

ASSOCIATION OF LONG-TERM PROTON PUMP INHIBITORS USE WITH HYPOMAGNESEMIA

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Received : 14/08/2023
Received in revised form : 20/09/2023
Accepted : 04/10/2023

Keywords:

Proton Pump Inhibitors;
Hypomagnesaemia; Hypocalcaemia.

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DOI: 10.47009/jamp.2023.5.6.227

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2023; 5 (6); 1112-1115



Abstract

Background: Proton pump inhibitors (PPIs) are widely used to treat acid-related gastrointestinal diseases. The long-term potential side effects of PPIs are increasing - hypomagnesaemia, secondary electrolyte disturbances like hypocalcemia and hypokalemia (which leads to seizures, tetany, convulsions and cardiac arrhythmia). This study was selected to investigate the levels of serum magnesium in patients who have been on PPI therapy for at least 12 months. **Objective:** To find out whether hypomagnesaemia is found in chronic PPI users. **Material & Methods:** In this comparative study, data were extracted from adults attending General Medicine Outpatient Department, Government Medical College, Kozhikode. **Results:** From our analysis we found out that the mean serum magnesium for Group 1 (n=58) is 1.544 ± 0.254 and Group 2 (n=58) is 1.990 ± 0.181 . After statistical analysis the p value is found to be less than 0.001 that shows the test is statistically significant. **Conclusion:** Chronic use of Proton Pump Inhibitors in patients with acid-related gastrointestinal diseases are associated with hypomagnesaemia.

INTRODUCTION

Proton-pump inhibitor (PPI) drugs are inhibitors of gastric acid secretion (e.g., omeprazole, pantoprazole and rabeprazole). They inhibit the hydrogen-potassium adenosine triphosphatase enzyme system ('proton pump') of the gastric parietal cell. They are used more commonly for the prevention and treatment of dyspeptic symptoms, associated with oesophagitis, gastritis and peptic ulcer disease.^[1] They are well tolerated, but have side effects may occur and some adverse effects are potentially serious. PPIs are considered to have an excellent and acceptable safety profile in the short-term use. Long-term PPI therapy can lead to severe hypomagnesaemia, which is associated with fatigue, unsteadiness, paraesthesia, tetany, fits etc.^[1,2]

The PPIs are commonly used for the treatment of acid-related disorders than the other agents like histamine2-receptor antagonists (H2RAs), synthetic prostaglandin analogs, and anticholinergics. PPIs have patient tolerance, safety and superior acid suppressing capability than other agents.^[3] After absorption, PPIs pass through the gastric parietal cells where they concentrate within the secretory canaliculi. Then PPI undergoes acid-catalyzed cleavage of a sulfoxide bond into active sulfenic acid or sulfonamide, then they bind covalently to cysteine residues on the H⁺/K⁺ ATPase and act to inhibit acid secretion.^[3] This effect helps in healing

of gastroesophageal reflux disease (GERD), Barrett's esophagus, peptic ulcers and Zollinger-Ellison syndrome, non-steroidal anti-inflammatory drug (NSAID) associated peptic ulcer prevention, as well as for the eradication of *Helicobacter pylori*.^[3,4] Long time use of PPI may cause some adverse effects such as infections, impaired absorption of vital nutrients, kidney disease, hypergastrinemia, gastric cancer, pancreatic cancer etc.^[5] The inhibition of gastric acid secretion due to long term PPI use has been connected with increased risk *Clostridium difficile* infections and also other enteric infections like nontyphoid *Salmonella* and *Campylobacter* infections. The long term use of PPIs also results in the deficiency of vitamins like B12, vitamin C, minerals such as iron, calcium, magnesium etc.^[6]

Magnesium is necessary for more than 300 enzymatic reactions in the human body and also plays an important role in neuromuscular excitability and cell permeability which leads to muscle contraction.^[7] It is a cofactor for enzymes involved in protein synthesis, muscle & nerve transmission, neuromuscular conduction and regulation of blood glucose & blood pressure. It facilitates active transport of calcium and potassium ions across cell membranes, for the conduction of nerve impulses, contraction of muscle, maintaining vasomotor tone and normal heart rhythm. A constant fraction of ingested magnesium is absorbed

by simple diffusion and this absorption increases linearly with luminal concentrations.^[8] The maintenance of serum magnesium levels depends on the balance between GI absorption and the renal excretion. The reference interval for serum magnesium is approximately 1.6 - 2.6 mg/dL (0.66 - 1.07 mmol/L) for adults.^[9] Hypomagnesemia can be defined as a serum magnesium concentration of ≤ 1.6 mg/dl. Hypomagnesemia and hypocalcemia were observed in long term PPI use and some of the individuals presented with muscle cramps, paresthesia, Trousseau's sign, unsteady gait, atrial flutter and long pauses in electrocardiogram. All abnormalities were normal when PPIs were stopped and the patient required no supplementation.^[10] Though many studies have been done to find out various side effects of PPIs and PPI induced hypomagnesemia, very few studies are done in our Indian population. So, this research study is embarked to find out the association of hypomagnesemia in patients with long term use of PPI (North Kerala), who are attending the outpatient clinics of Govt. Medical College Kozhikode, Kerala.

MATERIALS AND METHODS

Study setting: Outpatient departments of Medicine and Department Biochemistry - Govt. Medical College, Kozhikode, Kerala - a tertiary care hospital.

Study design: Comparative study.

Inclusion Criteria

1. Patients from both gender above 18 years who had been on proton pump inhibitors for more than 12 months and similar age and sex matched apparently healthy individual who are not on proton pump inhibitors.
2. Patients who are willing to give valid informed consent.

Exclusion Criteria

1. Pregnant and lactating mothers
2. Any acute illness
3. Already known patients of renal diseases
4. Patient with chronic diarrhea
5. Acute and chronic liver failure
6. Patient with established malignant disease
7. Patients using magnesium depleting drugs like diuretics

Method

Patients from both genders above 18 years who had been on proton pump inhibitors for more than 12 months (Group-1) and age and sex matched apparently healthy individual who are not on proton pump inhibitors (Group-2), who are coming to the outpatient department of Medicine, Govt. Medical College, Kozhikode are included in this study.

Sample size: 116 patients

Study period: 1 year

Study variables: Serum magnesium

Details of the patients were collected in the proforma which includes name, age, gender,

address, occupation, history of PPI use (including its duration, treatment and any co-morbidities).

Laboratory investigations

Venous blood samples (5-8 ml) were collected from all patients in a vacutainer. The Study variable, serum magnesium was estimated in both groups I and II. The estimation was done in COBAS c-311 analyzer by using commercially available standard assay kits.

Statistical Analysis

Analysis was done using SPSS for Windows Version 22.0

Descriptive Statistics

Descriptive analysis of all the explanatory and outcome parameters was done using frequency and proportions for categorical variables, whereas mean & SD for continuous variables.

Inferential Statistics

Independent Student t test analysis was used to compare the mean magnesium levels (in mg/dl) between the two groups (group 1 & group 2).

Chi Square test and Mann Whitney test was used to compare the mean age (in years) and gender distribution of group 1 & group 2 having hypomagnesemia & those with normal magnesium levels.

Prevalence of Hypomagnesemia in both groups (1 and 2) was done using Chi square Test. The level of significance was set at $p < 0.05$.

RESULTS

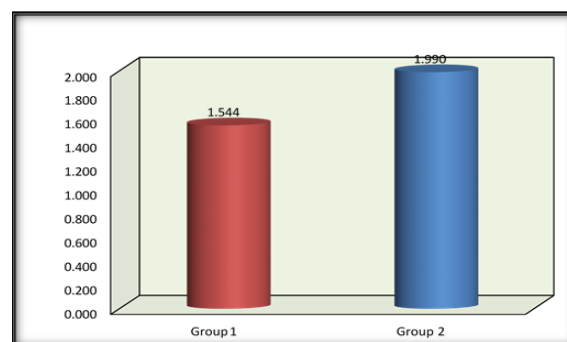


Figure 1: Mean Serum Magnesium levels (in mg/dL) between group 1 & group 2

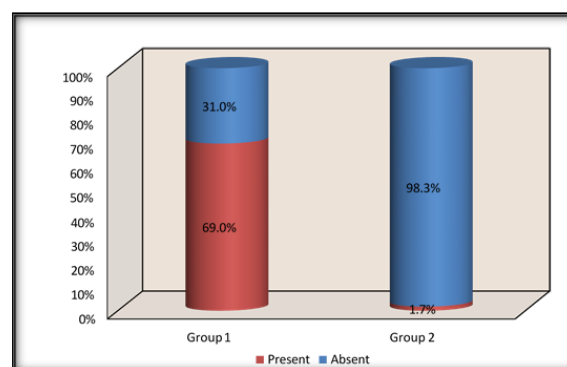


Figure 2: Prevalence of Hypomagnesemia between Group 1 & Group 2

The normal level of Magnesium in a healthy adult is 1.60-2.6 mg/dl. Magnesium levels lesser than this value will be considered as hypomagnesaemia. The mean serum magnesium in the group 1 was 1.544 ±0.25 and in the group 2 was 1.99±0.18, the p value is found to be <0.001, hence statistically significant. [Table 3]

Among the group 1, hypomagnesaemia was prevalent in 40 cases (69.0%) and remaining 18 cases (31%) presented with normal levels of magnesium. Among the group 2, hypomagnesaemia was prevalent in 1 case (1.7%) and remaining 57 cases (98.3%) presented with normal levels of magnesium.

Table 1: Age and gender distribution among 2 groups

Variable	Category	Group 1		Group 2	
		Mean	SD	Mean	SD
Age	Mean & SD	54.43	8.86	51.91	8.77
	Range	38 - 76		36 - 68	
		n	%	N	%
Sex	Males	38	65.5%	31	53.4%
	Females	20	34.5%	27	46.6%

Table 2: Comparison of mean Serum Magnesium levels (in mg/dL) between Group 1 & Group 2 using Independent Student t Test.

Parameter	Groups	N	Mean	SD	Mean Diff	P-Value
Serum Magnesium	Group 1	58	1.544	0.259	-0.446	<0.001*
	Group 2	58	1.990	0.181		

Table 3: Prevalence of hypomagnesaemia between Group 1 & Group 2 using Chi square Test

Variable	Category	Group 1		Group 2		P-Value
		n	%	n	%	
Hypomagnesaemia	Present	40	69.0%	1	1.7%	<0.001*
	Absent	18	31.0%	57	98.3%	

DISCUSSION

Our comparative study revealed that chronic use of PPI had significantly lowered S. Mg levels compared to PPI nonusers, which is also seen with the results reported by Gau et al.^[11] They reported that PPI users had significantly lower Serum Magnesium levels than nonusers of PPIs.

Among the total study patients, group 1 (n=58) and group 2 (n=58), it is found that there is a significant level of decreased magnesium levels in the individuals who are on PPI therapy for at least one year when compared to the individuals who are not on PPI therapy with the mean serum magnesium value of group 1 was 1.544 ±0.25 and in the group 2 was 1.99±0.18, the p value is found to be <0.001, which is statistically significant.

In 2006, a report published by Epstein et al. Reported PPI, omeprazole, was shown to be associated with hypomagnesaemia.^[12] Broeren et al. also showed that hypomagnesaemia was resolved after the replacement of omeprazole with a H2-blocker, ranitidine, but the re-replacement of ranitidine with pantoprazole resulted in recurrence. The same fluctuation was found for lansoprazole.^[13] Hoorn et al. reported a case of hypomagnesaemia in which the patient was treated with pantoprazole. They also documented another case in which the replacement of omeprazole with rabeprazole resulted in a further decrease in serum levels of magnesium.^[14] Some of the case reports by Tamura T et al in 2012 published with respect to PPI- long term use associated hypomagnesaemia.^[15]

CONCLUSION

This study confirmed that there was a significant level of hypomagnesaemia in patients who were on long term PPIs, when compared to the individuals who were not on PPI.

Limitations

- The sample size is small and duration of study is limited.
- Since this is a Cross sectional comparative study, temporality of association cannot be established. For that we need to conduct a longitudinal study.
- We only measured the total serum magnesium levels, but not free ionized or intracellular magnesium from the subjects. Although the serum magnesium level correlates fairly well with the intracellular free magnesium level, only 1 % of the total body magnesium exists extracellularly. Therefore, serum magnesium level may be an insensitive marker for intracellular magnesium deficiency.
- The influence of individual diet on magnesium levels was omitted.
- The individual effect of different PPIs wasn't studied clearly as our study was mainly concentrated on the class effect of PPIs.
- Urine magnesium was not measured. Completing studies that include measuring urine magnesium will be much more valuable.

Future Directions

As magnesium level was found to be decreased in chronic PPI use, it is advisable to screen the patients for serum magnesium in patients requiring long term PPI therapy.

Further care should be taken while prescribing magnesium depleting drugs like diuretics or other nephrotoxic drugs in patients who are on long term PPI therapy which may worsen the subclinical hypomagnesaemia.

Further trials should be done in future to know the effectiveness of magnesium supplementation and magnesium rich foods like almonds, cashews, peanuts, spinach etc. in preventing the hypomagnesaemia due to long term PPI use.

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