The Management of Hypomagnesaemia in Primary Care

Magnesium is a cofactor in enzyme systems involving energy metabolism and protein and nucleic acid synthesis. It also plays a role in the active transport of calcium and potassium ions across cell membranes, important to nerve impulse conduction, muscle contraction, and heart rhythm.

Normal plasma magnesium concentration ranges from 0.7 - 1.0mmol/L. Only about 1% total body magnesium is found in extracellular fluid; the remainder is in bone and soft tissue. About 25% of plasma magnesium is bound to albumin so high or low albumin concentrations will affect magnesium levels.

Changes in magnesium levels occur very slowly (over months or years). Serum magnesium does not always correlate with total body magnesium – it is possible to see a serum level within the reference interval, but a total body magnesium deficit with a chronic magnesium deficiency usually as a result of inadequate dietary magnesium. The reverse (a low serum level and normal total body magnesium) is also possible and is usually seen with drugs which increase excretion of magnesium.

Early signs of deficiency include loss of appetite, nausea, vomiting, fatigue, and weakness. As deficiency worsens, numbness, tingling, muscle contractions and cramps, seizures, personality changes, abnormal heart rhythms, and coronary spasms can occur. Severe deficiency can result in hypocalcaemia or hypokalaemia.

Magnesium deficiency has been associated with the following conditions:

- Gastrointestinal loss, including malabsorption, malnutrition, Crohn's disease, coeliac disease,
- Chronic alcoholism
- Poorly controlled type 2 diabetes
- Renal disorders
- Drug therapy – e.g. PPIs, diuretics, cisplatin, gentamicin, ciclosporin, foscarnet, amphotericin, pentamidine, citalopram, escitalopram.

In 2012 the MHRA advised that prolonged use of PPIs has been associated with case reports of hypomagnesaemia, some serious. They also advise that for patients expected to be on prolonged treatment, and especially for those who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and repeat measurements periodically during treatment.

Recommendation

DDES & ND CCGs advise that magnesium levels should be measured in patients who are symptomatic and/or are likely to have diminished magnesium levels because of their therapy (e.g. long term PPIs and/or other medicines) and pre-existing conditions.

Check for PPI use and stop PPI; if alternative gastro-protection is required then consider prescribing H2-receptor antagonist.

Magnesium Replacement

- Supplementation is recommended if magnesium levels fall below 0.4mmol/L (reference range 0.7 – 1.0mmol/L).
- At levels of between 0.4 and 0.7mmol/L, magnesium replacement should be considered in symptomatic patients or those at high risk of the effects of hypomagnesaemia.

NB: 1mg of magnesium is equal to 0.42mmol.

Management

- **Check for PPI use and stop PPI**; if alternative gastro-protection is required then consider prescribing H2-receptor antagonist.
- Prescribe Magnesium-L-aspartate (Magnaspartate) which is the preferred treatment for both adults and children as it is the only licensed preparation available.

Duration of treatment is dictated by the cause and severity of the deficiency. Prescribe an initial 5-7 days treatment and re-check the magnesium level weekly until it returns to the normal range 0.7 – 1.0mmol/L.

If magnesium-L-aspartate (Magnaspartate) is not effective in raising magnesium levels or if it is poorly tolerated, it is reasonable to try an alternative oral magnesium preparation. Magnesium hydroxide (off-label) or magnesium glycerophosphate (unlicensed) are alternatives. Please note that any unlicensed medicinal products may not have been assessed by the Licensing Authority against the criteria of safety, quality and efficacy. See table below for doses and formulations.

Dosing

Product	Licensed status in the UK	Recommended starting dose*	Cost of 7 day's treatment	Comments
Magnaspartate sachets (6.5g magnesium-L-aspartate oral powder)	**Licensed**	**1 sachet BD** (equivalent to 20mmol Mg^{2+} per day)	**£6.27** (£8.95 x 10 sachets)	Currently the only licensed oral supplement available and preferred option. Suitable for Oral/NG/PEG administration.
MagnaPhate (magnesium glycerophosphate 1g chewable tablets)	Unlicensed	**2 tablets TDS** (equivalent to 24mmol Mg^{2+} per day)	**£19.02** (£22.64 x 50 tablets)	Available from Arjun products Ltd.
Other brands of magnesium glycerophosphate 4mmol tablets	Unlicensed	**2 tablets TDS** (equivalent to 24mmol Mg^{2+} per day)	**Variable**	Brands include Neomag, and YourMAG. Available from Special Products Ltd, IDIS World Medicines and UL Medicines
Co-Magaldrox oral suspension (Maalox or Mucogel)	Not licensed for magnesium replacement therefore use is 'off-label'. Licensed as an antacid.	**5mls TDS** (equivalent to 24mmol Mg^{2+} per day)	Maalox = **£0.71** Mucogel = **£0.63**	Extra caution in renal impairment. May be useful to attenuate magnesium induced diarrhoea
Magnesium hydroxide oral suspension 83mg/ml, (1.424mmol/ml)	Not licensed for magnesium replacement, use is 'off-label'. Licensed as an antacid and a laxative.	**5mls TDS** (equivalent to 21mmol Mg^{2+} per day)	**£1.70**	Omega Pharma Ltd

The BNF states that for adults, magnesium may be given by mouth in a dose of 24mmol Mg^{2+} daily in divided doses.

Precautions for prescribing

- Patients with renal impairment are at higher risk of adverse effects from magnesium supplementation and it's generally advisable to dose conservatively where clinically appropriate.
- Additional electrolyte abnormalities are often associated with hypomagnesaemia, particularly calcium and potassium, it's therefore good practice to check and monitor these levels too.
- Patients who are taking concurrent digoxin may exhibit signs and symptoms of digitalis toxicity which require omission or reduction of digoxin dose until hypomagnesaemia is corrected.

As oral magnesium and other medicinal products may mutually influence each other's absorption, a time interval of 2 to 3 hours should generally be respected if possible. This specifically applies to:

- Fluorides and tetracycline: if they must be used, the doses must be separated by 2 to 3 hours or more to prevent their admixture in the gut.
- Aminoquinolines, quinidine and quinidine derivatives nitrofurantoin, penicillamine, iron, bisphosphonates, eltrombopag, nitroxoline: to avoid impairment of absorption, magnesium preparations should be taken 3 to 4 hours before or after the administration of those drugs.

Please refer to the current BNF for further information and details of interactions.

Adverse effects of magnesium supplementation

- Diarrhoea is the most common adverse effect following oral magnesium replacement, and can be minimised by using co-magaldrox suspension if supplementation needs to continue. However, co-magaldrox is not appropriate in patients with renal impairment.
- Hypermagnesaemia may occur in patients with renal failure but is unlikely in other patients with oral supplementation.

References

1. UKMi Medicines Q&A 111.5 What oral magnesium preparations are available in the UK and which preparation is preferred for the treatment and prevention of hypomagnesaemia? Accessed online via www.evidence.nhs.uk
2. UKMI Medicines Q&A 350.4 How is acute hypomagnesaemia treated in adults? Accessed online via www.evidence.nhs.uk
3. Joint Formulary Committee. British National Formulary (online). London: BMJ Group and Pharmaceutical Press. Available at http://www.medicinescomplete.com
4. Dorset CCG. The Management of Hypomagnesaemia in Primary Care. March 2014. Available here.

5. National Institute of Health. Office of Dietary Supplements. Magnesium. November 2013. Accessed via http://ods.od.nih.gov/
6. Barnsley CCG. Oral Magnesium Supplementation for Hypomagnesaemia. March 2016. Available here.
7. CDDFT. Hypomagnesemia protocol. June 2012.
8. Southern Derbyshire Pathology Guidelines. Hypomagnesaemia in Adults. Expires 30/6/18.
9. Nottingham University Hospital. Guideline for the Treatment of Hypomagnesaemia in Adults. Oct 2015.