definition of Mg deficiency (<50% Mg excretion in 24 h urine from 30 mmol Mg given in MLT), Mg deficiency was present in 85.7% of critically ill patients, whereas the frequency reported by others [11-13, 16], using the same definition (in ICU admitted patients), was 20-65%. According to the definition for Mg deficiency used by other authors [13, 17, 18] (<70% Mg excretion of the total Mg given) all subjects in our study could be considered Mg deficient.

Various factors such as protein-calori malnutrition, intravenous medication of Mg-free fluids, total parenteral nutrition and drugs such as loop diuretics, aminoglycosides and amphotericin B [22] put the patients in the ICU at risk for development of hypomagnesemia. We think the great prevalence of hypomagnesemia in our patients is due to not having standard enteral nutrition products and also not giving enough parenteral nutrion and supplements to the patients. In the present study furosemide infusion (1-2 mg/h) can not significantly increase magnesium excretion. This finding was noted in a study [16]. This study confirms that serum magnesium is not a reliable method to determine the magnesium status in critically ill patients.

The main aim of this study was to evaluate the effects of aminophylline infusion on the 24 h urine Mg content. Theophylline may induce hypomagnesemia. Mild diuresis is produced by combined effects of theophylline on renal hemodynamics and on tubular reabsorbtion [23]. On the other hand, an increase in the level of intra-cellular cyclic AMP due to inhibition of phosphodiesterases by theophylline, results in hypomagnesemia [24]. Many previous studies of theophylline-associated metabolic disturbances have assessed the relation of toxic serum theophylline concentrations [15]. Most of them evaluated serum Mg levels after single dose theophylline administration. Nowadays, we know that serum Mg is not a reliable marker to diagnose hypomagnesemia. There is only one article that evaluated effects of theophylline on urine Mg excretion [25]. In this study, 10 asthmatic women were enrolled in the study, and 300 mg aminophylline (serum theophylline concentration was 8.5 mg/l) was infused in 10 min. and patients' urine samples were collected for 6 h. Aminophylline infusion increased total urinary excretion of Mg by 59% compared to

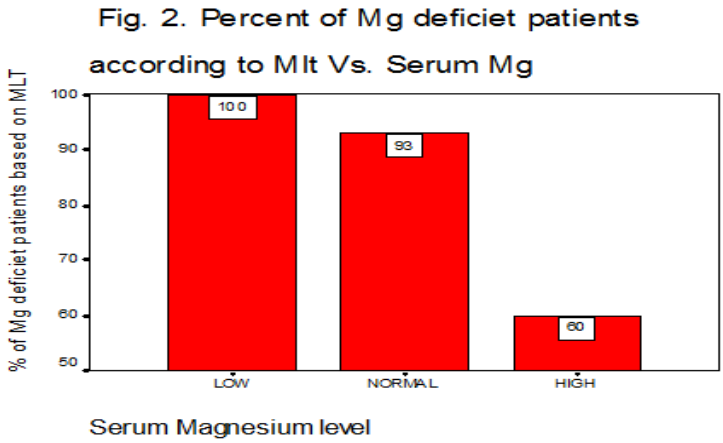

Figure 2. Percentage of Mg deficient patients according to MLT versus serum Mg level.

control without alteration in serum Mg levels. Our study was novel and is different from Knutsen's [25] because we did MLT with and without aminophylline infusion. In our study aminophylline infusion (serum theophylline concentration was 5.9 mg/l) could increase urine Mg excretion by 29.3% compare to control. In our study, both serum theophylline concentration and Mg excretion were lower than that amounts in Knutsen study [25]. Although in both of them there were no correlation between serum theophylline and Mg excretion.

We conclude that Mg deficiency is very common in our critically ill patients, specifically in patients who receive aminophylline.

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