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

Presenter
Title
Affiliation
Date

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

Disclaimer

The information in this presentation is not a substitute for clinical judgement in the care of a particular patient. CADTH is not liable for any damages arising from the use or misuse of any information contained in or implied by the information in this presentation.

The statements, conclusions and views expressed herein do not necessarily represent the view of Health Canada or any Provincial or Territorial Government.

Made possible through funding from Health Canada.

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

Statement of Disclosure

Outline

- **Didactic presentation**
  - Objectives
  - Background
  - Facts and Fallacies
  - Case-based review of evidence
- **Break into small groups - Case Studies**

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

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

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

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?

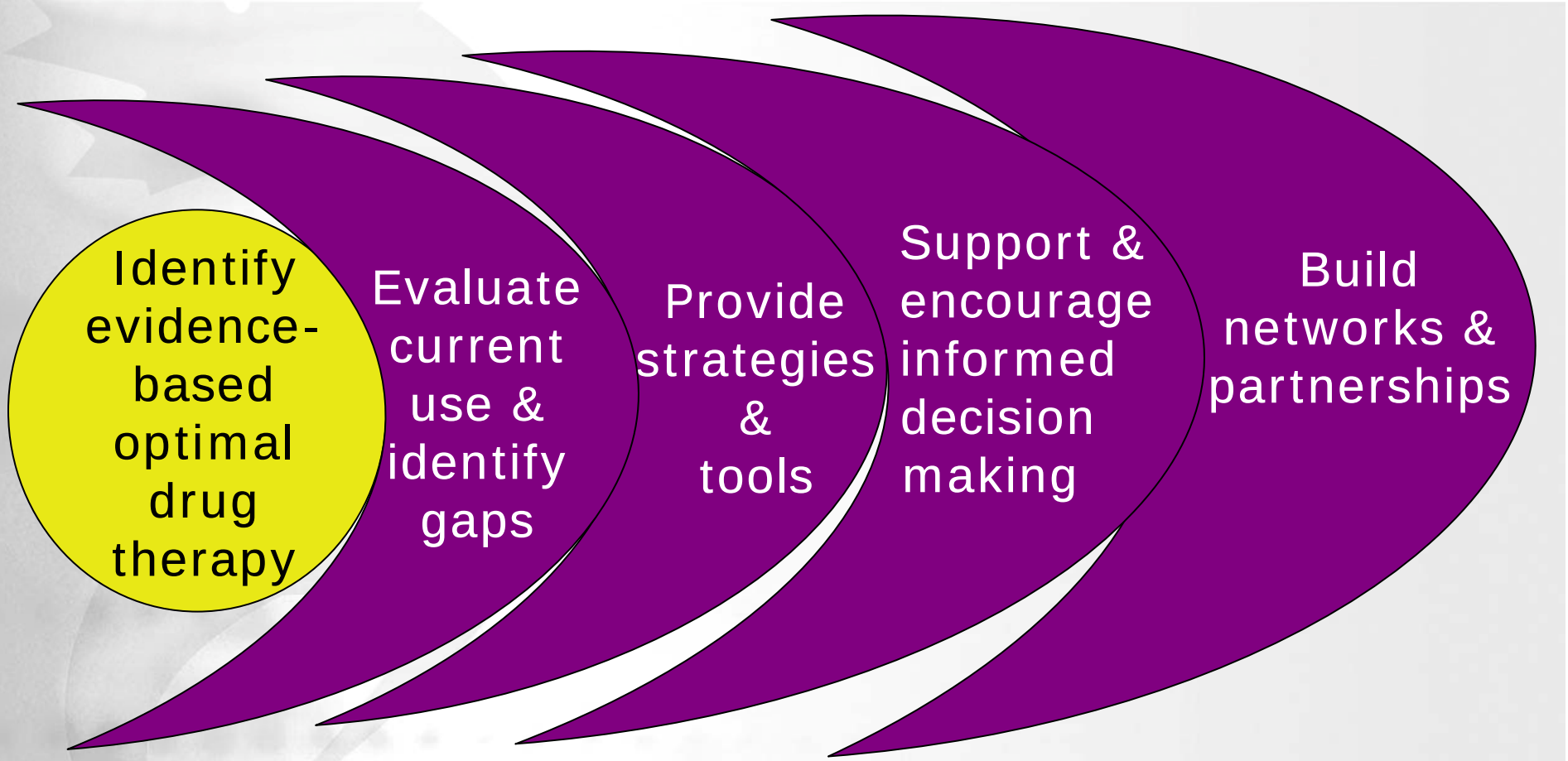
Canadian Agency for Drugs and Technologies in Health (CADTH)

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.

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

What is COMPUS?



Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

Why PPIs?

PPI topic selection criteria included:

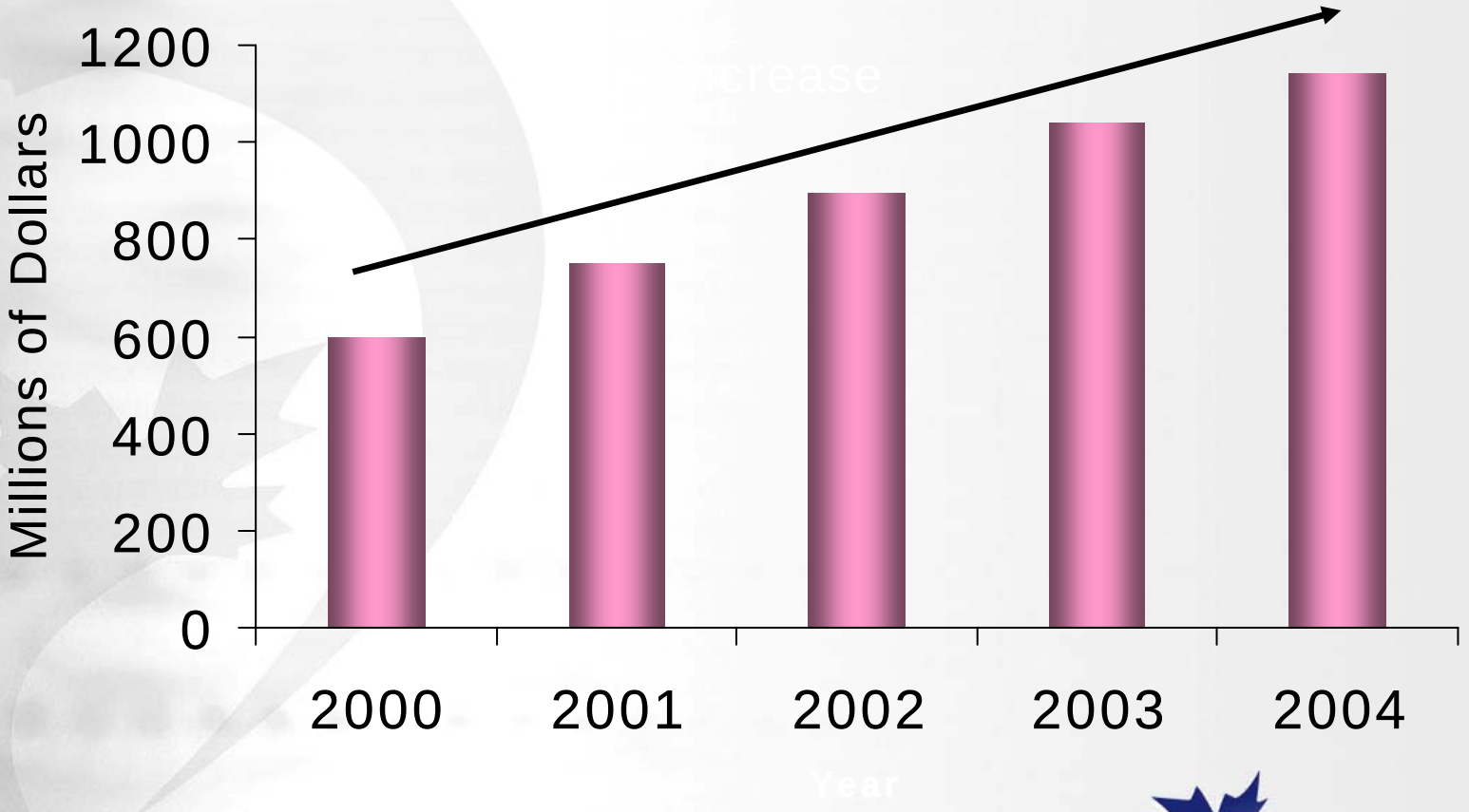
- Over- or under-use
- Size of patient population
- Potential impact on health outcomes and cost-effectiveness
- Potential to effect change
- Benefit to multiple jurisdictions
- Measurable outcomes

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

Why focus on PPIs?

Estimated total PPI retail pharmacy sales in Canada:



Source: IMS HEALTH, CANADA. Reprinted with permission of IMS HEALTH, CANADA

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

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

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

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

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

PPI Expert Review Panel (ERP)

BC	Dr. J. Rideout	Family Physician
AB	Dr. S. van Zanten	Gastroenterologist
AB	Dr. A. Thomson	Gastroenterologist
SK	Dr. M. Caughlin	Family Physician
SK	Dr. B. Schuster	Pharmacist
MB	Dr. L. Targownik	Gastroenterologist
ON	Dr. A. Holbrook	Clinical Pharmacologist
ON	Dr. M. Brouwers	Methodologist
ON	Ron Goeree	Health Economist
ON	Dr. M. Man-Son-Hing	Geriatrician
ON	Dr. J. Marshall	Gastroenterologist
NS	Pam McLean-Veysey	Pharmacist

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

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

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

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, *H. pylori* negative
- Now no further bleeding, ready to be switched to an oral PPI

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

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

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

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?

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

Double-dose PPIs

Double-dose PPIs are commonly used:

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

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

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

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:

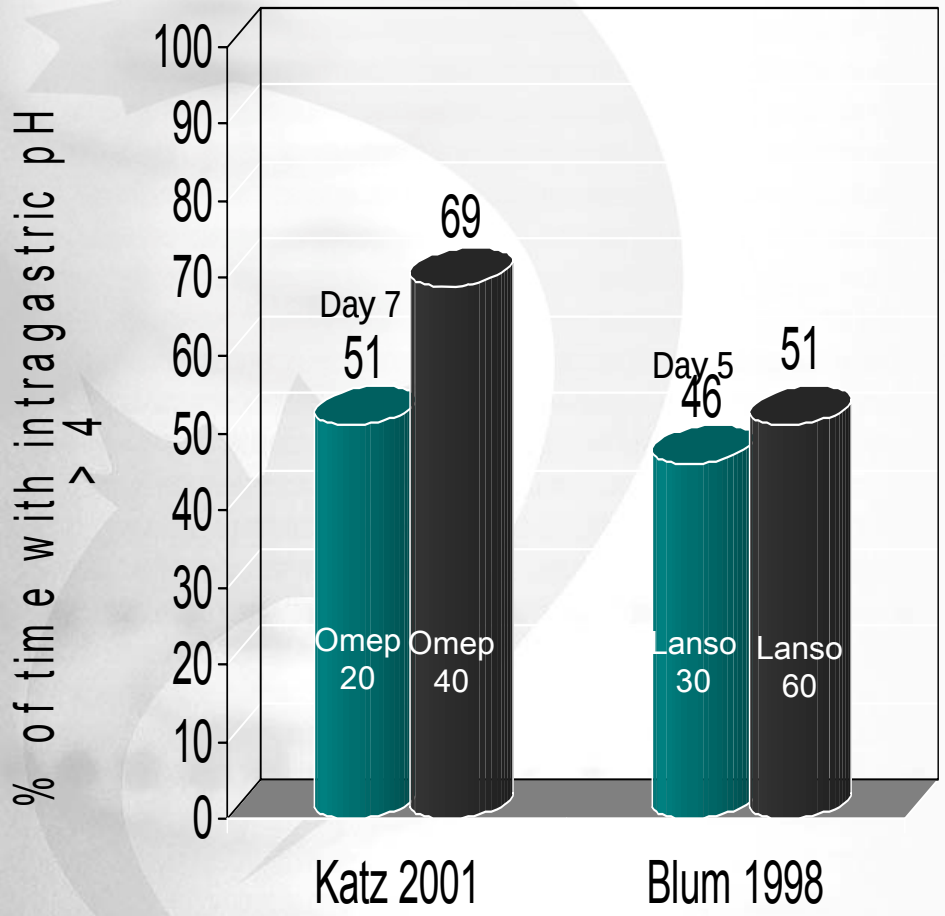
- Healing of duodenal ulcers
- Eradication of *H. pylori*

Jones 1987
Hunt 1986
Labenz 1995

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

PPI dose and intragastric pH



Increased PPI dose has a marginal effect on intragastric pH

Questionable clinical significance of this degree of difference of acid suppression

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

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

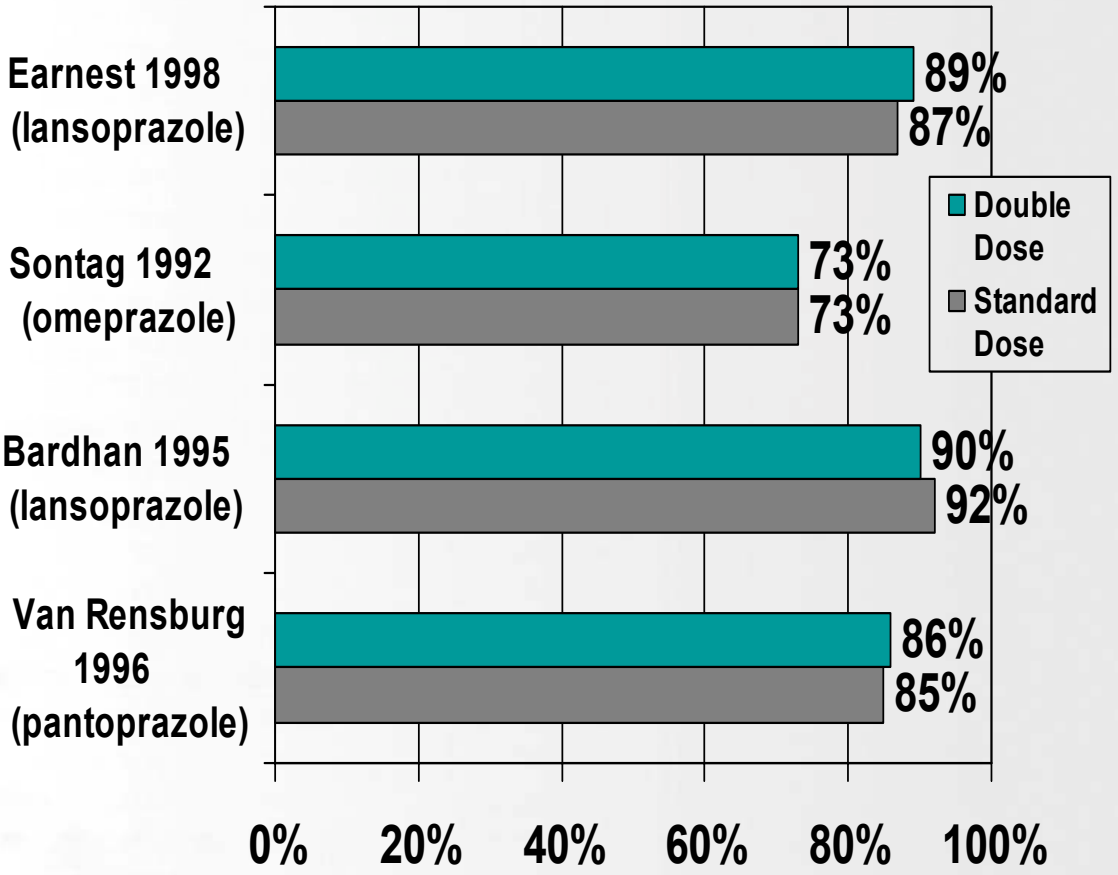
Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

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

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

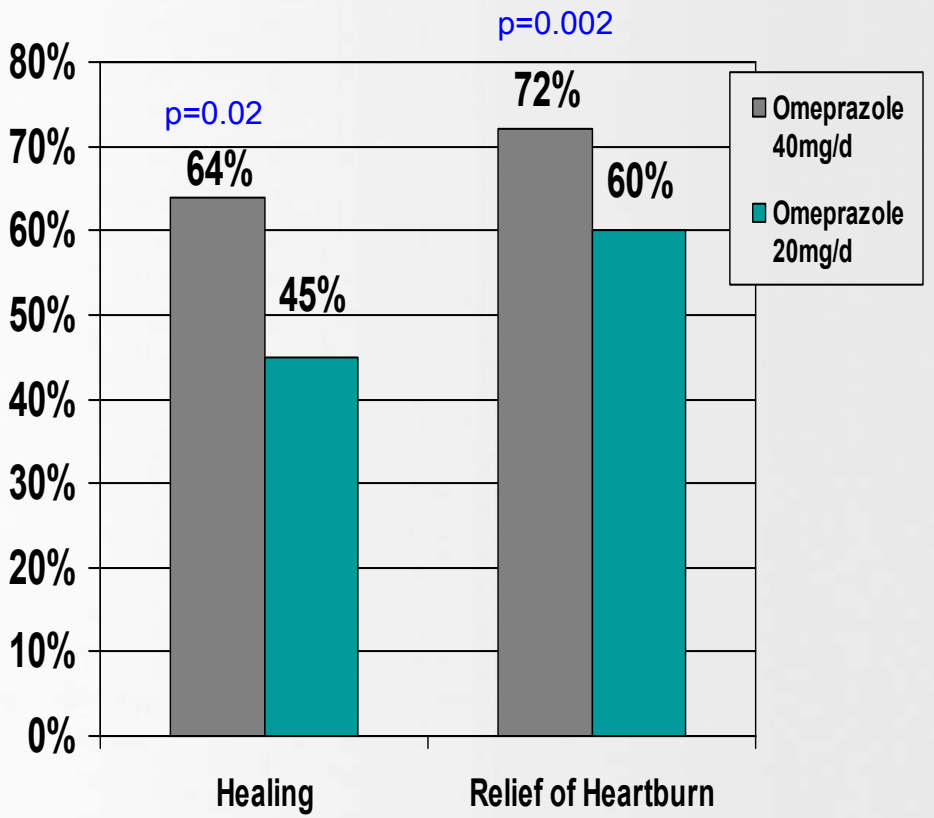
Double-dose PPIs: step-up therapy for non-responders

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



Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

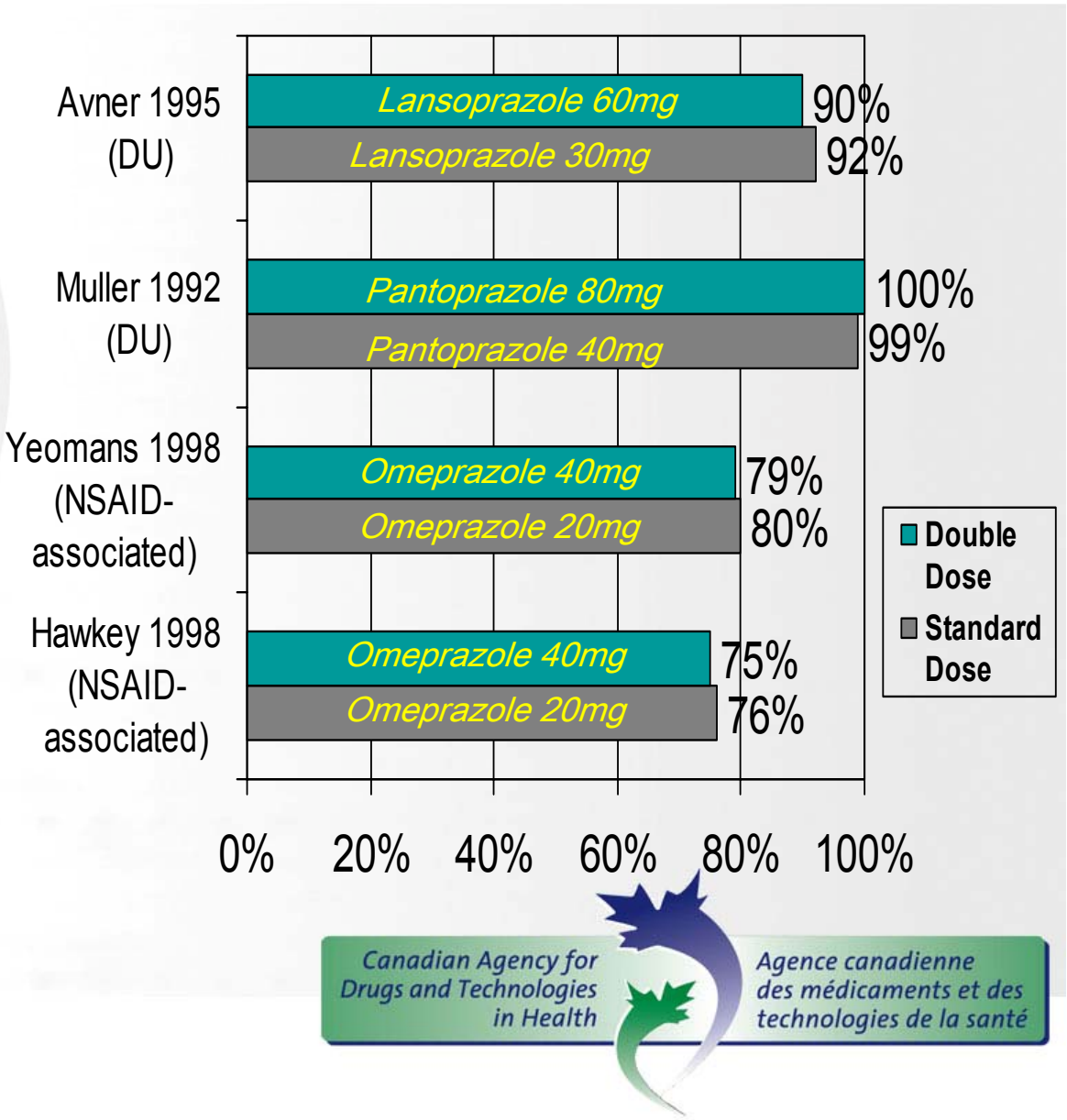
Bate 1993

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

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

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

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

Double-dose PPIs: conclusion

Aside from eradication of H. pylori, there are **no proven indications** for the use of double-dose PPIs

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

To review….

Who should be prescribed a double-dose PPI?

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

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

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?

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

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?

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

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

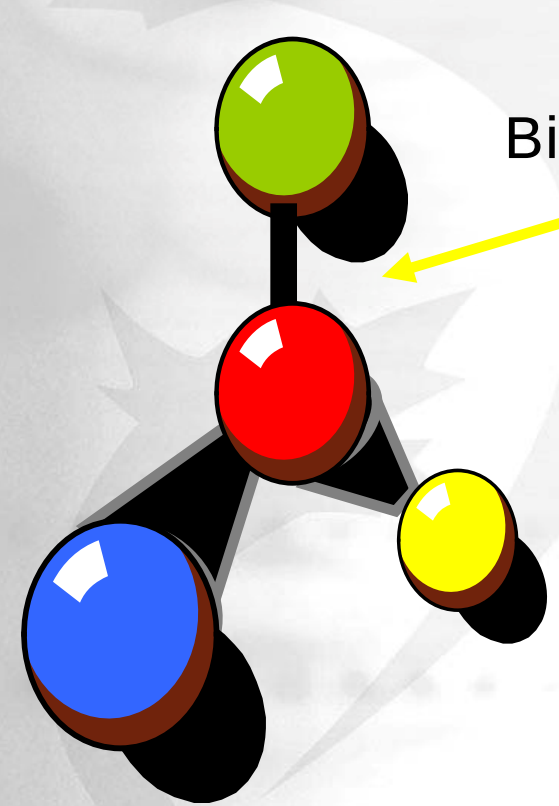
Canadian Agency for Drugs and Technologies in Health
Agence canadienne des médicaments et des technologies de la santé

Comparing the PPIs: What about esomeprazole?

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

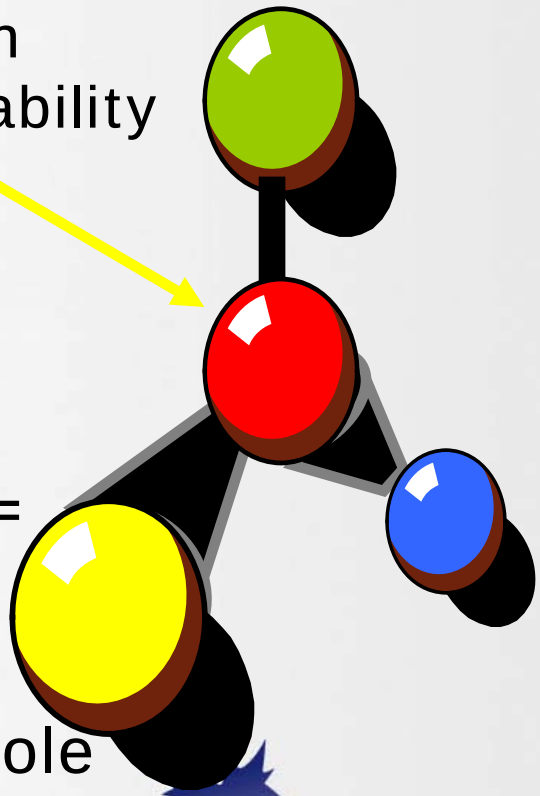
Low Bioavailability

High Bioavailability



R-Omeprazole

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

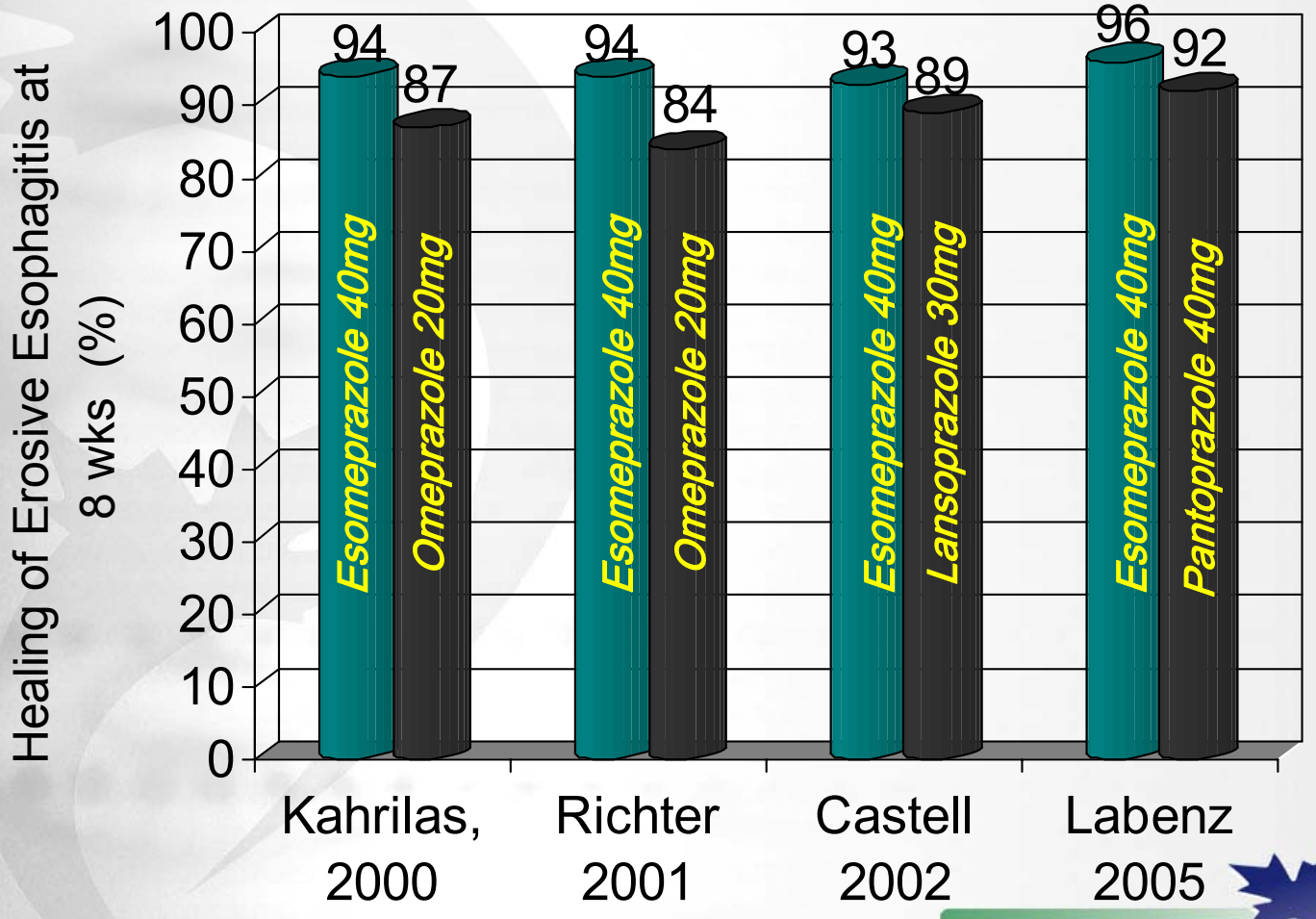


Esomeprazole

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

Comparing the PPIs: What about esomeprazole?



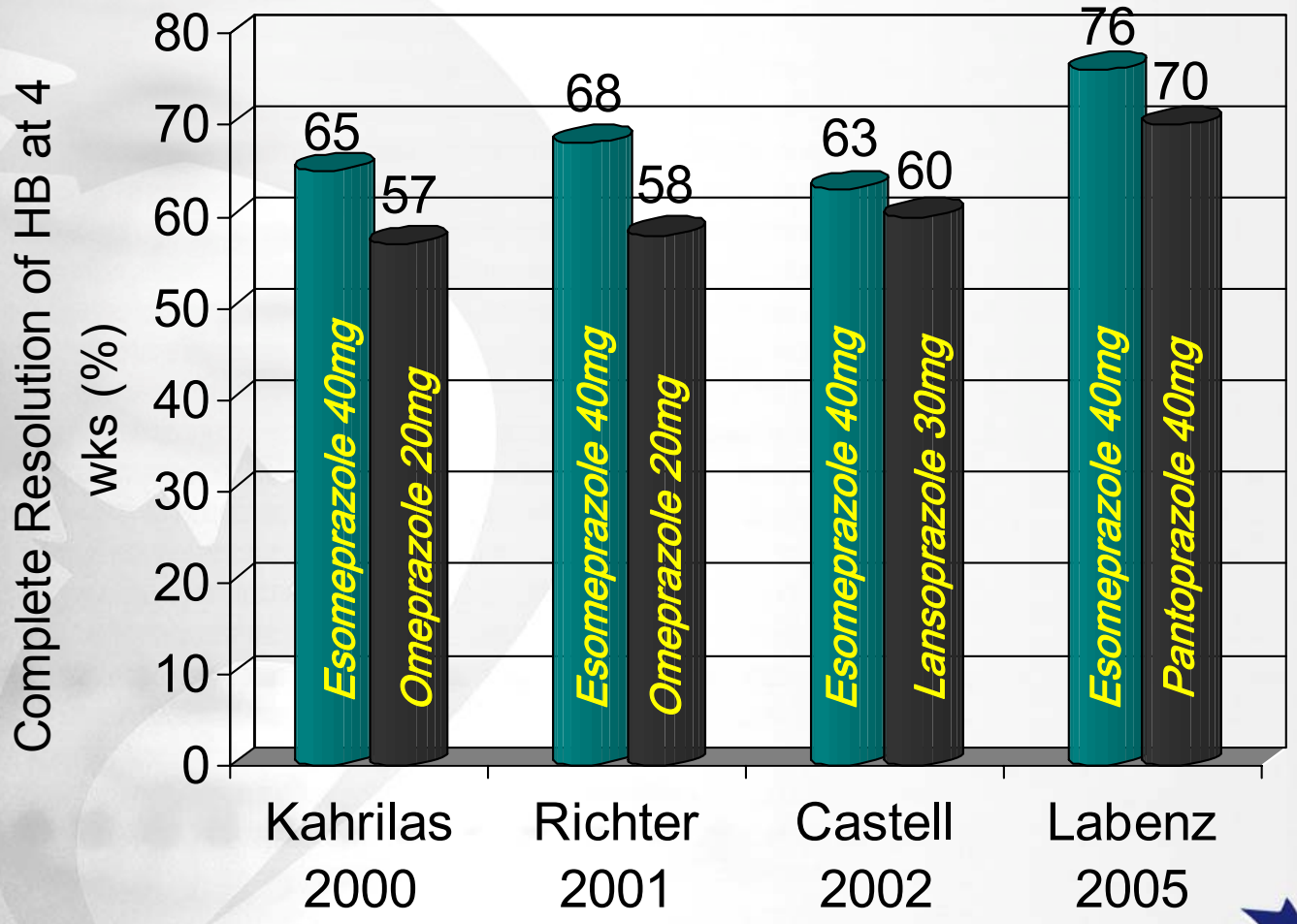
-p<0.05 for all comparisons

-Absolute differences range from 4 – 10%

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%

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

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

Canadian Agency for Drugs and Technologies in Health
Agence canadienne des médicaments et des technologies de la santé

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.

CADTH 2007
Vakil 2003

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

Regula 2006
McDonagh 2005

Canadian Agency for Drugs and Technologies in Health
Agence canadienne des médicaments et des technologies de la santé

Comparing PPIs: eradication of *H. Pylori*

- COMPUS identified 5 high-quality systematic reviews
- No significant differences in eradication rates across all PPIs, including esomeprazole

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

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

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

Practice implications

Prescribing may be optimized by focusing on lower cost PPIs

Standard Dose PPIs	Generic Omeprazole 20mg Daily	Pariet® Rabeprazole 20mg Daily	Pantoloc® Pantoprazole 40mg Daily	Prevacid® Lansoprazole 30mg Daily	Nexium® Esomeprazole 20mg Daily	Losec® Omeprazole 20mg Daily
Daily Price[Δ]	$1.25	$1.30	$1.90	$2.00	$2.10	$2.20
Approximate Monthly Price†	$43.00	$44.40	$61.20	$64.00	$66.80	$69.60

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

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?

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

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

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

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)

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

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

Canadian Agency for Drugs and Technologies in Health
Agence canadienne des médicaments et des technologies de la santé

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

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

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

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

Questions ?

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

References

1. 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/index.php/en/compus/current-topics/ppis (accessed 2007 Mar 28).

2. Armstrong D, Talley NJ, Lauritsen K, Moum B, Lind T, Tunturi-Hihnala H, et al. The role of acid suppression in patients with endoscopy-negative reflux disease: the effect of treatment with esomeprazole or omeprazole. Aliment Pharmacol Ther 2004;20(4):413-21.

3. Armstrong D, Marshall JK, Chiba N, Enns R, Fallone CA, Fass R, et al. Canadian consensus conference on the management of gastroesophageal reflux disease in adults: update 2004. Can J Gastroenterol 2005;19(1):15-35.

4. Avner DL, Movva R, Nelson KJ, McFarland M, Berry W, Erfling W. Comparison of once daily doses of lansoprazole (15, 30, and 60 mg) and placebo in patients with gastric ulcer. Am J Gastroenterol 1995;90(8):1289-94.

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

References

5. *Bardhan KD, Hawkey CJ, Long RG, Morgan AG, Wormsley KG, Moules IK, et al. Lansoprazole versus ranitidine for the treatment of reflux oesophagitis. UK Lansoprazole Clinical Research Group.* Aliment Pharmacol Ther *1995;9(2):145-51.*

6. *Bate CM, Booth SN, Crowe JP, Hepworth Jones B, Taylor MD, Richardson PD. Does 40 mg omeprazole daily offer additional benefit over 20 mg daily in patients requiring more than 4 weeks of treatment for symptomatic reflux oesophagitis?* Aliment Pharmacol Ther *1993;7(5):501-7.*

7. *Blum RA, Hunt RH, Kidd SL, Shi H, Jennings DE, Greski-Rose PA. Dose-response relationship of lansoprazole to gastric acid antisecretory effects.* Aliment Pharmacol Ther *1998;12(4):321-7.*

8. *Castell DO, Kahrilas PJ, Richter JE, Vakil NB, Johnson DA, Zuckerman S, et al. Esomeprazole (40 mg) compared with lansoprazole (30 mg) in the treatment of erosive esophagitis.* Am J Gastroenterol *2002;97(3):575-83.*

9. *Earnest DL, Dorsch E, Jones J, Jennings DE, Greski Rose PA. A placebo-controlled dose-ranging study of lansoprazole in the management of reflux esophagitis.* Am J Gastroenterol *1998;93(2):238-43.*

References

10. Fock KM, Teo EK, Ang TL, Chua TS, Ng TM, Tan YL. Rabeprazole vs esomeprazole in non-erosive gastro-esophageal reflux disease: a randomized, double-blind study in urban Asia. World J Gastroenterol 2005;11(20):3091-8.

11. Hawkey CJ, Karrasch JA, Szczepanski L, Walker DG, Barkun A, Swannell AJ, et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. Omeprazole versus Misoprostol for NSAID-induced Ulcer Management (OMNIUM) Study Group. N Engl J Med 1998;338(11):727-34.

12. Humphries TJ, Merritt GJ. Review article: drug interactions with agents used to treat acid-related diseases. Aliment Pharmacol Ther 1999;13 Suppl 3:18-26.

13. Hunt RH, Howden CW, Jones DB, Burget DW, Kerr GD. The correlation between acid suppression and peptic ulcer healing. Scand J Gastroenterol Suppl 1986;125:22-31.

14. Jones DB, Howden CW, Burget DW, Kerr GD, Hunt RH. Acid suppression in duodenal ulcer: a meta-analysis to define optimal dosing with antisecretory drugs. Gut 1987;28(9):1120-7.

References

15. Kahrilas PJ, Falk GW, Johnson DA, Schmitt C, Collins DW, Whipple J, et al. Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: a randomized controlled trial. The Esomeprazole Study Investigators. Aliment Pharmacol Ther 2000;14(10):1249-58.

16. Katz PO, Xue S, Castell DO. Control of intragastric pH with omeprazole 20 mg, omeprazole 40 mg and lansoprazole 30 mg. Aliment Pharmacol Ther 2001;15(5):647-52.

17. Labenz J, Stolte M, Blum AL, Jorias I, Leverkus F, Sollböhmer M, et al. Intragastric acidity as a predictor of the success of Helicobacter pylori eradication: a study in peptic ulcer patients with omeprazole and amoxicillin. Gut 1995;37(1):39-43.

18. Labenz J, Armstrong D, Lauritsen K, Katelaris P, Schmidt S, Schütze K, et al. A randomized comparative study of esomeprazole 40 mg versus pantoprazole 40 mg for healing erosive oesophagitis: the EXPO study. Aliment Pharmacol Ther 2005;21(6):739-46.

19. Martin de Argila C. Safety of potent gastric acid inhibition. Drugs 2005;65(Suppl 1):97-104.

References

20. McDonagh MS, Carson S. Drug class review on proton pump inhibitors: final report update 3. Portland (OR): Oregon Health & Science University; 2005.

21. Mönnikes H, Pfaffenberger B, Gatz G, Hein J, Bardhan KD. Novel measurement of rapid treatment success with ReQuest™: first and sustained symptom relief as outcome parameters in patients with endoscopy-negative GERD receiving 20 mg pantoprazole or 20 mg esomeprazole. Digestion 2005;71(3):152-8.

22. Muller P, Simon B, Khalil H, Lühmann R, Leucht U, Schneider A. Dose-range finding study with the proton pump inhibitor pantoprazole in acute duodenal ulcer patients. Z Gastroenterol 1992;30(11):771-5.

23. Qadeer MA, Phillips CO, Lopez AR, Steward DL, Noordzij JP, Wo JM, et al. Proton pump inhibitor therapy for suspected GERD-related chronic laryngitis: a meta-analysis of randomized controlled trials. Am J Gastroenterol 2006;101(11):2646-54.

24. Regula J, Butruk E, Dekkers CP, de Boer SY, Raps D, Simon L, et al. Prevention of NSAID-associated gastrointestinal lesions: a comparison study pantoprazole versus omeprazole. Am J Gastroenterol 2006;101(8):1747-55.

References

25. Richter JE, Kahrilas PJ, Johanson J, Maton P, Breiter JR, Hwang C, et al. Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. Am J Gastroenterol 2001;96(3):656-65.

26. Sontag SJ, Hirschowitz BI, Holt S, Robinson MG, Behar J, Berenson MM, et al. Two doses of omeprazole versus placebo in symptomatic erosive esophagitis: the U.S. Multicenter Study. Gastroenterology 1992;102(1):109-18.

27. Targownik LE, Metge C, Roos L, Leung S. The prevalence of and the clinical and demographic characteristics associated with high-intensity proton pump inhibitor use [Epub ahead of print]. Am J Gastroenterol 2007.

28. Vakil N, Fennerty MB. Direct comparative trials of the efficacy of proton pump inhibitors in the management of gastro-oesophageal reflux disease and peptic ulcer disease. Aliment Pharmacol Ther 2003;18(6):559-68.

29. van Rensburg CJ, Honiball PJ, Grundling HD, van Zyl JH, Spies SK, Eloff FP, et al. Efficacy and tolerability of pantoprazole 40 mg versus 80 mg in patients with reflux oesophagitis. Aliment Pharmacol Ther 1996;10(3):397-401.

References

30. Vavricka SR, Storck CA, Wildi SM, Tutuian R, Wiegand N, Rousson V, et al. Limited diagnostic value of laryngopharyngeal lesions in patients with gastroesophageal reflux during routine upper gastrointestinal endoscopy. Am J Gastroenterol 2007;102(4):716-22.

31. Yeomans ND, Tulassay Z, Juhász L, Rácz I, Howard JM, van Rensburg CJ, et al. A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal antiinflammatory drugs. N Engl J Med 1998;338(11):719-26.