MedicinesUpdateExtra

NHS Greater Glasgow and Clyde

# ORAL PROTON PUMP INHIBITORS

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- Proton Pump Inhibitors (PPIs) are one of the most commonly prescribed classes of drug
- PPIs are an effective treatment when used appropriately
- PPIs should only be prescribed where there is a clear indication
- PPIs are usually well tolerated
- Recent evidence suggests that PPIs may have potentially serious adverse effects such as fractures, hypomagnesaemia, subacute cutaneous lupus erythematosus, pneumonia and *Clostridium difficile* infection

## Introduction

Proton pump inhibitors (PPIs) have been available for over two decades, and since the introduction of lower cost generic PPIs, the use of these agents has continued to grow. In Scotland omeprazole was the most commonly prescribed drug by volume in the 2014 -2015 financial year (3.47 million items) and the 10th highest expenditure by gross ingredient cost (£11.54 million).[1] There is evidence that these agents may be prescribed excessively.[2] Over recent years evidence has emerged showing that PPIs may have previously unrecognised toxicities.

## Evidence

### Peptic Ulcer Disease

When prescribed for peptic ulcer disease, PPIs offer acid suppression, ulcer healing and symptomatic relief superior to that provided by any other anti-secretory therapy.[3] Four to eight weeks of full dose PPI treatment should be offered to people with peptic ulcer who have tested negative for *Helicobacter pylori (H. pylori)* and are not taking non-steroidal anti-inflammatory drugs (NSAIDs).[4]

### NSAID induced ulcers

NSAIDs increase the risk of dyspepsia and ulceration. Up to 25% of long term users of NSAIDs develop peptic ulcers. [3] PPIs have been shown to be superior to alternative treatments in both the healing of NSAID induced ulcers, and in preventing recurrences of these ulcers.[3] Refer to the NHS Greater Glasgow and Clyde (NHSGGC) oral NSAID guideline available via Staffnet for information on the use of PPIs to prevent NSAID induced ulcers. [5] Eight weeks of PPI therapy should be offered to those with a peptic ulcer related to NSAID use.[4]

### *Helicobacter pylori* eradication

*H. pylori* has been associated with both gastric and duodenal ulcers. Successful eradication of *H. pylori* with a PPI in combination with appropriate antimicrobial agents has been shown to facilitate ulcer healing and decrease the incidence of ulcer recurrence in *H. pylori* positive patients.[3] PPIs are normally prescribed in combination with antibiotics for one week, however, local guidance suggests that in complicated cases PPIs may need to be continued for a further three weeks after *H. pylori* eradication.[6]

### Gastro-Oesophageal Reflux Disease

PPIs are effective both for controlling symptoms of gastro-oesophageal reflux disease (GORD) and healing oesophagitis.[3] Initial treatment with a PPI should be given for 4-8 weeks but long-term treatment may be required in patients with severe oesophagitis.[4,6]

## Choice of PPI

Although studies exist comparing different PPIs, and some may suggest superiority of one agent over another, current NICE guidance does not recommend any particular PPI.[4] The NICE Guideline Development Group considered that a class effect could be assumed for all PPIs and the choice of agent should be based on patient preferences and clinical circumstances.[4]

Of the five PPIs licensed for use in the UK (esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole), only lansoprazole and omeprazole are included on the NHSGGC Formulary.[7] When choosing a PPI it should be noted that the licensed indications and the potential for interactions may differ between individual drugs.

## Safety

PPIs are usually well tolerated. The most common side effects include headaches, nausea, abdominal pain, constipation, flatulence, diarrhoea, rash and dizziness.[8] Recent reports have suggested that PPIs may be associated with additional, potentially more serious, adverse effects.

### Adverse effects reported by the MHRA

### Fractures

As PPIs reduce gastric acidity, it has been postulated that they may inhibit absorption of calcium from the diet, which, in turn, may lead to a reduction in bone mineral density and increased fracture risk.[9] However, a published review article, which examined the literature concerning the effects of PPIs on calcium absorption, stated that it is not possible to determine with any certainty whether PPIs affect calcium absorption.[10]

Meta-analyses have found a modest association between PPI use and fracture risk.[11-15] However, only epidemiological studies were available for evaluation. Some authors have reported that the risk of fracture increases with duration of use but this finding is inconsistent.

In 2012, the Medicines and Healthcare products Regulatory Agency (MHRA) issued advice in relation to the increased risk of fractures with prolonged PPI therapy.[16] No specific monitoring is recommended for patients on PPI therapy but they state that patients at risk of osteoporosis should be treated according to current clinical guidelines and have an adequate intake of calcium and vitamin D.

A more recent systematic review suggests that the modest effect of PPIs on fracture risk could be due to confounding factors.[17] Although the majority of studies did adjust for

confounding factors, residual confounding cannot be excluded.[17]

### Hypomagnesaemia

Symptoms of hypomagnesaemia include muscle twitches, tremor, vomiting, fatigue, delirium, arrhythmias and convulsions. These may begin insidiously and so the cause may be overlooked.

PPIs have been associated with hypomagnesaemia but the mechanism by which they cause this effect is not fully understood. It has been suggested that PPIs may reduce magnesium absorption or reduce active transport of magnesium from the intestine.[18]

In 2012, the MHRA issued advice to consider monitoring of serum magnesium levels in patients expected to be on long term treatment, especially if they are taking digoxin or other medicines known to cause hypomagnesaemia.[19] NHSGGC biochemistry have advised that levels should be checked only for patients who:

- have symptoms of hypomagnesaemia,
- have hypokalaemia or hypocalcaemia,
- are taking digoxin,
- have other causes of magnesium deficiency, eg prescribed diuretics, malabsorption syndromes, stoma losses.

Most of the evidence for the association between PPIs and hypomagnesaemia comes from case reports. A systematic review of published cases found this side effect to be a class effect with a variable onset of duration (median 5.5 years; range 14 days to 13 years). Discontinuation resulted in recovery within 4 days and rechallenge led to recurrence within 4 days.[20]

Observational studies have also investigated the association of PPIs with hypomagnesaemia. A systematic review including a case control study, two retrospective cohort studies and six cross-sectional studies found a statistically significant increased risk of hypomagnesaemia with PPI use. However, the authors concluded that they could not definitively determine causality due to heterogeneity between the studies.[18]

### Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) is characterised by polycyclic erythematous scaly plaques or confluent psoriasiform papulosquamous lesions, which may be accompanied by arthralgia. In September 2015 the MHRA advised that several cases of SCLE associated with PPIs have been reported both in the literature and on Yellow Cards.[21]

A case control study compared 234 patients diagnosed with SCLE with a control group from the general population to evaluate the association between exposure to suspected drugs (including PPIs) and a subsequent diagnosis of SCLE. The odds ratio (OR) for PPIs was 2.9 (95% CI 2.0-4.0). However, the authors concluded that a causal relationship cannot be established from this study and the pathogenesis underlying the disease is not fully understood.[22]

A more recently published retrospective medical chart review of patients diagnosed with SCLE identified 24 patients with PPI-induced SCLE. The authors found that PPI-induced SCLE seemed to be a class effect and that the onset was on average eight months after taking a PPI. However cases have been reported within a week of taking a PPI and up to years after starting.[23]

Considering the extensive use of PPIs, very few cases of SCLE have been reported. However, the evidence so far suggests a possible causal effect. The MHRA have advised that if a patient taking a PPI develops lesions (especially in sun-exposed areas) accompanied by arthralgia, SCLE should be considered as a potential diagnosis and the PPI should be stopped unless it is imperative that it is continued.[21]

### Other emerging adverse effects

### Pneumonia

Reduced gastric acidity may also increase pneumonia risk. The increase in gastric pH due to PPI use could allow gastric colonization with bacteria that if aspirated could cause pneumonia.[24]

A meta-analysis examined the published observational data and concluded that short term but not long term PPI exposure may be associated with a higher risk of community acquired pneumonia (CAP).[25] An additional publication found that the risks of CAP and hospital acquired pneumonia (HAP) increased with PPI use. The results suggested that the overall risk of pneumonia decreased with longer duration of PPI therapy and this effect was most apparent within the first seven days of acid suppression therapy. Additionally higher doses of PPI was more strongly associated with pneumonia.[26]

However, other authors have suggested that the effects observed may be due to confounding.[27] A recent large cohort study found that PPIs were not associated with an increased risk of hospitalisation for CAP and the authors suggested the positive results of previous studies were likely due to confounding and early cases of pneumonia being misdiagnosed as GORD.[28]

### *Clostridium difficile (C. difficile)*

PPI use has been suggested as a risk factor for *C. difficile* infection (CDI). This is because the gastric juice is more bactericidal at low pH and the host therefore becomes more susceptible to bacterial infections as gastric pH increases.[29]

Meta-analyses have found an association between PPI use and an increased risk of CDI[30-33] and of *C. difficile* recurrence.[31] Concomitant use of PPIs and antibiotics was also found to increase the risk to an excess of that conferred by either treatment alone.[31] However, the evidence was from case-control and cohort studies and of limited quality, so is insufficient to establish a definite causal link.

Although the evidence is limited, recently published guidelines from Health Protection Scotland state that PPIs are a major risk factor for CDI and recommend that they are stopped where possible in patients with suspected CDI.[34]

## Interactions

PPIs are known to have various significant interactions with other drug classes including anticoagulants, antiepileptics, antifungals and antivirals.[35] Most of these are due to the metabolism of PPIs by hepatic cytochrome P450 enzymes. The extent to which drugs within the class are metabolised by these enzymes may differ to some extent.[36] The BNF (see www.medicinescomplete.com) or individual Summary of Product Characteristics (see www.medicines.org.uk) should be checked for each drug.

The interaction between PPIs and clopidogrel has been much discussed in the literature in recent years. It is still unclear if there is definitely a clinically significant interaction as the available data are conflicting. Although

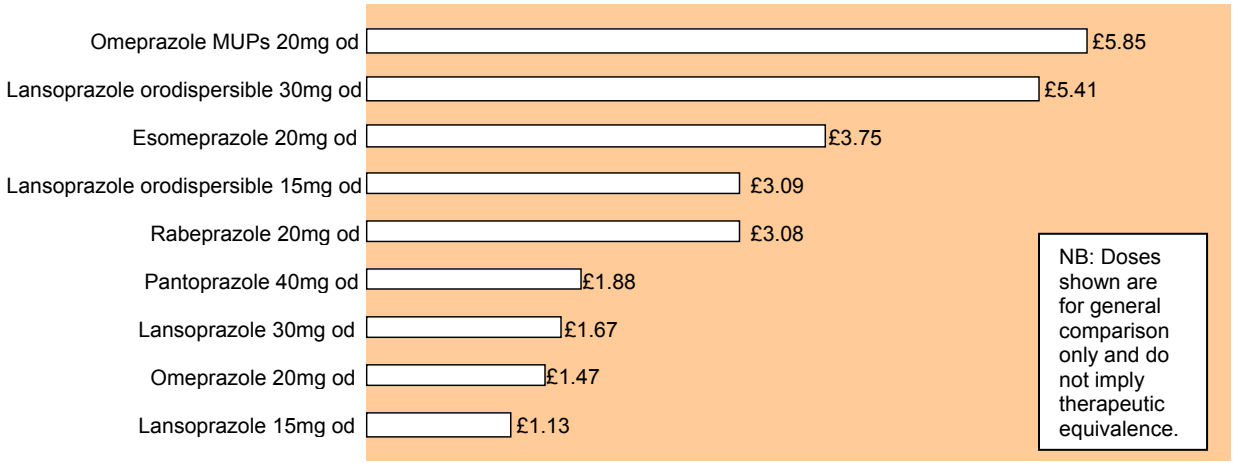
there is extrapolation from in vitro studies that some PPIs may be less likely to interact with clopidogrel there does not appear to be any evidence from clinical practice that any one PPI is better than another in this respect. Prescribers should consider the risk of GI side effects versus the risk of adverse cardiac events when considering co-prescription of a PPI and clopidogrel.[37] If a PPI is considered essential lansoprazole would be the Formulary choice. Further guidance on this is available from UK Medicines Information [38]

## Place in Therapy

Lansoprazole and omeprazole remain the choices on the NHSGGC Formulary.[7]

As with all medicines, the risks versus the benefits of PPI use should be considered when prescribing. Use should be restricted to the recommended durations as much as possible and dose reduction or as required use should be considered as appropriate.[4] Local guidance is available on the recommended durations for all acceptable indications.[6] As with all medicines, it is good practice to document the reason for initiating PPIs when prescribing. When PPIs are started in secondary care the indication, expected duration of treatment, and any required review or monitoring should be communicated to the primary care team on discharge. Similarly, it is good practice to document this information when initiating a PPI in primary care.

**Cost for 28 days treatment (Scottish Drug Tariff November 2015)**

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Produced by NHS Greater Glasgow and Clyde Medicines Information Service ♦ Approved by the Medicines Utilisation Subcommittee of the ADTC♦ Tel: 0141 211 4407 Email: medinfo@ggc.scot.nhs.uk