PostScRxipt - ExtRa

NHS Greater Glasgow and Clyde

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ORAL PROTON PUMP INHIBITORS

- **There is currently a lack of evidence to suggest superior clinical efficacy of one oral proton pump inhibitor over any other.**
- **Proton pump inhibitors display similar dose-response relationships with similar potencies and efficacies at the equivalent dose.**
- **The decision to select one proton pump inhibitor over another is likely to be based on the agents' licensed indication, patient tolerability and cost.**
- **Omeprazole and lansoprazole capsules, prescribed generically, for these reasons, are the Drugs of Choice across NHS Greater Glasgow.**

Introduction

There are currently 5 oral proton pump inhibitors (PPIs) available in the United Kingdom – omeprazole, lansoprazole, rabeprazole, pantoprazole and esomeprazole. However, only two, omeprazole and lansoprazole, are available on the Glasgow *Formulary*.

PPIs are used in a variety of gastro-intestinal (GI) disorders; such as, dyspepsia, gastro-oesophageal reflux disorder (GORD), NSAID-associated peptic ulcer, *Helicobacter pylori* (*H.pylori*) eradication, acute upper GI bleeding and Zollinger-Ellison syndrome. It is important to note that the licensed indications vary amongst the PPIs.

The widespread use of PPIs has raised questions regarding their cost-effective use. There are also questions about whether there are any clinically significant differences between the PPIs available. This bulletin considers *which PPI*? The place in therapy of PPIs, treatment vs. maintenance doses is not considered.

Evidence

Effectiveness of PPIs can be measured in several ways: surrogate markers such as changes in intragastric pH or clinical markers including rates of healing and resolution of symptoms.

Control of intragastric pH

PPIs owe their clinical efficacy to their ability to inhibit H^+, K^+ -adenosine triphosphate in gastric parietal cells, resulting in suppression of gastric acid secretion. The amount of time that intragastric pH is greater then 4.0 is a parameter that is frequently used to evaluate the pharmacodynamics and clinical effects of treatment with PPIs in patients with acid related diseases.

Two 5-way crossover studies, in *H.pylori* negative patients with symptoms of GORD, were randomised to esomeprazole 40 mg, omeprazole 20 mg, lansoprazole 30 mg, rabeprazole 20 mg or pantoprazole 40 mg daily.[1,2] Both studies demonstrated that esomeprazole 40 mg was superior compared with the other 4 PPIs in maintaining intragastric pH above 4 for a significantly higher mean percentage of the 24-h period. The clinical significance of these types of studies is unclear as it cannot be assumed that a quantitatively greater degree of suppression of intragastric pH translates into a demonstrable advantage in healing rates or resolution of symptoms in clinical practice.

Treatment of acute GORD

A meta-analysis comparing lansoprazole 30 mg and omeprazole 20 mg showed no significant difference in healing rates between these two proton pump inhibitors at 4 and 8 weeks.[3]

Another meta-analysis found no statistically significant differences in healing rates at 4 and 8 weeks, either between individual agents (lansoprazole 30 mg, rabeprazole 20 mg and pantoprazole 40 mg) or these PPIs combined versus omeprazole 20 mg.[4] There was no improvement in overall heartburn symptom resolution with lansoprazole, pantoprazole and rabeprazole compared with omeprazole at 4 weeks.

A third meta-analysis found no significant difference in the healing rates of lansoprazole 30 mg, pantoprazole 40 mg or rabeprazole 20 mg at 4 or 8 weeks when compared with omeprazole 20 mg.[5] However, esomeprazole 40 mg significantly increased healing compared with omeprazole 20 mg at 4 and 8 weeks. Similar outcomes were reported by another meta-analysis.[6] Esomeprazole, as the s-isomer of omeprazole, claims greater activity than the racemic omeprazole due to the significantly lower activity of the r-isomer.[7] In this case, the licensed dose of esomeprazole (40mg) is not just double that of omeprazole (20mg), but is equivalent to greater than double the 20mg omeprazole dose on account of the greater activity of the s-isomer. The ADTC concluded that this was insufficient justification to add esomeprazole to the *Formulary*.

Maintenance treatment of GORD

One meta-analysis found that lansoprazole 15 mg was more effective for maintaining healing than omeprazole 10 mg (at 12 months) but significantly less effective than esomeprazole 20 mg (at 6 months), lansoprazole 30 mg or omeprazole 20 mg (at 6 and 12 months).[8] No significant difference was found between lansoprazole 30 mg and omeprazole 20 mg for maintenance of healing at 12 months.[9]

One study randomised 243 patients with healed erosive oesophagitis to rabeprazole 10 mg, rabeprazole 20 mg or omeprazole 20 mg and followed them for 5 years. No difference in maintenance of healing of erosive oesophagitis was shown between the groups at 1-year or in the 123 patients who completed the 5-year study.[10,11]

Peptic ulcer disease

One meta-analysis compared the efficacy of different PPIs in the treatment of peptic ulcer disease.[6] No significant differences in ulcer healing rates were demonstrated

between lansoprazole 30 mg and omeprazole 20 mg, rabeprazole 20 mg and omeprazole 20 mg or lansoprazole 30 mg and omeprazole 40 mg after 4 weeks. However, pantoprazole 40 mg was statistically superior to omeprazole 20 mg in ulcer healing. The finding for pantoprazole was at odds with the original trials (they did not show any significant differences between pantoprazole and omeprazole) but this anomaly is not explained by the authors.

Prevention and treatment of NSAID-associated ulcers

No randomised controlled trials (RCTs) were found demonstrating the superiority of a particular PPI for this indication.

Helicobacter pylori (H.pylori)

A meta-analysis showed no difference between omeprazole and lansoprazole based triple therapies for *H.pylori* eradication of 7 days or more.[12] A more recent meta-analysis found no difference in PPIs (omeprazole, lansoprazole, rabeprazole and esomeprazole) when used in standard triple therapy for *H.pylori* eradication.[13] A third meta-analysis concluded that pantoprazole achieved similar cure rates to those of omeprazole and lansoprazole when co-prescribed with antibiotics for the eradication of *H.pylori*.[14]

'On demand' therapy

Esomeprazole and rabeprazole are the only PPIs approved for 'on-demand' symptomatic treatment of GORD.[15,16]

Only 2 trials comparing different PPIs given on-demand have been published. One considered esomeprazole 40 mg and omeprazole 20 mg.[17] Unsurprisingly, statistically fewer tablets were used in the esomeprazole group than in the omeprazole group. The second trial involved omeprazole 20 mg and lansoprazole 30 mg.[18] The average number of doses taken was similar for omeprazole and lansoprazole as was the proportion keeping their reflux symptoms controlled (95% and 96% respectively).

Patient preference

Observational studies have attempted to measure rates of humanistic outcomes in patients converted from one PPI to another. Some of these studies have demonstrated that such a switch leads to more severe symptoms, increased adverse effects and decreased patient satisfaction[19-21] whereas other studies have not indicated loss of symptom control or adversely affected patient perceived outcomes of PPI therapy.[22-24] However, there are limitations to such studies; e.g. they are unblinded, not randomised and there is potential for patient recall bias.

In a double-blind cross-over study 240 patients were randomised to omeprazole 20 mg daily or rabeprazole 20 mg for 4 weeks and then to the other agent for a further 4 weeks.[25] Results showed that that the majority of patients could be switched to another PPI, without noticeable difference in maintenance of primary symptom control. Most patients already controlled by a PPI would be willing to try another.

Safety

The PPIs are predominately metabolised by the CYP2C19 and CYP3A4 isoforms of cytochrome P450 and, theoretically, could interact with other drugs metabolised by these enzymes or by inducers or inhibitors of these enzymes, although the potential for such interactions based on metabolic pathways may be exaggerated.[26] However, caution is advised when these agents are prescribed concomitantly with other agents metabolised by the same enzyme system (refer to individual agents SPCs for details [http://emc.medicines.org.uk/]).

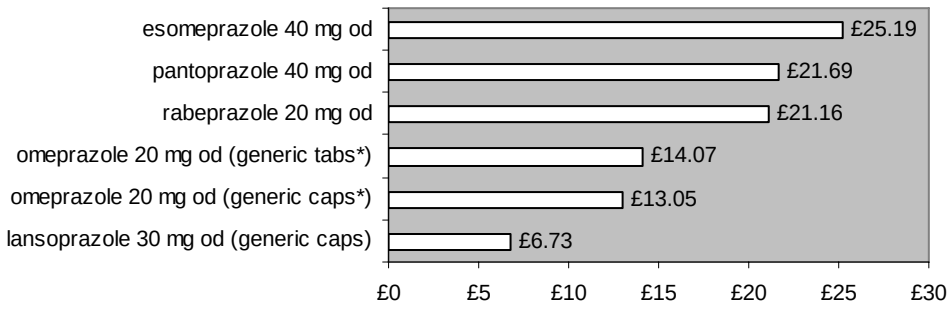
Place in Therapy

There is currently a lack of evidence to suggest superior clinical efficacy of one oral proton pump inhibitor over any other. Proton pump inhibitors display similar dose-response relationships with similar potencies and efficacies at the equivalent dose.

The decision to select one proton pump inhibitor over another is likely to be based on the agents' licensed indication, patient tolerability and cost. Omeprazole and lansoprazole capsules, prescribed generically, for these reasons, are the Drugs of Choice across NHS Greater Glasgow.

How much do they cost?

Cost for 28 days treatment (Scottish Drug Tariff/MIMS April 2006)



NB: Doses shown are for general comparison only and do not imply therapeutic equivalence.
* prices for generic omeprazole tablets and capsules based on Scottish Drug Tariff March 2006; the prices for April 2006 have not yet been released. A reduction in the cost of omeprazole is anticipated.

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