Therapeutic Reviews

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Magnesium *AHFS 28:12, 56:04 & 56:12*

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Indications: Hypomagnesemia, constipation, arrhythmia, eclampsia, †asthma, †myocardial infarction.

Pharmacology

Magnesium is the second most abundant intracellular ion after potassium. It is involved in numerous enzymatic reactions and is a co-factor for many biological processes, most of which use ATP. It is important for bone mineralization, muscular relaxation and neurotransmission. About half of the total body magnesium is in soft tissue, the other half in bone, with less than 1% present in blood.[1-3] Intracellular magnesium is mostly bound to ribosomes, phospholipids and nucleotides.[1]

The estimated average requirement for magnesium in adults is ~265mg for females and ~350mg/24h for males.[4] However, magnesium intake is falling as the use of processed and fast-foods increases, and about half of the US population does not meet this requirement.[3,5] Thus, the incidence of chronic magnesium deficiency is probably increasing, with possible health implications, but is unrecognized because of the diagnostic limitations of serum magnesium (see below).[3,5]

Magnesium competes with calcium for absorption in the small intestine, probably by active transport. The normal serum magnesium is 1.5–1.91mEq/L. However, some have argued that for optimal health, the lower limit for serum magnesium should be considered to be 1.7mEq/L.[3] This is based on a progressive increase in the frequency of magnesium deficiency seen with serum levels between 1.7mEq/L and 1.5mEq/L (from <10% to 90%), which is associated with an increased risk of morbidity, e.g., impaired glucose tolerance, type 2 diabetes mellitus, and mortality, e.g., sudden cardiac death.[3,5]

Magnesium is excreted by the kidneys, 6–24mEq/24h. Magnesium and calcium share the same transport system in the renal tubules and there is a reciprocal relationship between the amounts excreted.

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Magnesium deficiency can result from:

- *reduced intake*, e.g., an inadequate dietary intake (common)
- *reduced absorption*, e.g., small bowel resection, cholestasis, pancreatic insufficiency, diarrhea, stoma, fistula, PPI (rare and generally with prolonged use, i.e., >1 year)[6,7]
- *increased excretion*, e.g., alcoholism, diabetes mellitus, interstitial nephritis, diuretic phase of acute tubular necrosis, hyperthyroidism, hyperparathyroidism, hyperaldosteronism, drug-induced (aminoglycosides, amphotericin, anti-epidermal growth factor receptor monoclonal antibodies, cisplatin, cyclosporine, loop diuretics).

The risk of hypomagnesemia with cisplatin is dose-dependent and increases with cumulative doses (40% cycle 1 → 100% cycle 6).[8] It can persist for 4–5 months, and sometimes years, after completing treatment.[9,10] Although generally mild and asymptomatic, it can be severe and symptomatic.

Hypomagnesemia is an emerging toxicity of anti-epidermal growth factor receptor monoclonal antibodies, e.g., cetuximab, panitumumab.[11,12] The risk increases in the elderly, in those with a higher baseline serum magnesium, and with duration of treatment (e.g., 5% <3 months → 50% >6 months of cetuximab).[11] It is reversible, with magnesium levels returning to normal 4–6 weeks after discontinuation of treatment.[11]

When magnesium deficiency develops acutely, the symptoms may be obvious and severe, particularly muscle cramps, which aids diagnosis (Box A). In chronic deficiency, symptoms may be insidious in onset, less severe and non-specific.

In animal studies, magnesium deficiency results in an increased release of substance P and other mediators from nerve endings. These activate immune cells to release histamine and cytokines, producing a pro-inflammatory state and increased levels of oxygen-derived free radicals and nitric oxide. Manifestations include:[13-15]

- cutaneous vasodilation → erythema and edema
- leukocytosis
- inflammatory lesions in cardiac muscle
- atherogenesis
- increased levels of oxidative stress
- hyperalgesia.

In humans, the incidence of magnesium deficiency increases with aging (due to poor diet, reduced intestinal absorption, increased urinary loss, etc.) and obesity. Magnesium deficiency, aging and obesity are all associated with low-grade inflammation and increased oxidative stress. This has led some to postulate that magnesium deficiency is a contributing factor to age- and obesity-related diseases such as diabetes mellitus, cardiac failure, some cancers (e.g., breast, colon), and hypertension.[14,16-19] In support of this, an inverse relationship between serum magnesium and CRP has been demonstrated in patients with cardiac failure, with magnesium supplementation attenuating the elevated CRP.[20] The underlying mechanisms remain to be clarified, but in part may relate to magnesium acting as a natural "calcium antagonist."[5] Thus, in magnesium deficiency, intracellular calcium levels increase, activating processes which contribute to inflammation.[18]

Serum magnesium is associated with muscle performance, e.g., in the elderly[21] and in patients with coronary artery disease.[22] In the latter, the use of magnesium supplements improved exercise capacity. However, evidence that the use of magnesium supplements or the correction of mild magnesium deficiency, e.g., in patients with diabetes, is of consistent benefit is lacking.[2]

Hypomagnesemia (and hypokalemia) are risk factors for drug-induced *torsade de pointes* arrhythmia. Thus, when using a drug known to prolong the QT interval, e.g., methadone, monitoring of serum electrolytes is generally recommended in patients with cardiac disease or other risk factors for prolonged QT, and in those at risk of electrolyte imbalance, e.g., because of vomiting, diarrhea or diuretics.[23,24]

Hypermagnesemia is rare and is seen most often in patients with renal impairment who take OTC medicines containing magnesium. Serum concentrations >8mEq/L produce drowsiness, vasodilation, slowing of atrioventricular conduction and hypotension. Over 12mEq/L, there is profound CNS depression and muscle weakness (Box A). Calcium gluconate IV is used to help reverse the effects of hypermagnesemia.

Box A. Symptoms and signs of magnesium deficiency and excess

Magnesium deficiency	Magnesium excess
Muscle	Muscle
weakness	weakness
tremor	hypotonia
twitching	loss of reflexes
cramps	Sensation of warmth (IV)
tetany (positive Chvostek's sign)	Flushing (IV)
Paresthesia	Drowsiness
Apathy	Slurred speech
Depression	Double vision
Delirium	Delirium
Choreiform movements	Hypotension
Nystagmus	Cardiac arrhythmia
Seizures	Respiratory depression
Prolonged QT interval	Nausea and vomiting
Cardiac arrhythmia, including *torsade de pointes*	Thirst
Increased pain (?)	Hypermagnesemia
Hypomagnesemia (not always)	
Hypokalemia	
Hypocalcemia	
Hypophosphatemia	

When drugs such as cisplatin cause severe renal wasting of magnesium, hypomagnesemia is generally present and aids diagnosis. If necessary, this can be confirmed by the high urinary excretion of magnesium. In deficiency states which develop more insidiously, the serum magnesium is an insensitive guide to total body stores and hypomagnesemia is not always present.[25,26] In this situation, the finding of a low urinary excretion of magnesium may help the diagnosis. Currently, the best method for detecting magnesium deficiency is the magnesium loading test (Box B).[25,27,28]

Box B. The magnesium loading test[27]

Collect pre-infusion urine sample for urinary magnesium (Mg)/creatinine (Cr) ratio. Measure Mg and Cr in mg/L; divide the Mg value by the Cr value to calculate the Mg/Cr ratio.

By IVI over 4h, give 0.2mEq/kg (2.4mg/kg) of elemental magnesium, using magnesium sulphate 500mg/mL (4mEq or 48.6mg elemental magnesium/mL) diluted to 50mL with 5% dextrose (glucose).

Simultaneously, start a 24h urine collection for magnesium and creatinine. Measure the total amounts of magnesium and creatinine excreted in mg (*not* the concentrations in mgl/L).

Calculate % magnesium retention:

$$1 - \left[\frac{\text{24h urinary Mg (mg)} - (\text{pre-infusion urinary Mg/Cr ratio (mg/L)} \times \text{24h urinary Cr (mg)})}{\text{dose of elemental magnesium infused (mg)}} \right] \times 100$$

>50% retention implies definite deficiency.

If it is not possible to perform a magnesium loading test, hypokalemia (±hypocalcemia) not responding to potassium supplementation should raise the possibility of magnesium deficiency, and a trial of magnesium replacement therapy should be considered.[2]

Magnesium blocks calcium channels including the NMDA-receptor channel and this probably accounts for its analgesic effect (Box C).[29-32] However, despite the overall positive outcome from numerous RCTs, the role of magnesium as an analgesic in palliative care is yet to be determined and ideally such use should be in the setting of a clinical trial.

Box C. Magnesium as an analgesic

A number of studies have explored the effects of magnesium, mainly as an adjuvant analgesic for postoperative pain, with mixed results.

A systematic review of 14 studies concluded that there is no convincing evidence of reduced postoperative pain intensity or decreased analgesic requirements when magnesium was used as an adjuvant.[33]

However, of numerous RCTs undertaken since this systematic review, all but two have reported reduced postoperative pain and decreased analgesic requirements.[34-47]

Further, eight RCTs of spinal magnesium have all reported lower pain scores and decreased analgesic requirements.[48-55]

In a RCT of PO magnesium in patients with neuropathic pain, although the frequency of pain paroxysms and the emotional component of behavior improved, there was no overall difference in pain intensity or quality of life[56]

Cancer cells preferentially accumulate magnesium, which is used to activate or inhibit various metabolic and genetic pathways in order to promote cell survival and proliferation.[57] Animal studies suggest that magnesium deficiency inhibits the growth of the primary cancer but exacerbates metastatic disease, possibly by enhancing inflammation.[57] The relevance of these findings for patients is unknown.

Cautions

Generally, parenteral magnesium should not be given to patients with heart block or severe renal impairment. Risk of hypermagnesemia in patients with renal impairment.

Undesirable Effects

Flushing, sweating and sensation of warmth IV; diarrhea PO. Also see features of magnesium excess in Box A.

Dose and Use

Severe (serum magnesium <1mEq/L) and symptomatic hypomagnesemia generally necessitates replacement with >2mEq/kg of magnesium; the route of choice is IV, given in divided doses over 3–5 days.[2,58]

Mild or asymptomatic hypomagnesemia may be treated PO. If the cause of the magnesium deficiency persists, PO maintenance therapy will be needed.

In mild–moderate renal impairment, reduce IV replacement doses by 50% and monitor plasma magnesium daily. In severe renal impairment, avoid IV replacement if possible.

Prevention of Deficiency

- magnesium-rich foods, e.g., meat, seafood, green leafy vegetables, cereals and nuts
- potassium-sparing diuretics also preserve magnesium, e.g., amiloride.

IV Correction of Chronic Deficiency

Because the degree of deficiency is difficult to determine from the plasma magnesium, replacement is empirical, guided by symptoms, plasma magnesium and renal function. Guidelines vary; the following are examples.

Serum magnesium <1mEq/L with symptoms (life-threatening), e.g., arrhythmia, seizure

- give 16mEq IV over 1 min
- give as 4mL of magnesium sulfate 500mg (4mEq)/mL diluted to 10mL with 0.9% saline
- follow with IVI replacement as below.

Serum magnesium <1mEq/L with symptoms (not life-threatening)

- on the first day give about 1mEq/kg, then 0.5mEq/kg daily for 2–5 days until the deficiency is corrected
- give as an appropriate dose of magnesium sulfate 500mg (4mEq)/mL added to 250mL 0.9% saline or 5% dextrose
- infuse over a convenient time interval, e.g., 1.5h; ensure the infusion rate is restricted to ≤1.2mEq/min to avoid exceeding the maximum renal tubular resorption capacity for magnesium
- if undesirable effects occur, e.g., hypotension, increase the infusion time, e.g., up to 4h.

IV is the parenteral route of choice. If PO and IV routes are not feasible, options include (in order of preference):

- IM magnesium sulfate: in severe deficiency, give 0.5–1mEq/kg/24h as above in divided doses, e.g., multiple injections q4–6h of magnesium sulfate 500mg (4mEq)/mL; can be painful
- CSCI magnesium sulfate: data are limited, but use of an isotonic solution is recommended, i.e., 50mEq of magnesium sulfate in 100mL WFI.[59,60]

Serum magnesium >1mEq/L and <1.5mEq/L without symptoms

Begin with a trial of PO replacement. The main limiting factor is diarrhea, as magnesium salts are generally poorly absorbed PO and have a laxative effect. It is uncommon with doses <80mEq/24h, and the risk is reduced by a gradual introduction and by taking magnesium with or after food. None of the PO products is licensed for magnesium deficiency and products include those used normally as antacids or laxatives, e.g.:

- magnesium oxide tablets:
  - ➢ start with 400mg b.i.d. with food
  - ➢ increase weekly by 400mg/day
  - ➢ usual maximum 400mg q.i.d. (80mEq/24h)
- Milk of Magnesia® 5mL q.i.d. with food (56mEq/24h).

Generally, 6–12months of treatment is required to fully correct a deficiency. If poorly tolerated or ineffective, use IV replacement as above.

PO maintenance

To prevent recurrence of the deficit, prescribe magnesium ~48mEq/24h in divided doses with food. PO is used unless poorly tolerated or ineffective, e.g., malabsorption.

Supply

This is not an exhaustive list.

Magnesium *sulfate*

Injection 50% (500mg/mL), elemental magnesium 4mEq/mL, 2mL, 10mL, 20mL and 50mL vials = $1, $1.50, $2 and $4 respectively.

Magnesium *oxide*

Tablets 400mg (elemental magnesium 20mEq), available OTC.

Magnesium *hydroxide*

Oral suspension 400mg (elemental magnesium 14mEq)/5mL, available OTC as Milk of Magnesia®; *do not store in a cold place.*

Abbreviations/Key

†	Off-label use
ATP	Adenosine triphosphate
CNS	Central nervous system
CRP	C-reactive protein
CSCI	Continuous subcutaneous infusion
GI	Gastrointestinal
IM	Intramuscular
IV	Intravenous
IVI	Intravenous infusion
OTC	Over the counter (i.e., obtainable without a prescription)
PO	Per os, by mouth
PPI	Proton pump inhibitor
RCT	Randomized controlled trial
WFI	Water for injection

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