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Original Investigation

Proton Pump Inhibitors and Hypomagnesemia in the General Population: A Population-Based Cohort Study

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Background: Proton pump inhibitor (PPI) use has been associated with hypomagnesemia in case reports and hospital-based cohort studies. Our objective was to determine whether PPI use is associated with hypomagnesemia in the general population and whether this is also found in histamine 2 receptor antagonist (H2RA) users.

Study Design: Prospective cohort study.

Setting & Participants: 9,818 individuals from the general population (Rotterdam Study).

Predictor: PPI use and H2RA use compared to no use.

Outcomes & Measurements: Serum magnesium and hypomagnesemia (serum magnesium ≤ 1.44 mEq/L). Analyses were adjusted for age, sex, body mass index, kidney function, comorbid conditions, and alcohol and diuretic use.

Results: Serum magnesium level was 0.022 mEq/L lower in PPI users (n = 724; 95% CI, −0.032 to −0.014 mEq/L) versus those with no use. PPI use was associated with increased risk of hypomagnesemia (n = 36; OR, 2.00; 95% CI, 1.36-2.93) compared to no use. Effect modification was found between the use of PPIs and loop diuretics; in participants using loop diuretics (n = 270), PPI use was associated with a further increased risk of hypomagnesemia (n = 5; OR, 7.22; 95% CI, 1.69-30.83) compared to no use. The increased risk with PPIs was only seen after prolonged use (range, 182-2,618 days; OR, 2.99; 95% CI, 1.73-5.15). Including dietary magnesium intake into the model did not alter results (available for 2,504 participants, including 231 PPI users). H2RA users (n = 250) also had a lower serum magnesium level (−0.016 [95% CI, −0.032 to −0.002] mEq/L) and increased risk of hypomagnesemia (n = 12; OR, 2.00; 95% CI, 1.08-3.72) compared to those with no use, but no interaction with loop diuretics.

Limitations: Cross-sectional analysis with single serum magnesium measurement.

Conclusions: PPI use is associated with hypomagnesemia in the general population. Prolonged PPI use and concomitant loop diuretic use are associated with a stronger risk increase. Similar but weaker associations were found in H2RA users, except for interaction with loop diuretics.

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INDEX WORDS: Epidemiology; proton pump inhibitor (PPI); acid-suppressive medication; hypomagnesemia; magnesium; intestinal magnesium loss; diuretics; histamine 2 receptor antagonist (H2RA); TRPM6; drug safety; population-based cohort; Rotterdam Study.

Proton pump inhibitors (PPIs) are currently the main therapy for gastroesophageal reflux disease, peptic ulcer disease, non-ulcer dyspepsia, and prevention of gastropathy with the use of nonsteroidal anti-inflammatory drugs.[1] The broad spectrum of indications and the favorable safety profile have made them one of the most frequently used pharmaceuticals.[1,2] Because of their widespread and often long-term use, the safety of PPIs has received attention since their first introduction. Since 2006, cases of severe hypomagnesemia have been reported in association with the use of PPIs, sometimes accompanied by secondary hypokalemia and hypocalcemia.[3] Severe hypomagnesemia may result in tetany, convulsions, or cardiac arrhythmias.[4] Although mild hypomagnesemia is often asymptomatic, it may still be relevant because population studies have shown that even mild hypomagnesemia is associated with increased risk of diabetes mellitus,[5] osteoporosis,[6] cardiovascular disease,[7,8] and mortality.[9] Cases of severe hypomagnesemia have not been reported with the use of histamine 2 receptor antagonists (H2RAs), although a recent study showed that their long-term use is also associated with hypomagnesemia.[10]

At present, the evidence for the association between PPI use and hypomagnesemia is based on case

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reports (for review, see[1]), 6 studies in hospitalized patients,[2,11-15] and 1 study in ambulatory patients.[10] The latter study was important because of its size (95,000 participants) and the suggestion that PPI-induced hypomagnesemia also occurs in the community. Our objective was to analyze the association between PPI use and risk of hypomagnesemia in a population-based cohort with systematic measurements of serum magnesium. We also analyzed whether prolonged duration of PPI use and concomitant diuretic use were associated with increased risk of hypomagnesemia. Finally, we also assessed the association between the use of H2RAs and hypomagnesemia.

METHODS

Study Design, Setting, and Population

This cross-sectional analysis was performed within the Rotterdam Study, a prospective population-based cohort that started in 1990. The first cohort comprised 7,983 persons older than 55 years living in a suburb of the city of Rotterdam, the Netherlands. Starting in 2000, the first cohort was extended with a second cohort of 3,011 persons (aged ≥ 55 years). In 2006, the cohort was extended again with a third cohort of 3,932 persons (aged ≥ 45 years) living in the research area who had not yet been included. Follow-up examinations were conducted periodically. We used the third visit of the first cohort, with 4,797 remaining participants, and baseline visits of the second and third cohorts. These visits were identical in design. All 11,740 eligible participants gave written informed consent to participate in the study and to obtain information from their treating physicians. All participants underwent the same examinations and had identical blood measurements. Detailed information for design, objectives, and methods of the Rotterdam Study are described elsewhere.[16] The Rotterdam Study complies with the Declaration of Helsinki and has been approved by the Medical Ethics Committee of the Erasmus Medical Center and by the Dutch Ministry of Health, Welfare and Sport, implementing the "Wet Bevolkingsonderzoek: ERGO (Population Study Act: Rotterdam Study)."

Measurement of Serum Magnesium

Of 11,740 eligible participants, serum magnesium was available for 9,883, of whom 56 did not give consent to use their pharmacy data, we were unable to retrieve prescription data for 2 participants, and 7 were excluded because of combined use of PPIs and H2RAs. The study population therefore consisted of 9,818 participants. Serum magnesium was measured in all participants at the same time by the Department of Clinical Chemistry of the Erasmus Medical Center using a Roche/Hitachi Cobas c501 analyzer. The cutoff for hypomagnesemia was determined by calculating the mean minus 1.96 standard deviation in participants who did not use acid-suppressive medication, which resulted in a cutoff of 1.44 mEq/L.

Assessment of Medication Use

We used data from visits from 1997 through 2008 because PPI use became more widespread during this period and PPIs were not sold over the counter in this period in the Netherlands. Drug exposure has been monitored continuously since January 1, 1991, through computerized pharmacy records of all outpatient-filled prescriptions within the pharmacies in the district.[17] For each participant, the prescription period was calculated by dividing the total number of dispensed tablets per prescription by the prescribed daily number. Repeat prescriptions that were filled within 7 days after ending a previous one were considered as one single episode of continual use. If the date of serum magnesium measurement was within the prescription period, the participant was classified as being exposed. Cumulative prescription days could also be determined on the basis of this method. Dosage was expressed as standardized "defined daily doses" according to the definition of the World Health Organization.[18] In addition to prescription drugs, we also had interview data for self-reported use of vitamin and mineral supplementation (including magnesium) for 9,282 participants.

Assessment of Dietary Magnesium Intake

Daily magnesium intake was available for a subgroup of 2,504 participants, of whom 2,246 participants did not use acid-suppressive medication, 231 used PPIs, and 27 used H2RAs. Daily magnesium intake was assessed by using an extensive semiquantitative food frequency questionnaire.[19-21] Dietary energy and magnesium intake were calculated using the Dutch Food Composition Table.[22] Energy-adjusted magnesium intakes were computed as the unstandardized residuals from a linear regression model in which total caloric intake served as the independent variable, and absolute nutrient intake, as the dependent variable. Because residuals have a mean of zero and thus include negative values, the predicted mean magnesium intake of the study population (300 mg/d) was added to the residuals.[23]

Assessment of Covariables

Assessment of anthropometrics in the Rotterdam Study was described previously.[16] We defined diabetes mellitus as fasting serum glucose level ≥ 126.1 mg/dL, nonfasting serum glucose level ≥ 200 mg/dL (only if fasting serum was unavailable), or use of oral blood glucose-lowering drugs or insulin. Body mass index was calculated as weight in kilograms divided by squared height in meters. Information for prevalent stroke and coronary heart disease was determined on the date that blood was drawn from participants and obtained through linkage with general practitioners working in the study area and adjudicated by medical doctors and a neurologist and cardiologist. Blood pressure was measured twice during study visits, and prevalent hypertension was determined on the basis of average systolic blood pressure ≥ 140 mm Hg and/or average diastolic blood pressure ≥ 90 mm Hg or the use of blood pressure–lowering medication. Information for alcohol consumption was obtained during a home interview and categorized as yes or no. Estimated glomerular filtration rate was calculated with calibrated creatinine values using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation and was expressed as milliliters per minute per 1.73 m^2.[24]

Statistical Analysis

Mean ± standard deviation and frequency with percentage were used to report continuous and discrete variables, respectively. One-way analysis of variance and χ^2 tests were used for baseline comparisons. When studying the possible association between PPI use with serum magnesium or hypomagnesemia, H2RA users were excluded from the analysis and vice versa.

We used multivariable linear regression to investigate the association with serum magnesium and multivariable logistic regression to investigate the association with hypomagnesemia. All analyses were performed using a crude model and a model adjusted for age; sex; body mass index; estimated glomerular filtration rate; prevalent diabetes mellitus, stroke, coronary heart disease, and hypertension; alcohol use; and use of thiazide or loop diuretics. Effect modification by diuretic use or diabetes mellitus was tested by inclusion of interaction terms. For significant interactions, analysis was stratified on this potential effect modifier. The effect of duration of use was analyzed by defining 3 different