Canadian Agency for Drugs and Technologies in Health

COMPUS Optimal Therapy Newsletter: Proton Pump Inhibitors

Three Questions

Which PPI Should I Choose?

At What Dose Should I Start?

What Won't A PPI Treat?

The Canadian Agency for Drugs and Technologies in Health recognizes the importance of these questions to physicians and the COMPUS Expert Review Panel has carefully reviewed the evidence to offer some practical guidance to the prescribing and use of PPIs.

COMPUS: Canadian Optimal Medication Prescribing and Utilization Service

April 2007

Three Questions to Ask When Starting a Proton Pump Inhibitor (PPI)

1 Which PPI Should I Choose?

You've decided to prescribe a PPI for your patient. You want what is best for your patient – both clinically and economically. You want the best clinical outcome possible but you don't want your patient or the healthcare system to pay more for that outcome than is necessary. With all of that in mind, which PPI should you choose?

Bottom Line:

There are no clinically important differences among equivalently-dosed PPIs in the treatment of most acid-related GI conditions.

PPI Pharmacology:

PPIs suppress gastric acid by irreversibly inhibiting the H^+/K^+-ATPase or the "proton pump" that secretes acid into the lumen of the stomach.[1] Since all five of the PPIs currently on the Canadian market have the same mechanism of action, it is expected that all would produce similar results at equivalent doses. Due to the irreversible binding of PPIs, subtle differences in pharmacokinetic properties may not significantly affect duration of action since new acid production requires regeneration of proton pumps.[1]

Evidence-based Support:

For gastroesophageal reflux disease (GERD),[2] including both endoscopy-negative reflux disease (ENRD) and esophagitis, no clinically important differences were found among standard doses of PPIs. The robust evidence supporting this conclusion includes six good-quality systematic reviews. While there are isolated exceptions, the majority of comparisons of PPIs for GERD showed no significant differences in short-term (four to eight week) and long-term (up to one year) studies.

For *H. pylori* eradication,[2] all PPIs have similar efficacy when used in triple-therapy regimens. Superiority of any one PPI was not suggested by any of the seven systematic reviews.

For NSAID ulcer prophylaxis,[2] indirect comparisons from a good quality systematic review and a direct comparison (omeprazole and pantoprazole) in a randomized control trial (RCT) found no clinically significant differences between the PPIs.

For NSAID ulcer healing,[2] the data is limited to a single good quality systematic review that included indirect comparisons of PPIs. These indirect comparisons suggest similar healing rates for the PPIs that have been studied (omeprazole and lansoprazole).

Limitations of the Evidence:

The evidence suggests that there are no clinically important differences among the various PPIs in the treatment of most acid-related GI conditions. This important message should not be clouded by isolated studies or comparisons between non-equivalent doses. However, the evidence is limited by the fact that direct comparisons have not been made for all agents in all indications. It should also be recognized that official indications for each brand of PPI may vary.

Implications for Clinical Practice:

With the evidence indicating that there are no clinically important differences among the PPIs for the treatment of common acid-related GI conditions, practitioners like you have the flexibility to choose lower-cost alternatives when prescribing PPIs, without compromising quality of care.

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This Optimal Therapy Newsletter is published by:

Canadian Agency for Drugs and Technologies in Health

The Canadian Agency for Drugs and Technologies in Health (CADTH) is a national body that provides Canada's federal, provincial and territorial health care decision makers with credible, impartial advice and evidence-based information about the effectiveness and efficiency of drugs and other health technologies.

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References

[1] Richardson P, Hawkey CJ, Stack WA. Proton pump inhibitors: pharmacology and rationale for use in gastrointestinal disorders. *Drugs* 1998:56(3):307-35.

[2] Canadian Agency for Drugs and Technologies in Health. Evidence for PPI use in gastroesophageal reflux disease, dyspepsia and peptic ulcer disease: scientific report. *Optimal Therapy Report - COMPUS* 2007;1(2). Available: http://www.cadth.ca

Made possible through funding from Health Canada.

2 At what dose should I start?

Now that you've chosen which PPI to prescribe for your patient, you need to decide at what dose to initiate therapy. The evidence reviewed and compiled in the COMPUS Scientific Report on PPIs can help to guide this decision.

Bottom Line:

There is little evidence that more is better. Studies comparing standard doses of PPIs to high doses have not shown superiority of starting with the higher dose in the treatment of most acid-related GI conditions. Standard-dose therapy should be the initial therapy for most patients.

PPI Pharmacology:

PPIs inhibit gastric acid secretion in a dose-dependent manner.[1] However, most studies comparing standard- and high-dose PPIs have not shown significant differences in clinical outcomes.[2]

Evidence-based Support:

For **erosive esophagitis**, [2] it appears that high-dose PPIs are no better than standard-dose therapy in initial treatment. Six RCTs showed no significant differences in healing rates during initial treatment (four to eight weeks) between standard- and high-dose regimens. The majority of evidence suggests that standard-dose therapy is adequate for the initial treatment of erosive esophagitis.

Esomeprazole 40mg is indicated for erosive esophagitis. Some, but not all comparisons of esomeprazole 40mg daily with standard daily-doses of PPIs have shown benefit, although the clinical importance of these differences is not clear.[2]

For **NSAID-induced ulcer healing**,[2] standard- and high-dose omeprazole therapy were studied in two RCTs. High-dose therapy was not significantly better than standard-dose therapy in these trials.

Limitations of the Evidence:

There is good evidence to suggest that it isn't necessary to use high-dose PPI therapy as initial treatment for GERD and NSAID ulcer healing. The evidence is less clear on when it might be appropriate to consider doubling the standard dose. The COMPUS Scientific Report noted that evidence was lacking related to the use of high/double dose therapy for uninvestigated GERD with severe symptoms and for uninvestigated GERD/ ENRD/erosive esophagitis patients who remain symptomatic on standard-dose therapy.[2] Higher-dose therapy may need to be considered in a small subset of patients who fail a reasonable (~ eight week) initial PPI trial at a standard dose.

Implications for Clinical Practice:

When initiating PPI therapy for your patients you can prescribe the standard daily dose knowing that the evidence shows this to be the best option.

3 What Won't a PPI treat?

There are times when the best decision is not to prescribe a PPI. The evidence presented in the COMPUS Scientific Report can help you decide when a PPI is not the best therapeutic option.

Bottom Line:

Current evidence would suggest PPIs are not efficacious in improving asthma, laryngeal symptoms or chronic cough that may be associated with GERD.

PPI Pharmacology:

PPIs are effective in reducing the production of acid, raising gastric pH and treating GI conditions that are related to acid production. Therapeutic benefits beyond this, although occasionally reported anecdotally, have not been shown in the available body of evidence.[2]

Evidence-based Support:

In the management of **asthma associated with GERD**,[2] a good quality systematic review suggested that treatment with PPIs did not improve FEV_1, morning peak expiratory flow, airway responsiveness or frequency of inhaler use.

For **laryngeal symptoms**,[2] evidence from a good quality systematic review suggested that PPIs performed no better than placebo in reducing symptoms such as throat clearing, sore throat, or hoarseness associated with reflux.

For **chronic cough**,[2] a good quality systematic review suggested there was no benefit of PPIs over placebo.

Implications for Clinical Practice:

Given that the evidence does not support the use of PPIs in certain clinical conditions such as asthma, laryngeal symptoms and chronic cough, you can choose not to initiate PPI therapy in these patients knowing this to be the best clinical option. Other therapy options can then be considered.

For full project details and intervention tools, please visit the CADTH web site:

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