Objectives

Review the use of Proton Pump Inhibitors (PPIs) in the treatment of

- GERD
- Dyspepsia
- Peptic ulcer disease (NSAID induced & H.Pylori)

Review evidence for following PPI issues

- Efficacy of one PPI vs. another
- Double-dose PPI as initial therapy
- Role in asthma, laryngeal symptoms & chronic cough associated with GERD

Which PPI should be used?

All PPIs are equally efficacious

Standard doses of PPIs may be used interchangeably when initiating therapy because there are no clinically important differences among the various PPIs in the treatment of most acid-related GI conditions.

PPI Standard doses

<table>
<thead>
<tr>
<th>PPI</th>
<th>Standard dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole (Losec)</td>
<td>20mg daily</td>
</tr>
<tr>
<td>Lansoprazole (Prevacid)</td>
<td>30mg daily</td>
</tr>
<tr>
<td>Pantoprazole (Pantoloc)</td>
<td>40mg daily</td>
</tr>
<tr>
<td>Rabeprazole (Pariet)</td>
<td>20mg daily</td>
</tr>
<tr>
<td>Esomeprazole (Nexium)</td>
<td>20mg daily</td>
</tr>
</tbody>
</table>

Evidence-based support

All PPIs are equally efficacious

GERD/ENRD/Esophagitis

- 6 good quality systematic reviews-no clinically important differences in standard doses PPIs
- Isolated exceptions, majority showed no differences
- Comparisons showing some degree of difference involved non-equivalent comparisons (e.g. high dose vs. standard dose)

H.pylori Eradication

- 7 systematic reviews: PPIs have similar efficacy when used in triple therapy regimens

NSAID Ulcer Prophylaxis

- 1 good quality systematic review 7 RCTs (indirect comparisons; formal stat methods not employed), and 1 RCT direct comparison: different PPIs reduce ulcer risk to a similar degree (the only direct comparison was of omeprazole vs pantoprazole)

NSAID Ulcer Healing

- 1 good quality systematic review 3 RCTs (indirect comparisons; formal stat methods not employed): similar healing rates for the PPIs that have been studied (omeprazole & lansoprazole)
Evidence-based limitations

All PPIs are equally efficacious

- Isolated studies may show superiority, balance against weight of evidence
- Caution for comparisons between non-equivalent doses of PPIs, e.g. omeprazole 20mg vs. esomeprazole 40mg
- No evidence regarding safety and efficacy of switching to a different PPI in patients successfully treated with a given PPI
- Not all comparisons have been made for all indications
- Official indications may be more limited in scope e.g. apomorphine not officially indicated for H. pylori eradication
- Balance evidence against need for patient individualization

Bottom line

All PPIs are equally efficacious

- There are no clinically important differences among standard doses, or equivalent doses of PPIs in the initial treatment of most acid related GI conditions.
- In most circumstances the data suggests clinicians may interchange PPIs with confidence.
- The equality of PPIs is supported by the majority of the available literature.

Implications to practice

Cost savings to the patient/society.

Simplify prescribing by focusing on lowest cost PPI.

<table>
<thead>
<tr>
<th>Standard Dose PPIs</th>
<th>Generic Omeprazole 20mg Daily</th>
<th>Pantoprazole 20mg Daily</th>
<th>Famotidine 40mg Daily</th>
<th>Lansoprazole 20mg Daily</th>
<th>Omeprazole 20mg Daily</th>
<th>Nexium 180mg Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily Price</td>
<td>$1.10</td>
<td>$1.30</td>
<td>$1.80</td>
<td>$2.00</td>
<td>$2.10</td>
<td>$2.20</td>
</tr>
<tr>
<td>Approximate Monthly Price†</td>
<td>$44.40</td>
<td>$44.40</td>
<td>$61.00</td>
<td>$64.00</td>
<td>$66.00</td>
<td>$69.00</td>
</tr>
</tbody>
</table>

Generic omeprazole 20mg and Pantelit (rabeprazole) 20mg are the cheapest "standard" dose PPIs on the Canadian market.

Using a PPI that costs $1.40/day vs. $2.20/day will save a patient almost $300 per year in drug costs.

Potential yearly savings

Society/Patients

Canada 2004 12.4 million PPI prescriptions

Imagine if 50% were changed from:

$2.20/day regimen → $1.25/day regimen

0.95 cents saved/day x 30 days x 6.2 million prescriptions:

$176 million dollars/year

What dose of PPI?

More may not always be better

- High or double-dose PPI, as initial therapy, is no better than standard daily dose therapy in the management of erosive esophagitis
- Research Gaps: double dose in GERD patients with severe symptoms or in patients who remain symptomatic after an initial course of standard dose therapy

Evidence based support

More may not always be better

- High or Double-dose PPIs for initial Rx Erosive Esophagitis
- 6 RCTs: 2 RCTs very good quality, 1 good quality, 3 poor quality grade 2-4 esophagitis
- Majority of evidence: no benefit for initial treatment
- Limitation: small number of trials, all of poor quality, specifically addressed Grade 2-4 esophagitis (more severe)
- Esomeprazole 40mg is approved dose for erosive esophagitis
- Some but not all trials of 40mg vs standard dose PPIs have shown benefit
- Clinical importance unclear
Evidence based support
More may not always be better

Double-dose initial Rx NSAID-induced ulcer
• 2 RCTs n=1476: double dose omeprazole was not superior to single dose
• both standard and double doses more effective than H2RA (NNT=4-9) and misoprostol (NNT=6-8)

Do not need double-dose PPI

The Evidence

(ASRONAUT Study): 541 patients with DU, GU, or >10 GI erosions receiving NSAIDs treated with omeprazole 20mg or 40mg, or ranitidine 300mg daily

Results for omeprazole 20mg vs. ranitidine:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tx failure</th>
<th>RR of failure (95% CI)</th>
<th>NNT (95% CI) for success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Failure</td>
<td>20% vs. 3%</td>
<td>0.68 [0.50-0.94]</td>
<td>4 [3, 6]</td>
</tr>
<tr>
<td>DU healing</td>
<td>8% vs. 19%</td>
<td>0.44 [0.24-0.82]</td>
<td>5 [3, 17]</td>
</tr>
<tr>
<td>GU healing</td>
<td>10% vs. 30%</td>
<td>0.44 [0.24-0.82]</td>
<td>5 [3, 17]</td>
</tr>
</tbody>
</table>

Results for double dose vs. standard dose omeprazole:
• Treatment failure: 21% vs. 20%, p>0.05 (NS)
• DU persistence: 12% vs. 8%, p>0.05 (NS)
• GU persistence: 13% vs. 16%, p>0.05 (NS)

Bottom line
Little evidence that more is better

Doubling the standard daily dose of PPIs, as initial therapy, is no better than standard daily dose therapy.

Standard dose should be the initial therapy.

Implications to practice
Cost savings

<table>
<thead>
<tr>
<th>Standard Dose PPIs</th>
<th>Generic Omeprazole 20mg Daily</th>
<th>Pariét Omeprazole 20mg Daily</th>
<th>Losec Omeprazole 20mg Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily Price</td>
<td>$1.25</td>
<td>$1.30</td>
<td>$1.90</td>
</tr>
<tr>
<td>Approximate Monthly Price</td>
<td>$43.00</td>
<td>$44.40</td>
<td>$66.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High Dose PPIs</th>
<th>Nexium 40mg Daily</th>
<th>Generic Omeprazole 40mg Daily</th>
<th>Losec Omeprazole 20mg Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily Price</td>
<td>$2.10</td>
<td>$2.50</td>
<td>$2.60</td>
</tr>
<tr>
<td>Approximate Monthly Price</td>
<td>$66.80</td>
<td>$78.00</td>
<td>$80.80</td>
</tr>
</tbody>
</table>

Evidence-based support

Asthma with concomitant GERD
One good quality systematic review (12 RCTs, n=432)
• PPI (omeprazole 20-80mg) or H2RA did not improve FEV1, PEF, airway responsiveness or use of inhalers
• 1 RCT (omeprazole 40mg vs placebo) reported improvement in nocturnal symptom score

PPIs: asthma, laryngeal symptoms & chronic cough use the right tool for the job

PPIs are not efficacious in the treatment of asthma, chronic cough and laryngeal symptoms that may be associated with GERD.
Evidence-based support

**Laryngeal symptoms with Reflux**
One good quality systematic review (5 RCTs, n=247)
- **No significant effect** on laryngo-pharyngeal symptoms (e.g., cough, throat clearing, globus, hoarseness, sore throat)

**Chronic cough with or without GERD**
One good quality systematic review

Chronic cough ≥ 3 weeks without respiratory symptoms/signs or systemic illness

**Cough score at various times**
- No benefit of PPI vs. placebo

**Limitations:**
- Small pooled sample size: analysis likely underpowered
- Heterogeneity in study population

**Bottom line PPIs: asthma, laryngeal symptoms & chronic Cough**

**PPI effective for treating GI disease**
Current evidence would suggest they are not efficacious in improving asthma, laryngeal symptoms or chronic cough that may be associated with GERD.

The use of PPIs for this indication should be discouraged.