Proton Pump Inhibitors (PPIs) and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Advisory guidance on when to initiate a PPI for gastro-protection

This document is intended as advisory it does not replace clinical judgement which is assessed on a case-by-case basis. As PPIs have become widely used, evidence has started to emerge regarding their long-term safety and potential for adverse effects. Clinicians when considering prescribing long-term PPIs should consider if the risks (see overleaf) outweigh the benefits.

Need for oral NSAID therapy reviewed and confirmed. Check if any additional OTC preparations have been taken.

Yes

Does patient have any contraindications to NSAIDs[1] (see below)

Yes → Consider alternative treatment

No

Assess risk for NSAID-induced GI adverse events[1,3,4,5,6]

History of ulcer complication or history of ulcer disease (non-bleeding)[2]

Yes → Test for H pylori; treat if infected

- Aged over 65 years.
- A high dose of an NSAID.
- A history of gastroduodenal ulcer, GI bleeding, or gastroduodenal perforation.
- Concomitant use of medications that are known to increase the likelihood of upper GI adverse events (for example, anticoagulants, corticosteroids, SSRI).
- A serious comorbidity, such as CV disease, hepatic or renal impairment (including dehydration), diabetes, or hypertension.
- Heavy smoking.
- Excessive alcohol consumption.
- Previous adverse reaction to NSAIDs.
- Prolonged requirement for NSAIDs.

***Lansoprazole 15mg OD** or appropriate cost effective PPI

Does patient have CV and or renal risk factors?[1]

Yes

For people with heart failure:
Severe heart failure — *do not prescribe NSAIDs.*
Mild to moderate heart failure — *do not prescribe a COX-2 inhibitor, diclofenac, or high-dose ibuprofen (2400mg or more daily).* Consider ibuprofen upto 1200mg daily, or naproxen up to 1000mg with a PPI*

For people with ischemic heart disease, cerebrovascular disease, or peripheral arterial disease:
Do *not prescribe a COX-2 inhibitor, diclofenac, and high-dose ibuprofen*
Consider ibuprofen up to 1200mg per day or naproxen up to 1000mg daily with a PPI*

For people with risk factors for CV disease or the elderly:
Consider ibuprofen up to 1200mg per day or naproxen up to 1000mg daily with a PPI*

Before commencing long-term treatment with a PPI* consider risks (see overleaf) vs benefits. Discuss possible side effects to expect. Advise patient to only take PPI during course of NSAID

No

Moderate to high risk:
If they have more than ONE risk factor consider naproxen or ibuprofen with a PPI* [8,9]

Before commencing long-term treatment with a PPI* consider risks (see overleaf) vs benefits. Discuss possible side effects to expect. Advise patient to only take PPI during course of NSAID.

Low risk:
If they have no risk factors consider naproxen or ibuprofen.

For hypertension and severe renal impairment please see over

For people with hypertension:
Avoid prescribing etoricoxib or high-dose ibuprofen in people with uncontrolled hypertension (blood pressure persistently above 140/90 mmHg). Consider ibuprofen up to 1200mg per day or naproxen up to 1000mg daily with a PPI* and whether increased blood pressure monitoring is needed. Etoricoxib and high dose ibuprofen should be avoided.

For people with severe renal impairment (estimated glomerular filtration rate [eGFR] less than 30 mL/minute /1.73 m2):
Avoid prescribing NSAIDs.

If eGFR between 30 and 50mL/minute/1.73 m2 avoid NSAIDs if possible or use with caution and monitor carefully. Monitor renal function 1–2 weeks after starting or increasing the dose of the NSAID, and then regularly thereafter.[1]

Monitoring and Review

- Use an alternative H2 antagonist if a PPI is not appropriate.[7]
- For people continuing to take NSAIDs after a peptic ulcer has healed, discuss the potential harm from NSAID treatment. Review the need for NSAID use (at least every 6 months and offer a trial of use on a limited, 'as-needed' basis.[2]
- Review long term PPI prescribing to reduce the potential risk of Clostridium difficile, bone fractures and to a lesser extent the risk of higher mortality in older patients, acute interstitial nephritis, community acquired pneumonia, hypomagnesaemia, vitamin B12 deficiency and rebound acid hypersecretion. There may be indications where the benefits of long-term PPI use outweigh the risks (e.g. Barrett's Oesophagus, oesophageal stricture dilation, and gastro-protection for NSAID treatment). Assess on an individual basis and review regularly.[10]

Key Points[1]

- Ensure that appropriate patients are regularly reviewed and monitored for side effects during treatment.
- Assess NSAID-induced gastrointestinal (GI) adverse events, cardiovascular (CV) and renal risk factors.
- PPI should be stopped when the NSAID is stopped. For other indications of PPI usages ensure there is a set duration/ review date.
- Avoid prescribing more than one NSAID at a time. Avoid concomitant use of an NSAID with low-dose aspirin (if possible) – if this is essential, monitor closely.
- Before commencing treatment risks need to be discussed and explained as below and documented in the patient's notes.
- Use the lowest effective dose and the shortest duration of treatment necessary to control symptoms.
- Smoking increases risks: if patient is a smoker offer smoking cessation services.

Contraindications[1]

- **Do not prescribe nonsteroidal anti-inflammatory drugs (NSAIDs) to people with:**
  - Active gastrointestinal (GI) bleeding, or active GI ulcer.
  - A history of GI bleeding related to previous NSAID therapy, or a history of GI perforation related to previous NSAID therapy.
  - A history of recurrent GI hemorrhage (two or more distinct episodes), or history of recurrent GI ulceration (two or more distinct episodes).
  - A history of hypersensitivity/severe allergic reaction to an NSAID (including aspirin) — for example, asthma, rhinitis, angioedema or urticaria.
  - Severe heart failure.
  - Severe hepatic impairment — serum albumin less than 25 g/l or Child-Pugh score of 10 or more.
  - Severe renal impairment — estimated glomerular filtration rate (eGFR) less than 30 mL/minute/1.73 m^2.

- **Do not prescribe COX-2 inhibitors, diclofenac, aceclofenac or high dose ibuprofen (morethan 2400 mg daily) to people with:**
  - Ischaemic heart disease.
  - Inflammatory bowel disease (COX-2 inhibitors only).
  - Peripheral arterial disease.
  - Cerebrovascular disease

- Congestive heart failure (New York Heart Association [NYHA] classification II–IV).

- **Do not prescribe etoricoxib or high dose ibuprofen to** people with uncontrolled hypertension (persistently above 140/90 mmHg).

Known risks associated with long term PPI use

Adverse effects of PPIs are usually mild and reversible and include headache, diarrhoea, nausea, abdominal pain, constipation, dizziness and skin rashes.[10] However long-term PPI treatment may be associated with uncommon, serious adverse effects such as:

Clostridium difficile infection (CDI)

As per NICE guidance NG199, it is good prescribing practice to review the continuing need for existing proton pump inhibitor (PPI) treatment in people with suspected or confirmed C. difficile infection. Although some associations have been made between PPI use and the risk of C. difficile infection or recurrence, there is no definitive evidence of a causal or exacerbator effect. Also, no evidence from systematic reviews or randomised controlled trials was found to support stopping current PPI treatment. It was therefore concluded that suddenly stopping a PPI during an acute episode of infection may cause additional gastric symptoms. Additionally, some people will need ongoing gastroprotection for a clinical indication. However, they were aware that many people may be taking a PPI without a clear indication, so concluded that the use and need for a PPI should be reviewed.[11]

Osteoporotic fractures

As per MHRA drug safety update - observational studies suggest there may be a modest increase in the risk of hip, wrist or spine fracture associated with high dose and long term (>1 year) PPIs. Risk increases with a longer duration of PPI use in post-menopausal women with a history of smoking, which is known to inhibit calcium absorption. Smoking and PPI use may have a synergistic effect on fracture risk mediated by impaired calcium absorption. The Medicines and Healthcare products Regulatory Agency (MHRA) advice issued in April 2012 stated “There is recent epidemiological evidence of an increased risk of fracture with long-term use of PPIs. Patients at risk of osteoporosis should be treated according to current clinical guidelines to ensure they have an adequate intake of vitamin D and calcium”.[12]

Hypomagnesaemia

The MHRA have warned of the risk of hypomagnesaemia following prolonged use of PPIs (>1 year). Serious manifestations of hypomagnesaemia include fatigue, tetany, delirium, convulsions, dizziness, and ventricular arrhythmia. 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.[8]

Community acquired Pneumonia

There is a small but significant increase in hospitalisation from pneumonia due to PPI exposure has been found. It has been suggested that the greatest risk of pneumonia is within 48 hours of starting PPI therapy. This is inconsistent with bacterial overgrowth as a mechanism of colonisation. PPIs take 5 days to reach steady state but bacterial overgrowth due to PPI use would require substantially longer periods of exposure. GORD may itself be a risk factor for pneumonia (om stomach content aspiration) and is a confounding factor. No specific interventions are recommended in clinical practice.[10]

Rebound hypersecretion

PPI withdrawal may induce rebound acid hypersecretion. This could present as a worsening of symptoms that couldbe mistaken for disease relapse. However, due to weaknesses in the studies it cannot be concluded if symptoms are clinically important in patients or lead to reuptake of acid-suppressive medication.[10]

Acute interstitial nephritis (AIN):

A rare association has been reported between acute interstitial nephritis and PPIs. It can occur between several hours and four months following treatment with a PPI. The standard treatment involves early diagnosis, withdrawing the causative drug, administering steroids and clinical assessment.[10]

Very low risk of subacute cutaneous lupus erythematosus:

PPIs are associated with very infrequent cases of subacute cutaneous lupus erythematosus (SCLE), a non-scarring dermatosis that can develop in sun-exposed areas as per a MHRA drug safety update. Consider stopping use of the PPI 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 reactionwith another.[14]

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