

Advice For Practitioners Regarding Hypomagnesaemia Associated With Proton Pump Inhibitor (PPI) Use

Summary

- Hypomagnesaemia is a rare but serious adverse reaction associated with PPI use
- Hypomagnesaemia has been reported in association with **all** PPIs
- Where a patient has hypomagnesaemia, stop PPI therapy, consider the need for magnesium replacement therapy and do not restart or substitute with another PPI
- There are no national guidelines on hypomagnesaemia
- Patients may approach you with conflicting information as the American FDA has issued advice on specific magnesium supplementation and routine testing

Background

The April 2012 issue of the MHRA Drug Safety Update (DSU) includes an article regarding hypomagnesaemia associated with the use of proton pump inhibitors (PPIs) (<http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON149774>).

In this article practitioners have been advised to:

- Consider measurement of magnesium levels before starting PPI treatment and periodically during prolonged treatment, especially in those who will take a PPI concomitantly with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics)
- Take into account any use of PPIs obtained over-the-counter

Advice

- **Prescribers in the East Kent health economy are advised NOT to carry out blanket testing of magnesium levels in all patients receiving long-term PPI therapy.**
- **Consider testing patients where there is suspicion of hypomagnesaemia and in patients who are also taking digoxin.**

This does however present a further opportunity for prescribers to routinely review patients on PPI therapy and discontinue treatment where treatment is no longer indicated.

Which drugs are affected?

This advice applies to all PPIs (esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole).

How frequently does hypomagnesaemia occur in patients taking long term PPI therapy?

The advice contained in the DSU is based on case reports of hypomagnesaemia in patients taking PPIs. The DSU states that severe hypomagnesaemia has been reported infrequently in patients treated with PPIs and that the incidence is unknown. The BNF states that hypomagnesaemia has been reported rarely in association with PPI use.

When could hypomagnesaemia be expected to occur?

Patients usually have symptoms of hypomagnesaemia after using PPIs for at least three months, and in most cases a year or longer. The mechanism is currently unknown.

Is there any difference in the occurrence of hypomagnesaemia between the PPIs?

Hypomagnesaemia has been reported with all PPIs and has recurred following substitution of one PPI with another. Therefore practitioners are advised NOT to substitute PPIs to avoid hypomagnesaemia.

What are the clinical signs and symptoms of hypomagnesaemia?

Most of the symptoms of hypomagnesaemia are non-specific, they may begin insidiously and can be overlooked. Symptoms may include loss of appetite, nausea, vomiting, muscle weakness, ataxia, tremor, convulsions, tetany, ventricular arrhythmias, ECG abnormalities, fatigue, dizziness, delirium, depression, psychosis, vertigo, hyperinsulinism.

Case reports of hypomagnesaemia associated with PPIs showed that most patients presented with several hypomagnesaemia symptoms and had been hospitalised in previous years. Often the diagnosis is first suspected because of hypocalcaemia and its symptoms or hypokalaemia which are often paired with hypomagnesaemia.

Other causes of hypomagnesaemia

There are many potential causes of hypomagnesaemia including diabetes, malabsorption syndromes, protein-calorie malnutrition, disorders of the parathyroid gland, chronic alcoholism, chronic diarrhoea, renal disorders causing reduced magnesium resorption, cirrhosis, pregnancy, and excessive lactation. Inherited causes also exist.

Which patients are at higher risk of hypomagnesaemia?

It has been suggested that higher dose PPI therapy may be linked to the development of hypomagnesaemia, as has longer duration of treatment and good adherence to therapy.

Patients taking other drugs which may lower magnesium may also be at increased risk of hypomagnesaemia e.g. loop and thiazide diuretics, laxatives, cisplatin, carboplatin, aminoglycoside antibiotics, pentamidine, amphotericin B, ciclosporin, tacrolimus, foscarnet, cisplatin and alcohol.

Which patients are at greatest risk as a result of hypomagnesaemia?

Patients taking digoxin are at greater risk of serious side effects of digoxin associated with hypomagnesaemia.

What should healthcare professionals do?

- Consider the need for a PPI prior to prescribing
- Consider whether the patient has additional risk factors for developing hypomagnesaemia
- Routinely review patients on long term PPI therapy
- When prescribing a PPI inform the patient of the risk of hypomagnesaemia and to be vigilant for the signs and symptoms of hypomagnesaemia
- If a patient who is taking PPI therapy presents with signs or symptoms suggestive of hypomagnesaemia and / or hypokalaemia, consider PPIs as a possible cause, and test magnesium level.
- If the patient is found to have hypomagnesaemia, stop the PPI.
- Where hypomagnesaemia is considered to be serious this should be reported to the MHRA via the Yellow Card system.

Correction of hypomagnesaemia

Stop PPI therapy. Plasma magnesium concentrations return to normal only after withdrawal of PPI treatment. Consider magnesium replacement.

There is no national guidance on the treatment of hypomagnesaemia. The reference range for serum magnesium is 0.7-1.0mmol/L. Magnesium replacement should be prescribed orally for mild hypomagnesaemia (asymptomatic). There are no licensed oral magnesium preparations in the UK. Severe hypomagnesaemia (<0.4mmol/L or symptomatic) will require intravenous replacement with magnesium sulphate. Magnesium replacement should be used with caution in patients with myasthenia gravis, patients with hepatic impairment at risk of developing renal impairment, patients with renal impairment and respiratory insufficiency. Oral magnesium salts commonly cause gastrointestinal irritation and diarrhoea.

The East Kent Hospitals University Foundation Trust's Pocket Electrolyte Guide advises.

- Oral
Magnesium glycerophosphate 4mmol tablets 1-2 tds (unlicensed)
Dose limiting side effect – diarrhoea (give with or after food)
Care in renal failure and hyperphosphataemia
- Intravenous
20mmol Mg²⁺ in minimum 50ml 0.9% NaCl or 5% glucose over at least 2.5 hours or
40mmol Mg²⁺ in minimum 100ml over at least 5 hours, daily for up to 5 days and
measure electrolytes: Mg²⁺ and Ca²⁺ (allows for urinary loss). N.B. licensed dose is
20mmol Mg²⁺ in 1L over 3 hours.
- If symptoms are severe e.g. serious arrhythmias (especially if hypokalaemic), 8mmol
(2g) over 10-15 minutes. Repeat if necessary. Monitor deep tendon reflexes at 15
minutes and continuous ECG.

Magnesium sulphate 50% contains 2mmol (0.5g) per ml.

Contraindicated in AV block and severe bradycardia

Caution in renal failure (reduce dose)

What about histamine 2 receptor antagonists (H2RAs)?

H2RA such as ranitidine or cimetidine have not been linked to hypomagnesaemia. Practitioners may wish to consider prescribing a H2RA in place of a PPI.

Advice for patients

Patients should be aware of and advised to report symptoms of hypomagnesaemia to a healthcare professional. A list of symptoms can be found on the patient information leaflet which should be provided when the PPI is dispensed.

Many common foods contain magnesium including green vegetables, wholemeal bread, wholemeal pasta, nuts, pulses such as kidney beans and lentils, soya beans, peas, baked beans, seafood. "Hard" water also contains magnesium salts.

Cost of testing

The cost of an individual test for hypomagnesaemia is not high (approximately £1.50) however when considering the number of people who are taking PPIs (approximately 30,000 in Kent and Medway) in addition to blood sampling staff time this would lead to a significant cost across the health economy. Phlebotomy cost is approximately £9 per patient but would not be an additional cost if magnesium were to be tested at the same time as other blood tests.

Please see East Kent Prescribing Group guidance on options for Licensed oral magnesium supplementation

<http://www.canterburycoastalccg.nhs.uk/about-us/prescribing-advice/?assetdet7576137=422000&categoryesctl10344807=13476>

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