Severe hypermagnesemia induced by magnesium oxide ingestion: a case series

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Abstract

Hypermagnesemia is generally considered an exceptional iatrogenic condition usually caused by magnesium-containing cathartics. In particular, this condition often develops when magnesium-containing cathartics are administered to elderly patients with renal insufficiency or bowel movement dysfunction. Although magnesium oxide (MgO) is widely prescribed as a laxative, serum magnesium concentration has not been examined in most cases. In this report, we present the cases of four elderly patients with constipation and symptomatic hypermagnesemia caused by MgO ingestion, one of which had a lethal course. All of the patients were older than 65 years and with renal dysfunction. In addition, they had difficulties in expressing their symptoms because of cerebrovascular events or dementia. These cases suggest that hypermagnesemia caused by magnesium-containing cathartics is more likely to develop than previously recognized and that physicians should be aware that patients with chronic kidney disease and the elderly are at risk of hypermagnesemia on magnesium administration. We recommend serum magnesium monitoring for high-risk patients after initial prescription or dose increase.

Keywords Hypermagnesemia · Magnesium oxide · Constipation · Chronic kidney disease · Cathartic

Introduction

Hypermagnesemia is generally an iatrogenic condition caused by magnesium-containing cathartics [1]. Magnesium oxide (MgO) is a commonly prescribed laxative in Japan and is used by almost 10 million individuals [2]. Although elderly patients with renal insufficiency or bowel disorders are at high risk for hypermagnesemia [1, 3], this condition has been considered exceptional because cases of acute magnesium toxicity have been poorly documented.

However, the Ministry of Health, Labour and Welfare in Japan alerted healthcare facilities in 2015 regarding the relationship between MgO use and hypermagnesemia [2]

because several severe cases ($n=29$) of iatrogenic hypermagnesemia had been reported in the past 3 years, and four of these patients had died. It is conceivable that severe hypermagnesemia is more likely to develop than we have expected because many physicians prescribe magnesium-containing cathartics to high-risk patients without serum magnesium examination and monitoring.

In this case series, we describe the clinical course of four elderly patients with constipation who developed severe symptomatic hypermagnesemia induced by MgO ingestion. The cases were observed within 3 months, and one patient died. The findings suggest that hypermagnesemia is a serious condition and occurs more often than previously recognized.

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Case report

Patient 1

An 88-year-old woman from a nursing home presented to our outpatient department reporting appetite loss and progressive generalized weakness for the past 3 days. She

had severe dementia, was bedridden, and had a history of stage 4 chronic kidney disease (CKD) with serum creatinine (SCr) levels of 2.7 mg/dL and an estimated glomerular filtration rate (eGFR) of 13.4 mL/min/1.73 m². MgO (660 mg/day) had been prescribed for the past 2 years. At the time of arrival, she appeared drowsy and had a blood pressure of 130/80 mmHg, regular pulse rate (59 beats per min [bpm]), and body temperature of 35.8 °C. Pale complexion and cutaneous dryness were detected on physical examination. Neurological examination revealed lethargy with a Glasgow Coma Scale (GCS) score of 10 (E4V1M5) and hypoactive Achilles tendon reflexes. Laboratory analysis revealed severe anemia (hemoglobin, 7.9 g/dL; hematocrit, 24.6%), acute kidney injury (SCr, 5.27 mg/dL; serum urea nitrogen, 62 mg/dL), hyperkalemia (7.0 mEq/L), and hypermagnesemia (6.9 mEq/L). Venous blood gas analysis revealed metabolic acidosis (pH, 7.292; pCO₂, 44.2 mmHg; bicarbonate, 19.5 mEq/L).

Electrocardiography (ECG) showed a sinus rhythm (59 bpm) and mild QT interval prolongation (467 ms). Hemodialysis was first considered to improve her magnesium levels. However, her family did not approve of the treatment. Hence, she was treated with a 20-mL intravenous infusion of 10% calcium gluconate to prevent arrhythmia and with intravenous isotonic fluids (normal saline, 1,000 mL/day for 11 days) plus loop diuretics (furosemide, 20 mg/day for 5 days) to increase the renal excretion of potassium and magnesium. The patient's drowsiness gradually improved after treatment. Her serum potassium and magnesium levels gradually decreased (2.7 and 4.0 mEq/L, respectively), and her SCr level improved to 4.0 mg/dL on the 14th hospital day (Fig. 1). She was discharged on the 15th hospital day.

Patient 2

A 95-year-old woman from a nursing home was presented to our outpatient department with loss of consciousness. Nursing home staff reported that her dietary intake had been reduced for the past 3 days and that she had become drowsy that morning. She had a history of stage 4 CKD with SCr level of 2.3 mg/dL and eGFR of 15.6 mL/min/1.73 m². She also had severe dementia with a Hasegawa Dementia Scale—Revised score of 6/30. Her regular medication included MgO (1320 mg/day) and furosemide (20 mg/day). On examination, she appeared drowsy, with a blood pressure of 128/74 mmHg, regular pulse rate of 67 bpm, and body temperature of 36.7 °C. Neurological examination revealed a comatose state with a GCS score of 10 (E4V1M5) and hypoactive Achilles tendon reflexes. Laboratory analysis revealed the following: anemia (hemoglobin, 9.3 g/dL; hematocrit, 28.6%), acute kidney injury (SCr, 3.56 mg/dL; serum urea nitrogen, 62 mg/dL), hyponatremia (126 mEq/L), and hypermagnesemia (6.1 mEq/L). Other electrolyte data

Fig. 1 Clinical course of patients 1, 2, and 3. *Cr* creatinine, *SCr* serum creatinine, *Mg* magnesium

were normal. Venous blood gas analysis demonstrated no acid–base disturbance (pH 7.434; pCO₂, 44.2 mmHg; bicarbonate, 25.7 mEq/L). There were no ECG abnormalities, including absence of bradycardia and QT interval change. The patient was treated with intravenous isotonic fluid infusion (normal saline, 1,000 mL/day for 11 days) plus loop diuretics (furosemide, 20 mg/day for 5 days) to enhance magnesium excretion. After treatment, her activity gradually improved, and serum magnesium level decreased to 2.1 mEq/L on the 11th hospital day. She was discharged on the 13th hospital day.

Patient 3

An 87-year-old woman developed right thalamic hemorrhage, resulting in mild left hemiparesis, and was admitted to the neurosurgery unit. She had a history of stage 3a CKD with an SCr level of approximately 2.0 mg/dL and eGFR of 18.6 mL/min/1.73 m². She also had hypertension, osteoporosis, and chronic hepatitis C, but no other history of central nervous system (CNS) disease. Oral medication included eldcalcitol (0.75 µg/day) and amlodipine (10 mg/day). On the 14th hospital day, 1,000 mg/day of MgO was prescribed for constipation, which was increased to 2,000 mg/day on the 26th hospital day because the constipation did

not improve. Consequently, she presented with appetite loss and lethargy. On the 29th hospital day, laboratory analysis revealed deterioration of renal function (SCr, 6.4 mg/dL) and hyponatremia (126 mEq/L). She was subsequently referred to the Nephrology Department. At the time of examination, her blood pressure was 126/58 mmHg, regular pulse rate was 65 bpm, and body temperature was 36.8 °C. On physical examination, the oral mucous membranes were dry and skin turgor was reduced. She was alert with a GCS score of 15, but presented with generalized weakness. Her Achilles tendon reflexes were hypoactive. Additional laboratory analysis revealed anemia (hemoglobin, 9.7 g/dL; hematocrit, 28.8%), hypercalcemia (corrected calcium, 11.7 mg/dL), and hypermagnesemia (magnesium, 7.6 mEq/L). Venous blood gas analysis revealed metabolic alkalosis with partial respiratory compensation (pH, 7.461; pCO₂, 46.2 mmHg; bicarbonate, 30.9 mEq/L). No ECG abnormalities were detected, including absence of bradycardia (66 bpm) and QT interval change (408 ms). The patient was administered intravenous isotonic fluid infusion (normal saline, 1000 mL/day for 11 days). After treatment, her serum sodium, corrected calcium, and magnesium levels gradually improved (136 mEq/L, 9.6 mg/dL, and 1.8 mEq/L, respectively); her SCr level improved to 3.7 mg/dL. Her activity also gradually improved. She started rehabilitation 2 days after the infusion was completed.

Patient 4

A 66-year-old woman in a comatose state was brought by ambulance from a local nursing home to our emergency department (ED). The nursing home staff reported that she had a 2-week history of constipation and started taking MgO (330 mg/day) 10 days before going into a coma. She had a history of atrial fibrillation and experienced left cerebral infarction 23 years prior, resulting in right hemiparesis and aphasia. She had relatively mild renal failure, with SCr level of 0.8 mg/dL and eGFR of 55 mL/min/1.73 m². On arrival at our ED, she was comatose with a GCS score of 7 (E1V1M5). Her systolic blood pressure was 78 mmHg and she had an irregular pulse rate (140 bpm) and body temperature of 34.6 °C. Physical examination revealed severe cyanosis of the face and abdominal distension with muscular defense. Laboratory analysis revealed severe hypermagnesemia (11.9 mEq/L). No other electrolyte abnormalities or severe renal failure (SCr, 0.66 mg/dL; serum urea nitrogen, 42 mg/dL) was observed. Arterial blood gas analysis revealed respiratory acidosis with hypoxemia (pH, 7.325; pO₂, 83.4 mmHg; pCO₂, 45.4 mmHg; bicarbonate, 20.5 mEq/L). ECG showed atrial fibrillation with tachycardia (142 bpm); the QT interval could not be calculated. Abdominal computed tomography revealed a prominently distended intestine and enormous fecal accumulation in the large intestine. Additionally, subserosal gas cysts were found in the wall of

the small bowel, and venous gas was observed in the hepatic portal vein (Fig. 2). Two hours after ED arrival, a digestive surgeon suspected acute colonic ischemia and intestinal perforation. Consultation with her family revealed that they did not wish for her to receive invasive therapy, including surgery or hemodialysis. Therefore, the patient was admitted and received fluid replacement therapy. However, her blood pressure decreased and she died 4 h after admission.

Discussion

Magnesium is the fourth most abundant cation in the body and second most prevalent intracellular cation [4]. It is key to the function of essential enzymes, including those related to the transfer of phosphate groups. Magnesium is also important in cellular cytoskeleton contraction and nerve conduction at the myoneural junction and can therefore affect neuromuscular and respiratory functions as well as skeletal and cardiac muscle functions [4, 5]. Homeostasis of the total body magnesium level depends mainly on gastrointestinal absorption and renal excretion and reabsorption. In particular, magnesium reabsorption within the kidneys principally occur at the epithelial cells of the cortical segment of the thick ascending limb of Henle's loop [6], and serum magnesium levels are strictly regulated between 1.5 and 1.9 mEq/L (i.e., 1.7–2.2 mg/dL or 0.75–0.95 mmol/L) [4, 6].

Hypermagnesemia is primarily induced when renal function is impaired and when a large amount of magnesium is loaded. Those at risk are the elderly patients with renal insufficiency or gastrointestinal disorders (active gastric ulcer disease, gastritis, colitis) that can enhance magnesium absorption [1, 3]. Clinical manifestations of hypermagnesemia are related to serum magnesium levels. Nausea, vomiting, bradycardia, and hypotension occur at a serum level of 4–7 mEq/L, whereas somnolence, loss of deep tendon reflexes, and prolongation of the QT interval occur at a serum level of 8–10 mEq/L. Comatose, muscle paralysis, complete AV block, and cardiac arrest can occur at serum levels greater than 12 mEq/L [7, 8].

Hypermagnesemia has been considered an exceptional condition because cases of acute magnesium toxicity have been poorly documented. However, the Ministry of Health, Labour and Welfare of Japan alerted healthcare facilities regarding the relationship between MgO use and hypermagnesemia in 2015 because severe iatrogenic hypermagnesemia cases had been reported [2]. Twenty-nine cases had been reported during the previous 3 years, and four of them had died. Additionally, several severe cases associated with cathartic MgO administration have been reported [9–14]. Table 1 summarizes seven case reports of adult hypermagnesemia induced by MgO ingestion during the past 10 years, including two dead cases. As shown in the table, the number

Fig. 2 Abdominal computed tomography of patient 4 showing a prominent distended intestine and enormous fecal accumulation in the large intestine. Additionally, subserosal gas cysts are found in the

wall of the small bowel (white arrow), and venous gas is observed in the hepatic portal vein (white arrowhead)

of published case reports of hypermagnesemia induced by MgO ingestion is limited.

Herein, we have reported cases of four elderly patients with constipation who developed severe hypermagnesemia caused by MgO ingestion, one of whom died. All of the patients had CKD and difficulty reporting their symptoms because of a history of cerebrovascular event or dementia. Notably, these cases were observed during a short 3-month period, when we were eager to check magnesium level at ED. The frequency of cases appears to be higher than previous reports. For example, eight cases of severe hypermagnesemia (plasma magnesium concentration above 6 mg/dL) were seen over a 5-year period in one retrospective study [1]. Horibata et al. [15] recently reported on the relationship between renal function and serum magnesium level in elderly outpatients treated with MgO. The CKD category G4 group had the highest serum magnesium concentration in the MgO group (3.0 mg/dL; range, 2.9–3.1 mg/dL). This finding suggests that there could be more patients who are likely to be predisposed to severe hypermagnesemia than previously recognized.

Among the four patients in our case series, patient 4, who presented with most severe hypermagnesemia and suspected acute colonic ischemia resulting in death, did not have severe renal failure and had a relatively lower MgO intake than did the other patients. Based on these data, we believe that

despite several reports of hypermagnesemia in patients with normal renal function [8, 16], these patients, including the four in our case series, may have had an underlying bowel hypomotility. Additionally, physiological studies indicate two different transport systems for magnesium in the intestine: an active transcellular transport and a passive paracellular pathway [17]. Compared with the active absorption via the transcellular pathway, passive magnesium absorption through the paracellular pathway increases linearly as magnesium intake increases without an obvious threshold [18]. A possible mechanism of action may be that distention of the colon due to impaired bowel movement could cause an increase in magnesium absorption and further deteriorate hypermagnesemia, causing prolonged hypotension and reduced intestinal circulation, which lead to continuous ischemia of the bowel wall and necrosis. Therefore, in this case, hypermagnesemia aggravated constipation and abruptly induced megacolon, hyporeflexia, and hypotension. Considering these findings, when prescribing MgO to elderly patients with CKD, physicians should start from a low dose to prevent symptomatic hypermagnesemia. In addition, that the serum magnesium level should be checked when MgO prescription is started or its dose is increased in high-risk patients. Furthermore, physicians should avoid long-term MgO prescription without serum magnesium monitoring in patients with CNS disorders such as

Table 1 Patient characteristics at presentation in our and reported cases of hypermagnesemia caused by MgO in adults

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Weng et al. [10]	So et al. [11]	Nakao et al. [12]	Nakao et al. [12]	Nakao et al. [12]	Kimura [13]	Hanada et al. [14]
Age (years)	88	95	87	66	72	64	37	86	32	80	85
Sex	F	F	F	F	F	M	F	F	F	F	F
Pulse rate (beats/min)	59	67	65	140	97	72	70	99	89	Not reported	50
Blood pressure (mmHg)	130/80	128/74	126/58	78/-	128/78	Approximately 80/40	69/21	94/27	130/95	Not reported	85/45
Glasgow Coma Scale (EVM) or state of consciousness	10 (E4V1M5)	10 (E4V1M5)	15 (E4V5M6)	7 (E1V1M5)	Lethargic, confused	E1V1M1	E1VTM1	E1V1M1	E1V2M5	Coma	Lethargy, altered level of consciousness
White blood cells (μL)	4460	5870	3570	9420	11,500	20,700	Not reported	Not reported	Not reported	Not reported	Not reported
Hemoglobin (g/dL)	7.9	9.3	9.7	13.4	8.7	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Cr (mg/dL)	5.27	3.56	6.4	0.66	1.9	2.8	2.3	1.1	1.3	2.9	4.4
SUN (mg/dL)	62	62	72	42	36.4	44	9.5	30.2	38.6	50.9	79.4
Na (mEq/L)	130	134	126	140	143	Not reported	131	129	147	Not reported	133
K (mEq/L)	7	5	4.1	4.2	3.8	5.1	2.5	4.7	3.3	Not reported	4.2
Cl (mEq/L)	102	96	89	106	Not reported	Not reported	103	96	102	Not reported	86
Ca (mg/dL)	8.4	8.1	10.6	9.7	7.7	8.7	9.7	8.7	8.9	Not reported	14.5
Corrected Ca (mg/dL)	7.7	8.7	11.7	10.5	9.9	Not reported	Not reported	Not reported	Not reported	Not reported	14.5
Mg (mEq/L)	6.9	6.1	7.6	11.9	6.2	9.2	12.8	14.2	13.1	4.3	8.4
Mg (mg/dL)	8.3	7.3	9.1	14.3	7.4	11.0	15.3	17.0	15.7	5.2	10.2
Arterial or venous blood gas	Venous	Venous	Venous	Arterial	Not reported	Not reported	Arterial	Arterial	Arterial	Arterial	Arterial
pH	7.292	7.434	7.461	7.325	Not reported	Not reported	7.306	7.492	7.426	Not reported	7.445
HCO ₃ ⁻ (mEq/L)	19.5	25.7	30.9	20.5	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	36.0
pCO ₂ (mmHg)	44.2	44.2	46.2	45.4	Not reported	Not reported	40.3	38.2	67.6	Not reported	Not reported
Daily dose of MgO (mg)	660	1320	2000	330	1000	1500	3000	2000	2000	Irregular dose	6000

Table 1 (continued)

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Weng et al. [10]	So et al. [11]	Nakao et al. [12]	Nakao et al. [12]	Nakao et al. [12]	Kimura [13]	Hanada et al. [14]
Background of gastrointestinal disease	Constipation	Constipation	Constipation	Constipation	Constipation	Gastric ulcer	Constipation	Constipation	Constipation	Constipation	None
CKD stage at baseline	Grade 5	Grade 4	Grade 4	Grade 3a	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Grade 2
Past history of CNS disease	Dementia	Dementia	Thalamic hemorrhage	Cerebral infarction with aphasia	None	Head injury	Schizophrenia	Cerebral infarction	Cerebral palsy	Dementia	None
ECG abnormality	QT prolongation	None	None	Atrial fibrillation with tachycardia	Prolonged PR and QT interval	PEA, and then junctional rhythm	Prolonged PR and QT interval	Prolonged PR interval	None	Not reported	Prolonged PR interval and bradycardia
Achilles tendon reflex test	Hypoactive	Hypoactive	Hypoactive	Not examined	Decreased	Not reported	Not reported	Not reported	Not reported	Not reported	Absence
Outcome	Recovered	Recovered	Recovered	Died	Died	Recovered	Recovered	Died	Recovered	Recovered	Recovered

M male, *F* female, *SUN* serum urea nitrogen, *Cr* creatinine, *Na* sodium, *K* potassium, *Cl* chloride, *Ca* calcium, *Mg* magnesium, *MgO* magnesium oxide, *CNS* central nervous system, *CKD* chronic kidney disease, *ECG* electrocardiography

cerebrovascular events or dementia because of the patients' difficulties in expressing their symptoms. If possible, physicians should consider alternative laxatives, such as anthraquinones (e.g., senna), diphenylmethanes (e.g., sodium picosulfate), or poorly absorbed sugars (e.g., sorbitol) [19].

We also observed that metabolic alkalosis, hypercalcemia, and kidney dysfunction coexisted in patient 3, who had been prescribed with activated vitamin D and MgO. Generally, increased renal tubular bicarbonate reabsorption by volume depletion and suppression of the parathyroid hormone in response to hypercalcemia and hypermagnesemia [20] could induce and maintain metabolic alkalosis. Based on these findings, in our case, excessive MgO and vitamin D could have caused the metabolic alkalosis and maintained the self-perpetuating cycle, resulting in severe hypermagnesemia.

Treatment for patients with hypermagnesemia requires increasing renal magnesium excretion through high-volume normal saline infusion and loop diuretic administration. Loop diuresis inhibits tubular reabsorption of magnesium in the thick ascending limb of Henle's loop. Hemodialysis should be considered when kidney function is impaired or the patient is symptomatic. Patients with symptomatic hypermagnesemia should be administered with intravenous calcium as a magnesium antagonist to reverse the neuromuscular and cardiac effects of hypermagnesemia [21]. In the cases reported herein where each patient had symptomatic hypermagnesemia, hemodialysis was indicated but was not performed, as their family did not consent.

In summary, we suggest that hypermagnesemia is more likely to develop in elderly patients than previously thought. Without close observation, hypermagnesemia can be fatal. Physicians do not have to discontinue MgO prescription, but should monitor serum magnesium level when they prescribe or increase MgO in high-risk patients to prevent symptomatic hypermagnesemia.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from all participants included in the study.

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