

Management of Hypomagnesemia in Cancer Patients Receiving Chemotherapy

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The prevalence of hypomagnesemia in the general population ranges from 2.5% to 15%.¹ In a study of 11,000 white urban Americans aged 45 to 64 years (probability sampling),² 2.5% had a magnesium (Mg) concentration below 0.7 mmol/L, and 5% had a Mg concentration below 0.75 mmol/L. Rates of hypomagnesemia for 4,000 African-Americans were twice as high as for Caucasians. It is also postulated that the higher range for normal serum Mg should be raised in developed countries, as dietary Mg deficiency is endemic there. One reason for this is because rain reduces the Mg content of crops, and food processing causes further large reductions in the Mg content of the diet.¹

Hypomagnesemia may be more prevalent among cancer patients than among the general population. This may be due to the fact that in addition to gastrointestinal (GI; diarrhea) or urinary Mg losses (diuretics, other drugs), malnutrition and decreased dietary Mg intake may hasten the development of Mg depletion.

Facts About Magnesium

Approximately 60% of total body Mg is located in bone, 38% is in the soft tissues (skeletal muscle and liver), and less than 2% is present in the extracellular fluid compartment. The serum levels do not necessarily reflect the status of total body stores. Serum concentration typically ranges from 1.8–2.5 mEq/L. Approximately one third of this concentration is protein-bound, and the free (unbound) fraction of Mg is the active component.

Less than 40% of dietary magnesium is absorbed throughout the small intestine (predomi-

nantly in the ileum) and in the colon. Elimination is predominantly renal. The threshold for urinary excretion is near the normal serum concentration. Therefore, when serum levels exceed 2.5 mEq/L, Mg excretion increases dramatically. Conversely, the kidneys retain a strong capacity to reabsorb Mg, and the main site for reabsorption is the thick ascending loop of Henle (Figure 1). Different factors, such as volume expansion, ethanol ingestion, hypercalcemia, and diuretic administration, may impair renal reabsorption. A minimal daily intake of 0.3 mEq/kg of body weight has been suggested to prevent deficiency. Infants and children tend to have higher daily requirements.

MAGNESIUM AND CARCINOGENESIS

Mg deficiency can paradoxically increase the risk of, or protect against, oncogenesis. Over 300 enzymes that influence the metabolism of carbohydrate, amino acids, nucleic acids and protein, and ion transport require Mg. Its roles in fatty acid and phospholipid acid metabolism that affects permeability and stability of membranes is being elucidated. It has been proposed that Mg is central in the cell cycle and that its deficiency is an important conditioner in precancerous cell transformation. In addition, immunocompetence (that eliminates transformed cells) is Mg-dependent. Mg supplementation of those who are deficient in Mg, such as chronic alcoholic patients, may decrease the emergence of some malignancies.^{3,4}

The effect of Mg on cancer produced by tumor transplants, or by chemicals, has depended on the time Mg supplementation or deficiency was induced relative to exposure to oncogenes.³ Optimal Mg intake may be prophylactic against the initiation of some neoplasms. Because cancer cells have high metabolic requirements, Mg supplementation alone is not indicated in the treatment of cancer.

Causes of Hypomagnesemia

Common causes of hypomagnesemia, which range from GI and renal to shifts from extracellu-

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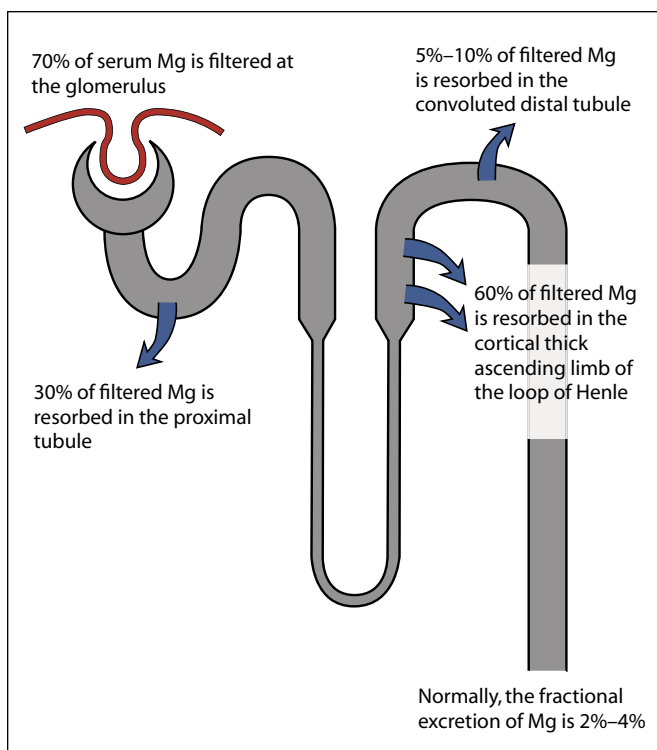


Figure 1 Handling of Magnesium (Mg) by the Kidneys

lar to intracellular fluid, are listed in Table 1. Moreover, many cancer drugs can lead to hypomagnesemia, such as cisplatin, interleukin-2, cyclosporine, enzastaurin, tacrolimus (Prograf; FK506), pegylated liposomal doxorubicin (Doxil), carboplatin (less severe than cisplatin), gallium nitrate (Ganite), dexyspergualin, and drugs against the epidermal growth factor receptor (EGFR) pathway (especially cetuximab [Erbix) and panitumumab [Vectibix]). Other drugs commonly used in cancer patients that can cause or contribute to chemotherapy-induced hypomagnesemia include aminoglycoside antibiotics, amphotericin B, pentamidine, gentamicin, and diuretics.⁵ This article will focus on cisplatin-based regimens, cyclosporine, and the EGFR inhibitor cetuximab.

CISPLATIN-BASED REGIMENS

Cisplatin causes hypomagnesemia in a large percentage of patients, and the incidence increases with the cumulative dose of cisplatin.^{6,7} Hypomagnesemia during cisplatin therapy may be acute or chronic. During the acute phase, apart from cisplatin, other factors contributing to Mg wasting include the use of diuretics and poor dietary intake of Mg.

Chronic hypomagnesemia starts to develop 3 weeks after initiation of chemotherapy and persists usually for several months. Occasionally, hypomagnesemia may persist for several years after completion of treatment. In chronic Mg wasting, patients usually present with hypocalcemia, renal Mg wasting, and hypokalemic metabolic alkalosis—a picture similar to Gitelman syndrome, with features consistent with a distal tubular defect. In addition, there may be a lesion in the proximal tubule, as

shown by increased excretion of B₂ microglobulin and N-acetyl-B-glucosaminase, which are markers of tubular cell damage.^{6,7}

Hypomagnesemia that persists long after the drug treatment has been stopped has been identified in cancer patients. This type of hypomagnesemia is caused by cisplatin-induced renal tubular defect in Mg reabsorption. The renal tubular lesion seems to be of the distal convoluted segment, like that of Bartter syndrome. Comparable renal tubular wasting occurs with the use of vinblastine, bleomycin, and cyclosporine. The observation of progressive lowering of blood Mg levels, despite gradual correction of urinary Mg loss over the week after a single dose (given to patients with lung cancer), suggested that besides causing damage to tubular function, cisplatin may also interfere with Mg cellular metabolism.^{6,7} Preventing the lowering of Mg levels by giving intravenous (IV) Mg infusions has prevented adverse effects of hypomagnesemia.

The anticancer activity of cisplatin has been linked to its effects on mitochondrial Mg and to nucleic acid Mg. Since tumor growth has been enhanced by supplementation with Mg, preventing or correcting the induced Mg depletion, it was anticipated that Mg administration to cancer patients under treatment might diminish the efficacy of the antineoplastic regimen.⁸ However, clinical experience has obviated that apprehension—Mg supplementation accompanying cisplatin treatment has not affected tumor growth rates in human patients, an effect that was confirmed in mice with induced fibrosarcoma or leukemia treated with cisplatin with and without Mg protection against nephrotoxicity.

Carboplatin, an analogue of cisplatin, causes less nephrotoxicity, and only 10% of patients treated with carboplatin develop hypomagnesemia.⁹

CYCLOSPORINE

Hypomagnesemia is seen with both short-term and long-term cyclosporine therapy, and symptomatic hypomagnesemia is seen especially in the elderly or in the presence of other associated conditions causing Mg loss.¹⁰ Cyclosporine causes increased Mg excretion. The hypomagnesemia is usually mild, asymptomatic, and does not necessitate stopping the medication, but occasionally severe symptomatic Mg deficiency is seen. Although total serum Mg concentration during cyclosporine treatment is variable, the ionized Mg concentration is low. Short-term cyclosporine treatment causes hypomagnesemia due to intracellular shift of Mg, whereas long-term treatment causes Mg deficiency as a result of renal Mg wasting.

The newer immunosuppressive agent tacrolimus can also produce hypomagnesemia.¹¹

EGFR INHIBITORS

Agents targeting the EGFR pathway offer promise for the treatment of patients with advanced cancer, particularly when the intent of standard chemotherapy is palliation. EGFR is overexpressed in numerous types of solid tumors, including colorectal cancer (CRC). EGFR activation is associated with proliferation, antiapoptosis, and metastatic spread, making

Table 1
Causes of Hypomagnesemia

Gastrointestinal
Diarrhea
Dietary deficiency (including protein-calorie malnutrition, parenteral and enteral feeding with inadequate magnesium, alcoholism, and pregnancy)
Familial magnesium malabsorption
Gastrointestinal fistulas
Inflammatory bowel disease
Laxative abuse
Malabsorption (sprue, steatorrhea, chronic pancreatitis), nasogastric suction
Surgical resection
Vomiting
Renal
Alcoholism
Diabetes
Diuretics (thiazide, loop, and osmotic/hyperglycemia)
Hypoparathyroidism
Hyperthyroidism
Hyperaldosteronism
Syndrome of inappropriate antidiuretic hormone secretion
Excessive vitamin D
Ketoacidosis
Hypercalcemia/hypophosphatemia
Tubular defects (primary magnesium wasting, Welt syndrome, Gitelman syndrome, renal tubular acidosis)
Shifts from extracellular to intracellular fluid
Acidosis (correction of)
Blood transfusions (massive)
Epinephrine
Hungry bone syndrome
Insulin/glucose/refeeding syndrome
Pancreatitis (acute)
Transdermal losses
Excessive sweating
Massive burns

this pathway a particularly compelling target for rational drug design.³ Currently, there are two classes of anti-EGFR agents: the monoclonal antibodies directed toward the extracellular EGFR domain (cetuximab, panitumumab) and small molecule tyrosine kinase inhibitors that inactivate the receptor enzyme activity (gefitinib [Iressa], erlotinib [Tarceva]).

The most important risk factors for hypomagnesemia in patients receiving EGFR-targeting monoclonal antibodies include duration of treatment, patient age, and baseline Mg level. Elderly patients are more susceptible to this toxicity. Interestingly, patients with higher baseline Mg levels tend to have more pronounced Mg wasting.¹²⁻¹⁴

Hypomagnesemia has emerged as a relatively common side effect of cetuximab and panitumumab therapy.¹²⁻¹⁹

Cetuximab: Although hypomagnesemia was not specifically

Table 2
Incidence of Hypomagnesemia in Pivotal Trials in Metastatic Colorectal Cancer

STUDY	AGENT	INCIDENCE OF GRADE 3/4 HYPOMAGNESEMIA
NCIC CO.17 ¹⁶	Cetuximab	5.8%
EPIC ¹⁴	Cetuximab	3.3%
CRYSTAL ¹⁵	Cetuximab	1.8%

Abbreviations: NCIC = National Cancer Institute of Canada; EPIC = Evaluation of 7E3 for the Prevention of Ischemic Complications; CRYSTAL = Cetuximab Combined With Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer

identified as an adverse event during clinical trials, Mg depletion has been noticed in half of patients treated with cetuximab alone or in combination with chemotherapy.¹²⁻¹⁷

A retrospective review of 154 consecutive patients treated for CRC at a single institution found 34 patients for whom serum Mg had been determined during treatment; 24% of these patients developed grade 3/4 hypomagnesemia (6, grade 3; 2, grade 4; Table 2).¹⁷

Neither the EPIC¹⁴ nor CRYSTAL¹⁵ study mandated monitoring of magnesium levels in enrolled patients. Unfortunately, only 20% of patients in the CRYSTAL study had an Mg level drawn sometime during treatment.¹⁵ This finding may in part explain the lower rate of hypomagnesemia noted in this study compared with the National Cancer Institute of Canada (NCIC) study.¹⁶

Schrag and colleagues¹³ postulated that cetuximab-induced Mg depletion may be related to the high expression of EGFR in the kidneys. After filtration through the glomerulus, approximately 70% of free extracellular Mg is reabsorbed in the thick ascending limb of the loop of Henle. The remainder is reabsorbed in the proximal and distal tubules. EGFR is highly expressed in the apical membrane of the loop of Henle and the distal tubules. The investigators suggested that cetuximab-induced EGFR blockade in the nephron reversibly impairs the active transport of Mg via interference with a specific cation channel, TRPM6. However, at this time, effects on the gut absorption of Mg cannot be ruled out.

A retrospective study¹⁷ from the Roswell Park Cancer Institute suggested a direct relationship between the duration of cetuximab exposure and hypomagnesemia. Tejpar et al¹² also found similar findings in a prospective study of 98 patients treated with EGFR-targeting monoclonal antibodies with or without chemotherapy (Table 3).

Panitumumab: Similar risks of hypomagnesemia have been seen with panitumumab treatment. In a randomized study of panitumumab versus best supportive care, 36% of 229 patients receiving panitumumab had some decline in magnesium levels, but only 3% developed grade 3/4 hypomagnesemia.^{18,19} The median magnesium levels decreased by 0.1 mmol/L in the panitumumab arm; hypomagnesemia (National Cancer Institute–Common Toxicity Criteria grade 3 or 4) requiring oral or IV electrolyte repletion occurred in 2% of patients. Hypo-

Table 3**Relationship Between the Duration of Cetuximab Exposure and Hypomagnesemia**

DURATION OF CETUXIMAB THERAPY	INCIDENCE OF GRADE 3/4 HYPOMAGNESEMIA
Fakih study¹⁷	
< 3 months	5%
3–6 months	23%
> 6 months	47%
Tejpar study¹²	
< 3 months	0
3–6 months	3%
> 6 months	12%

Table 4**Clinical Manifestations of Hypomagnesemia**

Tremor
Hyperactive deep tendon reflexes
Hyperreactivity to sensory stimuli
Muscular fibrillations
Positive Chvostek sign
Positive Trousseau signs
Carpopedal spasms progressing to tetany
Mental status changes:
Irritability
Disorientation
Depression
Psychosis
Reversible respiratory muscle failure may occur in severe hypomagnesemia

magnesium occurred 6 weeks or longer after the initiation of panitumumab. In some patients, hypomagnesemia was associated with hypocalcemia.

Patients' electrolytes should be periodically monitored during and for 8 weeks after the completion of panitumumab therapy. When combined with fluorouracil, oxaliplatin (Eloxatin), and leucovorin, panitumumab was associated with only a 4% incidence of grade 3/4 hypomagnesemia in the first-line treatment of metastatic colorectal cancer.²⁰ The low frequency of hypomagnesemia was likely related to the lack of stringent guidelines for magnesium monitoring.

Diagnosis**LABORATORY ANALYSIS**

The impact of hypomagnesemia is underestimated, largely because clinicians fail to measure Mg as part of the routine screening blood tests.²¹ For example, in a study of 381 consecutive admissions for hypomagnesemia at an inner-city hospital,²² approximately half the admissions went to intensive care units; the other half went to regular wards. Despite similar Acute Physiology and Chronic Health Evaluation (APACHE) scores at admission, hos-

pital mortality was twice as high for hypomagnesemic patients in both care settings.

The possible presence of hypomagnesemia should be suspected in cancer patients receiving the agents previously mentioned and in those with chronic diarrhea, hypocalcemia, refractory hypokalemia, and ventricular arrhythmia. Laboratory analysis by atomic absorption spectrophotometry is the most specific technique available to measure total serum Mg. Ion-selective electrodes for measurement of free Mg have been developed; however, their use has not been rigorously tested, and they currently are not readily available for clinical use.

If hypomagnesemia is confirmed, the diagnosis can usually be obtained from the patient's history. If no cause is apparent, the distinction between GI and renal losses can be made by measuring the 24-hour urinary Mg excretion or the fractional excretion of Mg on a random urine specimen. The latter can be calculated from the following formula:

$$FE_{Mg} = \frac{U_{Mg} \times P_{Cr}}{(0.7 \times P_{Mg}) \times U_{Cr}} \times 100$$

U and *P* refer to the urine and plasma concentrations of Mg and creatinine (Cr). The plasma Mg concentration is multiplied by 0.7, as only about 70% of the circulating Mg is free (not bound to albumin) and therefore able to be filtered across the glomerulus.

The normal renal response to Mg depletion is to lower Mg excretion to very low levels. Thus, daily excretion of more than 10 to 30 mg or a fractional excretion of Mg above 2% in a person with normal renal function indicates renal Mg wasting due, for example, to drugs such as cisplatin.

CLINICAL MANIFESTATIONS

The clinical manifestations of hypomagnesemia are categorized as cardiovascular, neuromuscular, and behavioral (Table 4).²³ Cardiovascular symptoms include ventricular tachycardia, ventricular fibrillation, atrial fibrillation, multifocal atrial tachycardia, ventricular ectopic beats, hypertension, enhancement of digoxin-induced dysrhythmia, and cardiomyopathies. Among the neuromuscular and behavioral symptoms are convulsions, confusion, psychosis, weakness, ataxia, spasticity, tremors, tetany, agitation, delirium, and depression.

ELECTROCARDIOGRAPHIC CHANGES

Hypomagnesemia may be associated with nonspecific electrocardiographic changes, including ST-segment depression, altered T waves, or loss of voltage. Severe Mg deficiency may cause PR prolongation or widened QRS complexes.

Management

The management of hypomagnesemia is based upon the grades of severity (Table 5). For grade 1 hypomagnesemia, no replacement strategy is necessary, as these patients are typically asymptomatic. For patients with grade 2 hypomagnesemia, a weekly IV replacement (4 g of Mg sulfate) for Mg levels of

Table 5**Grades of Severity of Hypomagnesemia: National Cancer Institute–Common Toxicity Criteria Version 3**

Grade 0	Within normal limits
Grade 1	< LLN–1.2 mg/dL or < LLN–0.5 mmol/L
Grade 2	< 1.2–0.9 mg/dL or < 0.5–0.4 mmol/L
Grade 3	< 0.9–0.7 mg/dL or < 0.4–0.3 mmol/L
Grade 4	< 0.7 mg/dL or < 0.3 mmol/L

Abbreviation: LLN = lower limit of normal

0.9–1.0 mg/dL seems to be effective. Oral Mg supplementation may be ineffective and poorly tolerated due to diarrhea.^{4,9} Patients with grade 3/4 hypomagnesemia are often symptomatic and are at increased risk of cardiac arrhythmia. Therefore, these patients should receive appropriate replacement.⁴ Most such patients do not complain of symptoms of hypomagnesemia; such symptoms tend to be attributed to cytotoxic chemotherapy. Correction of grade 3/4 hypomagnesemia can be challenging; frequent IV infusions via central venous access may increase the risk of infections.²⁴ In addition, risk associated with Mg salts should be kept in mind (see Box).

GENERAL GUIDELINES

Mg can be administered either orally in an oxide or gluconate form or parenterally as a sulfate salt. If hypomagnesemia is mild (ie, serum Mg levels > 1.2 mEq/L) and the patient is asymptomatic, oral replacement is appropriate. Little is understood about the uptake kinetics at the cell membrane level, so the optimal dosage to produce an effective intracellular uptake is unknown and varies from patient to patient.

In patients with normal renal function, if serum Mg levels are less than 1 mEq/kg, the estimated total body replacement requirement is approximately 4 mEq/kg of body weight. With renal impairment, these doses should be reduced by at least half. In emergent cases (eg, refractory ventricular tachycardia), 16 mEq (2 mL of a 10% solution) of Mg sulfate may be administered via IV over 5–7 minutes, as rapid IV administration can be life-threatening. Risks involved with IV Mg therapy include hypermagnesemia, hypocalcemia, and sudden hypotension. IV infusion rates should not exceed 67 mEq over 8 hours. Electrolyte levels and hemodynamic parameters should be continuously monitored during replacement under high infusion rates.

Weekly IV replacement is typically inadequate, as serum Mg levels tend to fall back to the low baseline level within 3 to 4 days. Our experience suggests that an initial strategy of IV replacement and monitoring of serum Mg every other day can aid to guide the frequency of replacement until a steady state is reached. We found that hypomagnesemia continues to worsen despite ongoing replacement in some patients, and stopping cetuximab or similar agents for a few weeks can be helpful. This approach can also be used in situations where patients need frequent Mg replacement but do not have a large tumor burden

Facts About Magnesium Replacement**Drug name**

Magnesium gluconate
500 mg contains 27 mg of elemental Mg

Adult dose

500–1,000 mg orally three times daily

Contraindications

Documented hypersensitivity, heart block, myocardial damage, hepatitis

Interactions

1. Concurrent use with nifedipine may cause hypotension and neuromuscular blockade
2. Mg may worsen neuromuscular blockade seen with aminoglycosides, tubocurarine, vecuronium, or succinylcholine
3. Mg may increase CNS effects and toxicity of CNS depressants, betamethasone, or ritodrine

Pregnancy

Safe in pregnancy

Precautions

1. Caution in renal failure
2. May alter cardiac conduction leading to heart block in digitalized patients
3. Monitor respiratory rate, deep tendon reflex, and renal function when administered parenterally
4. Caution when administering Mg dose, as it may produce significant hypertension or asystole
5. Diarrhea is the most common adverse effect

Drug name

Magnesium sulfate
1 g contains 8.12 mEq of Mg (98 mg of elemental Mg)

Adult dose

2 g IV solution over 20 min, then 1 g every 6 hours until levels are corrected

Precautions

1. May alter cardiac conduction leading to heart block in digitalized patients
2. Monitor respiratory rate, deep tendon reflex, and renal function when electrolyte is administered parenterally
3. Caution when administering Mg dose, as may it produce significant hypertension or asystole
4. Dilute to 5%–20% before IV administration; maximum concentration of 20%; rate of administration should be < 1.5 mL of 10% solution or equivalent per min (150 mg/min with ECG monitoring)
5. Rapid IV administration can lead to cardiac dysrhythmia, hypotension, flushing, sweating, and/or a sensation of warmth
6. In overdose, calcium gluconate (10–20 mL IV of 10% solution) can be given as an antidote for clinically significant hypermagnesemia; hypotension, hypocalcemia, respiratory depression, or venous irritation may occur

Abbreviations: Mg = magnesium; CNS = central nervous system; IV = intravenous; ECG = electrocardiographic

or other risk factors for cardiac arrhythmia. Usually, serum Mg levels correct within 6 weeks of stopping cetuximab.

DIET

A component of chlorophyll that is found in high concentrations in green leafy vegetables, Mg also is found in nuts, seeds, peas, beans, and cocoa. Dietary supplements may not be effective in patients with malnutrition or heavy alcohol consumption.

RECHALLENGE

If hypomagnesemia completely resolves after a 4- to 8-week break from cetuximab, rechallenge with such an agent is feasible. This rechallenge usually does not manifest grade 3/4 hypomagnesemia until patients receive an additional 6 to 8 weeks of cetuximab therapy. Oncologists at Roswell Park also found this approach to be successful in several patients with grade 4 hypomagnesemia.¹⁷

Conclusion

Hypomagnesemia is a relatively common side effect of

certain anticancer drugs, especially cisplatin, cyclosporine, and anti-EGFR agents, including cetuximab and panitumumab. Current data suggest a relationship between the duration of exposure to a certain anticancer agent and hypomagnesemia. Other risk factors that have been reported include a patient's age and the baseline magnesium level. Elderly patients are more susceptible to this toxicity. The impact of hypomagnesemia is underestimated largely because clinicians fail to measure magnesium levels. Since magnesium is a cofactor for more than 300 enzymes and is involved in numerous transport mechanisms, it is not surprising that hypomagnesemia is associated with significant morbidity. Therefore, we recommend a proactive approach in managing hypomagnesemia in cancer patients receiving such agents. Future studies are warranted to further understand this complication of anticancer drug therapy.

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