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Summary of 2009 Drug Effectiveness Review Project (DERP) Report of Proton Pump Inhibitors (PPIs)

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PPIs are utilized for a host of gastrointestinal maladies, primarily for the treatment of Gastro-Esophageal Reflux Disease (GERD) symptoms and peptic ulcers (gastric and duodenal), including those associated with Helicobacter pylori (H. pylori) gastritis or related to non-steroidal anti-inflammatory drug (NSAID) therapy.[1] The following is a summary of the 2009 DERP report on a PPI drug class review.

DERP is a collaboration of public entities, the Center for Evidence-based Policy and the Oregon Evidence-based Practice Center, who have joined together to produce systematic, evidence-based reviews of the comparative effectiveness and safety of drugs in many widely used drug classes.[2]

PPIs exert their gastric acid suppressing action by binding to hydrogen-potassium ATPase in gastric parietal cells thereby blocking the final step in the secretion of hydrochloric acid and inhibiting gastric acid secretion.[3] Currently there are five PPIs available: omeprazole (also available over-the-counter as omeprazole magnesium and in combination with sodium bicarbonate), lansoprazole, rabeprazole pantoprazole, and esomeprazole.

Key Questions for the DERP drug class review were:

1. What is the comparative effectiveness of different PPIs in patients with symptoms of GERD?
2. What is the comparative effectiveness of different PPIs in treating patients with peptic ulcer and NSAID induced ulcer?
3. What is the comparative effectiveness of different PPIs in preventing ulcer in patients taking an NSAID?
4. What is the comparative effectiveness of different PPIs in eradicating H. pylori infection?
5. Is there evidence that a particular treatment strategy is more effective or safer than another for longer-term treatment (more than 8 weeks) in patients with GERD?
6. What is the comparative safety of different PPIs in patients being treated for symptoms of GERD, peptic ulcer, and nonsteroidal anti-inflammatory drug-induced ulcer?
7. Are there subgroups of patients based on demographics, other medications, or comorbidities for which a particular medication or preparation is more effective or associated with fewer adverse effects?

1. Symptom relief and healing of GERD

Among the 16 head-to head trials, those with comparable doses did not find differences in symptom relief or healing of esophagitis. The only difference between proton pump inhibitors on the outcome of complete symptom relief at 4 weeks was in the comparison of esomeprazole 40 mg with omeprazole 20 mg; the pooled risk difference in 3 trials was 8% (95% CI 3-13), with a number needed to treat of 13. However, dose comparability between esomeprazole and omeprazole has not been established and it is believed that they are not equivalent due to differences in drug chemistry and pharmacology.[4]

With respect to healing rates, good evidence showed healing time for esophagitis did not differ between omeprazole, lansoprazole, pantoprazole, and rabeprazole at 4 and 8 weeks. The exception was esomeprazole 40 mg which was found to be better than omeprazole 20 mg and lansoprazole 30 mg but dose comparability remains uncertain; the pooled risk difference for omeprazole was 7% (95% CI 1-12) and a number needed to treat of 14 at 4 weeks and 5% (95% CI 1-9), number needed to treat is 20 at 8 weeks.

When healing rates of moderate to severe erosive esophagitis at 4 and 8 weeks were reviewed, esomeprazole 40 mg was found to be better than omeprazole 20 mg and lansoprazole 30 mg. Dose comparability is again an issue. The pooled risk difference in the 3 studies comparing omeprazole 20 mg with esomeprazole 40 mg was 16% at 4 weeks and 13% at 8 weeks (number needed to treat is 6 at 4 weeks, 8 at 8 weeks). Mixed differences were found between esomeprazole 40 mg and pantoprazole 40 mg where a higher healing rate occurred at 4 weeks with esomeprazole 40 mg, but no difference between the two at 8 weeks.

In prevention of relapse of healed esophagitis there was no difference between omeprazole, lansoprazole, and rabeprazole. The longest study (over 5 years) compared omeprazole with rabeprazole. Lower relapse rates were observed with esomeprazole 20mg compared with lansoprazole 15 mg or pantoprazole 20 mg at 6 months. For combined symptomatic and endoscopic remission rates after 6 months, no difference was found between esomeprazole 20 mg and pantoprazole 20 mg.

No difference was found between esomeprazole 20 mg and omeprazole 20 mg, pantoprazole 20 mg, or rabeprazole 10 mg for the symptom relief for nonerosive GERD (or presumptively treated symptoms). There was additional indirect evidence that suggests similar efficacy between all 5 PPIs for heartburn and complete symptom relief.

While statistically significant differences were noted in various esomeprazole comparisons, some of these studies are compromised by uncertain dose comparability and overall there were relatively small absolute clinical differences detected. In its review of the 2006 DERP PPI Report, the Oregon Health Resources Commission concluded there was no overall clinically significant difference between PPIs for esophagitis healing, relief of symptoms or prevention of relapse in adult patients with GERD.[5] Given this interpretation of similar effectiveness it is prudent to examine the comparative cost of treatment among the PPIs (Table 1).

Table 1.*

Generic	Brand	30-day supply
Omeprazole magnesium	Prilosec OTC	$30
Omeprazole	Generic	$35
Pantoprazole	Protonix	$80
Omeprazole	Prilosec	$90
Dexlansoprazole	Kapidex	$90
Pantoprazole	Generic	$110
Omeprazole/ Sodium Bicarbonate	Zegerid	$130
Lansoprazole	Prevacid	$160
Esomeprazole	Nexium	$180
Rabeprazole	Aciphex	$190

* Costs are 30-day average pharmacy reimbursement based on actual claim data from 5/1/09 - 6/30/09; Excludes rebate

2. Peptic Ulcer Treatment

For treatment of peptic ulcer with a PPI, 10 randomized controlled trials were reviewed and strong evidence was found that omeprazole 20mg and lansoprazole 30 mg are similarly effective for symptomatic relief and healing. In comparison, the evidence for pantoprazole, rabeprazole, and esomeprazole was less strong because only single studies involving comparison to omeprazole were available. Overall, no difference was found between all PPIs in healing rates or symptom relief.

For treatment of gastric ulcer, there was no difference in healing rates between rabeprazole and omeprazole nor was there a difference found in healing rates at 4 weeks between omeprazole, lansoprazole, or pantoprazole and H2 receptor antagonists.

2 & 3. NSAID Drug-Induced Ulcer

There was a paucity of data from the literature search for treatment and prevention of NSAID induced ulcer and no head-to- head trials available. The limited trials

that were available failed to prove any differences between PPIs. The trials available for prevention included omeprazole and lansoprazole with ranitidine and did not show any difference in rates of healing or eradication of symptoms.

4. Eradication of H. Pylori

With regard to the effectiveness of PPIs in eradication of H. pylori infection, the quality of evidence is only fair, but there seems to be no difference between the drugs based on this evidence.

5. Dosing Strategy Comparisons

The effectiveness of long-term treatment regimens with PPIs for GERD (greater than 8 weeks) was compared: standard dose versus low-dose PPI and standard dose compared with intermittent or on-demand PPI. The time in remission was longer with higher doses: omeprazole 20 mg, rabeprazole 20 mg, and lansoprazole 30 mg and rate of endoscopically verified remission at study end greater with high dose rabeprazole 20 mg. Similarly, the rate of relapse of symptoms was higher with lower doses of omeprazole, lansoprazole, and rabeprazole.

For healed erosive esophagitis, daily PPI (omeprazole 20 mg or esomeprazole 20 mg) was superior for relapse prevention of esophagitis or recurrence of symptoms versus 3 days a week or on-demand treatment at 6 months. For nonerosive esophagitis, there was no difference in symptom severity or return of symptoms between daily and on-demand regimens (lansoprazole 15 mg, 30 mg or rabeprazole 10 mg daily). In addition, no change in patient satisfaction and quality of life ratings occurred at end of the study.

When a PPI was compared with an H2 receptor antagonist, a daily PPI (pantoprazole 10 mg, 20 mg, or 40 mg) was superior to a daily H2 antagonist (ranitidine 300 mg daily) for relapse prevention of erosive esophagitis or GERD symptoms. When the same scenario was reviewed in children, omeprazole 0.7 mg/kg daily was no different than ranitidine 10 mg/kg daily or placebo at end of 3 months.

6. Comparative safety

The availability of comparative evidence on long-term adverse effects is limited and long-term, head-to-head clinical or observational comparative studies tailored to monitor adverse effects are lacking. Two long-term (48 weeks to 5 years) maintenance studies compared omeprazole to lansoprazole and found no difference in adverse events or withdrawals secondary to adverse events. Head-to-head comparisons for the short-term studies did not show a difference in rate of overall adverse events, serious adverse events or the rate of dropouts due to adverse events.

When noncomparative studies were reviewed on the potentially increased risk of colorectal cancer a study of less than one year duration was found to be statistically significant. Other findings included a significantly increased risk of community acquired clostridium difficile diarrhea in patients who were using a PPI, and mixed evidence of community acquired pneumonia. While the overall body of evidence for comparative harms between drugs was given a poor rating, these new studies are better quality than previously available and raise important concerns about long-term use of PPIs. The variation in the findings are related to the specifics of the populations studied, and the duration of exposure studied.

Since there are some concerns, prudent use of PPIs is needed to prevent increased risk of adverse events, increased pill burden and increase drug costs. Often PPIs are used for a longer duration than needed or for inappropriate reasons, such as uncomplicated heartburn. Patients are often not followed up for step-down therapy after symptom relief has occurred.[6,7] Provision of patient education and reinforcement of lifestyle modifications can mitigate overuse of PPIs and should not be overlooked.[8]

Printed patient education material on GERD and heartburn is available at http://medlineplus.gov. The direct links are:
GERD - http://www.nlm.nih.gov/medlineplus/tutorials/gerd/id159103.pdf
Heartburn-
http://familydoctor.org/online/famdocen/home/common/digestive/disorders/087.printerview.html

7. Patient Factors affecting effectiveness and/or adverse effects

Currently, there are insufficient numbers of head-to head studies with evidence of good quality that evaluate differences for patient subgroups. In two studies where differences in adverse effects were looked at based on age, gender, and racial groups, no difference was found. However, one open-label study of 320 patients with erosive esophagitis (mean age 77) found differences not seen in younger populations. These differences need to be confirmed.

Since the majority of PPIs are predominately metabolized by CYP2C19 and CYP3A4 enzymes, a deficiency in these may lead to a longer PPI half-life and a lower dose of PPI may be equally efficacious in affected populations (3% of whites and African Americans and 17% to 25% of Asians) and in the elderly. Despite this phenomenon, no dose adjustments are recommended and there is no difference in incidence of adverse effects. However, rapid metabolizers may experience a higher failure rate in H.pylori eradication due to lower drug levels.

Recently a restrospective Medco study of 16,690 post-PCI patients who were receiving clopidogrel for a year with or without concomitant PPI therapy highlighted the higher rates of major cardiovascular events (myocardial infarction unstable angina, transient ischemic attack/stroke, coronary revascularization, or cardiovascular death) in those patients who received a PPI. It appears that PPIs are associated with a decrease in the protective effects of clopidogrel.[9] Given the lack of clarity on the mechanism of the drug-drug interaction between clopidogrel and PPI's, all PPIs may be associated with a decrease in clopidogrel's protective effect and it is best to avoid concomitant use until further evidence becomes available. H2- blockers may be an alternative to PPIs but are not as effective at preventing GI bleeding.

Conclusion:

Given the evidence that overall there are small differences in PPIs for symptomatic relief and healing rates, it is prudent to keep in mind the cost of therapy when prescribing these agents to patients. Additionally, providing patient education materials on GERD and heartburn to reinforce of the importance of lifestyle modifications can curb unnecessary use of this drug class.

Reviewers:

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