The effect of omeprazole on urinary excretion of magnesium in children with peptic diseases

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Abstract

Purpose: This study aimed to assess the effect of omeprazole on urinary excretion of magnesium in children receiving omeprazole for treatment of peptic disease. What is the effect of omeprazole on urinary fractional excretion of magnesium?

Methods: This single-armed clinical trial study was conducted on 44 children with a diagnosis of acid peptic disease who was treated with omeprazole (1-2 mg/kg/day) for 3 months in Gastroenterology clinics of Imam Hossein hospital, 2021, Isfahan, Iran. Before and after the intervention, serum levels of magnesium and creatinine and urine magnesium and creatinine levels were measured by Pars Azmoon Kit based on the guideline of the kit. Then fractional excretion of magnesium (Mg) was calculated based on the formula.

Results: The mean urinary magnesium levels before and after intervention were 4.96±2.48 and 1.46±0.63, respectively (P<0.001). A significant decrease in serum Mg level was also observed after treatment versus before treatment (1.37±0.03 vs. 1.9±0.2, P<0.01). The mean fractional Mg excretion before and after therapy were 5.2±1.2 and 1.7±0.63, respectively (P<0.01). Serum creatinine level before and after therapy was 0.62±0.19 and 0.67±0.13, respectively (p=0.053). Urinary creatinine level was increased after intervention by 20.80±18.77 (p<0.001).

Conclusion: The cause of hypomagnesemia is not increased urinary loss of magnesium, conversely, the kidney effort to compensate for the drop in blood magnesium following omeprazole treatment, by reducing urinary excretion of it and saving magnesium ions in the body.

What Is Known

- Prolonged consumption of omeprazole can induce hypomagnesemia with unknown pathophysiology.

What Is New

- Fractional excretion of magnesium in urine reduced significantly with prolonged consumption of omeprazole.

Introduction

The acid peptic disease is caused by distinctive, but overlapping pathogenic mechanisms leading to excessive acid secretion or diminished mucosal defense (1). This disease represents a significant cost to healthcare due to its chronicity and relatively widespread prevalence.

Proton pump inhibitors (PPIs) as potent blockers of gastric acid secretion were the most effective therapeutic agents for this disorder (2, 3). The chemical structure of all PPIs is similar and their action is

also identical (4). They are administered in the lipophilic and membrane-permeable forms and inactive pro-drugs (4–6). Then they are absorbed from the small intestine into the blood and accumulated in acidic canaliculi of the parietal cells of the stomach. Here, protonated PPIs induce covalent binding between the PPI and specific cysteine residues of the gastric H+ ,K+ -ATPase (gHK-α) (a responsible enzyme in the secretion of hydrochloric acid by the gastric parietal cell), leading to inhibition of acid secretion (7, 8). Although the use of PPIs is associated with safety, hypomagnesemia is usually manifested after chronic use of PPIs. The causal link between the use of PPIs and the development of hypomagnesemia is demonstrated in patients with PPI-induced hypomagnesemia by a classical challenge–de-challenge–re-challenge protocol which led to the recovery of hypomagnesemia within de-challenge and fast reappearance of hypomagnesemia after re-challenge (9).

Patients with hypomagnesemia show symptoms of severe magnesium (Mg) depletion including convulsions, cardiac arrhythmia, seizures, and tetany (10). In addition, Mg deficiency has been implicated in various diseases such as osteoporosis, Parkinson's disease, asthma, hypertension, and osteoporosis (11).

Given that the prevalence of gastrointestinal diseases such as acid peptic disease in our country is high (4), the most effective therapeutic agents for acid peptic disorders are proton pump inhibitors, the effect of PPIs on Mg homeostasis is controversial (12) and no comprehensive study has been conducted in this regard in our country, this study aimed to assess the effect of proton pump inhibitors such as omeprazole on urinary excretion of Mg in children with the peptic disease.

Methods

This single-armed clinical trial study was conducted on 44 random children with a definitive diagnosis of acid peptic disease who was treated with omeprazole (1-2 mg/kg/day) for 3 months in gastroenterology clinics of Imam Hossein hospital, Isfahan in 2020.

Ethical Consideration

The current study was approved by the Ethical Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1399.953).

Inclusion and Exclusion criteria

Inclusion criteria were long-term treatment with omeprazole for at least 3 months, no liver disease, kidney disease, pancreatitis, diarrhea, and heart disease.

The dissatisfaction of families to continue treatment, the occurrence of side effects or intolerance to the drug, use of drugs that cause hypomagnesemia such as aminoglycosides, amphoteric, digoxin, tacrolimus during taking omeprazole caused those patients to be excluded from the study.

Measurements

Before and after the intervention, serum levels of magnesium and creatinine and urine magnesium and creatinine levels were measured by Pars Azmoon Kit based on the guideline of the kit. Fractional excretion of Mg was calculated based on the formula. Fractional excretion of Mg was calculated as:

$$\frac{U_{Mg} \times P_{Cr}}{(0.7 \times P_{Mg}) \times U_{Cr}} \times 100$$

Statistical analyses

The continued variable was described by mean ± standard deviation (SD) and categorical data was presented as frequency and percentage. Continuous variables were evaluated for normality using the Kolmogorov–Smirnov test. The change score from baseline was calculated for all outcomes. To compare the mean outcome before and after the intervention, paired t-test was used. The comparisons were conducted across gender and age subgroups. P-value < 0.05 was considered significant and all statistical analyses were carried out using IBM SPSS 25.0 (SPSS, IL, USA).

Results

22(50%) patients were female. Patients' age ranged from 4 to 15 years. The mean age was 6.39 ± 4.31, in which 26(56.8%) were six-year-old or less and 19(43.2%) were more than six years old.

Table 1 shows the mean ± SD of the outcome before and after intervention as well as the change from baseline. A significant difference was seen before and after treatment in terms of urinary (4.97 ± 2.49 vs. 1.47 ± 0.63, p < 0.001) and serum levels of Mg (1.92 ± 0.21 vs. 1.37 ± 0.25, P < 0.001). In addition, there was a significant difference before and after intervention regarding fractional Mg excretion (5.11 ± 1.32 vs. 1.64 ± 0.71, P < 0.001).

Serum Creatinine level was not significantly different before and after intervention (0.63 ± 0.19 vs. 0.67 ± 0.13, P = 0.053), while urinary Creatinine level increased after intervention (63.50 ± 15.71 vs. 42.70 ± 14.95, P = 0.001)

Table 1
Urinary and serum levels of Mg, fractional Mg excretion, serum and urinary Creatinine levels in 44 patients with peptic diseases

	before	after	change from baseline	r [c]	P [b]
Random Urinary Mg	4.97 ± 2.49[a]	1.47 ± 0.63	-3.50 ± 2.38	.296	< 0.001
Serum Mg	1.92 ± 0.21	1.37 ± 0.25	-0.55 ± 0.27	.319	< 0.001
Serum Creatinine	0.63 ± 0.19	0.67 ± 0.13	0.04 ± 0.14	.675	0.053
Urinary Creatinine	42.70 ± 14.95	63.50 ± 15.71	20.80 ± 18.77	.251	< 0.001
Fractional Mg excretion	5.11 ± 1.32	1.64 ± 0.71	-3.47 ± 1.17	.468	< 0.001

[a] Mean ± SD, [b] paired t-test, [c] Pearson correlation coefficient.

Table 2 shows the mean outcome before and after intervention as well as the change from baseline by gender groups. The change from baseline for all outcomes was the same for both males and females (P > 0.05).

Table 3 shows the mean outcome before and after intervention as well as the change from baseline by age group. The change from baseline for all outcomes was the same in both age groups for all outcomes (P > 0.05) except random urinary Mg. The reduction of urinary Mg was higher in children aged ≤ 6 years compared with > 6 years (-4.31 ± 2.53 vs. -2.43 ± 1.69, P = 0.008).

Table 2
Mean ± SD outcome before and after intervention and change from baseline in terms of gender

		female (n = 22)	male (n = 22)	p
Random Urinary Mg	before	5.00 ± 2.50	4.94 ± 2.53	
	after	1.44 ± 0.63	1.50 ± 0.64	
	Change	-3.55 ± 2.48	-3.44 ± 2.33	0.879
Serum Mg	before	1.91 ± 0.20	1.92 ± 0.23	
	after	1.34 ± 0.22	1.40 ± 0.28	
	Change	-0.57 ± 0.27	-0.52 ± 0.27	0.510
Serum Creatinine	before	0.65 ± 0.21	0.60 ± 0.18	
	after	0.70 ± 0.14	0.64 ± 0.12	
	Change	19.09 ± 19.21	22.50 ± 18.61	0.553
Urinary Creatinine	before	41.82 ± 17.25	43.59 ± 12.60	
	after	60.91 ± 17.19	66.09 ± 13.99	
	Change	19.09 ± 19.21	22.50 ± 18.61	0.553
Fractional Mg excretion	before	5.52 ± 1.30	4.71 ± 1.23	
	after	1.82 ± 0.85	1.46 ± 0.49	
	Change	-3.70 ± 1.22	-3.24 ± 1.09	0.201
[a] Paired t-test t				

Table 3
Mean ± SD outcome before and after intervention and change from baseline in terms of gender

		≤ 6 years (n = 25)	> 6 years (n = 19)	P[a]
Random Urinary Mg	before	5.85 ± 2.66	3.80 ± 1.67	
	after	1.54 ± 0.59	1.37 ± 0.68	
	Change	-4.31 ± 2.53	-2.43 ± 1.69	0.008
Serum Mg	before	1.90 ± 0.21	1.94 ± 0.21	
	after	1.33 ± 0.25	1.43 ± 0.25	
	Change	-0.58 ± 0.26	-0.51 ± 0.28	0.397
Serum Creatinine	before	0.51 ± 0.13	0.79 ± 0.15	
	after	0.62 ± 0.11	0.75 ± 0.12	
	Change	20.12 ± 18.40	21.68 ± 19.71	0.788
Urinary Creatinine	before	42.84 ± 16.96	42.53 ± 12.26	
	after	62.96 ± 14.60	64.21 ± 17.45	
	Change	20.12 ± 18.40	21.68 ± 19.71	0.788
Fractional Mg excretion	before	5.17 ± 1.13	5.03 ± 1.56	
	after	1.66 ± 0.65	1.62 ± 0.80	
	Change	-3.51 ± 1.02	-3.41 ± 1.36	0.781
[a] Paired t-test				

Discussion

The current study was conducted to assess the effect of omeprazole on urinary excretion of magnesium and fractional Mg excretion in children with peptic diseases and observed that there was a significant difference before and after treatment regarding fractional Mg excretion. In this regard, fractional Mg excretion was significantly decreased after omeprazole therapy. William et al. assessed the effect of the proton-pump inhibitor on fractional excretion of magnesium and demonstrated that proton-pump inhibitor use was associated with lower fractional excretion of urinary magnesium (13). Kuipers et al. demonstrated hypomagnesemia due to the use of proton pump inhibitors and reported that fractional magnesium excretion was low (3). The findings of both studies were consistent with our study. Moreover, the urinary Mg level was significantly reduced after the intervention. Moreover, the level of serum magnesium was significantly reduced in patients after intervention. William et al. reported that the mean daily urinary magnesium in PPI users and the non-PPI user was 84.6 ± 42.8 and 101.2 ± 41.1, respectively

(p = 0.01), indicating the reduction of urinary magnesium level in PPI users. The finding of this study was consistent with our study (13). Lameris et al. evaluated the effect of omeprazole on plasma level of Mg in rat models and observed that administration of omeprazole for 4 weeks in rat models had no effects on the plasma level of Mg (10). Faulhaber et al. assessed the effect of proton-pump inhibitors on serum Mg levels and observed no difference between the mean serum Mg level of PPI users and non-users (14). It seems that the reason for the difference between both studies and the current study was related to duration and different doses of omeprazole use. Famouri et al. assessed the effect of omeprazole in the treatment of gastroesophageal reflux disease and observed a decreased serum level of magnesium. This finding was consistent with the current study (15). Furthermore, they reported that the reduction of serum magnesium could affect the serum level of calcium and induce secondary hypocalcemia (15). Other studies also demonstrated severe hypomagnesemia as a side effect of PPIs in chronic users (16, 17). It seems that hypomagnesemia may be due to congenital defects in magnesium metabolism (14). Previous studies demonstrated that PPIs may affect passive Mg absorption in the small intestine (18–20) and induce magnesiotropic gene expression in mouse colon. Ortega et al., in another study, demonstrated 9 cases of severe hypomagnesemia in patients receiving omeprazole and reported that hypomagnesemia induced by omeprazole was due to deficient absorption of magnesium in the bowel and imbalance between active and passive transport in the intestinal lumen. It is assumed that impaired active transport occurred in patients with proton pump inhibitors due to intestinal pH changes (20). Hess et al. demonstrated the proton pump inhibitor-induced hypomagnesemia after 5.5 years of PPI use (12) and discontinuation of PPIs led to fast recovery within 4 days and re-challenge led to reoccurrence within 4 days. Cundy et al. demonstrated that the severe hypomagnesemia induced by long-term users of proton-pump inhibitors indicated a failure in the absorption of intestinal magnesium (16, 17). Macay et al. reported that the serum level of Mg should be checked annually in patients receiving long-term PPI therapy (21) and it can be partially compensated by a high dose of oral magnesium supplementation (16, 17). Another study also reported that histamine-2-receptor antagonists were the preferable alternative therapy in PPI-induced hypomagnesemia and prevented the reoccurrence of hypomagnesemia (12).

Moreover, serum creatinine level was increased after omeprazole therapy in the current study. Urinary creatinine level was also significantly increased after intervention treatment. Guedes et al. assessed the effect of omeprazole on the risk of chronic kidney disease and observed an association between the progression of chronic kidney disease and omeprazole use indicating a higher risk of chronic kidney disease among omeprazole users (22). Myers et al. assessed the effect of omeprazole in the treatment of acid-peptic disorder and observed that the use of omeprazole increased serum creatinine concentration(23). Therefore, the finding of this study indicated that omeprazole administration was associated with serious adverse effects such as renal failure. Varallo et al. also reported that treatment of digestive disorders with omeprazole increased serum creatinine levels and may contribute to kidney impairment development (24). Therefore according to the findings of our study and other studies, it seems that omeprazole therapy may be associated with the development of kidney impairment.

Powers of this study:

Confirming the effect of omeprazole on hypomagnesemia, was consistent with other studies.

It is for the first time that this subject is being discussed in Iran.

This study can be valuable Because there is a small number of studies in this field.

Limits of this study:

Parent's unwilling to repeat the tests after the treatment period.

Decrease in the number of patients referring to gastrointestinal clinics due to the covid 19 pandemic and as a result, data collection took so long.

Infants are not included in this study

Conclusion

Urinary and serum Mg levels and fractional Mg excretion decreased after treatment with omeprazole. The cause of hypomagnesemia is not enhanced urinary loss of magnesium, Conversely, The kidney effort to compensate for the drop in blood magnesium following omeprazole treatment by reducing urinary excretion of it and saving magnesium ions in the body.

Abbreviations

gHK-α Gastric H+ ,K+ -ATPase

Mg Magnesium

PPI Proton pump inhibitor

SD Standard deviation

Declarations

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Conflicts of interest/Competing interests: The authors declare no competing interests.

Availability of data and material: Data are available from the authors upon request.

Code availability: Not applicable

Authors' contributions: Fatemeh Famouri conceived and designed the study, acquired data, analyzed data, and drafted the manuscript. Nirvana Tavahen designed the study and critically reviewed the manuscript for relevant intellectual content. Hossein Gholami, Maryam Yazdi, Motahar Heidari- Beni contributed to the study conception and design and critically reviewed the manuscript for relevant intellectual content. All authors gave their approval to the final version of the manuscript.

Ethics approval: The Isfahan University of Medical Sciences reviewed and approved the study protocol (IR.MUI.MED.REC.1399.953).

Consent to participate: The participants were informed of the study objectives and purposes. Participation was voluntary. The Isfahan University of Medical Sciences waived the need for specific written informed consent for this survey study.

Consent for publication: Not applicable

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Figures

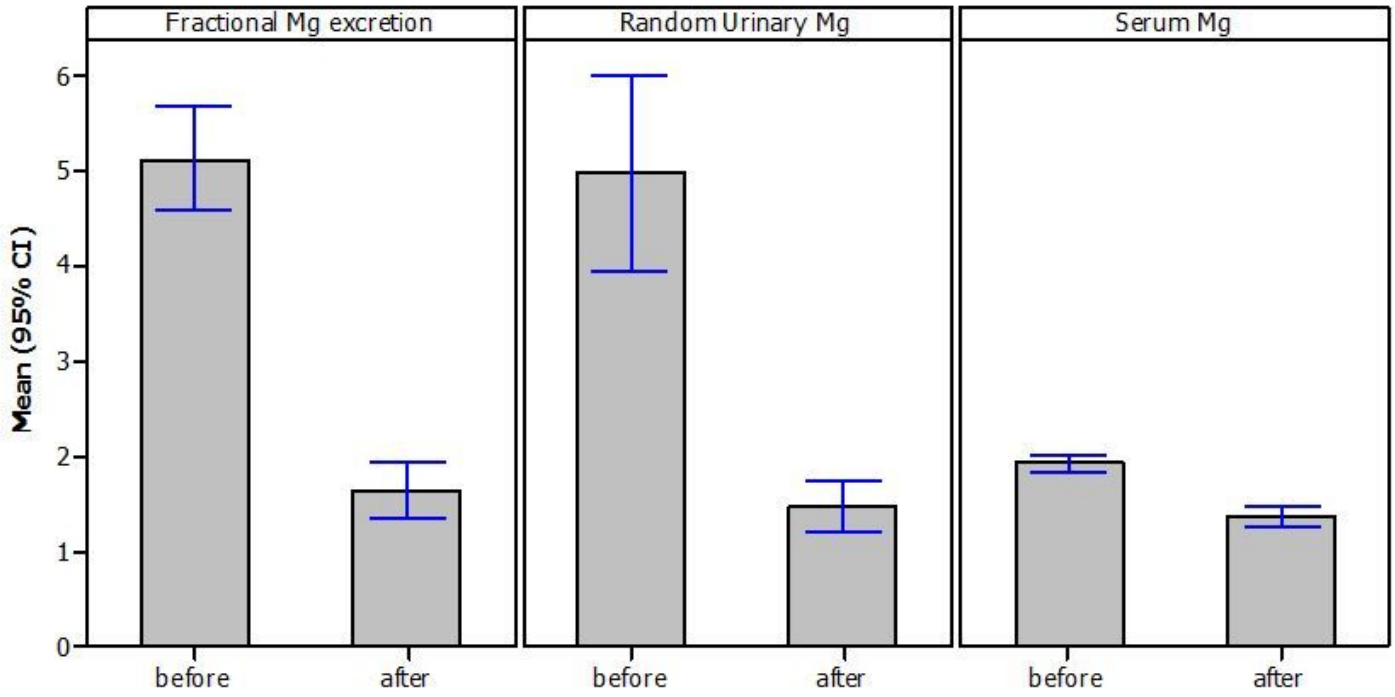

Figure 1

Mean (95% CI) outcomes before and after the treatment with omeprazole