

Drug Class Review on Proton Pump Inhibitors

Executive Summary

Marian McDonagh, PharmD
Susan Carson, MPH

Produced by
Oregon Evidence-based Practice Center
Oregon Health & Science University
3181 SW Sam Jackson Park Road
Mailcode: BICC
Portland, OR 97201-3098

Mark Helfand, MD, MPH, Director

The logo for Oregon Health & Science University (OHSU), consisting of the letters "OHSU" in a bold, black, serif font.

OVERVIEW

Proton pump inhibitors (PPIs) reduce stomach acid. PPIs act by blocking the enzyme system responsible for active transport of acid into the gastrointestinal lumen, namely the hydrogen/potassium adenosine triphosphatase (H^+/K^+ ATPase) of the gastric parietal cell, also known as the “proton pump.” Omeprazole, the first drug in this class, was introduced in 1988. Since then, four other PPIs have been introduced: lansoprazole (1995), rabeprazole (1999), pantoprazole (2000) and esomeprazole (2001).

PPIs are used to treat peptic ulcers (duodenal and gastric), gastroesophageal reflux disease (GERD), and to treat and prevent drug-induced ulcers (e.g., non-steroidal anti-inflammatory drugs [NSAIDs]). For peptic ulcer disease, PPIs are given with antibiotics to eradicate *Helicobacter pylori*, the bacteria that cause ulcers. For gastroesophageal reflux, which causes heartburn and acid regurgitation, the American Gastroenterology Association recommends that patients first try lifestyle modifications and over-the-counter medicines. Over-the-counter medications include antacids and histamine-2 receptor antagonists (H2-RAs, commonly called “H2-blockers”), such as cimetidine or ranitidine. If these lifestyle changes and over-the-counter medications do not completely control heartburn symptoms, PPIs or high doses of H2-RAs may be prescribed. Many clinicians use H2-RAs as the initial therapy for gastroesophageal reflux.

Key Questions

The key questions for this review were:

1. What is the comparative efficacy of different PPIs in adult patients with symptoms of GERD?
2. What is the comparative efficacy of different proton pump inhibitors in adult patients with peptic ulcer and NSAID-induced ulcer?
3. What are the comparative incidence and nature of complications (serious or life-threatening or those that may adversely effect compliance) of different PPIs in adult patients being treated for symptoms of gastroesophageal reflux, peptic ulcer, and NSAID-induced ulcer?
4. Are there subgroups of patients based on demographics, other medications, or co-morbidities for which one medication or preparation is more effective or associated with fewer adverse effects?

These questions, and the eligibility criteria for this systematic review, were developed and refined with input from a subcommittee comprised of local experts (pharmacists, primary care clinicians, and gastroenterologists)

METHODS

To identify articles relevant to each key question, we searched the Cochrane Library, MEDLINE, EMBASE, and reference lists of review articles. In electronic searches, we

combined terms for gastroesophageal reflux and peptic ulcer with terms for PPIs and relevant research designs. Electronic databases were searched from their launch to March 2003. Subcommittee members were invited to provide additional citations. Pharmaceutical manufacturers were invited to submit dossiers, including citations, using a protocol issued by the State of Oregon (<http://www.ohppr.state.or.us/index.htm>). All citations were imported into an electronic database (EndNote 5.0).

RESULTS

Comparative effectiveness and adverse effects of PPIs for GERD

Healing. Eight head-to-head trials and one good quality systematic review found no differences among omeprazole, lansoprazole, rabeprazole, and pantoprazole in healing rates at 4 and 8 weeks.

In two trials esomeprazole 40mg had higher 4-week and 8-week healing rates than omeprazole 20mg, but there are no head-to-head comparisons of omeprazole 40mg versus esomeprazole 40mg.

One trial of esomeprazole 40 mg versus lansoprazole 30 mg found better healing rates in the esomeprazole group. At 8 weeks the difference in adjusted crude healing rate was 3.4% corresponding to a number needed to treat of 29 (for every 29 patients treated with esomeprazole one additional patient was healed compared to lansoprazole).

There have been 3 trials that compare esomeprazole to another PPI, but because of concerns over lack of equivalence in doses used (omeprazole), method of reporting and analyzing results, and relatively small differences in healing rates these trials do not provide sufficient evidence that esomeprazole is more efficacious than any other PPI. Clear reporting of numbers of patients healed and unhealed at 4 and 8 weeks in these trials would help to clarify this.

Symptoms. Eight head-to-head trials found no difference in relief of symptoms between omeprazole, lansoprazole, rabeprazole, or pantoprazole. Twenty-four trials of omeprazole, lansoprazole, rabeprazole, or pantoprazole compared to an H2-RA, and a previous systematic review also found no differences.

A good quality study that measured symptoms and quality of life as primary endpoints found equivalent heartburn relief with omeprazole Multiple Unit Pellet System (MUPS) 20mg and pantoprazole 40 mg, but lansoprazole 30 mg was inferior. Patient satisfaction at 4 and 8 weeks was equivalent for all 3 PPIs, however.

Two studies found esomeprazole 40mg better at symptom relief on some, but not all, measures, than omeprazole 20mg. One good-quality study found better symptom relief on some, but not all, measures for esomeprazole 40 mg compared with lansoprazole 30 mg at 4 weeks and did not measure symptoms at 8 weeks.

Relapse Prevention. Three randomized controlled trials compared one PPI to another for long-term (6 months or more) maintenance therapy for esophagitis relapse prevention. Two of these found no differences in endoscopic or symptomatic relapse rates for lansoprazole versus omeprazole after 48 weeks of treatment, or rabeprazole versus omeprazole after 13, 26, and 52 weeks. The third trial compared relapse rates at 6 months in patients randomized to

esomeprazole 20 mg or lansoprazole 15 mg. According to life-table analysis, a higher proportion of patients in the esomeprazole group remained healed (83% vs 74%) over 6 months. More patients in the esomeprazole group remained healed across all grades of disease severity, whereas the efficacy of lansoprazole decreased with increasing severity of disease. No crude rates or numbers of patients remaining healed were presented. Because all patients enrolled had responded to esomeprazole for initial healing of esophagitis, the study may be biased towards esomeprazole.

A shorter-term trial of 36 patients with severe esophagitis compared omeprazole, lansoprazole, and pantoprazole for the prevention of relapse at 4 weeks. After 4 weeks, patients taking omeprazole had a lower rate of endoscopic relapse (10%) than those randomized to either lansoprazole (80%) or pantoprazole (70%). The relapse rates in the lansoprazole and pantoprazole groups are very high compared with other studies and, as in the esomeprazole versus lansoprazole study discussed above, had a selection bias in that all subjects had responded well to one of the study drugs before enrollment in the maintenance phase.

Adverse Effects. In head-to-head long-term maintenance studies, there was no difference in the number of adverse events reported or number of withdrawals due to adverse events in the different PPI treatment groups

In head-to-head comparisons of PPIs for short-term treatment of GERD, the proportion of patients withdrawing due to adverse events was very low, with most studies reporting 1% to 3%. No study found significant differences among treatment groups in the rate of withdrawals for adverse effects. The exception was one study of rabeprazole 10mg or 20mg versus omeprazole 20mg that reported 5% to 7% withdrawals for adverse events. The rate of attrition overall was somewhat high in this study (17%-24%) Reports of serious adverse events were low, and generally balanced among the drugs. Many of these incidences could be associated with pre-existing diseases.

Comparative effectiveness of PPIs for Peptic Ulcer and NSAID-induced ulcer

Duodenal Ulcer. The evidence is good for omeprazole and lansoprazole having similar effectiveness in both endoscopic healing and symptom relief. The pooled risk difference in absolute difference in proportion healed at 8 weeks for five trials of lansoprazole 30mg versus omeprazole 20mg once daily was not significant; -0.2 (95% CI, -3.0-2.6).

The evidence for pantoprazole, rabeprazole and esomeprazole is less strong, because there are only single studies for each drug compared to another PPI (all compared to omeprazole).

No study found significant differences in healing rate. Data from studies comparing PPIs to H2-RAs also indicate that there are no significant differences between the four PPIs studied (there are no studies of esomeprazole).

Symptom relief is an important measure in ulcer diseases, and does not always correspond to endoscopic healing. Method for assessment of symptom relief was not consistent across the studies, and reporting of findings was often limited to early time periods and just a few outcome measures (of many measured). Few studies found a difference in any of the many measures of symptom relief, and the lack of reported data at later time-points may indicate that symptom relief was equivalent.

Gastric Ulcer. There is little head-to-head comparative data of PPIs for the treatment of gastric ulcer, with only one study of rabeprazole versus omeprazole. No significant differences in healing rates were found. Data from studies of omeprazole, lansoprazole and pantoprazole compared to H2-RAs indicate no significant difference in the rate of healing at 4 weeks. Symptom relief was better in 3 of 12 measures for rabeprazole compared to omeprazole at 3 weeks or two measures and 6 weeks for a third measure (the measures significantly different at 3 weeks were not different at 6 weeks). Symptom relief was difficult to compare for the other drugs, with no head-to-head studies.

NSAID-induced Ulcer. There are no head-to-head trials, so the strength of the evidence for comparing PPIs is poor. Only three trials compared a PPI to another drug, two with omeprazole and one with lansoprazole. No important differences between PPIs could be discerned from these studies, with the confidence intervals for healing rates overlapping. However, the treatment success rates for all treatments varied widely among the trials, so confidence in this finding is low.

Prevention of NSAID-induced Ulcer. There are no head-to-head trials. A good quality systematic review and six subsequently published trials compared PPIs to placebo or other drugs. Only one trial included outcome measures for serious ulcer complications, and for some of the endoscopic ulcer findings, patients were asymptomatic. Based on development of new ulcers or serious erosions and on symptoms, there did not appear to be differences in the PPIs studied (omeprazole, lansoprazole and pantoprazole). However, because of the differences in patient populations, comparison groups, and outcome measure definitions, confidence in this finding is low.

Helicobacter Pylori Eradication. The data regarding comparative effectiveness of various PPIs for eradicating *H. pylori* is fair, with one systematic review, and 16 recent head-to-head trials. The significant heterogeneity among studies based on design, participants, and method of measuring outcomes lessen the strength of the evidence. These studies generally did not find a difference in eradication rate between the PPIs, with the exception of lower dose pantoprazole when compared to high dose pantoprazole or high dose omeprazole, and rabeprazole when compared to lansoprazole in one study. Symptom resolution was not assessed in these studies.

Adverse Effects. There are no head-to-head maintenance studies of ulcer, but three 12-month studies of duodenal ulcer maintenance compared a PPI to placebo or other anti-ulcer medications. In two of the studies, the withdrawal rates for placebo were higher than any of the drug arms. In one study, the withdrawal rates due to adverse events were unusually high in all groups, 17% for lansoprazole 15mg, 5.3% for lansoprazole 30mg and 21.5% for placebo over a 12-month period.

Subgroups

Head-to-head comparison studies did not adequately describe or analyze subgroups for differences in effectiveness, although two assessed differences in adverse effects based on age, gender and race with no differences found. There are studies which suggest that a lower dose of PPI may be equally effective in patients who are older or are deficient in the CYP2C19 liver

enzyme (3% of whites and African Americans and 17-25% of Asians). Only one of these studies was a head-to-head comparison, omeprazole versus lansoprazole, but no difference was found between the two. While there may be differing effects of the PPIs based on demographics, there is inadequate data to identify any difference between them.