ABSTRACT

Introduction: Proton pump inhibitors are seen to affect the serum vitamin B₁₂ and potassium levels. The aim of this study was to determine whether long-term proton pump inhibitor use (more than two years) was associated with an abnormal serum vitamin B₁₂ and serum magnesium status in the body.

Material and Methods: This prospective cross-sectional study enrolled 60 proton pump inhibitor (PPI) users, mean age: 50.78 (SD-10.14) years. Demographic data, serum levels of magnesium, vitamin B₁₂ and potassium were recorded. The reference level used for serum magnesium, vitamin B₁₂ and potassium were (1.8-2.4 mg/dl), (211-911 pg/ml), and (3.5-5.5 mEq/L) respectively.

Results: Among the enrolled 60 PPI users, the prevalence of low serum magnesium and low serum vitamin B₁₂ levels were 16 (26.67%) and 4 (6.67%) respectively. Mean PPI use was 5.123 years. From our study it was found that Low serum vitamin B₁₂ was associated with PPI use of more than four years whereas, low serum magnesium level was found irrespective of duration of PPI use.

Conclusion: Hypomagnesemia is common in long term PPI use and low vitamin B₁₂ is associated with more prolonged use.

Keywords: Food and Drug Administration, Clostridium difficile, Cardiac arhythmia, Transient receptor potential melasin, Hypokalemia, Achlorhydia.

INTRODUCTION

Proton-pump inhibitor (PPI) drugs (e.g. Omeprazole, Esomeprazole, Lansoprazole, Pantoprazole and Rabeprazole) are potent inhibitors of gastric acid secretion which blocks the hydrogen–potassium adenosine triphosphatase enzyme system (the ‘proton pump’) of the gastric parietal cell. They are widely used for the treatment and prevention of dyspepsia, associated with peptic ulcer disease, esophagitis and gastritis. Although they are well tolerated, they can have serious side effects. PPI therapy, by decreasing gastric acidity, can increase the risk of gastro-intestinal infections like Clostridium difficile enterocolitis. Recent reports reported that the long term use of PPI induces hypomagnesemia. On March 2, 2011, the U.S. Food and Drug Administration (FDA) issued a drug safety alert regarding long-time PPI use can cause low levels of serum magnesium.

The postulated mechanism of PPI-induced hypomagnesemia involves inhibition of intestinal magnesium absorption through transient receptor potential melatin (TRPM) 6 and 7 cation channels. Severe hypomagnesemia can cause tetany, malignant cardiac arrhythmias, generalized seizures, and other metabolic disturbances i.e. hypokalemia and hypocalcemia.

Vitamin B₁₂ (cobalamin) is an essential water-soluble nutrient acquired from animal-derived food sources meats, poultry, eggs, fish, shellfish and dairy products. Absorption of Vitamin B₁₂ requires peptic enzymes to cleave dietary B₁₂ from dietary proteins. This is primarily done by pepsin, which requires gastric acid to activate pepsin from its pepsinogen precursor. Vit B₁₂ absorption starts with peptic cleavage in the stomach, at acid pH of food-bound B₁₂ which then binds to salivary R protein complex in the duodenum; pancreatic enzymes release R-protein-bound B₁₂ which binds to IF. The B₁₂–IF complex is absorbed in the ileum and then transported in the blood bound to transcobalamin II. An enterohepatic cycle promotes the conservation of vit B₁₂. Without gastric acid, vit B₁₂ would not be cleaved from dietary protein and would not be able to bind with R-proteins, which protect vit B₁₂ from pancreatic enzymes. It has been hypothesized that since gastric acidity is essential for vit B₁₂ absorption, acid suppression by PPI can lead to malabsorption and ultimately vit B₁₂ deficiency from achlorhydia and atrophic gastritis. The aim of the study was to investigate whether long-term proton pump inhibitor use (more than two years) was associated with an abnormal serum vitamin B₁₂ and Magnesium status in body and also to evaluate the duration of PPI use and its association with hypomagnesaemia and low Vit B₁₂.

MATERIAL AND METHODS

This cross sectional study was done over a period of six months at TMC and Dr. B. R. Ambedkar Teaching Hospital after obtaining the ethical approval from institutional ethical committee. A total of 60 patients with long-term PPI use were included in the study after taking written informed consent from them.

Inclusion Criteria
1. Male / female subjects aged 18-65 yrs.
2. On PPI therapy more than two years.
3. Ability to comply with the requirements of the protocol and be available for study visits over six months.

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4. Willing to participate in the study.

Exclusion Criteria
1. Subjects aged < 18 and >65 yrs.
2. Patients on vitamin B₁₂ and magnesium supplementation over last six months.
4. Diseases which interferes vitamin B₁₂ absorption i.e. Achlorhydria, Hypochlorhydria, Pernicious anemia, Gastrectomy, Chronic pancreatitis, Malabsorption syndrome, Small intestinal bacterial overload, Short bowel syndrome, Crohn’s disease, Celiac sprue, etc.
5. Drugs which interferes vitamin B₁₂ and magnesium level on body i.e. Diuretic, Metformin, Potassium, Chloramphenicol, Angiotensin converting enzyme inhibitors, beta blockers, Digitalis, Gentamycin, Amphotericin B, Cisplatin etc.

Calculation of Sample Size:

\[ n = \frac{4 \times p \times q}{L^2} \]

Where \( p = \) Prevalence = 13% (Prevalence as per the study, “Association of Proton pump inhibitor with Hypomagnesaemia: A cross sectional study at a Tertiary care Hospital of Anand District.”)

\[ q = (100-p) = 87 \% \text{, } L = \text{Allowable error (absolute) } = 9 \% \]

By the formula, \( n = 4 \times p \times q / L^2 \)

Calculated sample size = 55.

Extra 10% sample added to compensate any incomplete data
So, final sample size = 60.

**STATISTICAL ANALYSIS**

All relevant data so collected were entered in the master chart and analyzed using IBM SPSS Statistics 20. Results obtained were based on descriptive statistics.

**RESULT**

Of the 60 participants, male were 30 (50%) and female 30 (50%). Age >45 years were 45 (75%) and <45 years were 15 (25%). Mean age was 50.78 years. The prevalence of participants with low serum magnesium and low serum vitamin B₁₂ levels were 16 (26.67%) and 4 (6.67%) respectively. The prevalence of PPI users with low serum magnesium and low serum vitamin B₁₂ levels in younger (<45 years) were 2 (12.5%) and 0 (0%) respectively and among older (>45 yrs) were 14 (87.5%) and 4 (100%) respectively (table-1). Mean PPI use was 5.123 years.

**DISCUSSION**

In 2011, Cundy T et al. reported 30 cases of severe hypomagnesaemia in patients on PPI therapy. In 2008, Agarwal et al. reported a 43-year-old man, on high-dose omeprazole for reflux esophagitis for 3 years developed symptomatic hypomagnesaemia and hypocalcaemia and withdrawal of PPI therapy led to normalized level in 6 wks and symptoms in 12 wks. In 2008, Cundy et al. reported 2 patients with severe hypomagnesaemia and hypocalcemic seizures, and who were on long-term PPI therapy. In 2006, Epstein et al. reported two patients on PPI therapy presented with tetany due to hypomagnesaeic hypoparathyroidism, and withdrawal of the PPI normalized the metabolic abnormalities. In 1980, Steinberg WM et al. reported the effect of cimetidine on the uptake of protein-bound cyanocobalamin, the excretion of radio-active cyanocobalamin decreased from 2.3% to 0.2% after a morning dose of cimetidine300 mg. In 1994, Macuard et al. reported that treatment of healthy subjects with omeprazole 20 mg or 40 mg daily for 2 weeks resulted in decreased vitamin B₁₂ absorption as measured by a modified Schilling test. Cyanocobalamin absorption was reduced from 3.2% to 0.9% in those who received 20 mg omeprazole, and from 3.4% to 0.4% in those who received 40 mg omeprazole.

In our cross-sectional study, prolonged acid suppression due to proton pump inhibitor use was associated with significantly low S. Magnesium level among 16 patients (26.67%) and low serum vitamin B₁₂ level in 4 patients (6.67%). All age groups of patients using long term PPI were equally involved with low serum Mg level, suggesting that age is not a factor influencing S. Mg level in chronic PPI users (figure-1). Whereas, low S. Vit B₁₂ levels are found in older aged patients with chronic PPI use. From our study it was found that Low serum vitamin B₁₂ was

![Figure-1: Age Distribution of low serum magnesium and low serum vitamin B₁₂ level](#)

**Table 1:** Demographic data of long term PPI users in relation with low serum magnesium and low serum vitamin b12 level.
Serum Vitamin B12 (vit B12) and Serum Magnesium

Our cross-sectional study revealed significantly lower serum Mg level and serum Vit B12 level in long term PPI users and it implies that long-term use of PPIs could be associated with subclinical Mg and vit B12 insufficiency or deficiency status. Hypomagnesaemia was seen irrespective of duration and age of long term PPI use, however low vit B12 was found in older individuals after more prolonged use. Our study also revealed that since different types of PPIs were involved with hypomagnesaemia, collectively we could conclude that it was a class effect of all types of PPIs. Future studies that include non PPI users as a control group and other prospective studies that include pre-treatment and post-treatment S. Mg and S. Vit B12 levels when initiating PPI therapy will provide more direct evidence for the association of PPIs with S. Mg and S. vit B12 levels and shall clarify its underlying mechanism(s) involved. Limitations of our study were: Sample size was small, duration of study was short, and serum levels of magnesium and vit B12 were not recorded prior to the study.

REFERENCES


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