Prescribing guideline

For

Managing Proton Pump Inhibitors
Balance of risks and benefits

Prescribing guideline developed by:
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Based on document prepared by:
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November 2012

Date approved: June 2016

Review Date: June 2018
Proton Pump Inhibitors - Balance of Benefits against Risks

Proton pump inhibitors (PPIs) are widely used for different indications (see BNF\(^1\), NICE CG184\(^2\) (dyspepsia), NICE CG177\(^3\) (osteoarthritis), NICE CG79\(^4\) (rheumatoid arthritis), NICE CG88\(^5\) (low back pain) and eMedicines\(^6\). Although there are risks associated with prescribing, their role in patient care is invaluable and prescribing in line with NICE guidelines is still encouraged.

Over the last few years there have been a number of MHRA alerts and other reports highlighting the risks associated with PPIs.\(^7\) Most of these risks / side effects are associated with long term treatment and high doses.

Studies suggest 87% of patients on long-term PPIs in primary care for reflux could be stepped down to a low dose PPI plus an alginate or an alginate alone.\(^8\)

Carrying out annual / regular medication reviews to ensure PPIs are prescribed for appropriate indications, used at **the lowest effective dose** (consider if stepping down dosage is appropriate, including PRN usage) and for **the shortest period of time** will help to manage some of the risks associated with PPIs. Where NSAIDs, antiplatelets, anticoagulants, dual antiplatelet therapy, combination of antiplatelet therapy or anticoagulants with NSAIDs, glucocorticosteroids, SSRIs are indicated, gastro-protection should be considered in presence of other risk factors (e.g. over 65 years of age, previous or current history of peptic ulcer especially with complications). Note PPIs are more effective than H\(_2\) receptor antagonists for prevention of bleeding. However, ranitidine may be considered as alternative.\(^9\) For detailed advice see local guidance available from the gastroenterology directorate at STH.\(^9\)

Prescribers should also discuss the risks with patients so that a more informed choice can be made and to increase awareness of the potential risks / side effects. Any that may arise can then be identified promptly and managed appropriately.

If prescribers do come across any unexpected reaction to any medicinal product this should, where appropriate, be reported to the Commission on Human Medicines (CHM) using the **yellow card reporting form**. Reporting should be carried out for prescribed drugs and also for those medicines obtained by patients over the counter.

**Local guidance** is available from the gastroenterology directorate at STH highlighting the clinical indications for PPIs and where step down or change to a H\(_2\) receptor antagonist may be appropriate.\(^9\)

The table below looks at some of the risks associated with PPIs and points to consider when managing patients on PPIs in practice.

PLI covering “Management of GORD in Primary Care” was held in March 2015 and can be accessed here.
### Risk to consider

**Clostridium difficile**

Although not proven, there is observational evidence to link PPI usage with *C. difficile* infections (CDI).\(^{11,12}\)

A diagnosis of *C. difficile* infection (CDI) should be considered for PPI users with diarrhoea that does not improve.

[Public Health England guidelines](https://www.gov.uk/government/publications/clostridium-difficile-infection-cdi-guidance-for-managing-and-treating-cdi) for managing and treating CDI recommend that consideration be given to stopping or reviewing the need for PPIs in patients with or at high risk of CDI.\(^{11}\)

- The use of PPIs or H\(_2\)RAs during the antibiotic treatment phase had no effect on *C. difficile*-associated diarrhoea recurrence rates.
- Studies show that concurrent use of PPI with treatment for CDI was associated with a 42% increased relative risk of recurrent infection 15 to 90 days afterwards. Risks were highest among those older than 80 years and those receiving antibiotics not targeted to CDI. Other mechanisms include impairment of leukocytes and other immune responses and antimicrobial properties of PPIs.\(^{13,14}\)
- Risk of CDI in the general population taking PPIs is low; risk is greater in hospitalised patients taking antibiotics.\(^{12}\)
- H\(_2\)RAs carry lower risk of CDI than PPIs, however, the risk of CDI is higher than in cases where no acid suppressants were used.\(^{15}\)

### Considerations/management

**Rebound acid hypersecretion**

and protracted dyspepsia may occur after stopping prolonged treatment with a PPI.\(^{16,17}\)

When reviewing PPI usage at medication review consider reducing dose slowly to avoid rebound acid hypersecretion. Co-prescribing an antacid may also help to manage this.

- After prolonged PPI use for more than 2 months consider weaning down dose rather than stopping abruptly to avoid rebound hyperacidity.
- Consider reviewing PPI use: stop or reduce a PPI or convert to H\(_2\) receptor antagonists/ alginates/ antacids as clinically appropriate.

**Increased risk of fractures with long term use of PPIs**\(^{7}\)

At medication reviews consider if stepping down is appropriate (including PRN use). Patients should also have their osteoporosis risk assessed and, if needed, treated according to current clinical guidelines to ensure they have adequate intake of calcium and vitamin D (NICE guidance is available for [primary](https://www.nice.org.uk/guidance/ng27) and [secondary](https://www.nice.org.uk/guidance/ng26) prevention of osteoporosis in post-menopausal women).

Two meta-analyses suggest the risk of fractures in elderly patients increase by 10-40% above baseline, especially if PPIs are used in high doses and over long durations (>1 year). However, other factors may contribute to the increase in fracture risk.\(^{20,21}\)
<table>
<thead>
<tr>
<th>Hypomagnesaemia—</th>
<th>In practical terms it may therefore be sensible to measure magnesium levels:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged use of PPIs has been associated with hypomagnesaemia.⁷</td>
<td>• before starting treatment and periodically in patients who are also taking digoxin or other medication that may cause hypomagnesaemia (e.g. diuretics) or patients with malabsorption syndromes</td>
</tr>
<tr>
<td>The MHRA advises prescribers 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.</td>
<td>• if a patient presents with symptoms of hypomagnesaemia (e.g. muscle twitches, tremors, vomiting, tiredness, loss of appetite) while taking PPIs</td>
</tr>
<tr>
<td>Interactions with clopidogrel (also see BNF Appendix 1 for full list of other drug interactions with PPIs)¹,⁷</td>
<td>Both omeprazole and esomeprazole reduce the antiplatelet effect of clopidogrel. Consider other PPIs; lansoprazole (Sheffield Formulary choice), pantoprazole and rabeprazole in patients taking clopidogrel. An H₂-blocker (except cimetidine) or antacids may be more suitable in some patients.</td>
</tr>
<tr>
<td>Mask symptoms of gastric cancer²³</td>
<td>At regular medication review check for symptoms of gastric cancer (e.g. bleeding, dysphagia, recurrent vomiting or weight loss).</td>
</tr>
<tr>
<td>Iron deficiency anaemia – although there is a theoretical risk of anaemia due to the increased pH in the stomach potentially reducing the absorption of iron, evidence in practice is lacking.²⁴</td>
<td>In practice, if treating a patient for iron deficiency anaemia and they are being prescribed a PPI, review need for PPI and consider this as being a potential interaction if anaemia not corrected.</td>
</tr>
<tr>
<td>Community acquired pneumonia - there are reports of an increased susceptibility to infections in patients using PPIs, including community acquired pneumonia (CAP).²⁵,²⁶</td>
<td>Evidence suggests patients are at greater risk of CAP if PPI treatment has been started within the previous 30 days. Extra vigilance is needed if patient presents with symptoms of respiratory infection. As above PPIs should only be used where there are clear indications.</td>
</tr>
<tr>
<td>There may be an association between long-term PPI use and higher mortality in older patients.²⁷</td>
<td>In older patients discharged from acute care hospitals, the use of high-dose PPIs may be associated with increased 1-year mortality. This risk appears to increase with higher doses.²⁷</td>
</tr>
<tr>
<td></td>
<td>The risk appears to increase with higher doses, but RCTs including frail, older patients are needed. PPIs may interfere with absorption of nutrients, exacerbating the risk of malnutrition common in older people.</td>
</tr>
</tbody>
</table>
Very low risk of subacute cutaneous lupus erythematosus (SCLE), a non-scarring dermatosis that can develop in sun-exposed areas.\(^7,28\)

Very infrequent cases of subacute cutaneous lupus erythematosus (SCLE) have been reported in patients taking PPIs. Drug-induced SCLE can occur weeks, months or even years after exposure to the drug. If a patient treated with a PPI develops lesions—especially in sun-exposed areas of the skin—and it is accompanied by arthralgia:

- advise to avoid exposing the skin to sunlight;
- consider subacute cutaneous lupus erythematosus as a possible diagnosis;
- consider discontinuing PPI treatment unless it is imperative for a serious acid-related condition; a patient who develops SCLE with a particular PPI may be at risk of the same reaction with another;
- in most cases, symptoms resolve on PPI withdrawal; topical or systemic steroids might be necessary for treatment of SCLE only if there are no signs of remission after a few weeks or months.

Drug-induced SCLE can occur weeks, months or even years after exposure to the drug.\(^7\)

Acute interstitial nephritis (AIN)\(^29,30,31\)

AIN is a rare complication of PPI use.\(^29\)

Medications account for 60% of cases of AIN, including antibiotics, NSAIDs, diuretics and PPIs. All of the PPIs have been implicated. (Please note that the main limitation of this evidence is that data is restricted to case reports.) The standard treatment involves early diagnosis of AIN, withdrawing the causative drug, administering steroids depending on the degree of acute kidney injury and clinical assessment.\(^29,30\)

Vitamin B12 deficiency\(^32\)

At present there is little evidence to suggest vitamin B12 monitoring is required routinely in all patients on PPIs. However, the effects of long-term treatment should be monitored.

A review of PPI side effects found mixed results from studies of PPI use and vitamin B12 deficiency suggesting that any risk of decreased vitamin B12 levels is clinically insignificant and a normal diet will safeguard against a clinically relevant deficiency when taking a PPI. The elderly and malnourished may be at a higher risk, as they are more likely to have borderline baseline levels.\(^32\)

Potential association between long-term PPIs and increased risk of MI\(^33,34\)

Recent retrospective studies showed that gastroesophageal reflux disease patients exposed to PPIs to have a 1.16 fold increased association (95% CI 1.09–1.24) with myocardial infarction. Survival analysis in a prospective cohort found a two-fold (HR = 2.00; 95% CI 1.07–3.78; P= 0.031) increase in association with cardiovascular mortality.

These findings are hypothesis generating, and a prospective randomized study in the general population (inclusive of both lean and obese individuals) is required before changing clinical practice. Pre-clinical findings show that PPIs may adversely impact vascular function. These data-mining studies support the association of PPI exposure with risk for MI in the general population.\(^33,34\)
References

1. BNF. Available at: https://www.medicinescomplete.com/mc/bnf/current/ (Accessed on 27/5/16)
6. eMedicines, Available at: http://www.medicines.org.uk/emc/
7. MHRA. Drug Safety Update. Available at: https://www.gov.uk/drug-safety-update?keywords=proton+pump+inhibitors&first_published_at%5Bfrom%5D=&first_published_at%5Bto%5D=


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.1,2

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.2,4 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.3,5

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® is the only licenced product for treating hypomagnesaemia.6,7,8 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.7

Local guideline is available from Clinical Chemistry at STH covering “The investigation of hypomagnesaemia in adult”.11

References
6. BNF  
7. UKMi. Q&A 111.2. What oral magnesium preparations are available in the UK and which preparation is preferred for the treatment and prevention of hypomagnesaemia? Available through NICE Evidence Search at www.evidence.nhs.uk  
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, immunosuppressants (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, intestinal fistula
5. History of alcoholism

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

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

Magnesium supplementation:
Up to 24 mmol/d of oral Mg may be given in adults (see below) in divided doses.
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.

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.

Avoid in severe renal impairment.

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

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

Patient may consider:
- dietary sources of magnesium (Appendix 2)
- 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

<table>
<thead>
<tr>
<th>Product*</th>
<th>Content &amp; Form</th>
<th>Licensed status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium-L-Aspartate (Magnaspartate®)</td>
<td>Oral powder (10mmol Mg per sachet)</td>
<td>Licensed</td>
</tr>
<tr>
<td>Magnesium glycerophosphate (Magnaphate®)</td>
<td>Tablets 97mg (4mmol of Mg)</td>
<td>Food supplement</td>
</tr>
<tr>
<td>Magnesium glycerophosphate</td>
<td>Tablets 97mg (4mmol of Mg)</td>
<td>Unlicensed</td>
</tr>
<tr>
<td>Magnesium citrate (MagAsorb®)</td>
<td>Tablets 150mg (6.2mmol of Mg)</td>
<td>Food supplement</td>
</tr>
<tr>
<td>Magnesium carbonate</td>
<td>Capsules 121mg (5.26mmol Mg per caps)</td>
<td>Unlicensed</td>
</tr>
</tbody>
</table>

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

**Magnaphate® is manufactured under GMP standards
Appendix 2.

Guide on dietary sources of magnesium

Overview. Magnesium is the second most abundant mineral in the human body and is needed as a cofactor in many enzyme systems. Magnesium has a vital role in skeletal development (half of the body’s magnesium is in the skeleton), protein synthesis, muscle contraction and neurotransmission. Magnesium is metabolically linked to calcium.

Requirement. The reference nutrient intake (RNI) for adults over 19 is:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>300 mg/day</td>
</tr>
<tr>
<td>Women</td>
<td>270 mg/day</td>
</tr>
<tr>
<td>Lactating women</td>
<td>320 mg/day</td>
</tr>
</tbody>
</table>

Absorption and bioavailability. About 20 – 50 % of dietary magnesium is absorbed (mainly in the small intestine), and 1, 25 dihydroxyvitamin D is needed for this process. Protein may enhance the absorption of magnesium.

Fibre rich foods decrease the bioavailability of magnesium.

Free phosphate may hinder magnesium absorption due to insoluble complexes being formed.

Dietary sources of magnesium.

Magnesium is present in many foods. A varied diet should be encouraged.
The table below shows the foods which are the richest sources of magnesium.

<table>
<thead>
<tr>
<th>Food</th>
<th>Magnesium (mg) / 100 g food</th>
</tr>
</thead>
<tbody>
<tr>
<td>All bran</td>
<td>210</td>
</tr>
<tr>
<td>Bran flakes</td>
<td>130</td>
</tr>
<tr>
<td>Cornflakes</td>
<td>14</td>
</tr>
<tr>
<td>Fruit’n’fibre</td>
<td>60</td>
</tr>
<tr>
<td>Muesli – no added sugar</td>
<td>90</td>
</tr>
<tr>
<td>Puffed wheat</td>
<td>140</td>
</tr>
<tr>
<td>Shredded Wheat</td>
<td>130</td>
</tr>
<tr>
<td>Sultana Bran</td>
<td>120</td>
</tr>
<tr>
<td>Weetabix</td>
<td>120</td>
</tr>
<tr>
<td>Wheatgerm</td>
<td>270</td>
</tr>
<tr>
<td>Rye crispbreads or Oatcakes</td>
<td>100</td>
</tr>
<tr>
<td>Wholemeal bread</td>
<td>76</td>
</tr>
<tr>
<td>White bread</td>
<td>24</td>
</tr>
<tr>
<td>Wholemeal scones</td>
<td>75</td>
</tr>
<tr>
<td>Food</td>
<td>Magnesium (mg) / 100 g food</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Sardines, canned</td>
<td>52</td>
</tr>
<tr>
<td>Whitebait, fried</td>
<td>50</td>
</tr>
<tr>
<td>Jacket potato – eaten with skin</td>
<td>32</td>
</tr>
<tr>
<td>Sweet potato, boiled</td>
<td>45</td>
</tr>
<tr>
<td>Baked beans in tomato sauce</td>
<td>31</td>
</tr>
<tr>
<td>Aduki / red kidney / black eye / mung / soya beans, boiled</td>
<td>45 - 60</td>
</tr>
<tr>
<td>Tofu, steamed then fried</td>
<td>67</td>
</tr>
<tr>
<td>Spinach</td>
<td>34</td>
</tr>
<tr>
<td>Bananas</td>
<td>34</td>
</tr>
<tr>
<td>Figs, dried</td>
<td>80</td>
</tr>
<tr>
<td>Almonds</td>
<td>270</td>
</tr>
<tr>
<td>Brazil nuts</td>
<td>410</td>
</tr>
<tr>
<td>Cashew nuts</td>
<td>250</td>
</tr>
<tr>
<td>Hazelnuts</td>
<td>160</td>
</tr>
<tr>
<td>Macadamia nuts</td>
<td>100</td>
</tr>
<tr>
<td>Mixed nuts</td>
<td>200</td>
</tr>
<tr>
<td>Peanuts</td>
<td>210</td>
</tr>
<tr>
<td>Chocolate, plain</td>
<td>100</td>
</tr>
<tr>
<td>Chocolate, milk</td>
<td>55</td>
</tr>
<tr>
<td>Milk</td>
<td>11 (1 pint of milk contains approximately 60 mg magnesium)</td>
</tr>
</tbody>
</table>

References.


Chris Rudd
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March 2013
Reviewed: February 2016