ORIGINAL ARTICLE

The Association between Omeprazole Dosing and Hypomagnesemia in Patients with Cardiovascular Disorders

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Abstract

Background: Patients with acute coronary syndrome should be treated with proton-pump inhibitors (PPIs) to decrease the gastrointestinal complications and hemorrhage associated with antiplatelets use. Hypomagnesemia associated with PPIs is not confirmed yet but if it is confirmed, it may explain the reason of cardiovascular risks associated with PPIs use. **Aims:** The aims of this study were to determine the association between omeprazole and hypomagnesemia, study the effect of different omeprazole doses in the occurrence of hypomagnesemia, and study the factors that may contribute to this hypomagnesemia. **Methods:** Over a 1-year period, all patients receiving omeprazole for more than 1 year admitted to the cardiac care unit were enrolled in this study. Patients were divided to three groups according to the omeprazole doses. The association between omeprazole dose and the presence of hypomagnesemia was assessed and compared between the three groups. **Results:** A total of 105 patients were enrolled in this study. The mean follow-up duration during hospitalization was 5.2 ± 2.9 days. All factors that may affect the incidence of hypomagnesemia were compared between the three groups and there was not any statistically significant difference between the three groups in relation to patient's age, sex, presence of diabetes mellitus, and concurrent use of digoxin or diuretics. The incidence of hypomagnesemia between the 3 groups was not statistically significant but it was clinically significant. **Conclusion:** The hypomagnesemia associated with omeprazole may be dose related. This hypomagnesemia may explain the occurrence the cardiovascular events (arrhythmias and sudden death) after omeprazole use, but further studies are needed.

Key words: Proton-pump inhibitors, hypomagnesemia, omeprazole, cardiovascular disorders, dosing

INTRODUCTION

Aspirin is considered as the cornerstone in decreasing the cardiovascular complications pre- and post-catheterization and stent placement. Clopidogrel is another antiplatelet that can be added to aspirin in those patients. Gastrointestinal (GI) complications such as gastric ulcer and bleeding are associated with prolonged aspirin use. Clopidogrel also may delay the healing of gastric insult and exacerbating the GI complications after aspirin administration.[1] Patients with acute coronary syndrome (ACS) should be treated with proton-pump inhibitors (PPIs) to decrease the GI complications and hemorrhage associated with antiplatelets use.[2] Recently, many studies found an association between PPIs use and cardiovascular events and death. These studies tried to find the correlation between PPIs and the increased risk of cardiovascular complications especially in patients with ACS.[3-5] One hypothesis was studied by Holmes *et al*. who explained that there is a drug interaction between PPIs and clopidogrel. They concluded that PPIs may compete with clopidogrel and inhibit its activation by CYP2C19. This interaction will decrease the clopidogrel's activity in preventing clotting formation and subsequently increases the coronary thrombosis and myocardial infarction (MI) risks.[6] Other studies revealed the same effects of antiplatelets failure and increase in the coronary thrombosis and MI risks in patients received PPIs and Ticagrelor. These findings oppose the previous one, because Ticagrelor is not activated by CYP2C19.[7,8] Another

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possible explanation was PPIs may decrease the absorption of clopidogrel and Ticagrelor through reducing in the gastric pH.[9] However, this hypothesis was rejected, because H2 blockers also reduce the gastric pH without an increase in cardiovascular risks.[7,8] The mechanisms by which PPIs increase cardiovascular complications still unknown. In 2006, Epstein *et al.* published a report discussing the electrolyte changes of PPIs, they mentioned that omeprazole is associated with hypomagnesemia.[10] Many other case reports were published to confirm the relationship between omeprazole use and hypomagnesemia.[11-15] Their findings include: Hypomagnesemia is associated with prolonged PPIs use, symptoms of hypomagnesemia occur if Mg levels decrease to <0.5 mmol/L, the mechanisms by which this hypomagnesemia occur still unknown, hypokalemia and hypocalcemia may also occur with hypomagnesemia, Mg replacement was effective for temporary relief of symptoms. Cundy and Mackay reported that PPI withdrawal may reverse the hypomagnesemia.[16] Mg deficiency may lead to atherosclerotic lesions, because Mg plays a role in myocardium damage after occlusion of the coronary artery in animal experiments. Human experiments revealed that Mg administration during the first 24 h after Mihas beneficial effect in the mortality rates. Intracellular Mg depletion may be present even if the serum Mg is normal. This observation was determined by muscle biopsy in patients with normal serum Mg levels and evidence of Mg stores depletion. Hypoalbuminemia may also affect the measured Mg levels as one-third of magnesium is bounded to the serum albumin.[17] Mg depletion may affect potassium flow through channels during phase 4 of the action potential.[18] Mg also affects the calcium flow through the sarcoplasmic reticulum, its effect is similar to the Ca – channel blockers.[19] Nowadays, it is confirmed that Mg administration decreases the incidence of arrhythmias and death which enhances the survival in patients with MI.[20] Hypomagnesemia associated with PPIs is not confirmed yet but if it is confirmed it may explain the reason for cardiovascular risks associated with PPIs use. The main objectives of this study are to determine the association between omeprazole and hypomagnesemia, study the effect of different omeprazole doses in the occurrence of hypomagnesemia, and study the factors that may contribute to this hypomagnesemia.

MATERIALS AND METHODS

Design

This was prospective observational evaluation with descriptive analysis.

Setting

The critical care unit (CCU) at Prince Sultan Cardiac Center – Saudi Arabia.

Patients

Over a 1-year period, all patients receiving omeprazole for more than 1 year admitted to the CCU were enrolled in this study. Patients were excluded if there is no follow-up for the magnesium level, receiving laxatives congaing magnesium, or H-2 receptor antagonist.

Patients follow-up

The principle investigator of this study was a clinical pharmacist consultant working in the cardiology center and she was responsible for monitoring CCU patients. During her daily follow-up of the patients, magnesium, potassium, calcium, and serum creatinine levels were assessed and recorded for each patient until the patient's discharge. Hypomagnesemia was defined as any magnesium level <0.8 mmol/L. Omeprazole doses and the use of any other drugs that may cause hypomagnisemia were also recorded and all patients' characteristics that may contribute to the risk of hypomagnesemia were collected. Patients characteristics included were patient's age, gender, the presence of diabetes mellitus, or the use of diuretics and/or digoxin during omeprazole use.

Patients' groups

To study the effect of omeprazole doses on the magnesium levels, patients were divided into three groups:

Group I: All patients prescribed omeprazole 20 mg/day

Group II: All patients prescribed omeprazole 40 mg/day or 20 mg/twice daily

Group III: All patients prescribed omeprazole 40 mg/twice daily

Statistical analysis

Data were presented as the mean ± SD. ANOVA was used to compare between the three groups and $P < 0.05$ was considered statistically significant. SPSS was used (version 18.0, Chicago, IL, USA).

RESULTS

A total of 105 patients were enrolled in this study. The mean follow-up duration during hospitalization was 5.2Â ± 2.9 days. Table 1 shows the patients' demographics. All factors that may affect the incidence of hypomagnesemia were compared between the three groups and there was not any statistically significant difference between the three groups in relation to patient's age, sex, the presence of diabetes mellitus, and concurrent use of digoxin or diuretics. About 76% of patients in Group I had ACS, as shown in Table 1. The incidence of hypomagnesemia associated with omeprazole use is shown in

Table 2, there was not any statistically significant difference between the 3 groups in the incidence of hypomagnesemia but there is clinically significant difference. Table 2 also shows that there is a statistically significant difference between the three groups in the serum creatinine elevation. This means increasing the Omeprazole doses may be associated with hypomagnesaemia and deterioration in kidney functions as presented by serum creatinine elevation. Potassium and calcium serum levels were also monitored, but as shown in Table 2, there was not any statistically significant difference between the three groups. The serum potassium and calcium levels were within the normal ranges in all groups. Figures 1–3 shows the detected serum magnesium levels in the three groups. As shown in these figures, increasing omeprazole doses were associated with an increase in the incidence of hypomagnesemia.

DISCUSSION

As shown in Table 2 and Figures 1–3, omeprazole use is associated with hypomagnesemia. Our findings were consistent with the results of three other studies conducted in the USA, Alhosaini *et al*. conducted a study on 62 hemodialysis patients and concluded that PPIs are associated with hypomagnesemia.[21] El-Charabaty *et al*. also conducted a study on a total of 262 intensive care patients with cardiac arrhythmias and their conclusion was the same as our conclusion.[22] Gau *et al*. study was conducted on 487 inpatients and their conclusion was PPIs use causes hypomagnesemia.[23] The same findings were found by Kim *et al*. in Korea.[24] Many other studies could not confirm the association between PPIs use and hypomagnesemia, Biyik *et al*. conducted a study on a total of 238 outpatients in Turkey and concluded that Mg level was the same between PPIs and Non-PPIs users.[25] The same findings were detected by Faulhaber *et al*. in Brazil,[26] Koulouridis *et al*. in the USA,[27] and Van Ende *et al*. in Belgium.[28] Another case report concluded that severe hypomagnesemia along with hypocalcemia and hypokalemia were associated with prolonged use of PPIs.[10] Hypocalcemia and hypokalemia were not detected in this present study, as shown in Table 2. About 76% of the enrolled patients were receiving loop diuretic (Furosemide) and 29% were receiving potassium sparing diuretics (Spironolactone). The use of diuretics did not affect the incidence of hypomagnesemia associated with omeprazole use in this present study. These findings were comparable with those of William *et al*. in the USA, who conducted a study on a total of 278 outpatients and

Table 1: Patients' demographics that may affect the occurrence of hypomagnesemia

Patients' characteristics	Group I (*n*=63) *n*. (%)	Group II (*n*=27) *n*. (%)	Group III (*n*=15) *n*. (%)	*P*-value (Statistically significant if<0.05)
Age elderly >65 years	24 (38%)	14 (50%)	3 (20%)	0.55
Sex (Male)	51 (81%)	16 (62%)	10 (69%)	0.532
Diabetes mellitus	36 (57%)	12 (44%)	3 (20%)	0.31
Use of digoxin concurrently with omeprazole	14%	11%	20%	0.92
Use of diuretics concurrently with omeprazole				
Furosemide	57%	88%	83%	0.16
Spironolactone	25%	33%		0.82
Underlying Cardiovascular diseases				
Acute coronary syndrome (Angina, STEMI, NSTEMI)	48 (76%)	9 (33%)	3 (20%)	0.018*
Heart failure	15 (24%)	14 (50%)	8 (50%)	0.11
Arrhythmias	9 (14%)	3 (11%)	3 (20%)	0.90

n.: Number, *: Statistically significant

Table 2: Electrolytes and serum creatinine levels of the studied groups

Electrolytes and serum creatinine levels	Group I (*n*=63) Mean±SD#	Group II (*n*=27) Mean±SD#	Group III (*n*=15) Mean±SD#	P-value (Statistically significant if <0.05)
Serum Magnesium mmol/L	0.85±0.16	0.94±0.14	0.97±0.17	0.073*
Serum creatinine µmol/L	117±31	127±51	146±36	0.040*
Serum calcium mmol/L	2.215±0.1321	2.1722±0.071	2.1933±0.1477	0.68
Serum Potassium (mEq/L)	3.9±0.15	3.92±0.19	3.94±0.20	0.94

*: Statistically significant, #: Standard deviation

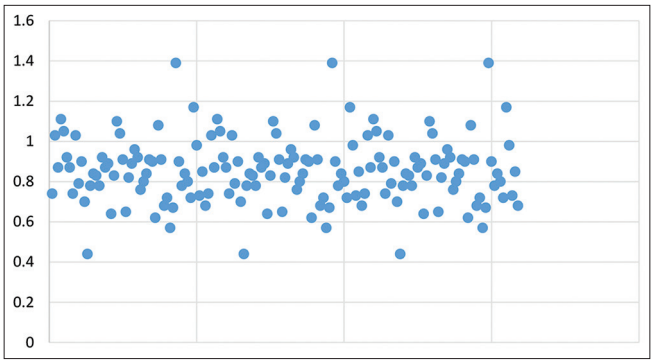

Figure 1: The detected serum magnesium levels (mmol/L) in Group I

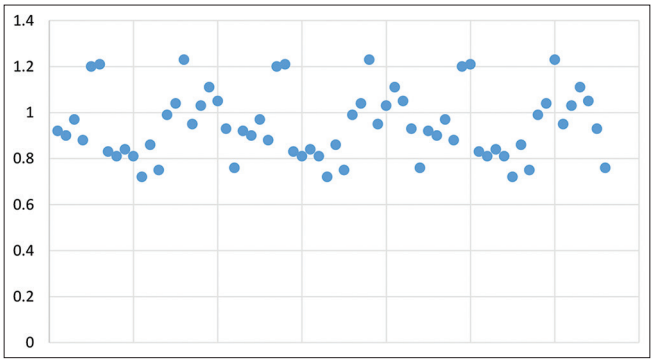

Figure 2: The detected serum magnesium levels (mmol/L) in Group II

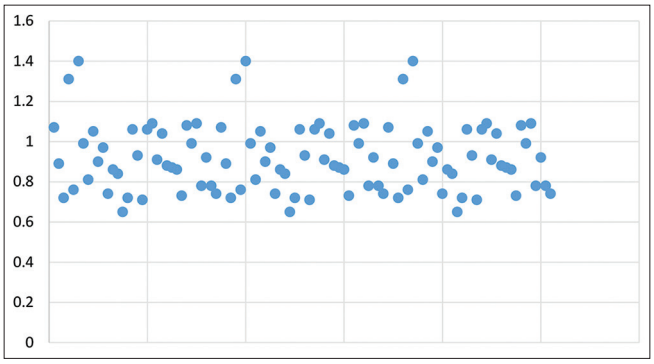

Figure 3: The detected serum magnesium levels (mmol/L) in Group III

concluded that diuretics use will not modify the effect of PPIs on Mg.[29] Different findings were revealed Danziger *et al*.[30] and Lindner *et al*.,[31] who concluded that hypomagnesemia was significantly associated with the use of PPI or both PPIs concurrently with diuretics. The effect of age on the incidence of hypomagnesemia was studied and as shown in Table 1, age did not affect the incidence of hypomagnesemia. Another study conducted by Sumukadas *et al*. on 196 elderly patients, concluded that lower incidence of magnesemia was detected in PPIs users renal dysfunction.[32] Regarding the deterioration in renal functions, Table 2 shows that there is an association between the increase in omeprazole dose and the increase in serum creatinine. Many other studies documented that acute interstitial nephritis[33] and acute kidney injury[34] may occur with prolonged omeprazole use. Another study concluded that PPI use[35] or its associated hypomagnesemia[36] may be a risk factor for chronic renal failure. Up to our knowledge, this is the first study conducted to determine the effect of different omeprazole doses in the occurrence of hypomagnesemia. The patients received omeprazole in three different doses 20mg daily, 40 mg daily and 40 mg twice daily. Another study conducted by Lazarus *et al*. concluded that the risk of hypomagnesemia is higher if PPI is given every 12 h than if it is given every 24 h. Their study design compared the frequency of omeprazole administration, not the total dose/day.[37]

CONCLUSION

Omeprazole use is associated with hypomagnesemia. This hypomagnesemia may be dose related, the incidence of hypomagnesemia was higher with omeprazole dose of 40 mg twice daily. This high dose was also associated with an elevation in the serum creatinine. Hypomagnesemia associated with prolonged omeprazole use may explain the occurrence the cardiovascular events (arrhythmias and sudden death) after omeprazole use. Further studies should be conducted to confirm these findings.

ETHICAL APPROVAL

The study was approved by the research and training center of Prince Sultan Cardiac Center

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