Esomeprazole:

**Licensed indications**

1. Gastro-Oesophageal Reflux Disease (GORD)
2. Eradication of *Helicobacter pylori*
3. Patients requiring continued NSAID therapy
4. Prolonged treatment after IV induced prevention of rebleeding of peptic ulcers.
5. Treatment of Zollinger Ellison Syndrome

**Relative potency**

Kirchheiner et al conducted an analysis to provide estimates of the relative potencies of PPIs based on peer-reviewed published data on gastric pH effects. Based on the mean 24-h gastric pH, the relative potencies of the five PPIs compared to omeprazole were 0.23, 0.90, 1.00, 1.60 and 1.82 for pantoprazole, lansoprazole, omeprazole, esomeprazole, and rabeprazole, respectively.

**Prescribing guidance**

In its briefing on dyspepsia in 2006, the NPC stressed that it was more important that PPIs are used appropriately, rather than debating which one to use and reiterated NICE recommendations from 2000 that the least expensive PPI should be used. It was highlighted in a related commentary that the newer PPIs offered no advantages in terms of clinical efficacy, long-term safety, or cost, and omeprazole and lansoprazole are both available generically and are thus suitable first choices.

A DTB review from 2006 noted that published comparative trials for reflux and *Helicobacter Pylori* eradication used around 2-4 fold higher doses of esomeprazole than comparator drugs, and no trials have demonstrated a therapeutic advantage of esomeprazole over other PPIs when the treatments are given at equivalent doses.

**Evidence in GORD**

In a systematic review and meta-analysis (AstraZeneca sponsored), Gralnek et al evaluated healing rates and symptom relief achieved with esomeprazole (40mg) compared with other PPIs in patients with erosive oesophagitis (EO).

They reported a 10% (relative risk, 1.10; 95% CI, 1.05 to 1.15) and 5% (1.05; 1.02–1.08) relative increase in probability of healing, with esomeprazole versus alternative PPIs at 4 and 8 weeks, respectively. At 8 weeks, there was an absolute risk reduction (ARR) of 4% and NNT of 25. I.e. 25 patients with EO would need to be treated with esomeprazole instead of an alternative PPI to achieve 1 additional case of healed EO. The effectiveness of esomeprazole was inversely proportional to baseline EO severity; the calculated NNTs by Los Angeles grade of EO (grades A–D) were 50, 33, 14, and 8, respectively. There was also an 8% (1.08; 1.05–1.11) relative increase in probability of GORD symptom relief at 4 weeks, translating into an ARR of 4% and NNT of 25, i.e. 25 patients with EO would need to be treated with esomeprazole instead of an alternative PPI to provide GORD symptom relief in 1 additional patient with EO after 4 weeks of treatment. There was a 22% relative increase in the reported incidence of headache with esomeprazole compared with other PPIs (1.22; 1.03–1.44), but no observed difference in the reported rates of diarrhoea, abdominal pain, nausea, or total adverse events between the various PPIs.
The researchers conclude from their meta-analysis that compared with alternative PPIs, esomeprazole provided a statistically significant but only modest degree of improved effectiveness in the healing of EO, and this appears to be largely limited to those individuals with more severe erosive disease (LA grades C and D). In addition, there was no evidence of a clinically meaningful improvement in symptom relief with esomeprazole compared with alternative PPIs. They suggested that the clinical benefit of esomeprazole might be important in more severe erosive disease.\(^6\)

According to an appraisal of this review by the Centre for Reviews and Dissemination, “the authors’ conclusion about overall benefit is appropriate given the evidence presented. However, the conclusion about greater benefit for more severe disease should be considered with caution given the limited details of the methods used and the results generated.” The appraisers added that the choice of PPI is likely to be best made on multiple factors such as disease presentation, drug cost, availability and patient tolerability, and further research is required to establish whether any clinical advantage is provided by esomeprazole, using an a priori definition of clinically meaningful improvement.\(^7\)

The systematic review (AstraZeneca sponsored) by Edwards et al compared the standard-dose PPIs (esomeprazole 40mg, lansoprazole 30mg, omeprazole 20mg and pantoprazole 40mg) with omeprazole 40mg in the healing of severe EO [LA classification C and D or equivalent] to obtain some insight into how patients who have failed on a previous standard-dose PPI might respond to an alternative treatment. They acknowledged that esomeprazole 40mg has not been compared with omeprazole 40mg in a head-to-head RCT. Among the four PPIs compared with omeprazole 20mg as the baseline treatment in the mixed treatment comparison, esomeprazole 40mg was the only one to demonstrate statistically significantly higher healing rates at 4 weeks (odds ratio, 1.84, 95% CrI: 1.50 to 2.22) and at 8 weeks (1.91, 95% CrI: 1.13 to 2.88). The authors note that despite the absence of direct comparison in a RCT of the European-licensed double and standard-dose PPIs for endoscopic healing, the results from the mixed treatment comparison suggest that “empirical management of patients who fail to respond to standard-dose PPIs with esomeprazole 40mg may reduce the need to refer patients to secondary care for further investigation and lead to cost savings in primary care.”\(^8\) According to an appraisal of this review by the Centre for Reviews and Dissemination, “overall, the findings of the review appear to be supported by the data, but caution is advised given the levels of unexplained statistical heterogeneity detected.”\(^9\)

Unpublished data from a randomised, double-blind study comparing esomeprazole with omeprazole at equivalent, head-to-head doses (40mg/d) in 320 patients with moderate or severe EO (LA grades C or D) indicated statistically significantly better healing rates with omeprazole at 8 weeks: 73.1% (95% CI, 66.1 to 80.0) vs. esomeprazole 61.8% (54.2 to 69.4), \(p=0.0422\), absolute risk reduction 11.3% and NNT= 9.\(^{12}\) These data were published in 2005 but do not seem to have been fully published so an assessment of the results cannot be undertaken.\(^{10}\)

In their review of esomeprazole in the treatment of GORD, Kalaitzakis et al noted that despite data from clinical trials and meta-analyses indicating higher rates of healing of erosive GORD and a greater proportion of patients with sustained resolution of heartburn with esomeprazole 40mg than omeprazole 20mg, lansoprazole 30mg, or pantoprazole 40mg, it was not clear whether these statistically significant differences were of major clinical importance.\(^{11}\)

**H. pylori eradication**

In a meta-analysis of 11 RCTs, including 2159 subjects, esomeprazole triple therapy was found to be effective in the treatment of *H. pylori*, with eradication rates comparable to previously studied PPI-based triple therapies. The mean *H. pylori* eradication rates with esomeprazole + antibiotics was 86%, a rate
comparable with other PPI therapies, 81%.

According to an appraisal of this paper by the Centre for Reviews and Dissemination, “the authors’ conclusion about the probable comparability of esomeprazole and omeprazole does not appear to be supported by the evidence presented, and so may not be reliable.”

Zollinger Ellison disease and NSAID cover.

There are no head to head studies of esomeprazole and other PPIs in Zollinger Ellison disease and for NSAID cover.

Summary

In EO, the data suggest a statistically significant, albeit modest improvement in the healing of EO with esomeprazole 40mg, compared to other PPIs to which it has been compared, though this appears to be largely limited to those individuals with more severe erosive disease. It is not clear whether these statistically significant differences were of major clinical importance, and the suggestion that it might be more effective for more severe disease requires further investigation. In addition, there was no evidence of a clinically meaningful improvement in symptom relief of EO with esomeprazole compared with alternative PPIs. A study of the relative potency of PPIs based on intragastric pH noted that esomeprazole was 1.6 times more potent than omeprazole. However, in the first study comparing equivalent head to head doses of esomeprazole and omeprazole (40mg), statistically significantly better healing rates at 8 weeks were actually reported for omeprazole. As these data remain unpublished, further analysis of the data is not possible. The probable comparability of esomeprazole and omeprazole in HP eradication has been suggested by a meta-analysis but its findings have been called into question. There are no head to head studies of esomeprazole and other PPIs in Zollinger Ellison disease and for NSAID cover.

Therefore based on the current literature, it is difficult to establish if esomeprazole offers a clinically significant advantage over other PPIs, and thus its place in therapy remains to be determined.

Ref

5. Anon. New drugs from old. DTB 2006; 44 (10): 75
APPENDIX 17


