Proton pump inhibitors

Compliance with a mandated step-up program

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abstract

OBJECTIVE To assess compliance with a step-up approach to proton pump inhibitor (PPI) therapy before implementation of a new provincial policy to promote histamine-type 2 receptor antagonist (H_2RA) use before PPI therapy.

DESIGN Population-based, retrospective, open cohort study using prescribing and medical procedure data from January 1, 1995, to April 30, 1999.

SETTING Health administration databases for the universal health care system in Ontario.

PARTICIPANTS Approximately 1.4 million residents of Ontario older than 65 years.

MAIN OUTCOME MEASURES Proportion of patients who received a trial of H_2RA therapy or gastrointestinal diagnostic testing 12 months before starting PPI therapy in 1996.

RESULTS Among the 25870 patients who met study criteria in 1996, about 63% had received H_2RAs 12 months before starting PPI therapy and 73% had had a trial of H_2RAs or gastrointestinal diagnostic testing. Repeat analysis for January through April 1999, following the new policy implementation, showed that about 72% of patients had had a trial of H_2RAs within 12 months of starting PPI therapy.

CONCLUSION A modest gain (9%) in compliance with using H_2RA therapy within 12 months before starting PPI therapy was seen following introduction of the step-up intervention. In future, costs and benefits of potential interventions should be carefully considered before implementing new policies.

résumé

OBJECTIF Évaluer la conformité à une approche progressive à l'endroit de la thérapie au moyen de l'inhibiteur de la pompe à protons (IPP) avant l'implantation d'une nouvelle politique provinciale visant à promouvoir le recours à l'antagoniste du récepteur de type 2 de l'histamine (ARH_2) avant une thérapie à l'IPP.

CONCEPTION Une étude rétrospective non contrôlée de cohortes, basée dans la population et fondée sur les données concernant les ordonnances et les interventions médicales du 1er janvier 1995 au 30 avril 1999.

CONTEXTE Les bases de données administratives du système de services universels de santé en Ontario.

PARTICIPANTS Environ 1,4 million de résidents âgés de plus de 65 ans en Ontario.

PRINCIPALES MESURES DES RÉSULTATS La proportion de patients ayant suivi une thérapie d'essai à l'ARH_2 ou subi une épreuve de diagnostic gastro-intestinal 12 mois avant d'amorcer une thérapie à l'IPP en 1996.

RÉSULTATS Au nombre des 25 870 patients qui répondaient aux critères de l'étude en 1996, environ 63% avaient suivi une thérapie à l'ARH_2 12 mois avant de commencer un traitement à l'IPP et 73% avaient eu une thérapie d'essai à l'ARH_2 ou une épreuve de diagnostic gastro-intestinal. Une réplique de l'analyse effectuée de janvier à avril 1999, à la suite de la mise en œuvre de la nouvelle politique, a fait valoir que 72% des patients avaient suivi une thérapie d'essai à l'ARH_2 dans les 12 mois précédant le début de leur traitement à l'IPP.

CONCLUSION Un gain modeste (9%) dans la conformité au recours à une thérapie préalable à l'ARH_2 avant d'amorcer un traitement à l'IPP a été observé à la suite de l'instauration d'une politique d'intervention progressive. À l'avenir, il y aurait lieu d'examiner rigoureusement les coûts et les avantages d'interventions éventuelles avant l'implantation de nouvelles politiques.

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Dyspeptic symptoms are common among elderly people; nearly a quarter of them complain of frequent abdominal pain.[1] Acid suppressant drugs, primarily histamine-type 2 receptor antagonists (H_2RAs) and proton pump inhibitors (PPIs), are commonly prescribed to manage dyspeptic symptoms, reflux, and peptic ulcers.

Growing concern has focused on the widespread and often unnecessary use of PPIs for minor symptoms[2,3] because of its substantial cost. Although many studies have suggested that PPI therapy is more cost-effective than H_2RAs for certain indications,[4-6] misuse could be widespread if many patients are receiving PPIs for unlicensed indications, such as nonspecific abdominal pain.[7] Furthermore, long-term outcomes could be similar for patients using PPIs and patients using H_2RAs when they are used intermittently,[8] and a step-up approach starting with a prokinetic agent or H_2RA might be more cost-effective than initial treatment with a PPI.[9] A step-up approach was accepted by most participants at the 1996 Second Canadian Consensus Conference on the Management of Patients with Gastroesophageal Reflux Disease (GERD).[10]

McBride et al[11] demonstrated that H_2RA use within 6 months of starting PPI therapy was low (approximately 20% in Ontario's elderly population). They used Ontario Drug Benefits (ODB) data from fiscal year 1992. In contrast, compliance with a step-up approach to using H_2RAs 12 months before starting PPI therapy was shown to be approximately 70% in an Australian population in 1996.[12]

The Ontario government requires use of H_2RAs before PPI initiation for its beneficiaries under the ODB program. It has deemed PPIs "limited use" drugs in an attempt to curtail rising costs. Patients presenting with severe disease on endoscopic examination or with procedurally or clinically diagnosed GERD who have not responded to at least 8 weeks of H_2RA therapy within the past 12 months and patients with pathologic hypersecretory conditions, such as Zollinger-Ellison syndrome and *Helicobacter pylori*–positive peptic ulcers, however, can use PPIs as primary therapy. A way of electronically verifying prior H_2RA use within 12 months of PPI initiation was also implemented on December 31, 1998, to improve compliance with the new policy.

While use of PPIs in Ontario has increased over the past several years, growing awareness of cost-containment initiatives and changing practice patterns could reflect greater compliance with ODB reimbursement criteria than previously reported. The primary objective of this study was to determine use of H_2RA therapy and gastrointestinal diagnostic procedures, both separately and together, in the 12 months before PPI initiation among elderly people in Ontario in 1996. (The PPIs considered were lansoprazole, omeprazole, and pantoprazole; H_2RAs considered were cimetidine, famotidine, nizatidine, and ranitidine.)

We also explored the relationship between patient and physician demographics and compliance with a step-up approach to PPI use and the effect of extending the observation period from 12 to 36 months. As a secondary objective, we compared use of H_2RAs before PPI therapy in 1996 to that during the first four months of 1999 to estimate the effect of the government-mandated step-up approach.

METHODS

Study design and data sources

We conducted a population-based, retrospective cohort study using administrative databases. Patients aged 66 years and older who started PPI therapy between January 1 and December 31, 1996, were included for analysis.

The ODB database was used to identify medications elderly patients were prescribed during the observation period. This database is maintained by the Ontario Ministry of Health (MOH) and includes encrypted patient identifiers, prescription dates, and drug identification numbers for all Ontarians 65 or older who make claims under the program. All Ontario residents 65 or older not residing in chronic care hospitals are eligible for government subsidization of prescription drugs through this program. Because data were available only for those 65 and older, the study was confined to an elderly population.

Study entry date was defined as first prescription of a PPI recorded in the ODB during the study period. The ODB data were reviewed for PPI use for a year before study entry, and those using PPIs within 1 year of study entry were excluded from analysis. Patients with no history of ODB claims were excluded to ensure that all patients in the study were using the system throughout the study period. All patients treated for

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H pylori eradication were also excluded; these patients were identified using ODB claims for specific antibiotics (ie, amoxicillin, clarithromycin, or a combination of metronidazole and tetracycline) within 3 days of the index PPI prescription.

Duration of drug therapy was estimated using the World Health Organization's "defined daily dose" criteria.[13] Number of procedures was based on claims recorded in the Ontario Health Insurance Plan (OHIP) database. All permanent residents of Ontario are covered by OHIP, and major diagnostic procedures are recorded in its database (each claim cites patient, physician submitting the claim, procedure performed, and service date). Follow-up management strategies were assessed for 365 days following study entry using the same databases and methods we used for pretreatment data.

Patient and physician demographics (ie, birth year, sex, and medical specialty) were ascertained using the MOH's Registered Persons Database and Human Resources Registry, both of which contain such information and use encrypted identifiers for all residents and practising physicians in Ontario.

The primary outcome measure was the proportion of patients who received a trial of H_2RA therapy or gastrointestinal diagnostic testing within 12 months of starting PPI in 1996. Compliance with the step-up approach was defined as the proportion of patients who received a trial of H_2RA therapy in the 12 months before PPI initiation. Although as a secondary outcome measure we examined compliance with the step-up approach in the first 4 months of 1999 following implementation of the new government policy, too few data were available to allow analysis of prior gastrointestinal diagnostic testing during that time.

Use of secondary data and encrypted identifiers to protect confidentiality, and formal confidentiality agreements between the MOH and the Institute for Clinical Evaluative Sciences and its faculty to use these databases for research purposes, made formal ethics approval unnecessary.

Statistical considerations

In addition to descriptive statistics, logistic regression analyses were conducted to assess the relationships between H_2RA use before PPI initiation and patient and physician age and sex, use of gastrointestinal diagnostic testing, and medical specialty. Age was entered as a continuous variable. Medical specialty was treated as a categorical variable with four levels: family practice, internal medicine, gastroenterology, and other. Relationships between long-term PPI use and age, sex, prior or subsequent H_2RA use, prior or subsequent gastrointestinal diagnostic testing, and medical specialty were also assessed using logistic regression.

RESULTS

Patient population

Approximately 6% (n = 78 008) of all Ontario residents 65 and older were prescribed PPIs in 1996. For this study, 25 870 subjects were eligible for initial review (**Table 1**). Average age of subjects was 75 years (standard deviation [SD] 6.7 years), and about 62% were women (n = 16 104).

Pretreatment strategies

Within a year before receiving PPI prescriptions, 63% of patients (n = 16 345) were prescribed a trial of H_2RA therapy and 31% underwent gastrointestinal diagnostic testing (**Table 2**). Most (95%) of the H_2RA-treated patients (n = 15 538) received at least 4 weeks of H_2RA therapy (mean duration of H_2RA therapy was 187 ± 143 days). Approximately 73% of study patients received a trial of H_2RA therapy, gastrointestinal diagnostic testing, or both during this time. Extending the assessment period to 24

Table 1. Exclusions: *Initial number of study candidates was 78 808; number of subjects assessed was 25 870.*

EXCLUSION 1 (41 398 [53.1%] EXCLUDED)
• Chronic proton pump inhibitor (PPI) use
• Use of PPI within 365 days of date of entry
EXCLUSION 2 (6655 [8.5%] EXCLUDED)
• Cannot verify Ontario Drug Benefits coverage
• No claims for medication for 1 year before date of entry
EXCLUSION 3 (4085 [5.2%] EXCLUDED)
• Apparent *H pylori* eradication therapy
• Received exclusion antibiotics within 3 days of date

Table 2. Pretreatment interventions

INTERVENTION	N (%)
Diagnostic procedure only	2641 (10.2)
H_2RA trial only	11 024 (42.6)
Diagnostic procedure and H_2RA trial	5321 (20.6)
Neither	6884 (26.6)

and 36 months before PPI initiation revealed step-up compliance rates for a trial of H_2RA therapy alone to be about 71% and 73%, respectively. Compliance rates for trials of H_2RA therapy, gastrointestinal diagnostic testing, or both were found to be 81% and 84%, respectively, for 24 and 36 months before PPI initiation.

After adjusting for patient age, pretreatment diagnostic assessment, and physician birth year, sex, and specialty in multivariate analysis, men were significantly less likely to have received a trial of H_2RA therapy within 12 months of PPI initiation than women (odds ratio [OR] 0.83, 95% confidence interval [CI] 0.79 to 0.88). In similar analyses, men were also significantly more likely to undergo pretreatment diagnostic testing than women (OR 1.18, 95% CI 1.11 to 1.25).

Prescriber information

Specialty and demographic data for prescribers was divided into family medicine, internal medicine, gastroenterology, and other specialty categories and was available for 89.4% (n = 23116) of all doctors giving a first prescription for PPIs (**Table 3**). After controlling for patients' age, sex, prior H_2RA therapy, and physicians' age and sex in multivariate analysis, family physicians were more likely to comply with the step-up approach than other physicians (OR 1.23, 95% CI 1.14 to 1.32). Similar analyses revealed that patients receiving first prescriptions for PPIs from family physicians were less likely to undergo gastrointestinal diagnostic testing (OR 0.54, 95% CI 0.50 to 0.58) than patients treated by gastroenterologists.

Changes in compliance over time

The analysis was repeated for patients started on PPI from January 1, 1999, to April 30, 1999, following step-up policy implementation on December 31, 1998, to assess any immediate effect. Approximately 72% of patients (4652/6464) had a trial of H_2RA therapy before PPI initiation.

Table 3. Prescribing physicians' characteristics and number of initial prescriptions for proton pump inhibitors

	NO. OF PRESCRIPTIONS	AGE		MEN
SPECIALTY	N (%)	MEAN (SD)	MEDIAN (IQR)	(%)
Family medicine	19 477 (84.3)	48.2 (10.7)	47 (14)	85.6
Internal medicine	2664 (11.5)	60.0 (10.5)	50 (16)	90.4
Gastroenterology	706 (3.1)	44.0 (7.6)	43 (13)	97.2
Other	269 (1.2)	47.0 (7.1)	47 (9)	87.4

IQR—interquartile range, SD—standard deviation.

DISCUSSION

This study demonstrates that compliance with a step-up approach using a trial of H_2RA therapy before PPI initiation, while not yet perfect, is much better than previously measured,[11] with rates similar to those in an Australian study.[12] About 73% of patients received a trial of H_2RA therapy, underwent gastrointestinal diagnostic testing, or had both in the 12 months before PPI initiation. When the period before PPI initiation is extended to 24 or 36 months, the proportion of patients treated increases to 81% and 84%, respectively. These findings suggest a favourable compliance rate for the 1996 cohort. If only H_2RA therapy is considered, a modest gain of approximately 9% in the proportion of patients receiving it can be observed between 1996 (63%) and the first 4 months of 1999 (72%).

These observations raise issues concerning the need for and value of the policy on PPI use. Increasing drug costs are a growing concern for governments who pay. As newer, more expensive therapies for common disorders emerge, there will be a growing need to discourage their use in situations where other efficacious but less expensive therapies already exist. The cost of such initiatives could outweigh the benefits if perceived gains are modest, which is often the case when compliance with desired behaviour is already high. The cost avoided as a result of decreased PPI use should be considered against the costs of program implementation and operation and any effect on clinical outcomes. In addition to tangible monetary costs, intangible costs, such as added work and time for busy physicians and quality of life for patients must also be considered. An accurate assessment of such trade-offs requires further investigation.

Unlike results of a previous study in Ontario,[11] our study showed that women were more likely to receive a trial of H_2RA therapy before PPI initiation than men. Symptoms presented by women might have been perceived as less severe than those presented by men, so perhaps women were treated relatively less aggressively.[14] Family physicians were also found to be more likely to try H_2RA therapy before PPI initiation, but it could be argued that more severe cases requiring immediate PPI therapy would have been referred to specialists.

This study has limitations given its observational nature and the data sources used. First, the indication for which PPI was prescribed and the severity of illness were unknown, and an accurate assessment of conditions that

would preclude a trial of H_2RA therapy was not possible. Second, results of this study apply only to older people and might not be generalizable to younger people. Third, although trials with H_2RA therapy or diagnostic testing before PPI initiation were examined in this study, other methods of management, such as use of antacids or prokinetic agents, were not explored. A previous study, however, found use of these strategies without H_2RA therapy was rare.[12]

Despite these limitations, the findings of this study provide further insight into use of PPI therapy and physicians' practice patterns among elderly people. Such insight could be valuable in future policy planning.

CONCLUSION

Results of this study indicate that most patients treated with PPIs have previously received a trial of H_2RA therapy, gastrointestinal diagnostic testing, or both. A modest gain in compliance with prior use of H_2RA therapy of approximately 9% following introduction of a new step-up policy was observed. In light of these findings, future policy decisions should more carefully consider the possible costs and benefits of interventions before implementing policies.

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Contributors

Dr Mamdani, *the primary author, contributed substantially to conception and design of the study and to data acquisition and analysis.* **Dr Tu** *and* **Dr Jaakkimainen** *contributed to conception and design of the study and to data interpretation.* **Ms Bica** *contributed to design of the study and to data acquisition and analysis.* **Dr Hux** *contributed to conception and design of the study and to data analysis and interpretation.*

Competing interests

Dr Hux is a career scientist with the Ontario Ministry of Health and all authors receive salary support from the Institute for Clinical Evaluative Sciences in Toronto. GlaxoWellcome Inc gave an unrestricted educational grant to support this study.

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Editor's key points

- Before a mandatory step-up program for proton pump inhibitor (PPI) prescriptions in Ontario, 73% of patients older than 65 had received a trial of histamine-type 2 receptor antagonist (H_2RA) therapy or gastrointestinal diagnostic testing before starting PPI treatment.
- The mandatory program resulted in a modest rise in prior H_2RA therapy of 9%.
- Family physicians were more likely to comply with the step-up program than internists or gastroenterologists were.

Points de repère du rédacteur

- Avant la mise en œuvre d'un programme progressif obligatoire préalable à l'ordonnance de l'inhibiteur de la pompe à protons (IPP) en Ontario, 73% des patients de plus de 65 ans avaient suivi une thérapie d'essai à l'antagoniste du récepteur de type 2 de l'histamine (ARH_2) ou subi une épreuve de diagnostic gastro-intestinal avant d'amorcer un traitement à l'IPP.
- Le programme obligatoire ne s'est traduit que par une modeste hausse de 9% dans le recours à une thérapie préalable à l'ARH_2.
- Les médecins de famille étaient davantage susceptibles de se conformer au programme progressif que ne l'étaient les internistes ou les gastro-entérologues.

References

1. Talley NJ, O'Keefe EA, Zinsmeister AR, Melton LJ. Prevalence of gastrointestinal symptoms in the elderly: a population-based study. *Gastroenterology* 1992;102(3):895-901.
2. Bateman DN. Proton-pump inhibitors: three of a kind? *Lancet* 1997;349:1637-8.
3. Roberts SJ, Bateman DN. Prescribing of antacids and ulcer-healing drugs in primary care in the north of England. *Aliment Pharmacol Ther* 1995;9(2):137-43.
4. Walan A, Eriksson S. Long-term consequences with regard to clinical outcome and cost-effectiveness of episodic treatment with omeprazole or ranitidine for healing of duodenal ulcer. *Scand J Gastroenterol Suppl* 1994;210(Suppl):91-7.
5. Harris RA, Kuppermann M, Richter JE. Proton pump inhibitors or histamine-2 receptor antagonists for the prevention of recurrences of erosive reflux esophagitis: a cost-effectiveness analysis. *Am J Gatroenterol* 1997;92(12):2179-87.
6. Hillman AL. Economic analysis of alternative treatments for persistent gastro-oesophageal reflux disease. *Scand J Gastroenterol Suppl* 1994;201(Suppl):98-102.
7. Bashfrod JNR, Norwood J, Chapman SR. Why are patients prescribed proton pump inhibitors? Retrospective analysis of the link between morbidity and prescribing in the General Research Database. *BMJ* 1998;317:452-6.
8. Bardhan KD, Muller-Lissner S, Bigard MA, Porro GB, Ponce J, Hosie J, et al. Symptomatic gastro-oesophageal reflux disease: double blind controlled study of intermittent treatment with omeprazole or ranitidine. *BMJ* 1999;318:502-7.
9. Eggleston A, Wigerinck A, Huijghebaert S, Dubois D, Haycox A. Cost effectiveness of treatment for gastro-oesophageal reflux disease in clinical practice: a clinical database analysis. *Gut* 1998;42:13-6.
10. Beck IT, Champion MC, Lemire S, Thomson AB, Anvari M, Armstrong D, et al. The Second Canadian Consensus Conference on the Management of Patients with Gastroesophageal Reflux Disease. *Can J Gastroenterol* 1997;11(Suppl B):7-20B.
11. McBride JE, Pater JL, Dorland JL, Lam Y-M. Extent and variation of omeprazole prescribing in an elderly population of Ontario. *Ann Pharmacother* 1997;31:411-6.
12. McManus P, Marley J, Birkett DJ, Lindner J. Compliance with restrictions on the subsidized use of proton pump inhibitors in Australia. *Br J Clin Pharmacol* 1998;46(4):409-11.
13. World Health Organization Collaborating Centre for Drug Statistics Methodology. *ATC index with DDDs*. Geneva, Switz: World Health Organization; 1999.
14. Kudenchuk PJ, Maynard C, Martin JS, Wirkus M, Weaver WD. Comparison of presentation, treatment, and outcome of acute myocardial infarction in men versus women (the Myocardial Infarction Triage and Intervention Registry). *Am J Cardiol* 1996;78(1):9-14.