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Acid-Base and Electrolyte Teaching Case

Treatment of Hypomagnesemia

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Serum magnesium concentration is determined by the interplay of intestinal absorption and renal excretion. Hypomagnesemia can occur as a result of insufficient magnesium intake, increased gastrointestinal or renal loss, or redistribution from extracellular to intracellular compartments. A number of drugs are known to cause hypomagnesemia, including proton pump inhibitors (PPIs). We report the case of a patient with symptomatic hypomagnesemia due to short bowel syndrome and PPI therapy. Investigations revealed low 24-hour urinary magnesium excretion and secondary hypocalcemia. PPI treatment was withdrawn and the patient was managed with intravenous and oral magnesium and calcium replacement. This teaching case provides an evidence-based discussion of the treatment of hypomagnesemia.

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INDEX WORDS: Hypomagnesemia; treatment; intravenous magnesium sulfate; oral magnesium salts; proton pump inhibitor.

Note from Feature Editor Jeffrey A. Kraut, MD: This article is part of a series of invited case discussions highlighting either the diagnosis or treatment of acid-base and electrolyte disorders. The present case discussion is the second of 2 articles describing a physiologic-based approach to the diagnosis or treatment of hypomagnesemia. In this article, Drs Ayuk and Gittoes present their approach to the treatment of hypomagnesemia; in the first teaching case, Dimke et al[1] described their approach to the evaluation of hypomagnesemia.

INTRODUCTION

Serum magnesium concentration is determined by the interplay of intestinal absorption and renal excretion. Hypomagnesemia can occur as a result of insufficient magnesium intake, increased gastrointestinal or renal loss, or redistribution from extracellular to intracellular compartments.[2] Conditions such as inflammatory bowel disease and short bowel syndrome, which are associated with diarrhea, malabsorption, or steatorrhea, can result in magnesium loss. A number of drugs are known to cause hypomagnesemia, with recent attention focusing on proton pump inhibitor (PPI) therapy. This report describes the case of a patient with inflammatory bowel disease who was on PPI therapy and presented with symptomatic hypomagnesemia. We discuss the management of hypomagnesemia, proposing treatment regimens based on available evidence.

CASE REPORT

Clinical History and Initial Laboratory Data

A 61-year-old woman presented with anorexia, vomiting, weakness, paraesthesia, and carpopedal spasm. She had longstanding Crohn disease and had undergone segmental small-bowel resection on 2 occasions, complicated by short bowel syndrome. Multiple courses of high-dose prednisolone had left her with significant dyspepsia, and in addition to mesalamine and loperamide, she had been treated with omeprazole for the previous 2 years. On examination, she was tachycardic and appeared volume depleted, with blood pressure of 90/60 mm Hg. Body temperature was 37.2°C and respiratory rate was 24 breaths/min. Chvostek sign was positive. Initial blood test results showed multiple electrolyte abnormalities (Table 1).

Additional Investigations

Subsequent investigations revealed a plasma intact parathyroid hormone (PTH) concentration of 31 (reference range, 14.6-62.7) pg/mL and 25-hydroxyvitamin D level of 21 ng/mL. The patient's 24-hour urinary magnesium excretion was 0.6 (reference range, 4-16) mEq/24 h.

Diagnosis

Hypomagnesemia due to malabsorption and PPI drug use, with secondary hypocalcemia.

Clinical Follow-up

Intravenous electrolyte replacement was undertaken with electrocardiogram monitoring. The patient received a loading dose of 2 g (16 mEq) of magnesium sulfate over 1 hour, followed by 5 g (40 mEq) of magnesium sulfate diluted in 1 L of 0.9% saline solution over 24 hours. Through separate intravenous access, one 10-mL ampule of 10% calcium gluconate diluted in 50 mL of 5% dextrose solution was infused gradually over 10 minutes, followed by an infusion of 10 ampules of 10 mL of 10% calcium gluconate in 1 L of 0.9% saline solution at a rate of 50 mL/h. Omeprazole therapy was stopped and replaced with ranitidine. Oral magnesium and calcium supplementation was initiated concurrently and continued when intravenous replacement was stopped. After 48 hours, her electrolyte levels had normalized and the patient was discharged from the hospital. A week later, serum magnesium and calcium levels were normal and treatment with oral supplements was stopped. To date, there has

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Table 1. Initial Investigation Results

Investigation	Result	Reference Range
Serum sodium (mEq/L)	131	134-146
Serum potassium (mEq/L)	3.6	3.4-5.2
Serum-adjusted calcium (mg/dL)	5.9	8.4-10.4
Serum magnesium (mEq/L)	0.36	1.4-1.9
Phosphate (mg/dL)	2.9	2.5-4.3
SUN (mg/dL)	30.8	9-21
Creatinine (mg/dL)	1.2	0.6-1.3
eGFR (mL/min/1.73 m^2)[a]	43	

Note: Conversion factors for units: serum-adjusted calcium in mg/dL to mmol/L, ×0.2495; serum magnesium in mEq/L to mmol/L, ×0.5; phosphate in mg/dL to mmol/L, ×0.3229; SUN in mg/dL to mmol/L, ×0.357; serum creatinine in mg/dL to μmol/L, ×88.4.

Abbreviations: eGFR, estimated glomerular filtration rate; SUN, serum urea nitrogen.

[a]GFR estimated using the MDRD (Modification of Diet in Renal Disease) Study equation.

been no recurrence of electrolyte disturbances, and her dyspeptic symptoms are well controlled with ranitidine.

DISCUSSION

The patient presented with symptomatic hypomagnesemia. The cause of hypomagnesemia often can be obtained from the history, and a number of potential contributors were apparent immediately in our patient. Severe Crohn disease with small-bowel resection and intestinal failure can lead to malabsorption of electrolytes.[3] Hypomagnesemia may be caused by secondary hyperaldosteronism due to salt and water loss, loss of absorptive area, or nonabsorbed fatty acids binding magnesium and forming soaps within the gut lumen, preventing absorption.[4] Although there is a high prevalence of vitamin D deficiency in patients with Crohn disease, hypocalcemia in this case most likely was due to suppression of PTH secretion and action by hypomagnesemia because 25-hydroxyvitamin D concentration was satisfactory and PTH level was inappropriately normal. The normal serum phosphate concentration confirms the lack of action of PTH.

The management of hypomagnesemia is based on the severity; symptoms rarely occur at magnesium levels >1 mEq/L. General recommendations for the management of hypomagnesemia are provided in Fig 1, but local guidelines are likely to exist and should be consulted.

Due to poor absorption, large doses of oral magnesium preparations cause gastrointestinal side effects. Therefore, patients with symptomatic hypomagnesemia should receive intravenous magnesium therapy, and oral replacement should be reserved for asymptomatic patients. Mild asymptomatic hypomagnesemia

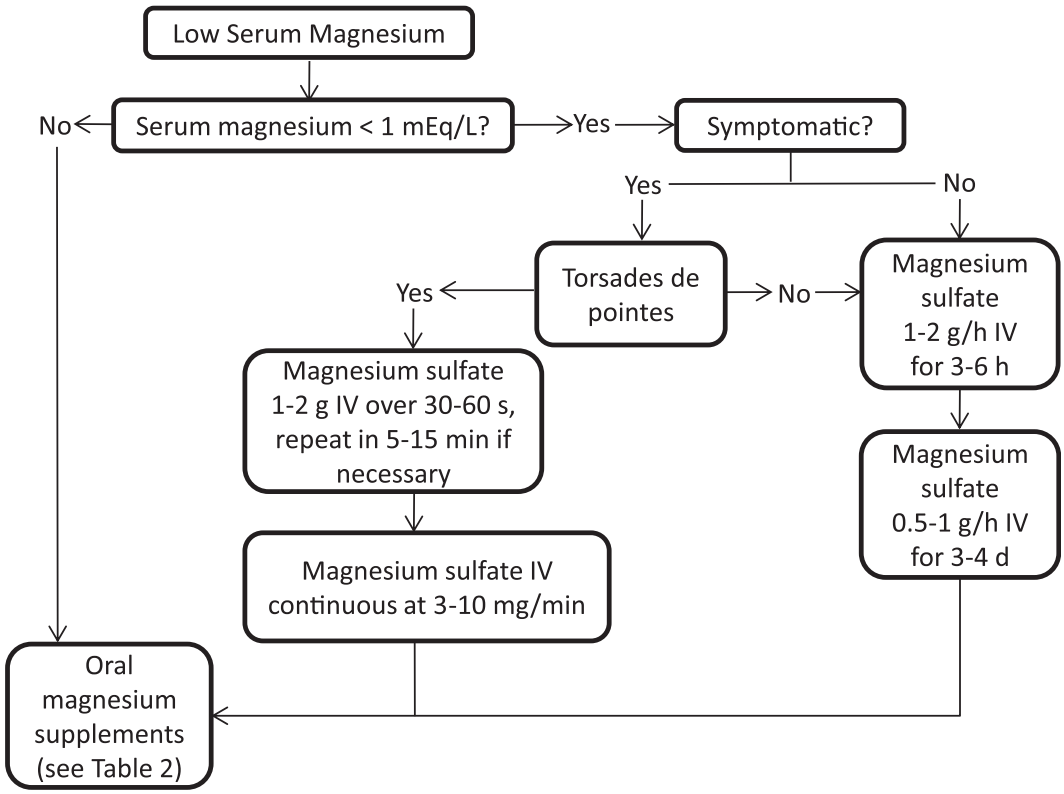

Figure 1. Treatment of hypomagnesemia. Abbreviation: IV, intravenous.

may be replenished by a diet rich in magnesium, but dietary supplements may not be sufficient to normalize magnesium levels in patients with malnutrition or heavy alcohol consumption.[5] The richest dietary sources of magnesium are whole grain cereals, green vegetables, beans, nuts, and seafood.[6] Meats, fish, vegetables, fruits, and chocolates have intermediate magnesium content. Magnesium in drinking water is thought to account for only ~10% of the daily magnesium intake.[7] Refining, processing, or cooking food can significantly deplete magnesium content.[8]

Most commonly, intravenous magnesium is available as a magnesium sulfate formulation: 1 g of magnesium sulfate contains 100 mg (4 mmol or 8 mEq) of elemental magnesium. Injectable magnesium sulfate preparations are 10%, 20%, or 50% solutions; when used intravenously, the latter, which contains 0.5 g of magnesium sulfate per 1 mL (4 mEq/mL), requires dilution with sodium chloride 0.9% or 5% glucose solution to a magnesium concentration ≤20%. No studies have been performed to investigate the optimal regimen for magnesium replacement; however, consensus statements recommend administering 8-12 g of magnesium sulfate in the initial 24 hours, followed by 4-6 g/d for 3 or 4 days to replete body stores.[9] Alternatively, in severe but not life-threatening hypomagnesemia, an infusion of 1-2 g/h of magnesium sulfate can be administered for 3-6 hours, decreased to a rate of 0.5-1 g/h as a maintenance infusion.[10] The goal should be to achieve serum magnesium concentrations >0.8 mEq/L as quickly as possible. Maximum infusion rates generally should remain at <2 g/h, but in the treatment of acute life-threatening arrhythmias such as torsades de pointes, magnesium sulfate can be administered at 1-2 g intravenously over 30-60 seconds, a dose that can be repeated in 5-15 minutes.[11] Another option is to start a continuous infusion at a rate of 3-10 mg/min. This regimen was shown to be effective in 12 patients with torsades de pointes; in 9 of the 12 patients, the initial bolus of 2 g given in 1-2 minutes was associated with complete eradication of torsades de pointes and most ventricular premature beats.[11] In 3 patients, only a partial response was observed and therefore a second bolus was administered 5-15 minutes later. Infusion of magnesium sulfate (3-20 mg/min) was given to 9 of the patients after the initial bolus, in 3 due to partial response to the initial bolus, and in the others, preventively. Rapid intravenous administration can lead to cardiac arrhythmia, depression of neuromuscular function, hypotension, flushing, sweating, and/or a sensation of warmth. Cardiac monitoring and regular clinical assessment of respiratory rate and deep tendon reflexes should be undertaken. In patients with chronic kidney disease, the initial dose should be reduced to 25%-50% of the suggested dose for patients with normal kidney function.[2,12] Electrocardiogram monitoring is recommended with high doses and in elderly patients.

Although magnesium sulfate can be injected intramuscularly, this is painful for patients and generally is used only as a last resort for those lacking intravenous access.[13] Administering the undiluted 50% solution intramuscularly results in therapeutic serum levels in 60 minutes; 1-2 g of magnesium sulfate (2-4 mL of the 50% solution) can be given intramuscularly every 6 hours for 24 hours (a total of 4 doses).

Because plasma magnesium concentration is the primary determinant of magnesium reabsorption in the loop of Henle, an abrupt elevation in plasma magnesium concentration decreases the stimulus for magnesium retention. When the renal threshold for magnesium is exceeded, up to 50% of the infused magnesium will be eliminated in urine.[14] If measured immediately after a magnesium infusion, serum magnesium levels may be higher than anticipated because magnesium is slow to equilibrate between serum and intracellular spaces and tissues. However, this does not indicate repletion of body magnesium stores, and further supplementation with oral magnesium salts often is necessary.

Oral magnesium salts can maintain body magnesium concentrations after intravenous replacement or may be used for the treatment of chronic or asymptomatic hypomagnesemia. However, the gastrointestinal tract generally does not absorb them well and they can cause significant gastrointestinal side effects, in particular diarrhea. Available preparations, which provide 5-8 mEq (60-96 mg) of magnesium per tablet, are listed in Table 2.[15] For severe magnesium depletion, 6-8 tablets should be taken daily in divided doses. Two to 4 tablets daily generally are adequate for mild asymptomatic disease.[14] The bioavailability of oral magnesium preparations depends on the specific magnesium salt and its administration form. Due to its low cost, magnesium oxide commonly is used. There is some evidence to suggest that its bioavailability is lower than some of the other preparations, particularly when capsules are administered rather than effervescent tablets.[16] Sustained-release magnesium preparations, which include Slow Mag ([Purdue Products LP] contains magnesium chloride) and Mag-Tab SR ([Niche Pharmaceuticals Inc] contains magnesium lactate), generally are recommended because they are less likely to cause diarrhea. They also are less likely to cause abrupt elevation of serum magnesium concentrations, which would result in increased urinary magnesium excretion, thereby allowing the slow uptake of magnesium from serum into the cells.[14] If a particular magnesium salt is not effective or is tolerated poorly, another one should be considered.[17] In patients with chronic renal magnesium wasting or those with diuretic-induced hypomagnesemia for whom diuretic therapy cannot be discontinued, a

Table 2. Common Oral Magnesium Preparations

Supplement	Elemental Magnesium Content and Formulation	Recommended Adult Dosage
Magnesium oxide (MagOx)	61% elemental magnesium; 242 mg in 400-mg tablet	2 tablets daily
Magnesium hydroxide (Milk of Magnesia)	42% elemental magnesium; 167 mg in 400 mg/5 mL oral suspension	5-15 mL 4×/d
Magnesium citrate	16% elemental magnesium; 48 mg in 290 mg/5 mL oral solution	120-300 mL daily
Magnesium gluconate (Mag-G)	5% elemental magnesium; 27 mg in 500-mg tablet	1-2 tablets daily
Magnesium chloride (Mag-SR)	12% elemental magnesium; 64 mg in 535-mg tablet	2 tablets once daily
Magnesium lactate (Mag-Tab SR)	10% elemental magnesium; 84 mg in 840-mg tablet	1-2 tablets every 12 h
Magnesium aspartate hydrochloride (Maginex DS)	10% elemental magnesium; 122 mg in 1,230-mg dietary supplement granules	Mix in 4 oz water; take up to 3×/d
Magnesium carbonate	24% elemental magnesium; 121 mg in 500-mg capsules	2-3 tablets daily
Magnesium glycerophosphate (Glysmag)	10% elemental magnesium; 97 mg in 1-g tablets	1-2 tablets 3×/d

Adapted from Guerrera et al[15] with permission of the American Academy of Family Physicians.

potassium-sparing diuretic such as amiloride or triamterene may be a beneficial addition because they decrease magnesium excretion by increasing its reabsorption in the collecting tubule.[14]

PPI drugs inhibit gastric acid secretion and commonly are used for treating and preventing dyspeptic symptoms. A number of severe hypomagnesemia cases have been reported with the long-term use of PPIs.[18-20] The exact mechanism by which PPI drugs cause hypomagnesemia has not yet been elucidated, but low 24-hour urine magnesium excretion has been demonstrated consistently, signifying that it is not mediated by excess renal loss.[19,20] Partial correction of PPI-induced hypomagnesemia can be achieved with high-dose oral magnesium supplements, suggesting that the passive intestinal magnesium transport pathway remains functional and that PPI drugs may disrupt active transport across the intestinal wall by effects on *TRPM6* channel function.[19] Hypomagnesemia due to PPI therapy is thought to take years to develop, but generally resolves within 2 weeks of treatment with the PPI drug being discontinued.[20] After the serum magnesium level has been corrected, the serum magnesium level decreases rapidly if the PPI drug is reintroduced, reflecting the fact that despite achieving normal serum magnesium levels, magnesium stores remain depleted. If treatment with the drug cannot be discontinued, the use of pantoprazole, the least potent PPI drug, combined with oral magnesium supplements when necessary, may achieve acceptable control of reflux symptoms without hypomagnesemia.[20]

In summary, hypomagnesemia is relatively widespread, though the majority of patients remain asymptomatic. Causes include insufficient magnesium intake, increased gastrointestinal loss, increased renal loss, and drugs such as PPIs and loop diuretics. Mild asymptomatic hypomagnesemia may be replenished by a diet rich in magnesium. Patients with symptomatic hypomagnesemia require intravenous magnesium treatment, and oral replacement should be reserved for asymptomatic patients. Box 1 lists the key teaching points of this article.

Box 1. Key Teaching Points

- Serum magnesium concentration is regulated by the interplay of intestinal absorption and renal excretion
- Hypomagnesemia may result from insufficient magnesium intake, increased gastrointestinal or renal loss, or redistribution from extracellular to intracellular space
- The management of hypomagnesemia is based on the severity; symptoms rarely occur at magnesium levels >1 mEq/L
- Patients with symptomatic hypomagnesemia should be managed with intravenous magnesium, oral replacement should be reserved for asymptomatic patients
- Patients with decreased kidney function should receive 25%-50% of the initial dose recommended for patients with normal kidney function
- Oral magnesium salts typically are not well absorbed from the gastrointestinal tract and can cause significant diarrhea

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