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Original Article

Changes in serum magnesium concentration after use of a proton pump inhibitor in patients undergoing percutaneous coronary intervention

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Abstract

Background: Although cross-sectional studies have suggested a relationship between proton pump inhibitor (PPI) use and hypomagnesemia, no large-scale cohort study has been conducted to date. Here, we examined the changes in serum magnesium levels in response to PPI use. We hypothesized that PPI use might change the serum magnesium concentration.

Methods: Of the 2,892 patients hospitalized for percutaneous coronary intervention between January 2007 and May 2012, 1,076 patients with normal baseline (1.6–2.5 mg/dL) and follow-up serum magnesium concentrations were enrolled. These patients were divided into two groups: the PPI group and the control group.

Results: The mean follow-up period was 9.51 ± 2.94 months. The incidence of hypomagnesemia (< 1.6 mg/dL) was 0.4% (3/834) in the PPI group and 0.4% (1/242) in the control group ($P = 0.904$). The change in magnesium levels did not differ between the two groups, and this result was maintained in the analysis of covariance after adjusting for confounding factors ($P = 0.381$). Moreover, magnesium levels did not significantly differ between the long-term (duration of use ≥ 12 months, $n = 71$) and short-term PPI groups (duration of use < 12 months, $n = 763$), and the control group ($n = 242$; $P = 0.620$). The effect of PPI use on change in serum magnesium concentration was affected by the use of multiple diuretics (-0.01 ± 0.25 mg/dL; $P = 0.025$), although a single diuretic use with PPI did not alter the change in magnesium level (0.12 ± 0.27 mg/dL).

Conclusion: Changes in magnesium levels might be subtle after PPI use in patients with normal baseline magnesium values.

Introduction

Magnesium is the second most common intracellular cation and is involved in a wide range of cellular functions, including protein synthesis, enzymatic reactions, and the regulation of ion channels. Significantly low serum magnesium levels have been associated with bradycardia, hypotension, seizures, tetany, and death [1,2].

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Proton pump inhibitors (PPI) are widely used worldwide. They have been associated with a wide variety of side effects including renal failure, respiratory infections, *Clostridium difficile* colitis, and hip fractures [3–7]. There have been several case reports and case series of PPI-induced hypomagnesemia (PIH) with a wide array of symptoms, including cardiac arrhythmias and seizures [8–13]. A common characteristic of PIH might be the long-term use of PPIs (> 1 year duration) and the presence of severe hypomagnesemia. If the long-term use of PPIs could decrease the serum magnesium level, PPI use might be a risk factor in patients with coronary heart disease. Serum magnesium levels might be particularly important in patients with coronary heart disease who are taking PPIs.

Although some cross-sectional studies have suggested that PPI use could be related with hypomagnesemia [14–17], there was a lack of causal relation between PPI use and hypomagnesemia.

To address these questions, we examined the change in serum magnesium level after use of PPI in a retrospective cohort of 1,076 patients, who underwent percutaneous coronary intervention (PCI) in a tertiary medical center.

Methods

Study population

The study population consisted of all patients undergoing PCI from January 2007 to May 2012 at the Soonchunhyang University Cheonan Hospital, Korea.

Our exclusion criteria included the following: patients without follow-up magnesium data, baseline magnesium < 1.6 mg/dL, baseline magnesium > 2.5 mg/dL, hemodialysis patients, estimated glomerular filtration rate (GFR) of < 15 mL/min/1.73 m^2, and patients who were prescribed laxatives including magnesium or histamine-2 receptor antagonist. Baseline magnesium level was measured at admission to undergo PCI, and follow-up magnesium level was measured at readmission for follow-up coronary angiography or cardiac event. During this time, the patients taking PPIs were assigned to the PPI group. Blood sampling was carried out before the intravenous fluid therapy.

To investigate PPI use in relation to change in magnesium levels, patients were divided into groups (Fig. 1). First, patients were divided into the PPI group and the control group (those who did not use PPIs). Second, the PPI group was further divided into the short-term PPI group (duration of use < 12 months) and the long-term PPI group (duration of use ≥ 12 months). The Institutional Review Board of Soonchunhyang University Cheonan Hospital approved this study.

Study variables

To investigate the prescription of PPIs, details on duration of use and type were obtained. Using a dose conversion factor, a daily omeprazole equivalent dose was also calculated when the daily PPI dose was documented. In brief, a 20-mg oral dose of omeprazole was considered to have an equivalent therapeutic efficacy to 20 mg esomeprazole, 30 mg lansoprazole, 40 mg pantoprazole, and 20 mg rabeprazole. PPI intensity was defined as equivalent dose multiplied by duration (months) of PPI use.

To improve clinical relevance, several covariates of interest were collected: age, sex, diabetes mellitus, history of diuretics use, and selected laboratory variables (serum creatinine, calcium, albumin, potassium) obtained at the time of hospital admission or, if they are missing, within the 1st day of hospitalization. The GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation [18].

Statistical analysis

Data are presented as the mean ± standard deviation for continuous variables and frequency (in percent) for the categorical variables. The difference between groups was compared using the Student *t* test or analysis of variance for continuous variables and a Chi-square test for categorical variables. The effects of PPIs on changes in serum magnesium level were analyzed using analysis of covariance (ANCOVA), with the PPI group as the main factor, and adjusting for factors influencing the

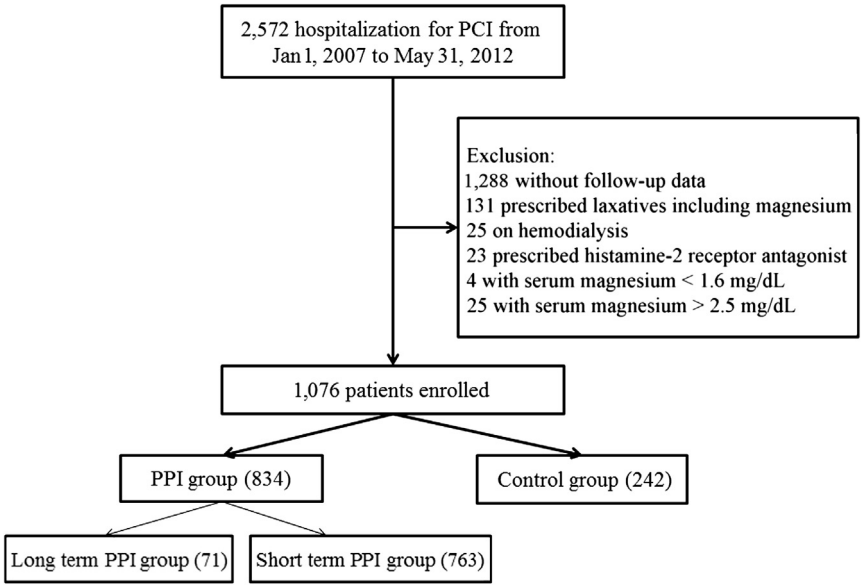

Figure 1. The flowchart illustrates the patients' inclusion and exclusion in this study. PCI, percutaneous coronary intervention; PPI, proton pump inhibitor.