Proton Pump Inhibitors and the Treatment of GERD, Dyspepsia, and NSAID-associated Peptic Ulcer Disease
Disclaimer

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Statement of Disclosure
Outline

• Didactic presentation
  • Objectives
  • Background
  • Facts and Fallacies
  • Case-based review of evidence

• Break into small groups - Case Studies
General objective

To facilitate optimal medication therapy in the treatment of gastroesophageal reflux disease, peptic ulcer disease and dyspepsia by providing an update on the evidence and research gaps around proton pump inhibitor use
Learning objectives

Upon completion of this workshop, participants will be able to:

- Define the appropriate role for PPIs in the management of upper GI tract conditions including: GERD, PUD, and Dyspepsia

- Understand the differences between the various PPIs and which PPI should be chosen for treatment
Learning objectives

• Understand the role of double-dose PPI therapy

• Define the role of PPI therapy in treatment of asthma and laryngeal symptoms

• Recognize clinical scenarios where PPIs may be inappropriately utilized and medication therapy should be reassessed
Where did the evidence come from?

Canadian Agency for Drugs and Technologies in Health (CADTH)

CADTH is an independent, not-for-profit agency funded by Canadian federal, provincial, and territorial governments to provide credible, impartial advice and evidence-based information about the effectiveness of drugs and other health technologies to Canadian health care decision makers.
What is COMPUS?

- Identify evidence-based optimal drug therapy
- Evaluate current use & identify gaps
- Provide strategies & tools
- Support & encourage informed decision making
- Build networks & partnerships
Why PPIs?

PPI topic selection criteria included:

- Over- or under-use
- Size of patient population
- Potential impact on health outcomes and cost-effectiveness
- Potential to effect change
- Benefit to multiple jurisdictions
- Measurable outcomes
Why focus on PPIs?

Estimated total PPI retail pharmacy sales in Canada:

Source: IMS HEALTH, CANADA. Reprinted with permission of IMS HEALTH, CANADA
PPI project process – evidence

- Identify, summarize and evaluate the clinical evidence in the form of evidence-based statements
- Produce reliable economic evidence
- Understand the current practice in Canada related to PPI prescribing and use
- Identify gaps in practice highlighting areas where current practice differs from the evidence
PPI project process – interventions

- Develop key messages regarding the evidence-based statements to address the gaps in practice
- Select interventions to support the key messages and effect change in the prescribing and use of PPIs
- Develop intervention tools for implementation
- Develop an evaluation framework to measure the effect of the interventions
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Proton Pump Inhibitor Facts and Fallacies
Case #1

Mr. B:

- 53-year-old male, otherwise healthy presents with a 1-year history of classical symptoms of GERD, now occurring daily
- minimal relief from over-the-counter antacids and H2RAs
- non-pharmacological measures (trial of weight loss, avoiding trigger foods) ineffective
Case #2

Ms. M

- 68-year-old female, past history of HTN, DM2, and osteoarthritis

- Admitted to hospital 3 days ago with upper GI bleed

- Endoscopy revealed an acute duodenal ulcer, treated with electrocautery and 3 days of intravenous pantoprazole infusion

- Had been using naproxen once daily, now discontinued, \textit{H. pylori} negative

- Now no further bleeding, ready to be switched to an oral PPI
Case #3

Mr. C:
- 77 year-old male, past Hx of IHD, previous CABG, HTN, COPD
- Current medications include ASA 81mg, once daily, amlodipine, ramipril
- Increasing pain from OA of the left knee, inadequate relief with acetaminophen
- You decide to initiate NSAID therapy in combination with a gastroprotective agent
To review….

- Mr. B: GERD refractory to OTCs/H2RAs
- Ms. M: acute GI bleed secondary to DU
- Mr. C: High-risk new NSAID user

Should any of these patients be prescribed a double-dose PPI?
Double-dose PPIs

**Double-dose PPIs are commonly used:**

- 15% of PPI users are using, on average, $\geq 1.5$ times the standard daily dose of PPIs at any given time; 7% are using $\geq 2$ times the standard daily dose

- More likely to be used in persons with
  - Advanced age
  - Comorbid Diseases
  - Multiple prescriptions

Targownik 2007
Double-dose PPIs: are they effective?

PPIs exert their effect by decreasing gastric acid secretion

• Promote an increase in intragastric pH
  • Higher pH levels = less gastric acidity

Degree of suppression of intragastric pH (% of time with intragastric pH > 4.0) is correlated with:

• Healing of duodenal ulcers
• Eradication of H. pylori

Jones 1987
Hunt 1986
Labenz 1995
Increased PPI dose has a marginal effect on intragastric pH

Questionable clinical significance of this degree of difference of acid suppression
Double-dose PPIs: GERD

Two clinical scenarios where double-dose PPIs are commonly used in patients with GERD:

A) initial therapy of GERD

B) “step-up” therapy in patients with continued symptoms or esophagitis on standard doses of PPIs
Double-dose PPIs: initial therapy of GERD

In the COMPUS review, 4 studies comparing initial therapy with high-dose PPI versus standard-dose PPI in healing and symptom relief in erosive esophagitis at 8 weeks:

- 2 lanso 30 vs. lanso 60
- 1 omep 20 vs. omep 40
- 1 panto 40 vs. panto 80

No differences in healing and symptom relief at 8 weeks

CADTH 2007
Double-dose PPIs: step-up therapy for non-responders

Only 1 non-blinded trial

Omeprazole 40 vs omeprazole 20 for subjects with symptoms/esophagitis after 4 weeks of omeprazole 20mg

Statistically significant improvement in heartburn relief and healing of esophagitis

Overall, evidence to support step-up therapy is poor

Bate 1993
Double-dose PPIs: peptic ulcer disease

Again, no difference in efficacy for healing of PUD (at 4 weeks for DU and at 8 weeks for NSAID-associated ulcer)

No role for double dose PPIs in the treatment of PUD

No evidence for step-up therapy for patients with non-healing ulcer
Double-dose PPIs: eradication of *Helicobacter Pylori*

- Double-dose PPIs are marginally superior to standard-dose PPI HP-eradication regimens

- One large meta-analysis
  - Double-Dose PPI: 84%
  - Standard-Dose PPI: 78%
  - \( p < 0.01 \), Number Needed to Treat: 16

- Though difference is marginal, treatment is short-term and of minimal economic concern
Double-dose PPIs

There are no studies evaluating double-dose PPIs in:

- Treatment of endoscopy-negative reflux disease
- Functional dyspepsia
- Prevention of NSAID-related peptic ulcer disease
Aside from eradication of H. pylori, there are no proven indications for the use of double-dose PPIs.
To review…

Who should be prescribed a double-dose PPI?

- Mr. B: GERD refractory to OTCs/H2RAs
- Ms. M: acute GI bleed secondary to DU
- Mr. C: High-risk new NSAID user
How about another case?

Ms. P
- 64-year-old woman with severe GERD
- Recent endoscopy reveals erosive esophagitis typified by multiple linear erosions
- Which PPI should she be prescribed?
Are all PPIs the same?

- There are currently 5 PPIs on the Canadian Market:
  - Omeprazole (Losec®, generics)
  - Lansoprazole (Prevacid®)
  - Pantoprazole (Pantoloc®)
  - Rabeprazole (Pariet®)
  - Esomeprazole (Nexium®)

- All PPIs target the same receptor which blocks gastric acid secretion (the proton pump)

- PPIs do differ in several respects (plasma half-life, pKa, hepatic vs. renal metabolism)

- Are these differences clinically significant?

Richardson 1998.
Comparing the PPIs: healing of erosive esophagitis

- In the COMPUS review: 6 systematic reviews were identified:
- No significant differences were detected in healing of erosive esophagitis and symptoms relief at 4 or 8 weeks for comparisons between standard doses of PPIs
- Esomeprazole 40 mg was marginally superior to standard dose omeprazole, lansoprazole, and pantoprazole in:
  - healing of erosive esophagitis (4 and 8 weeks)
  - symptom relief in patients with erosive esophagitis (4 and 8 weeks)

CADTH 2007  
Kahrilas 2000  
Richter 2001  
Castell 2002  
Labenz 2005  
Richter 2001
Comparing the PPIs: What about esomeprazole?

Omeprazole is composed of 2 enantiomers (mirror-image compounds)

R-Omeprazole

Low Bioavailability

Esomeprazole is similar to a double dose of omeprazole
40mg esomeprazole = 80mg omeprazole

S-Omeprazole

High Bioavailability

Esomeprazole
Comparing the PPIs:
What about esomeprazole?

- Healing of Erosive Esophagitis at 8 wks (%)

- p<0.05 for all comparisons
- Absolute differences range from 4 – 10%

Kahrilas, 2000
Richter, 2001
Castell, 2002
Labenz, 2005

Esomeprazole 40mg
Esomeprazole 40mg
Esomeprazole 40mg
Esomeprazole 40mg

Omeprazole 20mg
Omeprazole 20mg
Lansoprazole 30mg
Pantoprazole 40mg

-94 87 94 93 96
-87 84 89 92

-94
-100
-80
-70
-60
-50
-40
-30
-20
-10
-0

Canadian Agency for Drugs and Technologies in Health
Agence canadienne des médicaments et des technologies de la santé
Comparing the PPIs: What about esomeprazole?

- p<0.05 for all comparisons
- Absolute differences range from 2 – 8%

Complete Resolution of HB at 4 Wks (%)

Kahrilas 2000
Richter 2001
Castell 2002
Labenz 2005

Esomeprazole 40mg
Esomeprazole 40mg
Esomeprazole 40mg
Esomeprazole 40mg
Omeprazole 20mg
Lansoprazole 30mg
Pantoprazole 40mg

- p<0.05 for all comparisons
- Absolute differences range from 2 – 8%
Comparing the PPIs: endoscopy-negative reflux disease

• The majority of patients with GERD (approx. 70%) will have normal endoscopy

• In patients with normal endoscopy
  • No differences between the PPIs in symptom relief, including esomeprazole 40 mg vs. standard-dose omeprazole 20 mg

Armstrong 2005
Armstrong 2004
Fock 2005
Mönnikes 2005
Comparing the PPIs: peptic ulcer disease

- In direct comparisons, no significant differences in healing rates between:
- Standard-dose of Omeprazole and standard doses of:
  - Lansoprazole
  - Pantoprazole
  - Rabeprazole

- According to the COMPUS review, rates of ulcer healing in patients with NSAID-associated ulcer are similar among different PPIs.
Comparing PPIs: prevention of NSAID-related peptic ulcer disease

- Only direct comparison is for omeprazole vs. pantoprazole in one RCT

- Rates of endoscopic ulcer formation are similar for PPIs evaluated for this indication:
  - Omeprazole
  - Lansoprazole
  - Pantoprazole
Comparing PPIs: eradication of *H. Pylori*

- COMPUS identified 5 high-quality systematic reviews
- No significant differences in eradication rates across all PPIs, including esomeprazole
Comparing PPIs: side effects/drug interactions

- COMPUS did not specifically address the issue of drug interactions and side effects between PPIs

- There are no studies reporting any difference in the side-effect profiles of specific PPIs

- Rabeprazole and pantoprazole have less potential for drug-drug interactions due to their dual metabolism
  - Clinical significance is likely small, should not determine choice of PPI

Martin de Argila 2005
Humphries 1999
Comparing PPIs: summary

- Esomeprazole 40 mg is slightly more efficacious than other PPIs at standard doses, specifically for healing of erosive esophagitis
  - Small difference in benefit is insufficient in recommending its use over other PPIs

- All PPIs are equivalent for initial treatment of all other GI indications
  - endoscopy-negative reflux disease
  - erosive esophagitis
  - NSAID-associated ulcer disease (prevention and treatment)
  - HP eradication
Practice implications

Prescribing may be optimized by focusing on lower cost PPIs

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<th>Standard Dose PPIs</th>
<th>Generic Omeprazole</th>
<th>Pariet® Rabeprazole</th>
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One last case

Mr. P.

- 37-year-old male, previously healthy
- 2 month Hx of:
  - Sore throat, voice hoarseness, non-productive cough
- No SOB, no wheezing, no hemoptysis
- 0.5ppd smoker x 15 years
- No classical symptoms of GERD (heartburn/regurgitation/waterbrash)

*Should we consider empiric therapy with a PPI?*
PPIs for chronic laryngitis

- GERD is often suspected as a cause for chronic laryngeal symptoms, including:
  - Sore throat
  - Globus sensation (lump in throat)
  - Hoarseness
  - Cough

- Diagnosis is often based on the presence of laryngoscopic evidence of reflux
PPIs for chronic laryngitis

According to the COMPUS review...

PPIs are no better than placebo in relief of laryngeal symptoms
PPIs for chronic laryngitis

Meta-analysis of 8 placebo-controlled trials of chronic laryngitis:

- Enrolled patients with chronic laryngeal symptoms
- PPI subjects were no more likely to have symptom relief than placebo
- OR 1.28 (95% CI 0.94-1.74)

Qadeer 2006
PPIs for chronic laryngitis: some caveats

PPI response more likely in subjects with laryngeal symptoms + GERD confirmed by 24h pH testing

• Laryngeal signs and abN 24h pH test:
  • OR 1.58 (95% CI: 0.97 – 2.57)
• Laryngeal signs and no pH monitoring
  • OR 1.05 (95% CI: 0.76 – 1.44)

ENT-diagnosed laryngeal changes are very non-specific for GERD, while 24h pH testing is the gold standard for GERD

Qadeer 2006
Vavricka 2007
Armstrong 2005
PPIs and chronic laryngitis: summary

• PPIs are at best marginally effective in patients with laryngeal symptoms in the absence of classical GERD symptoms

• There are multiple other non-GERD related causes for laryngeal symptoms

• Therefore, no role for PPIs in the empiric management of laryngeal symptoms

• Can consider a referral to a GI specialist for 24h pH monitoring for laryngeal symptoms not responding to other interventions
COMPUS Key Messages

1. Double-dose PPIs are no more effective than standard-dose PPIs, except in HP eradication

2. There are few meaningful differences between the PPIs

3. PPIs are ineffective in the empirical management of chronic laryngeal symptoms
Questions ?
References


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