Original Article

The Effect of Omeprazole on Urinary Magnesium Excretion in Children with Peptic Diseases

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Abstract

Objective: This study investigates the impact of omeprazole on urinary magnesium (Mg) excretion in children undergoing treatment for peptic disease. Specifically, it examines how omeprazole influences the fractional excretion of Mg. **Methods:** This single-arm clinical trial was conducted from 2020 to 2021. With 44 children diagnosed with acid peptic disease who received omeprazole (1–2 mg/kg/day) for 3 months at the Gastroenterology Clinic of Imam Hossein Hospital, Isfahan, Iran. Serum and urine levels of Mg and creatinine were measured before and after the intervention using the Pars Azmoon Kit, following the kits guidelines. The fractional excretion of Mg was then calculated using standard formulas. **Findings:** The mean urinary Mg levels decreased significantly from 4.96 ± 2.48 mg/dL before treatment to 1.46 ± 0.63 mg/dL after treatment ($P < 0.001$). Serum Mg levels also significantly declined from 1.90 ± 0.20 mg/dL before treatment to 1.37 ± 0.03 mg/dL after treatment ($P < 0.01$). The mean fractional excretion of Mg decreased from 5.2% ± 1.2% before therapy to 1.7% ± 0.63% after treatment ($P < 0.01$). Serum creatinine levels showed a slight increase from 0.62 ± 0.19 mg/dL to 0.67 ± 0.13 mg/dL ($P = 0.053$), whereas urinary creatinine levels increased by 20.80 ± 18.77 mg/dL ($P < 0.001$). **Conclusion:** The observed hypomagnesemia is not attributable to increased urinary Mg loss. Instead, the kidneys appear to compensate for the reduced serum Mg levels by decreasing urinary Mg excretion, thereby conserving Mg in the body following omeprazole treatment.

Keywords: *Children, Magnesium, Omeprazole, peptic diseases*

Received: 28-01-2024.
Revised: 12-03-2024.
Accepted: 27-03-2024.
Published: 23-12-2024.

Introduction

Acid peptic disease arises from distinct yet overlapping pathogenic mechanisms that result in excessive acid secretion or reduced mucosal defense.[1] Due to its chronic nature and widespread prevalence, this condition poses a significant financial burden on healthcare systems.

Proton pump inhibitors (PPIs) are the most effective agents for managing this disorder, acting as potent blockers of gastric acid secretion.[2,3] The chemical structure of all PPIs is similar, and their action is identical.[4] They are administered as lipophilic, membrane-permeable prodrugs,[4-6] which are absorbed

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Website: https://journals.lww.com/jrpp

DOI: 10.4103/jrpp.jrpp_35_24

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How to cite this article: Famouri F, Tavahen N, Gholami H, Yazdi M, Heidari-Beni M, Momenzadeh M. The effect of omeprazole on urinary magnesium excretion in children with peptic diseases. J Res Pharm Pract 2024;13:53-7.

in the small intestine and subsequently accumulate in the acidic canaliculi of gastric parietal cells. Within these cells, protonated PPIs form a covalent bond with specific cysteine residues of the gastric H+, K+-ATPase (gHK-α), an enzyme critical for hydrochloric acid secretion, thereby inhibiting acid production.[7,8] Despite their efficacy, chronic use of PPIs is often associated with hypomagnesemia. The causal relationship between PPI use and hypomagnesemia has been demonstrated through challenge–de-challenge–re-challenge protocols, which showed that hypomagnesemia resolves upon discontinuing PPIs and recurs upon reintroduction.[9]

Hypomagnesemia can manifest as severe magnesium (Mg) deficiency symptoms, including convulsions, cardiac arrhythmias, seizures, and tetany. Mg deficiency has also been linked to various conditions, such as osteoporosis, Parkinson's disease, asthma, and hypertension.[1]

A study conducted in 2022 revealed a higher probability of hypomagnesemia in individuals who use PPI medications. The occurrence of hypomagnesemia was approximately 22% in people using PPIs, while it was around 16% in those who did not take these medications.[10]

Given the high prevalence of gastrointestinal disorders like acid peptic disease in our country,[4] PPIs are a cornerstone of treatment. However, their impact on Mg homeostasis remains controversial.[11] This study aims to evaluate the effect of omeprazole on urinary Mg excretion in children with peptic disease.

Methods

This single-arm clinical trial involved 44 children with a confirmed diagnosis of acid peptic disease, who were treated with omeprazole (1 mg/kg/day) for 3 months at the Gastroenterology Clinics of Imam Hossein Hospital, Isfahan, from February 2020 to March 2021. The Research Ethics Committee of Isfahan University of Medical Sciences reviewed and approved the study protocol (IR.MUI.MED.REC.1399.953). The participants were informed of the study objectives and purposes. Participation was voluntary.

Inclusion criteria required long-term treatment with omeprazole for at least 3 months and between 4 and 12 years of age. Exclusion criteria included family dissatisfaction with continuing treatment, drug side effects or intolerance, concurrent use of drugs known to cause hypomagnesemia, such as aminoglycosides, amphotericin, digoxin, and tacrolimus, and the patients have concurrent liver disease, kidney disease, pancreatitis, diarrhea, heart disease, hypothyroidism, aldosteronism, malabsorption syndromes, and taking Mg supplements.

Serum and urinary levels of Mg and creatinine were measured before and after the intervention using the Pars Azmoon Kit, following the manufacturer's guidelines. The fractional excretion of Mg was calculated through:

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

Continuous variables were expressed as mean ± standard deviation (SD), and categorical data were presented as frequency and percentage. The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. The change from baseline for all outcomes was calculated, and a paired *t*-test was employed to compare pre- and postintervention means. Comparisons were also made across gender and age subgroups. P <0.05 was considered statistically significant. All statistical analyses were performed using SPSS, version 25 (IBM Corporation).

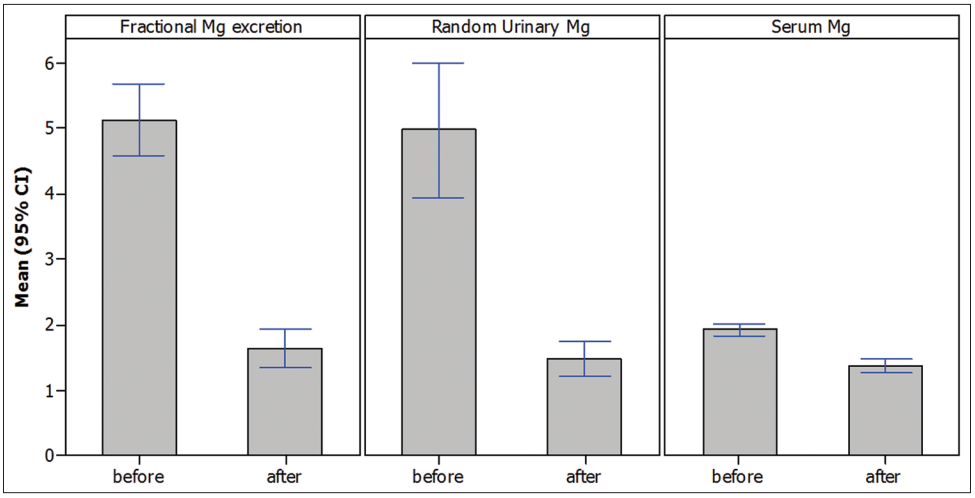

Figure 1: Mean (95% confidence interval) outcomes before and after the treatment with Omeprazole. CI = Confidence interval

Results

During this research, 44 children diagnosed with acid peptic disease received omeprazole (1 mg/kg/day) for 3 months at the Gastroenterology Clinic of Imam Hossein Hospital, Isfahan, Iran.

Among the 44 patients, 22 (50%) were female. Their ages ranged from 4 to 15. The mean age was 6.39 ± 4.31, and 26 (56.8%) were 6 years or less, whereas 19 (43.2%) were more than 6 years old.

Table 1 presents the mean ± SD of the outcomes (urinary and serum levels of Mg, fractional Mg excretion, serum, and urinary creatinine levels) before and after the intervention, as well as the changes from baseline. Significant differences were observed in urinary Mg levels (4.97 ± 2.49 vs. 1.47 ± 0.63, $P < 0.001$) and serum Mg levels (1.92 ± 0.21 vs. 1.37 ± 0.25, $P < 0.001$) before and after treatment. Fractional Mg excretion also significantly decreased (5.11 ± 1.32 vs. 1.64 ± 0.71, $P < 0.001$).

Serum creatinine levels did not change significantly (0.63 ± 0.19 vs. 0.67 ± 0.13, $P = 0.053$), but urinary creatinine levels increased after the intervention (63.50 ± 15.71 vs. 42.70 ± 14.95, $P = 0.001$). Figure 1 presents the mean (95% confidence interval) outcomes (Fractional Mg excretion, Rendom urinary Mg, Mg serums) before and after the treatment with omeprazole. (CI = Confidence interval).

Table 2 presents the mean urinary and serum Mg, fractional Mg excretion, and serum and urinary creatinine levels before and after the intervention and the changes from baseline, categorized by gender. The change from baseline for all outcomes was the same for males and females ($P > 0.05$).

Table 3 shows the mean outcome before and after intervention and 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, $P = 0.008$).

Discussion

This study investigated the impact of omeprazole on urinary Mg excretion and fractional Mg excretion in children with peptic diseases. We found a significant decrease in fractional Mg excretion following omeprazole therapy. William *et al*. reported that PPIs are associated with reduced fractional urinary Mg excretion.[12] Similarly, Kuipers *et al*. observed hypomagnesemia linked to PPI use with low fractional Mg excretion.[13] These findings align with our results.

In addition, urinary Mg levels were significantly reduced after the intervention, and serum Mg levels decreased significantly posttreatment. William *et al*. found that the mean daily urinary Mg levels were 84.6 ± 42.8 mg in PPI users compared to 101.2 ± 41.1 mg in non-PPI users ($P = 0.01$), indicating a reduction in urinary Mg among PPI users, which is consistent with our findings.[12]

In contrast, Lameris *et al*. reported no effect of omeprazole on plasma Mg levels in rat models after 4 weeks of administration.[14] Similarly, Faulhaber *et al*. found no significant difference in mean serum Mg levels between PPI users and nonusers.[15] The discrepancies between these studies and our research may be attributed to variations in the duration and dosage of omeprazole administration.

Famouri investigated omeprazole's impact on serum Mg levels in treating gastroesophageal reflux disease and observed a decrease in serum Mg, which aligns with our results. Furthermore, they reported that reducing serum Mg could affect the serum calcium level and induce secondary hypocalcemia.[16] Other studies have reported severe hypomagnesemia as a side effect of long-term PPI use.[17,18] Hypomagnesemia may result from congenital abnormalities in Mg metabolism[15] or the effects of PPIs on passive Mg absorption in the small intestine.[7,19,20] Rodríguez Ortega *et al*. identified nine cases of severe hypomagnesemia in patients on omeprazole, attributing it to impaired Mg absorption and an imbalance between active and passive transport in the intestinal lumen, likely due to changes in intestinal pH.[20] Hess *et al*. found that

Table 1: Urinary and serum levels of magnesium, fractional magnesium excretion, serum, and urinary creatinine levels in 44 patients with peptic diseases

Variable	Before treatment	After treatment	Change from baseline	r^c	P^b
Random urinary Mg	4.97±2.49[a]	1.47±0.63	−3.50±2.38	0.296	<0.001
Serum Mg	1.92±0.21	1.37±0.25	−0.55±0.27	0.319	<0.001
Serum creatinine	0.63±0.19	0.67±0.13	0.04±0.14	0.675	0.053
Urinary creatinine	42.70±14.95	63.50±15.71	20.80±18.77	0.251	<0.001
Fractional Mg excretion	5.11±1.32	1.64±0.71	−3.47±1.17	0.468	<0.001

[a]Mean±SD, [b]Paired *t*-test, [c]Pearson correlation coefficient. SD=Standard deviation, Mg=Magnesium

Table 2: Outcomes before and after the intervention, and the changes from baseline, categorized by gender

Variable	Female (*n*=22)	Male (*n*=22)	*P*[a]
Random urinary Mg			
Before	5.00±2.50	4.94±2.53	0.879
After	1.44±0.63	1.50±0.64	
Change	−3.55±2.48	−3.44±2.33	
Serum Mg			
Before	1.91±0.20	1.92±0.23	0.510
After	1.34±0.22	1.40±0.28	
Change	−0.57±0.27	−0.52±0.27	
Serum creatinine			
Before	0.65±0.21	0.60±0.18	0.553
After	0.70±0.14	0.64±0.12	
Change	19.09±19.21	22.50±18.61	
Urinary creatinine			
Before	41.82±17.25	43.59±12.60	0.553
After	60.91±17.19	66.09±13.99	
Change	19.09±19.21	22.50±18.61	
Fractional Mg excretion			
Before	5.52±1.30	4.71±1.23	0.201
After	1.82±0.85	1.46±0.49	
Change	−3.70±1.22	−3.24±1.09	

Data are reported as mean ± standard deviation. [a]Paired *t*-test. Mg=Magnesium

Table 3: Outcomes before and after the intervention, and the changes from baseline, categorized by age group

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

Data are reported as mean ± standard deviation. [a]Paired *t*-test. Mg=Magnesium

PPI-induced hypomagnesemia persisted after 5.5 years of use, with rapid recovery upon discontinuation and recurrence upon re-challenge.[11] Cundy and Mackay suggested that severe hypomagnesemia in long-term PPI users indicates a failure in intestinal Mg absorption.[18] Mackay and Bladon recommended annual monitoring of serum Mg levels in patients on long-term PPI therapy and suggested high-dose oral Mg supplementation as a partial remedy.[21] Histamine-2 receptor antagonists have also been proposed as an alternative therapy to prevent and manage PPI-induced hypomagnesemia.[11]

In our study, serum creatinine levels increased following omeprazole therapy, and urinary creatinine levels rose significantly after treatment. Guedes *et al*. found an association between omeprazole use and the progression of chronic kidney disease, indicating a higher risk among omeprazole users.[22] Myers *et al*. reported increased serum creatinine concentrations with omeprazole use in treating acid-peptic disorders.[23] These findings suggest that omeprazole may be linked to significant adverse effects, such as renal impairment. Varallo *et al*. also observed elevated serum creatinine levels with omeprazole treatment, potentially contributing to kidney dysfunction.[24] Thus, our results, along with those from other studies, suggest that omeprazole therapy may be associated with the development of kidney impairment.

This study has several notable strengths. It confirms the effect of omeprazole on hypomagnesemia, aligning with findings from existing literature. This research addresses a topic that has yet to be extensively explored in Iran, providing valuable insights into a field with limited studies. The study contributes essential data to understanding omeprazole's impact on Mg levels, an area with relatively few investigations.

However, some limitations must be considered. Requiring follow-up tests proved challenging due to parental reluctance, which affected the study's comprehensive data gathering. Furthermore, the data collection process was extended because of reduced patient referrals to gastrointestinal clinics during the COVID-19 pandemic. Finally, the study should have included infants, limiting the findings' generalizability to younger populations.

After treatment with omeprazole, urinary and serum Mg levels and fractional Mg excretion decreased. The resulting hypomagnesemia is not due to increased urinary Mg loss. Instead, the kidneys compensate for reduced blood Mg levels by reducing urinary excretion and conserving Mg ions.

Acknowledgments

We thank the Imam Hossein Laboratory team for their cooperation.

Authors' Contribution

F. Famouri contributed to Conceptualization,

methodology design, and study supervision. Data curation and validation were performed by M. Yazdi and H. Gholami. N. Tavahen contributed to the investigation and manuscript drafting. M. Heidari-Beni gathered and analyzed the data. M. Momenzadeh contributed to the manuscript drafting and editing.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Kavitt RT, Lipowska AM, Anyane-Yeboa A, Gralnek IM. Diagnosis and treatment of peptic ulcer disease. Am J Med 2019;132:447-56.
2. Toh JW, Ong E, Wilson R. Hypomagnesaemia associated with long-term use of proton pump inhibitors. Gastroenterol Rep (Oxf) 2015;3:243-53.
3. Kieboom BC, Kiefte–de Jong JC, Eijgelsheim M, Franco OH, Kuipers EJ, Hofman A, *et al*. Proton pump inhibitors and hypomagnesemia in the general population: a population-based cohort study. American Journal of Kidney Diseases 2015;66:775-82.
4. Naderian H. Model of ulcer peptic patients' quality of life predictors based on path analysis of the PRECEDE model in Sanandaj. Razi J Medical Sciences 2013. p. 1-9.
5. Kinoshita Y, Ishimura N, Ishihara S. Advantages and disadvantages of long-term proton pump inhibitor use. J Neurogastroenterol Motil 2018;24:182-96.
6. Hannan FM, Kallay E, Chang W, Brandi ML, Thakker RV. The calcium-sensing receptor in physiology and in calcitropic and noncalcitropic diseases. Nat Rev Endocrinol 2018;15:33-51.
7. Thongon N, Penguy J, Kulwong S, Khongmueang K, Thongma M. Omeprazole suppressed plasma magnesium level and duodenal magnesium absorption in male Sprague-Dawley rats. Pflugers Arch 2016;468:1809-21.
8. Lameris AL, Hess MW, van Kruijsbergen I, Hoenderop JG, Bindels RJ. Omeprazole enhances the colonic expression of the Mg(2+) transporter TRPM6. Pflugers Arch 2013;465:1613-20.
9. Gröber U, Schmidt J, Kisters K. Magnesium in prevention and therapy. Nutrients 2015;7:8199-226.
10. Anna Vermeulen Windsant-van den Tweel AM, Derijks HJ, Gadiot NP, Keijsers CJ. Proton pump inhibitors and hypomagnesemia in older inpatients: An observational study. Sr Care Pharm 2022;37:623-30.
11. Hess MW, de Baaij JH, Gommers LM, Hoenderop JG, Bindels RJ. Dietary inulin fibers prevent proton-pump inhibitor (PPI)-induced hypocalcemia in mice. PLoS One 2015;10:e0138881.
12. William JH, Nelson R, Hayman N, Mukamal KJ, Danziger J. Proton-pump inhibitor use is associated with lower urinary magnesium excretion. Nephrology (Carlton) 2014;19:798-801.
13. Kuipers MT, Thang HD, Arntzenius AB. Hypomagnesaemia due to use of proton pump inhibitors--a review. Neth J Med 2009;67:169-72.
14. Lameris AL, Nevalainen PI, Reijnen D, Simons E, Eygensteyn J, Monnens L, *et al*. Segmental transport of Ca^{2+} and Mg^{2+} along the gastrointestinal tract. Am J Physiol Gastrointest Liver Physiol 2015;308:G206-16.
15. Faulhaber GA, Ascoli BM, Lubini A, Mossmann M, Rossi G, Geib G, *et al*. Serum magnesium and proton-pump inhibitors use: A cross-sectional study. Rev Assoc Med Bras (1992) 2013;59:276-9. doi: 10.1016/j.ramb.2012.12.007.
16. Famouri F. Forough Derakhshani, Yahya Madihi, Armindokht Shahsanai. Electrolyte disturbances in children receiving omeprazole for gastroesophageal reflux disease. J Res Med Sci 2020;25:106.
17. Koyyada A. Long-term use of proton pump inhibitors as a risk factor for various adverse manifestations. Therapie 2021;76:13-21.
18. Cundy T, Mackay J. Proton pump inhibitors and severe hypomagnesaemia. Curr Opin Gastroenterol 2011;27:180-5.
19. Suksridechacin N, Kulwong P, Chamniansawat S, Thongon N. Effect of prolonged omeprazole administration on segmental intestinal Mg(2+) absorption in male Sprague-Dawley rats. World J Gastroenterol 2020;26:1142-55.
20. Rodríguez Ortega P, Rebollo Pérez I, Laínez López M, Roldán Mayorga E, Hernández Lavado R, Creagh Cerquera R. Severe hypomagnesemia and hypoparathyroidism induced by omeprazole. Endocrinol Nutr 2013;60:156-7.
21. Mackay JD, Bladon PT. Hypomagnesaemia due to proton-pump inhibitor therapy: A clinical case series. QJM 2010;103:387-95.
22. Guedes JV, Aquino JA, Castro TL, Augusto de Morais F, Baldoni AO, Belo VS, *et al*. Omeprazole use and risk of chronic kidney disease evolution. PLoS One 2020;15:e0229344.
23. Myers RP, McLaughlin K, Hollomby DJ. Acute interstitial nephritis due to omeprazole. Am J Gastroenterol 2001;96:3428-31.
24. Varallo FR, de Nadai TR, de Oliveira AR, Mastroianni PC. Potential adverse drug events and nephrotoxicity related to prophylaxis with omeprazole for digestive disorders: A prospective cohort study. Clin Ther 2018;40:973-82.