IJBPAS, December, 2015, 4(12): 6724-6732

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

THE PREVALENCE OF HYPOMAGNESEMIA IN GASTROESOPHAGEALREFLUX DISEASE(GERD) PATIENTS TAKING APROTON PUMP INHIBITOR(PPI) IN ISFAHAN, IRAN,CASE-CONTROL STUDY

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ABSTRACT

Introduction: Proton pump inhibitors (PPI) have several adverse effects such as hypomagnesemia inlong-termuse,we decided to analyze the relationship between serum magnesium level and taking of this group of drugs. **Materials and methods**: This case-control study was carried out on a number of 160 subjects (case n= 80, control n= 80). The case group consisted of 80 patients taking a PPI and the control group consisted of 80 healthy subjects who didn't takea PPIand magnesium-rich supplements. Serum magnesium level in these two groups was measured, the data was transferred to a computer and was analyzed using SPSS Software version 21. **Results**: Based on the results of this study, the prevalence of hypomagnesemia in control and case subjectswere 2 persons (2.5%) and 10 subjects (12.5%) respectively, which was statistically significant (P<0.05). There was no significant relationship between age,sex, and

duration of PPI use with reducing of serum magnesium level in the groups (P>0.05). **Conclusion:**This study showed that taking a PPI in GERD Patientsis associated with increasing risk of hypomagnesemia and these patients should be regularly evaluated in terms of hypomagnesemia and be treated if necessary.

Keywords: Proton pump inhibitor, hypomagnesemia, gastroesophageal reflux disease

INTRODUCTION

Proton pump inhibitors (PPI) reduce gastric acid secretion by inhibiting the proton pump in the parietal cells of stomach and this property is used for treatment of gastroesophageal reflux disease (GERD), Zollinger–Ellison Syndrome (ZES),and along with antibiotics for eradication of Helicobacter pylori (H. pylori). Recently, there are 6 drugs in this group of drugs which consist of the following: omeprazole, esomeprazole, dexlansoprazole , pantoprazole, lansoprazole, and rabeprazole (1).

PPI with short-term use causes few side effects. However, using a PPI for long period of timecauses side effects such as: reduction ofvitamin B12 serum level(2), increased risk of bone fractures(3), infections (including: clostridium difficile infection(4), pneumonia(5), etc.), hypomagnesemia(6,7) and etc.

Magnesium is rich in green vegetables, fruit, fish, cereals, grains, nuts, and chocolate. Magnesium, as an auxiliary factor, plays an important role in the body's biological activities. Many physical activities are dependent on enzymes in which magnesium acts as an auxiliary substance and the lack of this element can cause muscle spasm, cardiovascular diseases, diabetes mellitus, hypertension, neurological disorders, migraine, and osteoporosis (8-10).

Due to the hypomagnesemia with taking a PPI and the lack of conducted studies related to hypomagnesemia and taking of this group of drugs in Iran, we decided to study about prevalence of hypomagnesemia in GERD Patients Taking a PPI, so that through diagnosis of hypomagnesemia proper treatment can be applied. As a result, fatal outcome of hypomagnesemia can be prevented in these patients.

MATERIALS AND METHODS

This research was a case-control study which approved by Ethics Committee of Islamic Azad University, Najaf Abad Branch, from April 2014 until July 2015, in Dr.Shariati Hospital (Isfahan, Iran), on the patients with GERD. The number of this case study divided into two groups those are called case

and control groups and these subjects agreed to participate in this study. The subjects in the case groupwere patients with GERD takinga PPI group of drugssuch as omeprazole, pantoprazole and etc. The subjects in the control group were selected among the healthy persons those are not suffering from GERD and not taking magnesium-rich supplements as well.

The inclusion criteria were the persons with GERD who had used the PPI group of drugs for more than six months and were not suffering from other causes of hypomagnesemia such as: acute and chronic diarrhea, steatorrhea, mal absorption, small intestinal bypass surgery, uncontrolled diabetes, hypercalcemia, thiazide diuretics, nephrotoxics (aminoglycosides, amphotericin B, cisplatin, pentamidine, cyclosporine), dysfunction of in the loop of Henle and the distal tubule, etc. Moreover, the patients who have not done the measurement of serum magnesium level were excluded from the study.

The sample size is required for this study, by the means of sample size estimation formula for comparison of the averages that are mentioned below and by considering 95% confidence level, 80% minimum power of study and standard deviation of serum magnesium level in healthy persons which was equals 2 and the difference minimum between the two groups which was considered as 0.8 and also by considering the sample size of similar previous studies was estimated as 80 persons in each group.

The sampling method in this study was simple random sampling method and the subjects in the sample were selected among the patients referring to the internal clinic of Dr. Shariati Hospital in Isfahan.

In this study, 160 subjects who were divided into two groups of 80 (case and control groups) were selected. The researcher asked the studied subjects about their age, gender and taking aPPI group of drugs (name, dosage and duration of use). The researcher introduced both groups to Dr.Shariati Hospital Laboratory, in a fasting state, in order to measure the serum magnesium level. The selected method for measurement of magnesium in our study is the Xylidyl blue in alkaline environment with photometric method with the kit of Pars Azmun Company. Normal serum magnesium level in our study was considered as 1.7-2.1 mg/dl (11,12). Hypomagnesemia refers to people's serum magnesium level less than 1.7 mg/dl.

The demographic data including age, sex, prescribed PPI group of drugs (name, dosage and duration of use) and serum magnesium

level were provided in a special form in this purpose.

Subsequently, the data of the studied subjects was entered in Excel program and was eventually entered in SPSS program version 21, and it was analyzed by using $\chi 2$ and t tests and Pearson correlation. the p-value less than 0.05 was considered as statistically significant. In addition, the data of the studied subjects was entered in the data collection forms without mentioning their names and it remained protected by the researchers. The researchers were committed to the principles of the Helsinki Convention in all the stages of this research.

FINDINGS AND RESULTS

174 subjects participated in this study and 14 subjects (10 subjects in the control group and 4 subjects in the case group) were excluded from the study due to lack of measurement ofserum magnesium level and the number of 80 subjects were entered into the case group and the number of 80 were entered into the control group in this study.

In this study, among 160 individuals, 39 subjects (24.4%) were male and 121 subjects (75.6%) were female, and the age average was 44.9±15.8 years,and the age range was 16-85 years. Serum magnesium level of the subjects under study was 2±0.2 mg/dland the range of serum magnesium levelwas 1.1-2.64mg/dl,and 12 persons (7.5%) (Two in the control group and 10 in the case group) had hypomagnesemia and 148 persons (92.5%) had normal serum magnesiumlevel.

In the case group, 20 subjects (25%) used a dose of 20 mg ofomeprazole and 60 persons (75%) used a dose of 40 mg of pantoprazole. In this study, there was no statistically significant difference in terms of age and sex, between the control and case groups; but the prevalence of hypomagnesemia in the case group was more than the control group which was statistically significant (P=0.016). The demographic and biochemical features of the groups have been shown in table-1. Serum magnesium levels of the groups have been shown in diagram-1.

Based on Pearson correlation test, there was no statistically significant difference between the duration of taking a PPI (21.03±25.9 months) and the serum magnesium level(2.0±2 mg/dl) (P=0.696).

In the case group, the duration of used PPI was 24.3±27.3 months in the subjects with hypomagnesemia and 18.9±11.6 months in the subjects with normal serum magnesium level, and based on the t-test there was no statistically significant difference between the duration of used aPPI and serum magnesium level (p=0.624).

DISCUSSION

As the gastroesophageal reflux is one of the most common gastrointestinal diseases and PPIs are the most common groups of used drugs for treatment of this disease, they quickly improve the symptoms.

Short term of taking a PPIcauses few adverse effects. However, their long-term usage brings adverse effects such as: reduction of vitamin B12 serum level, the increasedrisk of fractures in the hip, the wrist and the spine, cardiac events, infections (clostridium difficile infection, pneumonia and etc.), hypomagnesemia and etc.

Magnesium balance is a function of intake and excretion. The average daily magnesium intake is 360 mg. About one-third of this element is absorbed principally in the small bowel through both a saturable transport system and passive diffusion.Two other processes occur in the gut: the secretion of approximately 40 mgin intestinal secretions; and the absorption of another 20 mgin the colon. In the healthy adult, there is no net gain or loss of magnesium from bone so that balance is achieved by the urinary excretion of the approximately 100 magnesiumthat is absorbed. Changes in intake are balanced by changes in urinary magnesium reabsorption, principally in the loop of Henle and the distal tubule.

Thepresumed mechanism of omeprazole is not at the level of the kidney since urinary magnesium excretion is appropriately low in such patients. Some patients have inappropriately low serum parathyroid hormone levels. It seems that low stomach PH is important for absorption of minerals. Metal ions are connectedwith the binding positions on diet fibers and may be replaced by hydrogen ions and facilitate re-absorption. The acid materials that enter the small intestine through the stomach help mineral salts to remain as a solution until they are absorbed. Omeprazole causes hypochlorhydria which can, theoretically, causeminerals deficiency although there is no evidence indicating that the use of omeprazole can inhibit the absorption of magnesium at least in the short-term.Although,its mechanism is not fully known, there is no doubt that the long-term use of omeprazole can be considered as a possible factor of hypomagnesemia (13-15).

Based on the results of this study, the average serum magnesium level in the case group was significantly less than the control group, and these results were same as the results Epstein et al and, Tamura et al (16), Matsuyamaet al (17), and Hess et al(18) studies. Due to the number of 12.5% prevalence of hypomagnesemia in the group

taking a PPIin this study, it can be said that hypomagnesemia is common among these patients.

In a study by Khosravi et al and Kim et al showed that less than one year of PPI use and will not cause hypomagnesemia but in studies by Hoorn et al (20) and Mackay et al (21) had reported the drop in serum magnesium level in patients who had used a PPI for more than a year.Food and Drug Administration (FDA) suggested that measurement of serum magnesium levels prior to initiation of PPI therapy and periodically during treatment in patients expected to be on PPIs for long periods of time (7) .In this study, no significant relationship was obtained between the duration of PPI use and the serum magnesium level. Moreover, the small sample size in our study might have led to the insignificance of this relationship and with the increase of the sample size, a significant relationship can be found between the duration of a PPI use and the serum magnesium level.

One of the strengths of this study has been done in Isfahan for the first time but the weakness of the study, comparison of hypomagnesemia in different kinds of a PPI group of drugs and different dosages of these drugs, has not been analyzed in this study and should be considered in subsequent studies.

CONCLUSION

This study showed that hypomagnesemia following the use ofa PPI group of drugs is common and the subject taking these drugs are recommended to use magnesium-rich foods and the serum magnesium level should be measured in them and they should be treated in case of hypomagnesemia as a result, fatal outcome of hypomagnesemia can be prevented in these patients.

ACKNOWLEDGMENT

We sincerely thank all patients participating in this study because it would be impossible without their cooperation. This research was supported by Najaf Abad Islamic Azad University.

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Table 1: The demographic and biochemical features of the groups

Variable		Groups frequency(%)		Groups Mean(±Standard Deviation)		p-value*
		case	control	case	control	
Sex	Male	18(22.5)	21(26.3)			0.58
	Female	62(77.5)	59(73.7)			
Age(year)				49.53±15.7	40.45±14.82	0
Serum Magnesiumlevel(mg/dl)				1.95±0.2	2.05±0.2	0.019
Hypomagnesemia	Yes	10(12.5)	2(2.5)			0.016
	N0	70(87.5)	78(97.5)			

***p-value less than 0.05 was considered as statistically significant.**

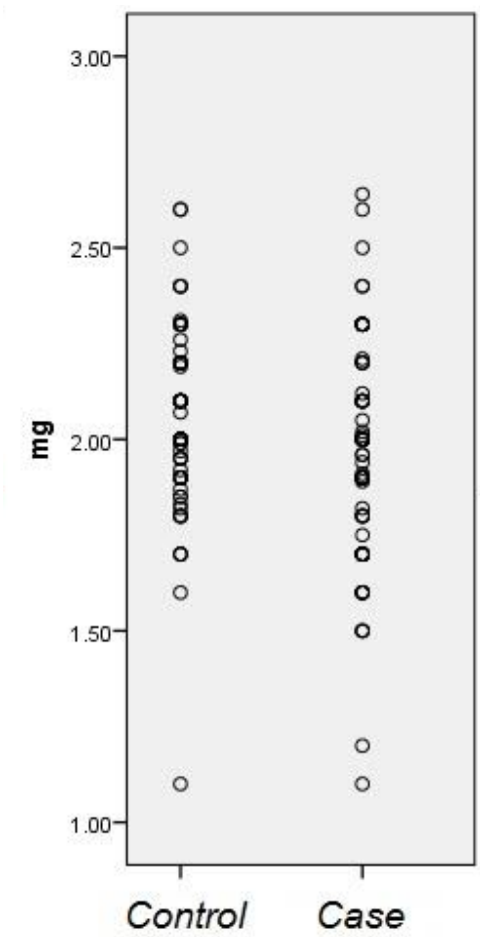

Diagram1: Serum magnesium levels of the groups.