THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

Comparative effectiveness of proton pump inhibitors

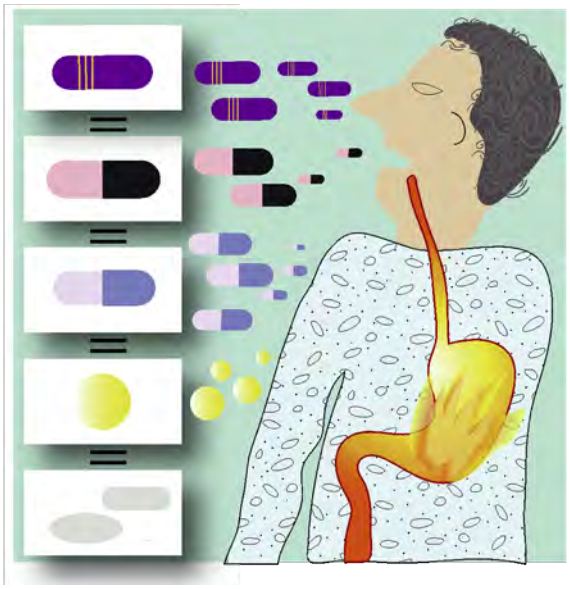
Six previous Therapeutics Letters reported information about the benefits and harms of different proton pump inhibitors (PPIs).[1-6] These drugs work by irreversibly inhibiting gastric H+K+ ATPase (the proton pump) in the stomach. They inhibit both basal and stimulated acid secretion and are used in a number of clinical settings: gastroesophageal reflux disease (GERD), reflux esophagitis, peptic ulcer disease (PUD), and symptoms associated with stomach acid such as heartburn and acid indigestion.

Are there any important differences between the different drugs in the class?

We have conducted two systematic reviews to compare the efficacy and safety of different PPIs: one in patients with symptomatic GERD and one in patients with PUD. A search up to March 2014 was done for all relevant randomized controlled trials (RCTs). RCTs were included if they compared two or more PPIs for at least 4 weeks in duration. We found 38 unique RCTs, in patients with GERD and 25 RCTs for patients with PUD. These 63 studies were retrieved, read and critiqued in detail. The critique included assessing each trial for features that may introduce bias in the trial findings.

Comparative trials of PPIs in adult patients with symptomatic GERD

Based on 26 RCTs in 23,789 patients, esomeprazole was not significantly different from other PPIs for most outcome measures: time to first resolution of symptoms; mortality; serious adverse events; withdrawal due to adverse events; and patients with at least one adverse event.[7] Quality of life scores were not reported.
Based on 13 RCTs in 7,532 patients, lansoprazole was not significantly different from other PPIs for most outcome measures: total relief of symptoms; relief of retrosternal pain; relief of dysphagia; time to first resolution of symptoms; endoscopic healing of esophagitis; recurrence or relapse of symptoms; mortality; serious adverse events; withdrawal due to adverse events; and patients with at least one adverse event.[7] Quality of life scores were not reported.



Comparative trials of PPIs in adult patients with symptomatic PUD

Based on 6 RCTs in 1753 patients, esomeprazole was not significantly different from other PPIs for most outcome measures: relief of heartburn; relief of epigastric pain; endoscopic healing of ulcer; mortality; serious adverse events; withdrawal due to adverse events; patients with at least one adverse event; or any specific adverse event. Total symptomatic relief, time to first resolution of symptoms, recurrence or relapse of symptoms, and quality of life scores were not reported. *H. pylori* eradication at 6 to 8 weeks did not differ between esomeprazole and omeprazole.[7]
Based on 19 randomized trials in 3,649 patients, lansoprazole was not significantly different from other PPIs for most outcome measures: *H. pylori* eradication; mortality; serious adverse events; withdrawal due to adverse events; and patients with at least one adverse event. Total symptomatic relief, time to first resolution of symptoms, recurrence or relapse of symptoms and quality of life scores were not reported.[7]

Overall Risk of Bias assessment

RCTs remain our best source evidence, but unfortunately can be biased.[8] Selection bias occurs if randomization and allocation of the patient to treatment are compromised. Performance and detection bias can result if the patients, investigators and outcome assessors are not blinded to the treatment group. Reporting bias occurs if the outcomes reported are those that show the desired results and if trials with positive results are published and those with negative results are not.[9]

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The 63 RCTs in these reviews were judged to have a high risk of selection, performance, detection and reporting bias. Thus the few significant differences in outcome measures found were thought to be most likely due to bias. In addition differences reported were small and were judged to not be clinically important.[7]

Applicability of evidence

The studies were mostly short-term (8-12 weeks) and excluded patients with any complications or co-morbidities so are mainly applicable to a relatively healthy population treated for short durations.[7]

What proportion of patients treated with PPIs will experience benefit of therapy?

The majority of patients (60 to 85%) with GERD experienced relief of heartburn at 4-8 weeks. In general symptom response rates were lower in patients with PUD compared to GERD. *H. pylori* eradication at 6 to 8 weeks was seen in 76 to 85% patients with PUD. Endoscopic healing at 4 to 8 weeks was seen in 66 to 82% patients with GERD or PUD. There is a wide variation in median time to first resolution of symptoms, ranging from 1 to 9 days in patients with GERD.[7]

Comparative overall safety of PPI

Harms were underreported in these short-term RCTs that directly compared different PPIs. Longer duration, head-to-head comparative RCTs specifically designed to monitor adverse effects have not been conducted. Based on observational studies, PPIs have been associated with an increased risk of the following adverse events: enteric infections (e.g. *C difficile*), spontaneous bacterial peritonitis, hospital and community acquired pneumonia, fractures, hypomagnesemia, acute interstitial nephritis, iron deficiency and vitamin B12 deficiency.[10,11] There have also been concerns that long-term treatment with PPI may lead to development of gastric polyps, gastric cancer, carcinoids and colorectal cancer.[1]

Are there differences in cost of PPIs?

The wide range of costs of PPIs in British Columbia is shown in the Table.

Table: PPI Cost Comparisons

Generic name	Brand name	Strength mg	Cost/pill Canadian $
Esomeprazole	Nexium	20	0.57
		40	0.57
Lansoprazole	Prevacid	15	0.43
		30	0.43
Lansoprazole	Prevacid FasTab	15	2.15
		30	2.15
Omeprazole	Losec	10	0.88
		20	0.44
Pantoprazole sodium	Pantoloc	20	1.38
		40	0.39
Pantoprazole magnesium	Tecta	40	0.20
Rabeprazole	Pariet	10	0.13
		20	0.26
Dexlansoprazole	Dexilant	30	2.38
		60	2.38

Conclusions

- **There is currently no convincing RCT evidence that one PPI is preferable to another for the management of GERD or PUD related symptoms or for endoscopically confirmed healing of esophagitis.**
- The risk of bias assessment of the 63 included RCTs indicated a high risk of selection, reporting, performance and detection bias.
- There are no long-term, head-to-head comparative RCTs specifically designed to monitor adverse effects of PPIs.
- Observational studies suggest that long-term use of PPIs is associated with a number of serious adverse effects.
- **The cost of different PPIs vary by over tenfold.**

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99 The draft of this Therapeutics Letter was submitted for review to 65 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

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