Safety of prolonged use (> 8 weeks) of Proton Pump Inhibitors (PPIs)

The Pan Mersey Safety subgroup recommends that prescribers should consider the safety issues of PPIs and prescribe accordingly

Prescribing of PPIs should be in accordance with NICE guidance CG184 for dyspepsia and gastro-oesophageal reflux disease (GORD), having addressed all potential safety issues. See algorithm page 3.

Recommendations

- Review PPIs 4-8 weeks after initiation to minimise the risk of safety issues listed below.
- Offer lifestyle advice to manage dyspepsia eg. healthy eating, weight reduction, smoking cessation, reduce alcohol and caffeine intake, and avoid food/drink that can worsen dyspeptic symptoms.
- Review and if possible, stop medication that may exacerbate dyspepsia eg. calcium channel blockers, nitrates, theophyllines, bisphosphonates, corticosteroids, NSAIDs, iron, anticholinergics.
- Follow local pathway and refer any patients with ‘gastric alarm features’. Stop all antisecretory drugs (PPIs and H2 antagonists such as ranitidine) for 14 days before an endoscopy.
- Test and treat for *Helicobacter pylori* where appropriate. Avoid PPI treatment for at least 14 days before testing to avoid a false-negative result.
-Prescribe a low acquisition cost PPI. There is no evidence that any PPI is more effective than another.
- It may be necessary to repeat short courses of PPI treatment (2-3 times a year) in order to control symptoms and/or promote healing.
- Repeat prescriptions should be reviewed at least annually; try stepping down to the lowest effective dose needed to control symptoms, or ‘as needed’ to manage their own symptoms.
- When stopping a long term PPI, counsel patient about rebound acid hyper-secretion and protracted dyspepsia. This is usually a short-term effect and goes within 2-4 weeks. To ensure that this does not occur, it is recommended that the dose is reduced gradually and that an alginate is prescribed regularly for at least two weeks to reduce the chance of this occurring.
- Avoid long term, frequent dose, continuous antacid therapy in functional dyspepsia where there is no obvious cause (it only relieves symptoms in the short term rather than preventing them).
- Indications where the benefits of long term PPI use outweigh the risks include Barrett’s oesophagus, oesophageal stricture dilation, history of ulcer complications (bleeding or perforation), Zollinger-Ellison syndrome, gastroprotection for NSAID treatment.

First choice PPIs in the Pan Mersey formulary are lansoprazole capsules and omeprazole capsules.
A clear definition of what is meant by ‘long term’ PPI use is lacking and there is an overall lack of randomised, controlled trials on the long term use of PPIs and adverse effects. Most studies are observational which have limitations. Adverse effects of PPIs are usually mild and reversible and include headache, diarrhoea, nausea, abdominal pain, constipation, dizziness and skin rashes.

PPI treatment may be associated with the following uncommon, serious adverse effects:

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Description</th>
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<tr>
<td><strong>Acute interstitial nephritis (AIN)</strong>(^4,5)</td>
<td>Medications account for 60% of AIN cases, and case reports have shown AIN to be a rare complication of PPI use. Early diagnosis of AIN and stopping the PPI are important to help avoid CKD developing and its consequences.</td>
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<tr>
<td><strong>Clostridium difficile infection (CDI)</strong>(^6,7)</td>
<td>The use of PPIs may increase the risk of recurrence of CDI. Recommend stopping PPI in patients diagnosed with CDI. Consider withholding a PPI for the duration of any future courses of broad spectrum antibiotics.</td>
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<tr>
<td><strong>Community acquired pneumonia (CAP)</strong>(^8)</td>
<td>Recent PPI exposure (within previous 30 days) has been associated with a small but significant increase in hospitalisation from pneumonia. GORD itself may be a risk factor for pneumonia (from stomach content aspiration).</td>
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<tr>
<td><strong>Hypomagnesaemia</strong>(^9)</td>
<td>Has been infrequently reported in patients treated with PPIs, mostly occurring after one year of treatment. Stop PPI and prescribe magnesium replacement (rated Amber) in patients with hypomagnesaemia. Consider measuring magnesium levels before starting PPI treatment and repeat periodically during prolonged treatment, especially in those also taking digoxin or diuretics.</td>
</tr>
<tr>
<td><strong>Increased mortality in older patients</strong>(^10)</td>
<td>This association appears to increase when older patients are prescribed high-dose PPIs. Recent findings suggest 50% to 80% of hospitalised older patients are inappropriately prescribed a PPI.</td>
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<tr>
<td><strong>Increased risk of bone fractures</strong>(^11,12)</td>
<td>Observational studies suggest a modest increase in the risk of hip, wrist or spine fractures, particularly in older patients, where the PPI dose is high, and taken for over a year. Other contributory factors include PPI use in post-menopausal women, with a history of smoking or obesity. Patients at risk of osteoporosis should be treated according to local clinical guidelines. Consider H2RAs as an alternative in these patients as no association has been reported with H2RA use and the risk of fractures.</td>
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<tr>
<td><strong>Rebound acid hypersecretion syndrome (RAHS)</strong>(^13)</td>
<td>Should be considered in patients taking a PPI long term, who previously experienced rapid recurrence of symptoms after PPI withdrawal. Consider gradual step-down PPI treatment, and prescribe an alginate for at least two weeks.</td>
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<tr>
<td><strong>Subacute cutaneous lupus erythematosus</strong>(^14)</td>
<td>There is a very low risk of SCLE in patients taking a PPI, particularly to sun-exposed areas of skin. In most cases SCLE resolves when the PPI is stopped.</td>
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<tr>
<td><strong>Vitamin B12 deficiency</strong>(^4)</td>
<td>Has been associated with the long term use of PPIs. Studies suggest that a normal diet will safeguard against a clinically relevant deficiency when taking a PPI. Older patients and the malnourished may therefore be at a higher risk of vitamin B12 deficiency.</td>
</tr>
</tbody>
</table>
Algorithm for process to review a patient on a PPI

Based on suggested methodology from Welsh Analytical Prescribing Support Unit

Is the patient receiving a PPI on a regular repeat prescription?

- Yes
  - Is there a clinical reason for prolonged treatment?
    - Yes
      - Maintain treatment with current PPI and agree period for review
      - Ensure the indication is documented in medical notes
      - Provide lifestyle advice
      - Monitor magnesium: Consider testing at baseline and a minimum of annually
      - Ensure adequate intake of calcium and vitamin D in patients at risk of fractures
    - No
      - Review prescription and address lifestyle issues
      - Can PPI be stopped or stepped down?
        - Step down: Consider as required PPI usage with regular self-care*
        - Stop PPI: Initiate gradual dose reduction, with co-prescription of alginate for at least two weeks to reduce rebound hypersecretion
        - Manage repeats: Remove from repeat prescribing and prescribe for specific durations
        - Record review in notes and monitor progress
  - No
    - Consider future step down where appropriate

- No
  - Symptom return
    - Use regular alginate
    - Revert to lowest effective PPI dosage as required for up to four weeks
    - Consider regular PPI use until symptoms resolve and then re-initiate step down with self-care*

*Self-care
- Patients should receive lifestyle advice and be advised to use alginates first line to control symptoms
- Drugs known to cause gastrointestinal adverse effects should be reviewed
References

1. NICE Guidance for dyspepsia and GORD CG184;
3. All Wales Therapeutics and Toxicology Centre. All Wales Proton Pump Inhibitor and dyspepsia resource pack. April 2013.
6. NPC Rapid Review. Increased risk of C. difficile infections and of fractures: two more good reasons to review PPI prescribing. 3 June 2010.
11. Drug Safety Update. Recent epidemiological evidence of an increased risk of fracture with long-term use of proton pump inhibitors (PPIs). 2012; 5(9): A2