MIL

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This Medicines Information Leaflet is produced locally to optimise the use of medicines by encouraging prescribing that is safe, clinically appropriate and cost-effective to the NHS.

Guidelines for the Acute Management of Hypomagnesaemia in Adults

This MIL summarises oral and intravenous (IV) treatments recommended within OUH for the acute replacement of magnesium in adult patients. It does not cover magnesium use in specialist circumstances such as pre-eclampsia, severe acute asthma or arrhythmia (refer to Medusa magnesium monograph for information[1]).

Magnesium plays an important role as a cofactor for DNA and protein synthesis, oxidative phosphorylation, neuromuscular excitability, enzyme activity and regulation of parathyroid hormone (PTH) secretion[2]. In adults, around 99% of magnesium is stored intracellularly (mainly in bones) therefore serum levels do not accurately reflect total body stores.[2,3] Extracellular (serum) magnesium is mainly ionised (free, physiologically active) but 30% is bound to albumin (inactive) and therefore hypoalbuminaemic states may cause the magnesium levels to appear falsely low.[2]

Recommendations within this MIL are not intended for patients with chronic kidney disease; people with impaired renal function may require alternative modifications to their care and should be discussed with clinicians responsible for their care on an individual basis.

Definition of hypomagnesaemia[4]

- Grade 1, mild: 0.5 -0.7mmol/L*
- Grade 2, moderate: 0.4 – 0.49mmol/L
- Grade 3, severe: 0.3-0.4mmol/L
- Grade 4, life-threatening: <0.3mmol/L

*an incidental finding of mildly low magnesium levels (low but 0.5mmol/L) may be attributed to normal pregnant physiology.

Diagnosis and measurements

Measurement of total serum magnesium is the method of choice. 24-hour urinary magnesium excretion can help distinguish between gastrointestinal and renal losses.[2]

When to check magnesium levels

- In presence of conditions and/or symptoms suggestive of hypomagnesaemia, as detailed below.
- Before starting, and during treatment with, systemic anti-cancer therapy (SACT).
- Before initiating proton pump inhibitors and then periodically during treatment, especially if patients are taking other magnesium lowering medicines.[5]
- Checking magnesium levels should also be considered in patients who have hypocalcaemia or hypokalaemia.

Causes of hypomagnesaemia[2,6,7]

Inadequate intake	• malnutrition • chronic alcoholism • magnesium-free intravenous fluids • long-term total parenteral nutrition
Increased gastro-intestinal losses	• diarrhoea • malabsorption
Increased renal losses	• renal impairment
Magnesium shift from extra- to intra-cellular space	• refeeding syndrome • correction of metabolic acidosis (e.g. diabetic ketoacidosis) • acute pancreatitis

Drugs	• thiazide and loop diuretics
	• proton pump inhibitors
	• amphotericin B
	• aminoglycoside antibiotics (e.g. gentamycin, tobramycin)
	• foscarnet
	• tacrolimus
	• pentamidine
	• systemic anticancer therapies, e.g.
	  ◦ cisplatin, carboplatin
	  ◦ ifosfamide
	  ◦ EGF-receptor antagonists (e.g. cetuximab, erlotinib)
	  ◦ Immunotherapy (e.g. pembrolizumab, nivolumab)

Signs and Symptoms[2,6,7]

Signs and symptoms of hypomagnesaemia are typically non-specific and rarely occur unless the magnesium level is less than 0.4mmol/L. They include:

- Gastrointestinal symptoms:
    - Anorexia, nausea
- Neuromuscular symptoms:
    - Tremors, tetany, cramps, seizures, ataxia, and muscle weakness
- Cardiovascular symptoms:
    - Arrhthymias and non-specific ECG changes, including ST-segment depression, altered T-waves, or loss of voltage (or PR prolongation and widened QRS complexes if severe)
- Behavioural symptoms:
    - Irritability, confusion, depression, drowsiness, and psychosis

Treatment

Treatment of the underlying cause should be considered in all cases. The route and dose of magnesium replacement should be selected on the basis of the severity of the clinical manifestations and the degree of hypomagnesaemia.[8]

Grade 1: Mild **0.5 - 0.7 mmol/L**	**Grade 2: Moderate** **0.4 - 0.5 mmol/L**	**Grades 3 / 4: Severe** **<0.4 mmol/L**
Replacement only required if symptomatic. Replacement should be oral unless there are other reasons for intraveneous (IV) replacement.	**Oral replacement is recommended, unless the patient is symptomatic or there are other reasons that intravenous replacement is necessary**	**Intraveneous replacement is strongly recommended** 12-lead ECG should be done, and hospital admission considered if QTc >500ms
FIRST LINE (oral): ***Preferred – licensed*** Magnesium aspartate 10mmol TWICE a day for 7 days *Alternative – unlicensed* Magnesium glycerophosphate 8mmol THREE times a day for 7 days **Intravenous** Magnesium sulphate 10mmol* in 100-1000ml sodium chloride 0.9% or glucose 5% over 90 minutes (*5ml magnesium sulphate 50% solution)	**ASYMPTOMATIC (oral):** ***Preferred – licensed treatment*** Magnesium aspartate 10mmol TWICE a day for 7 days *Alternative – unlicensed treatment* Magnesium glycerophosphate 8mmol THREE times a day for 7 days **SYMPTOMATIC (IV):** Magnesium sulphate 20mmol** in 100 - 1000mL sodium chloride 0.9% or glucose 5% over 3 hours **followed by 7 days of oral replacement (as grade 3/4)** (**10 mL magnesium sulphate 50% solution)	**ALL PATIENTS (IV & oral)** 20mmol magnesium sulphate** in 100-1000ml sodium chloride 0.9% or glucose 5% over 3 hours **followed immediately by 7 days of oral replacement:** ***Preferred – licensed*** Magnesium aspartate 10mmol TWICE a day for 7 days *Alternative – unlicensed* Magnesium glycerophosphate 8mmol THREE times a day for 7 days

Patient's medication should be reviewed, and any causative agents exacerbating hypomagnesaemia should be assessed. PPIs reduce absorption of magnesium from the gastrointestinal tract, and hypomagnesaemia is usually associated with chronic use or high doses. They are unlikely to be causative if started within the last few weeks. If alternative anti-acid treatment is required, treated with famotidine (a histamine-2 receptor antagonist) may be appropriate.

Notes:

Magnesium aspartate is contraindicated in patients with severe renal impairment (eGFR <30ml/min/1.73m^2), and IV magnesium dose should be reduced – replacement should be discussed with senior clinicians / renal team in these patients.

IV magnesium is generally well-tolerated. The majority of reported side-effects relate to symptoms of hypermagnesaemia, where too rapid, excessive / repeated doses have been administered within a short period of time. Symptoms of hypermagnesaemia include nausea, vomiting, flushing of the skin, thirst, hypotension, drowsiness, confusion, loss of tendon reflexes, muscle weakness, respiratory depression, cardiac arrthymias, coma, and cardiac arrest. If toxicity is suspected, magnesium replacement should be stopped immediately and calcium gluconate (an antidote) may be indicated. The medical team caring for the patient should be contacted immediately if toxicity is suspected.

Timing of treatment

Outpatients with asymptomatic Grade 1-2 hypomagnesaemia can usually have magnesium replacement delayed until the following morning where blood results come back out of hours. Patients with symptomatic or Grade 3 hypomagnesaemia may require more urgent replacement, and cases should be assessed individually by a senior clinican (SpR or consultant).

Monitoring following replacement

It can take months to replenish the body's magnesium stores, as by the time serum levels are reduced there has been substantial reduction in total body magnesium. Serum magnesium levels remain raised for approximately 48 hours after intraveneous replacement before the magnesium is redistributed into cells and serum levels fall.

Intravenous replacement:
People treated with IV magnesium replacement should have 7 days of oral replacement immediately following infusion and serum magnesium levels should be checked on subsequent regular blood tests following that.

- If serum magnesium levels stabilise and there are no symptoms of hypomagnesaemia, then further oral replacement is not required, and people should be encouraged to follow a high magnesium diet.
- For patients on systemic anticancer therapy - if levels are stable for four weeks, magnesium can be checked monthly with routine SACT bloods. The frequency of monitoring should be increased if the patient is unwell.

Oral replacement:
People treated with oral magnesium replacement should have magnesium levels checked on subsequent regular blood tests after completing replacement.

- If serum magnesium levels stabilise and there are no symptoms of hypomagnesaemia, then repeated oral replacement is not required. People should be encouraged to following a high magnesium diet.
- For patients on systemic anticancer therapy, levels should continue to be checked regularly. If levels are stable, magnesium can be checked monthly (but more frequently if the patient becomes unwell.

For patients treated with either intravenous or oral replacement – if serum levels are dropping, magnesium replacement should be repeated and prolonged oral replacement considered.

Dietary advice

In some patients, a balanced and varied diet can prevent magnesium deficiency. All patients with hypomagnesaemia should be advised to increase their intake of foods high in magnesium, for example avocados, leafy green vegetables, peas, beans, pulses, meat, fish, nuts, wholegrains, and dark chocolate. The "Food Sources of Magnesium (UK)" leaflet[11] should be offered to patients for further guidance.

Cautions

Magnesium therapy should be used with caution in:

- Chronic kidney disease
- Myasthenia gravis
- Heart block
- Hepatic impairment at risk of developing renal impairment
- Respiratory insufficiency

References

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