Int J Clin Exp Med 2015;8(11):21689-21693
www.ijcem.com /ISSN:1940-5901/IJCEM0015560

Original Article

Proton pump inhibitors use in hemodialysis patients and serum magnesium levels

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Received September 3, 2015; Accepted November 2, 2015; Epub November 15, 2015; Published November 30, 2015

Abstract: Hypomagnesemia is reported in patients who use proton pump inhibitors (PPIs). We investigated the effect of PPIs use on serum magnesium levels in hemodialysis patients. Our study was conducted in a hemodialysis center including 75 end stage renal disease patients. PPI use and duration were investigated. All patients were dialyzed using a dialysate magnesium level of 0.5-0.75 mmol/L. After at least one month of hemodialysis with the mentioned dialysate, laboratory tests were performed. Fifty-four patients (72%) used PPIs while 21 (28%) did not. The mean duration of PPI use was 42.5 ± 35 months. There was no significant difference between serum magnesium levels of patients who used and did not use PPIs (2.73 ± 0.3 vs. 2.88 ± 0.3 mg/dL, P = ns). There were 15 patients (20%) with a dialysate magnesium level of 0.5 mmol/l and 60 patients (80%) with a dialysate magnesium level of 0.75 mmol/L. The mean serum magnesium levels of patients with a dialysate magnesium level of 0.5 mmol/L was 2.45 ± 0.3 mg/dL while that of patients with a dialysate magnesium level of 0.75 mmol/L was 2.85 ± 0.3 mg/dL (P<0.0001). In hemodialysis patients, PPI use did not affect serum magnesium levels. The most important factor affecting the serum magnesium levels in hemodialysis patients is the dialysate magnesium concentration.

Keywords: Hemodialysis, proton pump inhibitor, magnesium

Introduction

Magnesium is vital for human cellular function. In advanced chronic kidney disease, the tubular secretion of magnesium becomes insufficient. Intestinal magnesium absorption occurs after dietary intake. This causes a positive magnesium balance, especially in end stage renal disease patients, that may cause hypermagnesemia [1, 2]. Although hemodialysis patients are more inclined towards hypermagnesemia, hypomagnesemia can also be seen [1, 3]. Diuretics such as furosemide and thiazide may also cause hypomagnesemia [1, 4]. Phosphate binders, laxatives, or antacids which contain magnesium may cause hypermagnesemia [5, 6]. Hypomagnesemia, which is related to increased cardiovascular risk in the general population [7], is found to be linked to an increased risk of both cardiovascular and non-cardiovascular mortality in hemodialysis patients [8, 9].

Proton pump inhibitors (PPIs) [omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole] are used for both gastroesophageal reflux disease and acid-related disorders. All PPIs inhibit the gastric acid pump and the gastric acid secretion [10]. Hypomagnesemia has been reported with long term PPI use [11-13]. We investigated the effect of PPI use on serum magnesium levels in hemodialysis patients.

Materials and methods

Our study was conducted in a hemodialysis center including 75 end stage renal disease patients. All patients were greater than 18 years of age and underwent hemodialysis for at least 4 months. The dialysate components of hemodialysis patients were as follows: sodium 138 mmol/L, potassium 2 mmol/L, chloride 105 mmol/L, acetate 3 mmol/L, bicarbonate 36 mmol/L, calcium 1.25-1.5-1.75 mmol/L, magnesium 0.5-0.75 mmol/L, glucose 1 g/L. After at least one month of hemodialysis with the above-mentioned dialysate, laboratory tests were performed. Plasma corrected calcium, phosphorus, albumin, and magnesium levels were measured. The normal range of serum magnesium was determined to be between 1.6 and 2.6 mg/dL. Dialysis adequacy (Kt/V) was calculated [14]. Patients were questioned on the

Table 1. Data of patients according to PPI use

	Patients who did not use PPIs (n = 21)	Patients who used PPIs (n = 54)	*p*-value
Gender (female/male)	8/13	27/27	ns
Age (years, mean)	60.7 ± 10	63.3 ± 11	ns
Duration of dialysis (months, mean ± SD)	56.3 ± 44	64.3 ± 54	ns
Plasma magnesium (mg/dl, mean ± SD)	2.88 ± 0.3	2.73 ± 0.3	ns
Plasma calcium (mg/dl, mean ± SD)	8.7 ± 0.6	8.8 ± 0.7	ns
Plasma phosphorus (mg/dl, mean ± SD)	4.7 ± 0.8	4.3 ± 0.9	ns
Plasma albumin (g/dl, mean ± SD)	3.9 ± 0.4	3.8 ± 0.3	ns
Kt/V (mean ± SD)	1.8 ± 0.3	1.7 ± 0.2	ns
Diuretics (yes/no)	4/17	12/42	ns
Diabetes Mellitus (yes/no)	7/14	15/39	ns
Dialysate magnesium 0.5 mmol/L/0.75 mmol/L	4/17	11/43	ns

PPIs: proton pump inhibitors; SD: standard deviation; ns: non-significant.

Table 2. PPI use according to dialysate magnesium concentrations

	Patients who do not use PPIs (n = 21)	Patients who use PPIs (n = 54)	*p* value
Dialysate magnesium concentration	Plasma magnesium (mg/dl, mean ± SD)	Plasma magnesium (mg/dl, mean ± SD)	
0.5 mmol/L	2.6 ± 0.1 (n = 4)	2.39 ± 0.3 (n = 11)	ns
0.75 mmol/L	2.94 ± 0.3 (n = 17)	2.81 ± 0.3 (n = 43)	ns

PPIs: proton pump inhibitors; SD: standard deviation; ns: nonsignificant.

use and duration of PPIs, diuretics, and magnesium-containing drugs. The magnesium units in the studies were mg/dL, mEq/L or mmol/L. To convert from mg/dL to mEq/L, divide by 1.2. To convert from mEq/L to mmol/L, divide by 2. To convert from mg/dL to mmol/L, divide by 2.4 [15].

The Kolmogorov-Smirnov test was used to determine whether continuous variables were normally distributed. Descriptive analyses were presented as the mean and standard deviations for normally distributed variables. Variables were compared using the Student's t-test, the Mann-Whitney U test, the chi-squared test, or Fisher's exact test, as appropriate. A *p*-value of less than 0.05 was considered statistically significant.

Results

Of 75 patients, 35 (47%) were female and 40 (53%) were male. The mean age of the patients was 62.6 ± 10 (range 37-84) years. The mean duration of the dialysis treatments was 62.1 ± 51 (range 4-246) months. Twenty-two patients (29%) had diabetes mellitus. None of the patients in our cohort utilized magnesium-containing tablets. Fifty-four patients (72%) used PPIs while 21 (28%) did not. The mean duration of PPI use was 42.5 ± 35 (range 3-144) months. There was no significant difference between serum magnesium levels in patients who did and did not use PPIs (P = ns; **Table 1**). Based on dialysate magnesium concentrations, this result did not change (P = ns; **Table 2**).

There were 15 patients (20%) with a dialysate magnesium level of 0.5 mmol/l and 60 patients (80%) with a dialysate magnesium level of 0.75 mmol/L. The mean serum magnesium level of patients with a dialysate magnesium level of 0.5 mmol/L was 2.45 ± 0.3 (range 1.98-2.73) mg/dL while that of patients with a dialysate magnesium level of 0.75 mmol/L was 2.85 ± 0.3 (range 2.26-3.67) mg/dL (P<0.0001). We did not have any hypomagnesemic patients. Six of 15 patients (40%) with a dialysate magnesium level of 0.5 mmol/L and 53 of 60 patients (88%) with a dialysate magnesium level of 0.75 mmol/L were hypermagnesemic.

Discussion

Magnesium balance is determined by the gastrointestinal, skeletal, and renal systems of healthy individuals. When oral magnesium intake decreases, intestinal absorption increases and

urinary excretion decreases. If oral intake continues to be insufficient, magnesium released from the bone into the serum. When dietary intake is high, urinary excretion of magnesium increases if the kidneys are healthy. Hypo- and hypermagnesemia may occur for a variety of reasons. PPIs use has been shown to cause hypomagnesemia [15].

In several case reports, hypomagnesemia was detected in patients who use PPIs and serum magnesium levels normalized once PPI treatment was stopped. Upon restarting PPI treatment, hypomagnesemia recurred [13, 16, 17]. Other studies link PPI use with hypomagnesemia [18]. Gau et al. evaluated serum magnesium levels of hospitalized patients and determined the serum magnesium levels of patients using PPIs to be lower than in those who did not use PPIs [19]. Lindner et al. reported about the frequent use of PPIs in patients who were admitted to the emergency department with hypomagnesemia [20]. In the general population, the risk of hypomagnesemia increased with PPI use. Long term PPIs use and concomitant use of loop diuretics increased the risk of hypomagnesemia [21]. In a different study, PPI-induced hypomagnesemia was defined as follows: age greater than 50, greater than one year of PPI use, concomitant diuretic (thiazides and loop diuretics) use or alcohol abuse, resolution after ceasing PPI use, recurrence after restarting PPI treatment, hypocalcemic hypoparathyroidism and hypomagnesemia accompanying hypokalemia [18].

In a study of hemodialysis patients, hypomagnesemia was reported to be linked to PPI use. As serum magnesium levels of patients on PPIs were found to be lower, a higher rate of PPI use was found in hypomagnesemic patients, as compared to normomagnesemic patients. In that study, the dialysate magnesium level was 0.5-0.375 mmol/L. They reported that hypomagnesemia might occur with PPI use in hemodialysis patients whose dialysate magnesium level was 0.5-0.375 mmol/L [3].

Transient receptor potential channel melastatin member 6 (TRPM6) and TRPM7 are newly discovered channels involved in active magnesium transport. TRPM6 is expressed in the renal distal tubule and the small intestine brush border membrane [15, 22]. Once absorbed from the intestine, magnesium is filtered from the glomerulus. 10% of filtered magnesium is reabsorbed through the renal proximal tubule while 50-70% is absorbed in the ascending limb of Henle's loop via paracellular passive diffusion. Distal active transcellular magnesium reabsorption depends on epithelial magnesium TRPM6 channels. Plasma magnesium are dependent upon the balance between intestinal absorption and renal excretion and both are controlled by TRPM6 channel expression. A decrease in number of intestinal or distal tubular TRPM6 magnesium channels may induce intestinal and urinary magnesium wasting leading to hypomagnesemia [23]. PPI-induced hypomagnesemia is thought to be caused by a decrease in intestinal magnesium absorption. PPIs change the intestinal pH, which decreases the activity of intestinal TRPM6. Accompanied by decreased intestinal magnesium absorption, patients with low dietary magnesium intake and/or increased urinary loss have a tendency towards hypomagnesemia [15, 24].

There are also studies which report that PPI use does not affect serum magnesium levels. Bıyık et al. found serum magnesium levels of outpatients under long-term PPI treatments to be within the normal range in the absence of other factors affecting serum magnesium levels. The serum magnesium levels of outpatients who have and have not been using PPIs were found to be similar [25]. In a different study, serum magnesium levels of patients using PPIs were determined to be normal and with no significant difference found between those who did and did not use PPIs [26]. Koulouridis et al. found that out-of-hospital PPI use was not associated with hypomagnesemia at the time of hospital admission in a hospital-based adult population [27].

Dialysate magnesium levels are one the most important determinants of serum magnesium levels in hemodialysis patients [6]. Serum magnesium levels were determined to be mildly hypermagnesemic when the dialysate magnesium levels were 0.75 mmol/L [6, 28, 29]. There are studies which report both hypermagnesemia and normomagnesemia with a dialysate magnesium level of 0.5 mmol/L [30, 31]. Navarro et al. demonstrated mild hypermagnesemia in 73% of patients in whom dialysate magnesium concentration was 0.5 mmol/L [31]. Saha et al. found normal serum magnesium levels with a dialysate magnesium concentration of 0.25-0.5 mmol/L [30].

In our study, we did not find a relationship between PPI use and hypomagnesemia. The serum magnesium levels of patients who did and did not use PPIs were similar. None of these patients had hypomagnesemia. According to the study which determined hypomagnesemia with PPI use in hemodialysis patients [3], relatively high dialysate magnesium levels (0.375-0.5 mmol/L vs. 0.5-0.75 mmol/L) may have prevented the hypomagnesemia. According to our study, the most important factor affecting serum magnesium levels was concentration of dialysate magnesium. Serum magnesium levels of patients with a dialysate magnesium concentration of 0.75 mmol/L were higher than with a dialysate magnesium concentration of 0.5 mmol/L. 40% of patients with a dialysate magnesium level of 0.5 mmol/L and 88% of patients with a dialysate magnesium level of 0.75 mmol/L were slightly hypermagnesemic. None of our patients had hypomagnesemia, including those with dialysate magnesium concentrations of 0.5 mmol/L.

In conclusion, PPI-induced hypomagnesemia was not detected in hemodialysis patients with dialysate magnesium concentrations of 0.5-0.75 mmol/L. In hemodialysis patients, the most important factor affecting serum magnesium was found to be dialysate magnesium concentrations.

Disclosure of conflict of interest

None.

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