Relationship between renal function and serum magnesium concentration in elderly outpatients treated with magnesium oxide

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A short running title: Magnesium level of the magnesium oxide users

Abstract

Aims: We investigated the relationship between renal function and serum magnesium concentration in elderly patients treated with magnesium oxide (MgO) in an outpatient setting of an urban hospital in Japan.

Methods: In the present study, 44 elderly outpatients (23 patients with constipation treated with daily oral MgO and 21 untreated patients in the control group) who visited Kameyama municipal medical center were enrolled. Variables were age, sex, weight, height, serum magnesium concentration, serum blood urea nitrogen level, serum creatinine level, use of other magnesium-containing supplements, and symptoms associated with hypermagnesemia. We calculated the estimated glomerular filtration rate (eGFR) and classified patients based on eGFR category.

Results: Compared to the control group, the MgO group showed a significantly higher concentration of serum magnesium [median 2.2 mg/dL (interquartile range 2.1–2.3) vs. 2.4 mg/dL (2.2–2.6), $P < 0.001$]. Hypermagnesemia (>2.6 mg/dL) was noted only in the MgO group. However, symptoms associated with hypermagnesemia occurred in patients from both groups, with no significant difference between groups. In the MgO group, significant difference was seen in the median serum magnesium concentration between eGFR categories ($P < 0.05$). The category G4 (eGFR 15–29 mL/min/1.73m^2) group had the highest serum magnesium concentration in the MgO group [3.0 mg/L (2.9–3.1)].

Conclusions: Elderly patients treated with MgO have higher serum magnesium levels compared to the control group. MgO should prescribed with caution in patients with low renal function as shown by a GFR category G3b or less (eGFR < 30 mL/min/1.73 m^2).
Keywords: elderly outpatients, estimated glomerular filtration rate, magnesium oxide, serum magnesium concentration.

Introduction

Constipation is a common health problem in the primary care setting.[1] The prevalence of constipation in elderly people is high, and laxatives are frequently prescribed for these patients.[2,3] Laxatives are classified into osmotic and stimulant types.[4,5] The most commonly used osmotic laxatives in Japan are made of magnesium oxide (MgO). MgO is annually used by 45 million Japanese people.[6] While MgO is a relatively safe drug, there is a potential risk of excessive absorption resulting in dose-dependent hypermagnesemia in patients with bowel disorder or renal insufficiency.[7] In 2008, the Ministry of Health, Labour, and Welfare Ministry of Japan alerted healthcare facilities about a relationship between the use of MgO and hypermagnesemia.[6]

Total body magnesium concentration mainly depends on gastrointestinal absorption and renal excretion.[8] Generally, renal function in the elderly is diminished, and drugs excreted from the kidney require a dose reduction.[9] According to a previous study on the correlation between intake of MgO and serum magnesium concentration in elderly inpatients, patients with decreased renal function have a higher serum magnesium concentration.[7] However, those results are not sufficient to establish a clear prescription criteria for MgO administration in elderly outpatients. Generally, physicians use estimated Glomerular filtration (eGFR) for evaluation of patient's renal function, and classify eGFR into GFR category based on a clinical guideline. Therefore, we investigated the correlation between renal function classified by using international guidelines and serum magnesium concentration in elderly patients treated with MgO in the outpatient setting of an urban hospital in Japan. And the aim of study was to provide a clear prescription criteria for MgO administration in elderly outpatients.

Method

Study participants

In the present study, we enrolled 44 elderly patients who visited Kameyama Municipal Medical Center from March 1, 2011 to October 31, 2011. Kameyama Municipal Medical Center is an urban small hospital in Kameyama City in the Mie prefecture and has 60 sick beds. Of 44 patients, 23 had chronic constipation treated with daily oral MgO, and

21 untreated patients included in the control group. All patients were aged 65 years or older. We excluded patients who had chronic renal failure receiving hemodialysis, cognitive impairment, or acute disease. We recorded age, sex, daily dose of MgO, intake of other magnesium-containing supplements, and symptoms associated with hypermagnesemia. Symptoms of hypermagnesemia were defined as skin flushing, lethargy, headache, somnolence, and nausea.[7,8,10,11] These symptoms were collected through personal interview. The study was approved by the local ethical committee at Kameyama city, and all participants signed an informed consent prior to their participation.

Clinical and laboratory measurements

Body weight and height were measured. Laboratory tests included measurements of serum magnesium concentration, blood urea nitrogen level, and serum creatinine level. We calculated the estimated glomerular filtration rate (eGFR) according to following equation suitable for the Japanese: eGFR = 194 $\times$ serum creatinine$^{-1.094}$ $\times$ age$^{-0.287}$ [$\times$ 0.739 if female].[12] According to the KDIGO (Kidney Disease: Improving Global Outcomes) 2012 Clinical Practice Guidelines, we classified the participants' renal function into GFR categories.[13] The GFR categories are classified into five groups: G1 (eGFR $\geq$ 90 mL/min/1.73m^2), G2 (60–89), G3a (45–59), G3b (30–44), G4 (15–29), and G5 (15>).

Statistical analysis

Continuous variables are presented as the median and interquartile range, and categorical variables are presented as the percentage. Patient age, body weight, height, and laboratory values were compared according to their intake of MgO using the Mann-Whitney U test, and other categorical data were compared using Fisher's exact test. In the MgO group, serum magnesium concentration according to GFR category was compared using the Kruskal-Wallis test. A P-value <0.05 was considered significant. All statistical analyses were carried out using EZR on R-commander (version 1.24 for Windows).[14]

Results

The clinical and laboratory characteristics of the study participants are shown in Table 1. There were no significant differences in age, sex, height, and weight between groups. Some participants in both groups had symptoms associated with hypermagnesemia, with no significant difference between groups. None of the patients took other magnesium- containing supplements. The median daily dose of MgO was 1.0g (1.0–1.5)

in the MgO group. Compared to the control group, the MgO group showed a significantly higher concentration of serum magnesium [median 2.2 mg/dL (interquartile range 2.1−2.3) vs. 2.4 mg/dL (2.2−2.6), P < 0.001], but there was no significant difference in serum blood urea nitrogen level, serum creatinine level, or eGFR values between groups.

Hypermagnesemia (≥2.6 mg/dL) was only seen in the MgO group (Figure 1), with the highest serum magnesium level being 3.1 mg/dL. We classified all participants into two groups according to the serum magnesium concentration; normal group and hypermagnesemia group, and found no difference in the incidence of symptoms associated with hypermagnesemia (Table 2).

In the MgO group, there was no significant correlation between age and serum magnesium concentration (r =0.238, P = 0.274). The number of patients in each GFR category group was not significantly different between the MgO group and the control group (Table 3).

In the MgO group, the median serum magnesium concentration was significantly different according to eGFR category (P < 0.05) (Table 4). The GFR category G4 (GFR 15−29 mL/min/1.73 m^2) group had the highest serum magnesium concentration in the MgO group [3.0 mg/L (2.9−3.1)].

Discussion

In our results, compared to the control group, the MgO group showed significantly higher concentration of serum magnesium. Furthermore, patients with low renal function, such as those in the GFR category G4 group (eGFR 15−29 mL/min/1.73 m^2) had the highest levels of serum magnesium in the MgO group. These results suggest that physicians take caution when prescribing MgO for elderly patients with decreased renal function less than G3b of GFR category.

Magnesium is the fourth most abundant cation in the body, and the second most prevalent intracellular cation. Total body magnesium levels depend mainly on gastrointestinal absorption and renal excretion. The kidney is the principal organ involved in magnesium regulation. Hypermagnesemia is rare and iatrogenic after intravenous magnesium or when magnesium-containing laxatives or supplements have been administered.[8,15] Those most at risk are the elderly and patients with bowel disorders or renal insufficiency. In other words, the cause of hypermagnesemia includes intake of magnesium-containing drugs, decreased renal excretion, and rarely, redistribution with acidosis.[8]

A previous study on 6,252 patients in Japan showed that only 51 patients (0.8%) had hypermagnesemia.[10] All 51 patients received treatment with magnesium-containing drugs, while only a portion of them had renal failure.-Another study on 996 patients with

electrolyte imbalance admitted to the emergency department in Turkey reported that only 10 patients (1.0%) were hypermagnesemic.[16] These two reports suggest that hypermagnesemia is a rare electrolyte disorder and an iatrogenic cause.

There are several reports on the correlation between intake of magnesium-containing laxatives and symptomatic hypermagnesemia worldwide. According to a case report in the United States, and South Korea, and two case reports in Japan, all patients had some degree of bowel disorder and all took magnesium-containing laxatives.[11,17,18,19] In these cases, hypermagnesemia had an iatrogenic cause.

Constipation is a common health problem in elderly.[2-5] A previous study showed that 70.7% of elderly residents of nursing homes in Spain have chronic constipation.[2] In another report in China, 18.1% of the elderly population has constipation.[3] Similarly, in Japan, constipation is expected as a common health problem in the elderly. Magnesium-containing laxatives, such as MgO, are the most commonly prescribed osmotic laxatives in Japan.[6] In addition over-the-counter magnesium-containing drugs such as antacids, many laxatives, and herbal supplements are easily available to the population.[8] In 2008, the Ministry of Health, Labour, and Welfare Ministry of Japan called attention to all healthcare facilities in Japan on the relationship between the use of MgO and hypermagnesemia, and recommended that the serum magnesium concentration of such drugs users be checked regularly.[6] However, serum magnesium concentration is not examined routinely in blood tests.[16] After this recommendation was announced, several studies examining the relationship between serum magnesium concentration and intake of MgO were performed in Japan.

In a study of children with functional constipation treated with MgO, the serum concentration of magnesium in the MgO group was significantly higher than in the control group.[20] The renal function of all participants were normal in that study, and the serum magnesium concentration decreased significantly with age. In our study, there was no significant correlation between serum magnesium concentration and age.

In another study in patients from facilities for the physically and psychiatric handicapped, whose age ranged from 9 to 82 years, and whose GFR values, which indicate renal function, were in greater than the G2 category, there were no significant correlation between serum magnesium concentration and duration of intake of MgO, the daily dose of MgO, or patient renal function.[21] In our study, the GFR values of our participants were classified into the G2, G3, or G4 category, and the median serum concentration of the G4 category group was significantly higher than that of the other groups.

In a study of 1,282 elderly inpatients over 65 years of age, the serum concentration of magnesium in the MgO group was significantly higher than that in the control group.[7]

In addition, the serum magnesium concentration was significantly higher in patient with eGFR less than 30mL/min/1.73 m^2 than in patients with eGFR more than 30 mL/min/1.73 m^2. According to KDIGO guidelines, patients with eGFR less than 30 mL/min/1.73 m^2 are classified into the G4 category. This result is similar to the finding of our study. However, differences with our study are that, in the previous study, the patients' renal function was not classified based on the KDIGO guidelines, and that inpatients were included. In that study, the GFR categories are uniquely defined into five groups: Group 1 (eGFR < 30 mL/min/1.73 m^2), Group 2 (30−59), Group 3 (60−89), Group 4 (90−129), and Group 5 (≤130).

In these three Japanese studies, no patients developed symptomatic hypermagnesemia. In our study, symptoms associated with hypermagnesemia were compared between the normal group (1.4−2.5 mg/dL) and hypermagnesemia group (≥2.6 mg/dL), but no significant differences were noted (Table 2). We also assessed symptoms of hypermagnesemia (skin flushing, lethargy, headache, somnolence, and nausea), but these symptoms are not disease-specific but rather common symptoms that may occur in patients who do not have hypermagnesemia. Generally, the symptomatic hypermagnesemia may develop when the serum magnesium concentration is greater than 4.8 mg/dL.[11] In fact, the maximum serum concentration of magnesium was 3.1 mg/dL in our study.

Our study had several limitations. First, our study included a small sample size. Second, we did not evaluate the conditions of the gastrointestinal tract of patients. Third, we did not check the patient's compliance with intake of MgO. However, there are also several strengths to our study. First, to the best of our knowledge, this is the first study to evaluate the serum magnesium concentration of elderly patients treated with MgO according to GFR category based on KDIGO guidelines. Second, since we investigated elderly outpatients, our results are useful to primary care physicians.

In conclusion, elderly patients treated with MgO had elevated levels of serum magnesium compared to patients not treated with MgO. In patients with renal function lower than a GFR category of G3b (GFR < 30 mL/min/1.73 m^2), physicians should prescribe MgO with caution.

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Disclosure statement

The authors declare no conflicts of interest.

References

1 Yamada T, Yoshimura M, Nago N *et al*. What is the common diseases and common health problems? - The use of ICPC in the community-based project -. *Jpn J Prim Care* 2000; 23: 80−89. (In Japanese)

2 Rey E, Barcelo M, Jimenez Cebrian MJ, Alvarez-Sanchez A, Diaz-Rubio M, Rocha AL. A nation-wide study of prevalence and risk factors for fecal impaction in nursing homes. *PLOS ONE* 2014. doi: 10.1371/journal.pone.0105281

3 Chu H, Zhong L, Li H, Zhang X, Zhang J, Hou X. Epidemiology characteristics of constipation for general population, pediatric population, and elderly population in China. *Gastroenterol Res Pract* 2014. doi: 10.1155/2014/532734

4 Liu LW. Chronic constipation: Current treatment options. *Can J Gastroenterol* 2011; 25 Suppl B: 22B−28B.

5 Gandell D, Straus SE, Bundookwala M, Tsui V, Alibhai SM. Treatment of constipation in older people. *CMAJ* 2013; 185 (8): 663−670.

6 Pharmaceuticals and Medical Devices Safety Information No. 252 (Bulletin on the Internet). Tokyo: Pharmaceutical and Food Safety Bureau. Ministry of Health, Labour, and Welfare of Japan; 2008 (cited 2015 Jan 19). Available from: http://www.info.pmda.go.jp/iyaku_anzen/file/PMDSI252.pdf. (In Japanese)

7 Saito N. Influence of impaired renal function and magnesium oxide administration on serum magnesium levels in elderly inpatients. *Nippon Ronen Igakkai Zasshi* 2011; 48: 263−270. (In Japanese)

8 Sharon M. Disorders Involving Calcium, Phosphorus and Magnesium. *Prim Care* 2008; 35 (2): 215−237.

9 Rothschild JM, Bates DW, Leape LL. Preventable Medical Injuries in Older Patients. *Arch Intern Med* 2000; 160: 2717−2728.

10 Hashizume N, Mori M. An Analysis of Hypermagnesemia and Hypomagnesemia. *Jpn J Med* 1990; 29 (4): 368−372.

11 Onishi S, Yoshino S. Cathartic-induced Fatal Hypermagnesemia in the Elderly. *Intern Med* 2006; 45 (4): 207−210.

12 Matsuo S, Imai E, Horio M *et al*. Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; 53: 982−992.

13 KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (Guideline on the Internet). 2013 (cited 2015 Jan 19). Available from:
http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf.

14 Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical

statistics. *Bone Marrow Transplant* 2013; 48 (3): 452–458.

15 Weisinger JR, Bellorin-Font E. Magnesium and phosphorus. *Lancet* 1998; 352: 391–396.

16 Balci AK, Koksal O, Kose A *et al*. General characteristics of patients with electrolyte imbalance admitted to emergency department. *World J Emerg Med* 2013; 4 (2): 113–116.

17 Khairi T, Amer S, Spitalewitz S, Alasadi L. Severe symptomatic hypermagnesemia associated with over-the-counter laxatives in a patient with renal failure and sigmoid volvulus. *Case Rep Nephrol* 2014. doi: 10.1155/2014/560746

18 Yoon HE, Kim YW, Ha KS, Sim EH, Go SW, Shin SJ. Hypermagnesemia Accompanied with Colonic Perforation in a Hemodialysis Patient. *Yonsei Med J* 2013; 54 (3): 797–800.

19 Kontani M, Hara A, Ohta S, Ikeda T. Hypermagnesemia induced by massive cathartic ingestion in an elderly woman without pre-existing renal dysfunction. *Intern Med* 2005; 44 (5): 448–452.

20 Tatsuki M, Miyazawa R, Tomomasa T, Ishige T, Nakazawa T, Arakawa H. Serum magnesium concentration in children with functional constipation treated with magnesium oxide. *World J Gastroenterol* 2011; 17 (6): 779–783.

21 Hamada S, Morimoto M, Mori K *et al*. Clinical analysis for the safety of patients receiving long-term treatment with magnesium oxide. *Nihon Byouin Yakuzaishikai Zassi* 2010; 46 (8): 1074–1078. (In Japanese)

Figure 1

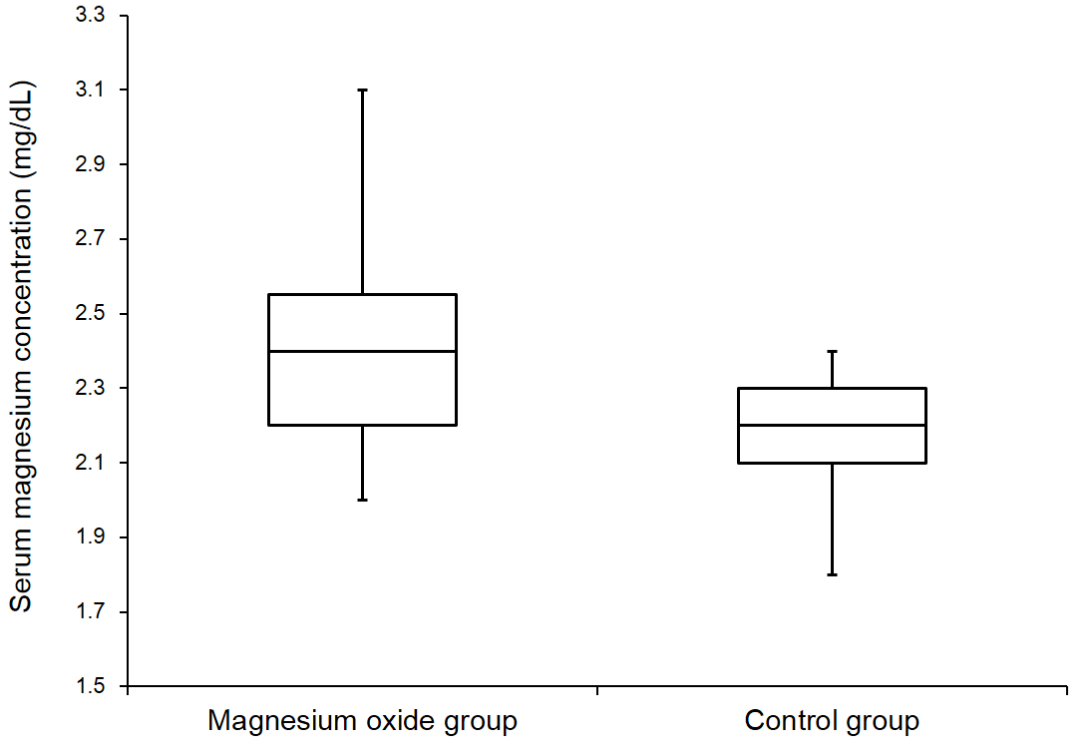

Figure legends

Figure 1. Serum magnesium concentration in the magnesium oxide group and in the control group

Table 1. Clinical and laboratory characteristics of the study participants

	Magnesium Oxide (n=23)	Control (n=21)	P-value
Age (years)	80.0 (77.5–85.5)	80.0 (76.0–85.0)	0.805
Sex (proportion of men, %)	34.8	42.8	0.758
Height (cm)	146.5 (143.0–157.0)	150.8 (144.0–157.0)	0.497
Weight (kg)	49.0 (42.7–61.8)	50.1 (45.2–62.7)	0.563
Symptoms of hypermagnesemia (number of patients)			
Skin flushing	1	2	0.599
Headache	3	6	0.272
Somnolence	3	6	0.272
Lethargy	5	5	1
Nausea	2	1	1
Intake of other magnesium-containing supplements (number of patients)	0	0	NA
Daily dose of MgO (g)	1.0 (1.0–1.5)	0	NA
Serum Mg (mg/dL)	2.4 (2.2–2.6)	2.2 (2.1–2.3)	<0.001
Serum BUN (mg/dL)	17.0 (14.5–21.0)	18.0 (15.0–19.0)	0.962
Serum Cr (mg/dL)	0.8 (0.7–1.2)	0.9 (0.7–1.0)	0.561
eGFR (mL/min/1.73 m^2)	50.6 (38.4–68.9)	60.8 (51.0–71.0)	0.269

Continuous variables are presented as the median and interquartile range, and the proportion of men is presented as the percentage. Symptoms of hypermagnesemia and intake of other magnesium-containing supplements are presented as the actual number. MgO, magnesium oxide; Mg, magnesium; BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration rate; NA, not applicable.

Table 2. Serum magnesium concentration and symptoms of hypermagnesemia

	Hypermagnesemia group (n=6)	Normal group (n=38)	P-value
Symptoms of hypermagnesemia (Number of patients)			
Skin flushing	0	3	1
Headache	1	8	1
Somnolence	1	8	1
Lethargy	2	8	0.606
Nausea	1	2	0.363

Hypermagnesemia defined as a serum magnesium concentration greater than 2.6 mg/dL, Normal serum magnesium concentration defined by a range of 1.6–2.5 mg/dL.

Table 3. Number of patients in each GFR category

	Magnesium Oxide (n=23)	Control (n=21)	P-value
GFR categories (mL/min/1.73 m^2)			
G1 ≥90	0	0	NA
G2 60–89	9	11	0.545
G3a 45–59	5	6	0.732
G3b 30–44	6	2	0.245
G4 15–29	3	2	1
G5 <15	0	0	NA

Data are presented as the actual number. GFR, glomerular filtration rate; NA, not applicable.

Table 4. Serum magnesium concentration in each GFR category in the MgO group

	Serum magnesium concentration (mg/dl)
GFR categories (mL/min/1.73 m^2)	
G1 ≥90	No case
G2 60−89	2.4 (2.2−2.5)
G3a 45−59	2.3 (2.2−2.4)
G3b 30−44	2.4 (2.3−2.4)
G4 15−29	3.0 (2.9−3.1)
G5 <15	No case
P-value	0.0451

Data are presented as the median and interquartile range. GFR, glomerular filtration rate; MgO, magnesium oxide.