

# Electrolyte disturbances in children receiving omeprazole for gastroesophageal reflux disease

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**Background:** Gastroesophageal reflux disease (GERD) is one of the common gastrointestinal diseases with various side effects. Proton pump inhibitor (PPI) drugs are widely used for their treatment and long-term ingestion, which results in an electrolyte imbalance. This study investigates the changes in serum magnesium, calcium, sodium, and potassium after long-term use of omeprazole in children. **Materials and Methods:** This cross-sectional study was conducted in 2016–2017 on 97 children and adolescents, aged 1–15 years, with GERD, in Isfahan, Iran. Enrolled were patients visiting a referral pediatric gastroenterology clinic (Imam Hossein and Amin Hospitals) examined by an academic pediatric gastroenterologist. Before and 4 weeks after omeprazole administration, clinical manifestations including lethargy, muscle spasm, dyspnea, nausea, vomiting, abnormal heartbeat and deep tendon reflexes, and Chvostek and Trousseau signs were recorded in a data-gathering form. In addition, fasting serum magnesium, calcium, sodium, and potassium were measured. **Results:** The McNemar test results showed that omeprazole can reduce sodium, calcium, and magnesium levels statistically significantly ( $P < 0.05$ ), but potassium levels do not have a meaningful reduction ( $P > 0.05$ ). **Conclusion:** Consumption of omeprazole might cause asymptomatic hypomagnesemia, hypocalcemia, and hyponatremia in children. Such side effects should be considered in the follow-up of children under treatment with this medication.

**Key words:** Electrolyte imbalance, omeprazole, proton pump inhibitors

**How to cite this article:** Famouri F, Derakhshani F, Madihi Y, Shahsanai A. Electrolyte disturbances in children receiving omeprazole for gastroesophageal reflux disease. *J Res Med Sci* 2020;25:106.

## INTRODUCTION

Gastroesophageal reflux (GER) is the reflux of gastric contents from lower esophageal sphincter to the esophagus, which ignores gender and age limitations.<sup>[1]</sup> Despite an unpleasant feeling, GER is a normal physiological phenomenon that usually has no harm to the esophagus. When GER produces signs and symptoms, it is called GER disease (GERD), which is pathologic and needs treatment. It is related to gastric acid as one of the most common disorders of the esophagus, which frequently responds to proton pump-inhibiting drugs.<sup>[2-5]</sup>

Proton pump inhibitor (PPI) drugs inhibit hydrochloric acid (HCl) secretion that can influence on H/K ATPase

pump in gastric parietal cells.<sup>[6]</sup> Therefore, it was widely used during the past three decades and prescribed as a treatment for peptic diseases in adults and children, so its prescription became 7.5 times more from 1999 to 2004.<sup>[7]</sup> It is also applied for treating a gastric ulcer, GERD, and *Helicobacter pylori* infection in children and adolescents.<sup>[7]</sup> Omeprazole is considered the first well-known drug, which has been mostly prescribed. Later, lansoprazole (1995), pantoprazole (1997), rabeprazole (1999), and esomeprazole (2001) have been entered into the field of privileged drugs.<sup>[2]</sup> In children, the side effects of PPI drugs are considered as minimum as possible.<sup>[8]</sup> Taking this medicine for more than 2 weeks may be associated with some side effects<sup>[9]</sup> including respiratory infections, some renal side effects, Vitamin B12 malabsorption, *Clostridium difficile* colitis,

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10.4103/jrms.JRMS\_637\_18

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**Submitted:** 25-Sep-2018; **Revised:** 26-Aug-2019; **Accepted:** 13-Jul-2020; **Published:** 26-Nov-2020

hip fractures, and blood magnesium reduction in children and adults.<sup>[9-12]</sup>

Magnesium reduction following PPI drug administration was first reported in 2006, but 2016 in children.<sup>[12]</sup> Subsequent studies have suggested that impaired intestinal absorption of magnesium is more likely to cause hypomagnesemia rather than enhanced urinary excretion.<sup>[13]</sup> The individual patient may clinically present with weakness, lethargy, nausea, vomiting, and hyperreflexia. Hypocalcemia is another electrolyte abnormality that can occur secondary to hypomagnesemia or decrease calcium absorption due to the elimination of the acidic environment that is essential for calcium absorption following H/K ATPase pump inhibition in gastric parietal cells by PPI.<sup>[14]</sup> Affected patients may exhibit paresthesia around the mouth, carpopedal spasm, convulsion, laryngospasm, bronchospasm, low blood pressure, arrhythmia, and prolonged QT interval.<sup>[15]</sup> Reduction of blood sodium is another electrolyte disorder following omeprazole use, which was reported only in some articles.<sup>[16]</sup> It can induce muscle weakness and lethargy, nausea, dizziness, drowsiness, muscle spasm, and rarely coma and convulsion.<sup>[17]</sup> The increasing urinary sodium loss could be the cause.<sup>[17]</sup> The inhibitory effect of omeprazole on H/K ATPase pump in gastric parietal cells may also create a vicious cycle in potassium absorption, which has also been reported in some literature, that causes nausea and vomiting, muscle weakness, arrhythmia, abnormal electrocardiogram, ileus, and abdominal distention.<sup>[18]</sup>

Because there are no studies in literature about electrolyte abnormalities rather than hypomagnesemia, we investigated the electrolyte disturbances in children receiving omeprazole for GERD.

## MATERIALS AND METHODS

### Data source

This study was carried out on children and adolescents (1–15 years old) with GERD. They were referred to a gastroenterology clinic of the Imam Hossein Children Hospital (Isfahan, Iran) in 2016–2017. They were examined by an academic pediatric gastroenterologist who prescribed omeprazole to them for a relatively long period, at least 1 month.

### Study design

This is a cross-sectional, single-group study conducted on 100 children and adolescents (1–15 years old) with GERD<sup>[1]</sup> who were eligible to receive omeprazole for at least 1 month. The diagnosis of GERD was done by the academic gastroenterologist who prescribed omeprazole to them

for treatment. The sample size was acquired based on the following formula:

$$n = \frac{z_{1-\alpha}^2 \times p(1-p)}{d^2}$$

where  $n$  is the minimum sample size,  $d$  is the desired level of significance (set at 0.05),  $z_{1-\alpha}$  is a confidence interval, and  $P$  is the prevalence rate in a target population from a previous study. To determine the largest sample size and the statistical accuracy of 0.1, 100 people were attained by considering the statistical domain of 95% and  $z_{(1-\alpha)}^2 = (1.96)^2$  and the prevalence of electrolyte abnormalities of 50%.

As  $\alpha = 0.05$ ,  $z_{1-\frac{\alpha}{2}} = 1.96$ ,  $P = 0.5$ , and  $d = 0.2 \times p$ , the sample size becomes:

$$n = \frac{1.96^2 \times 0.5 \times 0.5}{(0.2 \times 0.5)^2} = 96.04$$

Hence, at first, 100 individuals (who met the inclusion criteria) with GERD eligible for receiving omeprazole, entered the study after filling out the consent form. Eighteen children had exited the research because of the lack of regular drug consumption. Then, 19 children were substituted due to a significant drop in sample size, but again 4 patients left the study owing to the lack of proper omeprazole intake. Finally, a sample size of 97 children were involved in the analysis [Figure 1]. The omeprazole capsules, which were consumed in this study, were prepared from Abidi Company (Tehran, Iran). They were administered at a dose

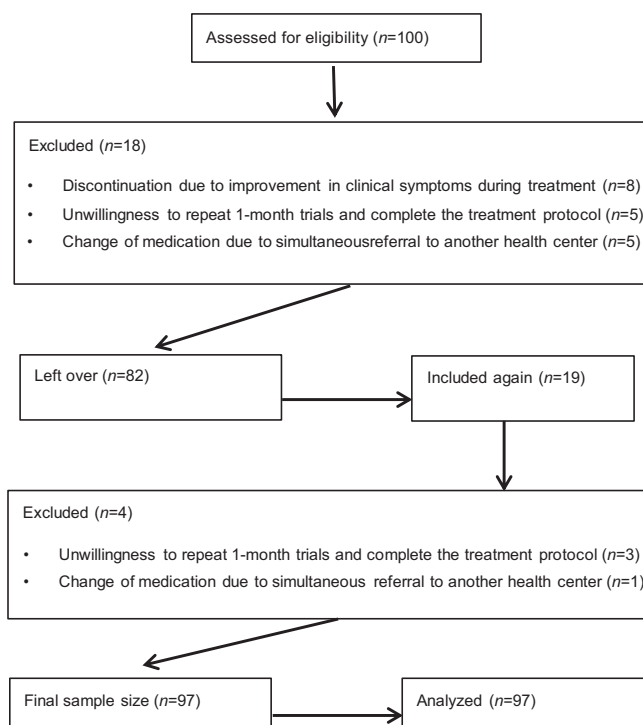


Figure 1: The diagram of the sampling

of 1 mg/kg/day divided into two doses, a maximum of 40 mg/day. The drug was ingested as nondissolved granules, which were mixed with yogurt, apple juice, or mashed apple, half or an hour before breakfast. At the beginning of treatment, the serum level of magnesium, calcium, sodium, and potassium was measured after 8 h fasting in the Imam Hossein Children Hospital laboratory by the DIRUI auto analyzer device (Dirui, Changchun, China). Precise history was taken about lethargy, muscle spasm, dyspnea, nausea, vomiting, and abnormal heartbeat. Physical examination was performed to check DTR, Chvostek, and Trousseau signs. All information regarding clinical manifestations was recorded in a checklist.

One month after starting omeprazole, the serum levels of magnesium, calcium, sodium, and potassium were measured again after 8 h of fasting. If serum levels of an electrolyte were observed as out of the normal range, the considered electrolyte was rechecked with the same blood sample. If the result was the same, it would be recorded, then the relevant history was taken again, and the previous physical examinations were repeated.

The acceptable serum level was considered 1.7–2.4 mg/dl for magnesium, 8.5–10.5 mg/dl for calcium, 135–145 for sodium mmol/l, and 3.5–5 mmol/l for potassium. Serum magnesium <1.7 mg/dl, calcium <8.5 mg/dl, sodium <135 mmol/l, and potassium <3.5 mmol/l were considered hypomagnesemia (magnesium reduction), hypocalcemia (calcium reduction), hyponatremia (sodium reduction), and hypokalemia (potassium reduction), respectively.<sup>[17,19]</sup>

#### Inclusion and exclusion criteria

Enrolled were 1–15-year-old children and adolescents who had been on omeprazole prescribed by an academic gastroenterologist for the treatment of GERD. Individuals with liver, kidney, pancreatic, and cardiovascular diseases; those with diarrhea; and patients who dissatisfied with receiving medication, or receiving other medications such as vitamins and minerals; and patients who have been on a special diet were excluded from the study. Individuals who had been noncompliant with medication; those who suffered from an allergy to any ingredients of the drug; those with intolerance to medication, or had lost to follow-up before the 1 month of the study; and those who have electrolyte disturbance at the beginning of the study were also excluded from this investigation.

#### Ethic

Approval of the University Research and Ethical Committee was acquired. The ethical code was 396045 and the project number was IR.MUI.REC.1396.3.045. Informed consent form was filled out by the participants' parents before entering the study.

#### Statistical analysis

In the current study, McNemar test was used for estimation of the relative frequency of reduction in each electrolyte, Chi-square and Fisher's exact tests were used for correlation between two genders in each electrolyte reduction, and independent sample *t*-test was used for determination of the relation between age and each electrolyte decrement before and after the intervention. Statistical analysis was done with IBM SPSS Statistics version 20 software (SPSS Inc., Chicago, IL).  $P < 0.05$  was considered statistically significant.

#### RESULTS

The study was carried out on 97 children and adolescents, which was composed of 55.7% girls and 44.3% of boys, with a age range of 1–15 years, a mean of 6.22 years, and a standard deviation of 2.86 [Table 1].

The McNemar test showed that the relative frequency of decreased serum sodium ( $P < 0.001$ ), calcium ( $P < 0.001$ ), and magnesium levels ( $P = 0.002$ ) had statistically significantly increased after omeprazole consumption. The serum potassium level did not decrease significantly after omeprazole ingestion [Table 2].

The Chi-square test revealed that the frequency of sodium ( $P = 0.77$ ) and calcium ( $P = 0.62$ ) reduction had not differed statistically significantly between the two genders after omeprazole ingestion. According to Fisher's exact test, no statistically significant difference was seen in the rate of serum magnesium reduction ( $P = 0.29$ ) between the two genders [Table 3].

According to independent *t*-test, age had no statistically significant relation with serum sodium ( $P = 0.27$ ) and magnesium ( $P = 0.75$ ) reduction. Meanwhile, there was a statistically significant relation between age and decrement of serum calcium after omeprazole ( $P = 0.04$ ) so that the mean age of children with and without calcium reduction was  $5.1 \pm 2.4$  and  $6.5 \pm 2.9$ , respectively.

The patients did not develop symptoms of lethargy; muscle spasm; dyspnea; nausea; vomiting; and palpitation

**Table 1: Distribution of the patients' age and sex**

Variable	n (%)	P
Gender		
Female	54 (44.3)	0.94
Male	43 (55.7)	
Age (years)		
<5	28 (28.9)	
5-9	52 (55.7)	
≥10	15 (15.4)	

<sup>a</sup>The probability of obtaining test results at least as extreme as the results observed during the test, assuming that the null hypothesis is correct

**Table 2: Distribution of electrolyte disorders before and after omeprazole**

Electrolyte disturbance	Before omeprazole, n (%) <sup>a</sup>	After omeprazole, n (%) <sup>b</sup>	P <sup>c</sup>
Sodium reduction <sup>a</sup>	1 (1.03)	17 (17.5)	<0.001
Calcium reduction <sup>b</sup>	2 (2.1)	16 (16.5)	0.001
Magnesium reduction <sup>c</sup>	0	10 (10.3)	0.002
Potassium reduction <sup>d</sup>	0	0	1

<sup>a</sup>Serum sodium <135 mmol/l; <sup>b</sup>Serum calcium <8.5 mg/dl; <sup>c</sup>Serum magnesium <1.7 mg/dl; <sup>d</sup>Serum potassium <3.5 mmol/l; <sup>e</sup>The number of patients (percent) before omeprazole consumption; <sup>f</sup>The number of patients (percent) after omeprazole consumption; <sup>g</sup>The probability of obtaining test results at least as extreme as the results observed during the test, assuming that the null hypothesis is correct

**Table 3: Distribution of electrolyte disturbance after omeprazole by sex**

Electrolyte disturbance	Male, n (%) <sup>d</sup>	Female, n (%) <sup>e</sup>	P <sup>f</sup>
Sodium reduction <sup>a</sup>	7 (16.3)	10 (18.5)	0.77
Calcium reduction <sup>b</sup>	8 (18.6)	8 (14.8)	0.62
Magnesium reduction <sup>c</sup>	6 (14)	4 (7.04)	0.29

<sup>a</sup>Serum sodium <135 mmol/l; <sup>b</sup>Serum calcium <8.5 mg/dl; <sup>c</sup>Serum magnesium <1.7 mg/dl; <sup>d</sup>The number of male patients (percent); <sup>e</sup>The number of female patients (percent); <sup>f</sup>The probability of obtaining test results at least as extreme as the results observed during the test, assuming that the null hypothesis is correct

or abnormal DTR, Chvostek, and Trousseau signs after 4 weeks of taking omeprazole.

## DISCUSSION

This research was conducted on children and adolescents who received omeprazole for a relatively long period (at least 1 month). The results indicated that taking omeprazole for more than 1 month could lead to some electrolyte disturbances such as decreased serum levels of sodium, calcium, and magnesium. However, no significant changes in serum potassium levels were observed. Because the reduction of serum magnesium can affect the level of serum calcium and induce secondary hypocalcemia, the decline of serum calcium in this research was perceived independent of the serum magnesium level. In the majority of individuals, the decreased level of calcium and magnesium had not occurred in the same patient. The present study also revealed that gender plays no significant role in electrolyte disorders and mostly depends on the period of omeprazole intake.

Some investigations have been targeted on the electrolyte abnormalities following omeprazole administration with some case reports in this setting. For the first time in 1993, Melville *et al.* reported a 4.7-year-old patient, a known case of Klippel–Feil syndrome, who had received omeprazole for gastrointestinal bleeding after surgical repair of the mandible. The authors marked hypokalemia and hyponatremia after 10 days.<sup>[16]</sup> After some workups, they found that the inappropriate hyperexcretion of sodium and potassium was the leading cause.<sup>[16]</sup> Nonetheless, no significant change in serum potassium was observed in the current study after 1 month of treatment with omeprazole. For the hospitalized older adults with PPI exposure, Gau

*et al.* found that these patients had higher serum potassium levels before admission than those who did not receive omeprazole.<sup>[20]</sup> The first possible reason for this variation may be that the participants in this study were children who usually have normal kidney function, whereas the mentioned study had been directed in older adults. These findings suggest that age has a positive effect on serum potassium levels, which is due to a relative decline in renal function in this age group.<sup>[20]</sup> The important point is that the current study does not include infants (<1-year-old) who have an immature kidney function. This variable may affect the serum potassium level after omeprazole ingestion. The second reason is that children who were involved in this study had not suffered from any important medical illness other than GERD. Meanwhile, those adults had older age with some underlying diseases where they even took some medications that could affect the serum potassium level.<sup>[20]</sup>

Hypomagnesemia was reported for the first time as a complication of PPI.<sup>[21]</sup> Later hypocalcemia and hypokalemia as consequence of hypomagnesemia following PPI administration were reported.<sup>[22]</sup> Regolisti *et al.* reported the case of a 65-year-old diabetic male who had taken lansoprazole for many years due to Barrett's esophagus.<sup>[15]</sup> This elderly male had developed profound hypomagnesemia (serum magnesium 0.42 meq/l) and secondary hypocalcemia along with serious signs and symptoms that resolved with ranitidine substitution and then recurred with pantoprazole consumption. Diabetes had been under control, but fractional excretion of magnesium had been increased. The interesting point is that despite receiving magnesium in conjunction with lansoprazole after treatment, hypomagnesemia had been reappeared.<sup>[15]</sup>

One systematic review was also directed regarding hypomagnesemia as a side effect of PPI.<sup>[23]</sup> This study showed that hypomagnesemia can develop after exposure to PPI beside hypokalemia and hypocalcemia in some cases.<sup>[23]</sup>

Most often, these electrolyte disturbances take place when PPI is administered with some medications such as cisplatin, carboplatin, and diuretics, or in patients with abnormal renal function.<sup>[23,24]</sup> This situation revealed that

the mentioned electrolyte disturbances were frequently observed in individuals aged more than 50 years who had received PPI for >1 year. The rationale for these events may be the reduction of magnesium absorption from the gastrointestinal tract, which frequently leads to hypocalcemic hypoparathyroidism and hypokalemia.<sup>[23]</sup> Hess *et al.* found that hypomagnesemia improved 4 days after discontinuation of PPI, which had not been developed by H<sub>2</sub>-blocking agents.<sup>[23]</sup> Fortunately, the current study did not show any evidence of the marked hypomagnesemia after 1 month, but significant decreased levels of serum magnesium, calcium, and sodium were observed. No considerable change in serum potassium was recorded. It may be due to the lack of the underlying illness in our patients as well as the lower age of the participants. Another important factor may be the lack of receiving the mentioned medications by the participants. Because the decreased levels of calcium have not had a correlation with the diminished serum magnesium in the present study, they have occurred separately.

Results of one clinical trial in 2014 indicated that chronic PPI consumer adults had lower levels of serum magnesium, which mostly drop down to the lower limit of normal, but in 4 of 30 patients, it dropped under 1.7 mg/dl without clinical manifestations.<sup>[11]</sup> This clinical trial is comparable to our trial, which indicates a statistically significant decrease in serum level of magnesium with the lack of signs and symptoms after 1 month of PPI consumption. However, there were similar results for serum calcium and sodium regardless of potassium in the current research.

One research on cats in 2016 did not demonstrate statistically significant decrement in serum magnesium, calcium, bone mineral density (BMD), and bone mineral content (BMC) after 30 and 60 days of receiving omeprazole.<sup>[24]</sup> Variation in body physiology may be the rationale for this diversity.<sup>[24]</sup> There is no clinical trial to evaluate serum sodium simultaneously with magnesium, calcium, and potassium levels following omeprazole consumption. Meanwhile, sodium level also statistically reduced significantly in the current research, but it has been in the normal range yet. Patients did not develop hyponatremia or relevant signs and symptoms.

The mechanism of electrolyte imbalance following omeprazole is undefined till now. In one investigation about the cause of susceptibility to fracture with chronic use of PPI, the investigators suggested that achlorhydria created by PPI ingestion might reduce the absorption of calcium carbonate in the fasting state, but more studies are required.<sup>[25]</sup>

Hypomagnesemia may be the result of decreased intestinal absorption or increased urinary loss of magnesium. Chen

*et al.* revealed that in the cases of hypomagnesemia after omeprazole consumption, the urinary excretion of magnesium had not been increased.<sup>[25]</sup> They suggested that the decreased intestinal absorption of magnesium may be the cause of this problem. However, more researches are needed to find out the reason.<sup>[25]</sup> In a 4.7-year-old child with hyponatremia and hypokalemia in one case report, urinary excretion of sodium and potassium had increased after receiving omeprazole for 10 days.<sup>[25]</sup>

The present research showed that the serum levels of sodium, calcium, and magnesium had significantly decreased after 1 month of omeprazole consumption. It would be an alarming sign that those decrements can progress to mark deficiencies, which relieve signs and symptoms. Thus, we suggest measuring serum electrolyte levels after 1 month of omeprazole consumption and thereafter. If significant decrement is observed, it can be replaced with other appropriate medications.

Although PPI drugs have a critical role in the treatment of acid peptic diseases in children and adults, special attention should be paid to their important side effects, including electrolyte disturbances, especially when the patients receive certain medications or have any underlying kidney disease. If the patients are required to take this medication for more than 1 month, they should be monitored for electrolyte imbalance and relative clinical manifestations. In the case of electrolyte imbalance or impending to it, PPI should be stopped and replaced by H<sub>2</sub>-blocking agents or other forms of antacids. In fact, regarding electrolyte disorders following omeprazole, the majority of investigations were carried out on adults. This clinical trial has been planned to evaluate this subject on children and adolescents.

### Limitations

1. Our research did not include infants < 1 year old who may have altered drug metabolism and immature renal function
2. The level of urinary magnesium, calcium, sodium, and potassium was not measured simultaneously with serum levels
3. Electrolyte levels had not been checked after 3 months because of either the limitation of time or patients' compliance with long-term treatment.

### CONCLUSION

PPI drugs can reduce serum levels of magnesium, sodium, and calcium when they are administered for >1 month. Therefore, the serial checking of these electrolytes can prevent serious signs and symptoms.

### Acknowledgments

We would like to thank the Imam Hossein Children's Hospital Laboratory for its cooperation. The ethical code was 396045 and the project number was IR.MUI.REC.1396.3.045.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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