Appendix 3

Managing hypomagnesaemia during PPI therapy - good practice guide

Background:

Use of proton pump inhibitors (PPI) has been recently associated with low magnesium levels, but the mechanism remains not fully understood. Low urinary magnesium excretion has been observed and may support the theory that it is likely related to reduced magnesium absorption from the intestine. Intestinal absorption of this ion normally proceeds in both a passive paracellular and an active transcellular manner. Long-term PPI users who are highly adherent to treatment can eventually deplete total body magnesium stores and present with severe complications of hypomagnesaemia.[1-3]

Regulatory bodies recommendations

The FDA and MHRA have both notified that PPI drugs may cause low serum magnesium levels if taken for prolonged periods of time.[4,5] In most cases, hypomagnesaemia occurred after one year of PPI treatment. However, some reports showed hypomagnesaemia after three months. Treatment of hypomagnesaemia generally requires magnesium supplements. In approximately one-quarter of the cases reviewed, magnesium supplementation alone did not improve low serum magnesium levels and the PPI had to be discontinued. Moreover, in a few cases in which the patients restarted taking a PPI, the hypomagnesaemia recurred, suggesting a PPI-related effect.[4,6]

Healthcare professionals may consider obtaining serum magnesium levels prior to initiation of prescription PPI treatment in patients expected to be on these drugs for long periods of time, as well as patients who take PPIs with medications such as digoxin, diuretics or drugs that may cause hypomagnesaemia. This is especially important because low magnesium can increase the likelihood of serious side effects. Healthcare professionals should consider obtaining magnesium levels periodically in these patients.

Good practice guide

Currently there are no national guidelines for hypomagnesaemia treatment. Magnaspartate® and Neomag® are the only licenced products for treating hypomagnesaemia.[7-9]

The flowchart presented below advises prescribers on the management of hypomagnesaemia and gives suggestions on the use of magnesium products. Oral magnesium products may trigger diarrhoea. Taking magnesium supplements with food may reduce side-effects.[8]

Local guideline is available from Clinical Chemistry at STH covering 'The investigation of hypomagnesaemia in adults'.[11]

References

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Management of hypomagnesaemia in PPI treatment in adults

See 'The investigation of hypomagnesaemia in adult (new diagnosis in adults)'
Check magnesium levels only if the patient belongs to a **risk group** i.e.:

1. Symptoms of hypomagnesaemia:
   - Mild hypomagnesaemia (serum magnesium <0.7mmol/L): weakness, fatigue, lethargy, muscle weakness, paraesthesia, cramps, hypertension, cardiac arrhythmias;
   - Severe hypomagnesaemia (serum magnesium < 0.4mmol/L): tetany, seizures, convulsions, cardiac arrhythmias, confusion, coma;
2. Drugs: e.g. PPIs, loop & thiazide diuretics, ciclosporin, digoxin, theophylline, immunosuppessants (tacrolimus, ciclosporin), chemotherapy (e.g. cisplatin)
3. Severe or refractory hypokalaemia or hypocalcaemia (reduced PTH secretion)
4. GI causes: chronic diarrhoea, malabsorption, short bowel syndrome, interstinal fistula
5. History of alcoholism, malnutrition

Consider PPIs for:
-shortest period of time
-in lowest effective dose

If long-term PPI therapy **and** if patient belongs to risk group then after 3-6 months check renal function, calcium, potassium levels, serum magnesium levels

If magnesium serum concentration level between **0.4 to 0.69 mmol/l** then consider:
- stopping PPI and starting supplementation of Mg
- if gastroprotection necessary consider H2RA
- if PPI absolutely necessary then continue Mg supplementation

If serum Mg level of **0.4 mmol/l or less** (asymptomatic or symptomatic) then consider referral to secondary care

If magnesium levels correct then continue PPI

Review after **one year** and then review on **annual basis**; if recurrent hypomagnesaemia and gastroprotection necessary then consider H2RA

Magnesium supplementation:
Up to 24 mmol/d of oral Mg (1-2 tablets three times a day) may be given in adults (see table below) in divided doses, adjusted according to the serum total magnesium level of the individual patient.
Dose can be limited by SEs(diarrhoea).
Monitor response weekly as normalisation may take 6- 8 weeks.
In patients requiring long-term supplementation the monitoring may take place at increased intervals, if Mg levels are found to be stable.[11]
In renal impairment: Mg can accumulate; Mg dose may need to be reduced by up to 50% due to an increased risk of toxicity, monitor frequently.[11]
Avoid in severe renal impairment.[6]
C/I: Severe renal impairment (GFR <30ml/min).

Patient may consider:

-dietary sources of magnesium

-purchasing OTC magnesium supplements:

Magnesium citrate, e.g. MagAsorb®, Mg 150mg (6.2mmol);
H&B Mg 300mg (12.4mmol)

Magnesium oxide, e.g. Boots, Mg 375mg tabs (9.4mmol)
H&B, Mg 250mg tabs (6.25mmol)

Choice of magnesium products

Product*	Content & Form	Licensed status
Magnesium glycerophosphate (**Neomag**®)	Chewable tablets 97mg (4mmol of Mg) (contains Aspartame)	Licensed
Magnesium-L-Aspartate (Magnaspartate®)	Oral powder (10mmol Mg per sachet)	Licensed

*If one oral Mg preparation is not effective in raising Mg levels then consider an alternative oral preparation.[6]