Differences in utilisation of gastroprotective drugs between 2001 and 2005 in Australia and Nova Scotia, Canada†

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ABSTRACT

Purpose This study aimed to compare use of histamine H2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs), 2001–2005, in the elderly and social security beneficiaries in Australia (AUS) and Nova Scotia, Canada (NS).

Methods Prescription dispensing data were collected for all subsidised H2RAs and PPIs. In AUS, dispensing data for concession beneficiaries were obtained from the Pharmaceutical Benefits Scheme database. In NS, data were sourced from the Pharmacare database. Relevant population data were used to convert to World Health Organisation Anatomic Therapeutic Chemical defined daily doses (2005) per 1000 beneficiaries per day (DDD/1000/day).

Results Overall use of gastroprotective agents was similar and rising in NS and AUS (100–160 DDD/1000/day) over this 5-year time window. However, the proportion of this use accounted for by PPIs was far higher in AUS (over 85% by 2005) than in NS (23% rising to 35% over the 5 years). In AUS, PPI use rose from 50 to about 140 DDD/1000/day over the 5 years, whereas PPI use in NS rose slowly to less than 60 DDD/1000/day by 2005. H2RA use in NS was always high (over 100 DDD/1000/day), whereas in AUS, H2RA use fell from 54 to around 24 DDD/1000/day over this period.

Conclusions AUS had much higher use of PPIs than NS over 2001–2005. The proportion of PPIs in all gastroprotective agents rose in AUS to be nearly 90%. The differences in utilisation during this time window could lead to differences in health outcomes from either lower gastro-intestinal bleeding risk or higher long-term adverse effects of PPIs. Copyright © 2013 John Wiley & Sons, Ltd.

KEY WORDS—gastroprotection; drug utilisation; international comparison; proton pump inhibitors; histamine H2 receptor antagonists; pharmacoepidemiology

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INTRODUCTION

Histamine H2 receptor antagonists (H2RAs) have been available since the 1980s with indications to treat and prevent peptic ulcer disease, gastro-oesophageal reflux disease and other gastro-intestinal (GI) disorders; proton pump inhibitors (PPIs) have been introduced more recently.1–3 Public subsidy for PPIs (which were manifely more expensive than H2RAs until the very recent introduction of generic products) has historically been strictly controlled in many jurisdictions, as the cost-effectiveness of increased expenditure resulting from widespread use was difficult to justify.4–8

More recently, adverse effects of long-term PPI use have been reported, including possible drug interactions, increased fracture risk (effects on bone mineralisation), rebound gastrin hypersecretion, magnesium deficiency and risk of some infections.9–17 Systematic reviews and recent meta-analyses confirmed slight increased risk of fracture in PPI users, with no increased risk detected in H2RA users.17–22 There is evidence that PPIs are superior to standard dose H2RAs to prevent serious upper GI bleeding from non-steroidal anti-inflammatory drug (NSAID)-induced ulcers.
The continued assessment of benefits and risks through rigorous evaluation of data generated from actual use of medicines is important as public subsidy decisions are often based on incomplete, early, clinical trial and modelling data. Currently, as long-term adverse effects are often not known when a medicine is first assessed for public subsidy, longer term public health benefits, risks and costs are not factored into the funding decisions. However, when data that suggest an altered cost–benefit performance become available, a case could be made for re-assessment of subsidy. Actual use data (rather than predicted use), real-life outcomes and known costs of treating resulting adverse effects could be incorporated in the benefit–risk profiles. Even a small increased relative risk for an adverse effect of low absolute risk can have high population health impacts. Policy makers and researchers have now begun evaluating ways of investigating benefits and harms over the lifecycle of approved medicines. One way of investigating such differences in population health effects due to longer term adverse effects is to assess differences in these outcomes in populations with historically different exposures to the medicines of interest.

Previous comparisons of utilisation of statin antilipemics, NSAIDs (COX-2 specific and non-specific), benzodiazepines and antidepressant medications between Nova Scotia, Canada (NS) and Australia (AUS) have been completed. In these studies, similar population groups were identified receiving publicly reimbursed medications, seniors (over 65 years of age) and social security recipients. Medication use was thus able to be compared for similar groups in the two jurisdictions. These analyses highlighted several areas of medication utilisation differences, recognising different influences on prescribing and use, and led to suggestions for improved use of these medications. As the validity of comparing across these administrative databases has been established, it is now timely, with the new, rare adverse events especially with long-term PPIs emerging as potential significant issues, to compare historical use of gastroprotective agents in similar populations in the two jurisdictions, AUS and NS.

AIM

The aim of this study was to compare use of H2RAs and PPIs (together called ‘gastroprotective agents’), during the 5-year period 2001–2005, in comparable groups of elderly and social security beneficiaries in two jurisdictions (AUS and NS).

METHODS

Prescription dispensing data were collected for all H2RAs and PPIs that were subsidised by the public pharmaceutical systems in AUS and NS, for eligible Seniors (above 65 years of age) and social security beneficiaries. These groups are aggregated as concession beneficiaries in the AUS Pharmaceutical Benefits Scheme (PBS) and in the Pharmacare programmes in NS.

In the relevant time window, 2001–2005, the H2RAs (World Health Organisation Anatomic Therapeutic Chemical (ATC) 2005 code A02BA) subsidised were ranitidine, cimetidine, famotidine and nizatidine, and the PPIs (ATC code A02BC) subsidised were omeprazole, lansoprazole, pantoprazole, rabeprazole (from 2002 in NS) and esomeprazole (from 2002 in both jurisdictions).

The NS Government Pharmacare programme is available to all seniors 65 years or older who have a valid NS Health Card and do not have private drug coverage (Seniors’ Pharmacare Programme) and to those receiving income assistance through the Department of Community Services (Community Services Pharmacare programmes). Older patients who have drug insurance from the Royal Canadian Mounted Police or Veterans Affairs Canada, eligible members of the First Nations or Inuit communities (i.e. registered Indians, Inuk and Innu individuals born in Canada), or those who use solely private drug insurance are not covered by the Pharmacare health insurance programme. Eligible Pharmacare beneficiaries are required to pay a yearly premium (Canadian Dollars $424 (2008)). In 2007, the annual maximum co-payment a senior would pay was $382. In NS, H2RAs and PPIs were reimbursable benefits with special maximum allowable cost. The special maximum allowable cost is the maximum amount Pharmacare reimburses pharmacies for one tablet or capsule of a defined product only (e.g. ParietR (rabeprazole) 10-mg tablet was the reimbursed product that was defined in May 2003, with 2 × 10 mg being the standard dose at that time). The patient then pays any difference between this cost and the cost of the actual prescribed medication. Additionally, PPIs required prior authorisation for reimbursement during this period, with strict criteria for coverage.

Medicare AUS is responsible for payment to community pharmacists for prescriptions reimbursed by the PBS in AUS. Prescriptions dispensed for reimbursable medicines are recorded and aggregated; de-identified data are publicly accessible. The data are presented aggregated by item number (a code given to each formulation of each medicine subsidised by the PBS).
The reimbursement system covers all permanent residents in AUS (PBS beneficiaries) with two classes of PBS beneficiaries: general and concession. Concession beneficiaries consist of those AUS residents eligible for the Commonwealth Seniors Health Card, Health Care Card and Pensioner Concession Card. These are people receiving old age or disability pensions, single parents, low-income families and other patients eligible for a social security benefit. They contribute a low co-payment ($AUS4.60, in 2005; with a ‘safety net’ total maximum co-payment of $239.20 for all subsidised medicines in the calendar year 2005). Neither PPIs nor H2RAs required prior authorisation in AUS during the study period; however, PPIs were a ‘restricted benefit’, with prescribers responsible for ensuring that patients met the defined restrictions (initial treatment for peptic ulcer disease (limited quantity), Zollinger–Ellison syndrome, gastro-oesophageal reflux disease, scleroderma oesophagus). H2RAs had no restrictions but are one of the groups of drugs in AUS subject to therapeutic group premiums, whereby the patient pays the difference in cost between the lowest-cost H2RA and the one that is actually prescribed.

In AUS, dispensing data for concession beneficiaries were obtained for the years 2001, 2002, 2003, 2004 and 2005 from the PBS database. In NS, these data were sourced from the provincial Pharmacare database. Relevant population data were used to convert all data to defined daily doses (DDD) per 1000 beneficiaries per day (DDD/1000/day), as described previously. DDD for each medication was defined according to the World Health Organisation ATC DDD 2005.33

Drug utilisation 90% (DU90%) for all gastroprotective drugs was also calculated for NS and for AUS. DU90% ranks the drugs accounting for 90% of those dispensed within the group of medicines being studied. Chi-squared analyses were used to compare proportions of PPIs and H2RAs used in each jurisdiction, with $p < 0.05$ considered a statistically significant difference (Microsoft Office Excel 2007).

RESULTS

The AUS concession beneficiaries numbered 4.95 million in 2005, accounting for approximately 24% of the whole population. Older Australians concession beneficiaries, those over 65 years of age, represented just over 40% of the concession beneficiaries. In NS, eligible beneficiaries numbered 185,864 in 2003/2004 (about 20% of the population), and approximately 60% of those were aged 65 or over (seniors).

Approved indications were similar in both AUS and NS—for H2RAs, these were dyspepsia, peptic ulcer disease and gastro-oesophageal reflux; for PPIs, these were dyspepsia, peptic ulcer disease, gastro-oesophageal reflux and Zollinger–Ellison syndrome, and indicated by regulatory authorities (although not approved for subsidy in either jurisdiction) for prevention and/or treatment of GI adverse effects of NSAIDs.

The overall use of gastroprotective agents in both jurisdictions, AUS and NS, increased during the 5-year period, 2001–2005. However, there were important differences in which actual medications were used and differences between the two jurisdictions in the relative use of PPIs compared with H2RAs.

H2RAs were used far more extensively in NS than in AUS each year over the period 2001–2005 (Figure 1). In 2005, more than four times as many DDD/1000/day for H2RAs were recorded in NS compared with AUS. In both jurisdictions, ranitidine accounted for almost all the H2RA use (90–95% in NS; 77–82% in AUS). The use of H2RAs declined over the period in AUS, whereas the total H2RA usage remained quite constant in NS.

In contrast, PPI use in AUS was far higher than in NS each year (Figure 2). PPI use also rose dramatically (over 150%) in NS between 2001 and 2005, whereas there was a slow rise in use over this time in NS. Omeprazole was the main PPI used in both jurisdictions, with esomeprazole use rising rapidly in AUS but not in NS during this time.

By 2005, the total use of all gastroprotective agents was similar (over 150 DDD/1000/day) in both jurisdictions (Figure 3), with AUS rising from a lower starting point in 2001. However, the proportion of use accounted for by PPIs was significantly higher in AUS (Figure 4) ($p < 0.05$ for each year). In AUS, PPI use rose from just below 50% in 2001 to over 85% in 2005, whereas in NS, this proportion rose from just over 20% to just over 30% between 2001 and 2005.

The DU90% for the two jurisdictions clearly shows the changes in prescribing over the 5-year period (Table 1) and reflects the major use of ranitidine in NS and of omeprazole with increasing esomeprazole in AUS over the period. The effects of the preferential listing policy to reimburse only omeprazole and, later, rabeprazole in NS are clear from the DU90%.

DISCUSSION

The total use of gastroprotective agents (H2RAs and PPIs) was similar in NS and in AUS, rising to over 150 DDD/1000/day by 2005 in the selected population groups (Pharmacare and PBS concession beneficiaries, respectively) comprising seniors and social security recipients. Both jurisdictions have similar overall...
gastroprotective drug usage for the indicated GI disorders treated in their populations. The interesting finding was the widely different proportions of this use accounted for by PPIs; by 2005, nearly 90% of use was for PPIs in AUS compared with only about 35% in NS. This difference in use was statistically significant ($p < 0.05$). However, it remains to be determined how clinically significant this difference is, in terms of benefits in health outcomes, adverse effects and cost.

We believe the main explanation for the differences in use of PPIs and H2RAs between the two countries is related to pharmaceutical policies, with more formulary restrictions being present in NS. PPIs are more potent acid suppressants than H2RAs and superior to H2RAs in treatment of gastro-oesophageal reflux disease; however many patients with milder forms respond well to H2RAs. There also is evidence that PPIs are more effective in preventing GI bleeding due to peptic ulcers in NSAID users when compared with H2RAs. Furthermore, PPIs have proven to be effective in the prevention and treatment of aspirin associated peptic ulcers. This is relevant as many seniors are taking aspirin and non-aspirin NSAIDs. In contrast, there are new data emerging indicating that PPIs have a higher rate of side effects of infections, low bone density and fractures although the absolute risk of these is low.

The differences in use of PPIs and H2RAs attributed to differences in restrictions for subsidy are clearly seen in the DU90% (Table 1). NS had more stringent reimbursement criteria to be met prior to approval for PPI prescription. NS was also far more directive about which PPI could be subsidised, depending largely on medicine acquisition costs for the purchaser (NS Government). In AUS, by contrast, 2001 marked the end of prior authorisation for PPIs, and this was reflected in the large increase in the use of these medicines. AUS has a monopsony purchasing power (essentially a single purchaser), as pharmaceuticals are subsidised nationally and the maximum price paid by the government determined for the whole country (population over 20 million). Cost-effectiveness studies are

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required for new medications and prices negotiated against appropriate comparators.\textsuperscript{42,43} New medications, such as esomeprazole, may gain a place in this market as AUS purchasing power, for the whole country, may force a lower cost on a new entrant to the existing market. Esomeprazole has a larger market in some jurisdictions, such as AUS, in part as a result of the influence of marketing (which is diminished by reimbursement criteria such as preferential listing policies in NS) and the monopsony purchasing power
of the PBS in AUS able to negotiate lower prices. In the USA, direct-to-consumer advertising has been shown to influence switching between different PPIs, but this form of advertising is not permitted in NS or AUS so would be less likely to influence choice in these jurisdictions. PPIs first became available in AUS in 1992 as ‘authority required’ benefits (which required prior approval from Medicare Australia). In 2001, in AUS, the prior authorisation restriction was changed to restricted benefits (no prior authorisation, but intended to be only prescribed for specific therapeutic uses). The dramatic change in use around this 2001 policy change has been reported for the whole Australian population previously, as well as in this current group of concession beneficiaries. What the current study adds is the dimension of how much this change influenced prescribing in comparison with another jurisdiction where the formulary restrictions on prescribing of PPIs were still applied with much more stringent reimbursement criteria. It is neither obvious that any specific clinical outcomes of GI diseases differ between the two jurisdictions nor is there any evidence of differences in prevalence of GI disorders that could account for differential utilisation, which makes it all the more important to ascertain whether any detriment resulted to the health of the population from such a high use of PPIs in AUS. The potential beneficial outcomes could include improved control of GI diseases in AUS as a result of more PPI use, but this is not tracked or documented and was not part of this study. Perhaps quality-of-life improvements; for example, improved control of gastro-oesophageal reflux disease symptoms, may have resulted in AUS from the higher proportional use of PPIs, but remain as yet undocumented. The other consideration is the amount of public money spent on PPIs, as H2RAs until very recently were much cheaper. Would the funding spent on PPIs have been better placed, from a public health perspective, in purchasing other health outcomes for Australian consumers?

Currently considerations about differences in long-term adverse outcomes have limited influence on how cost-efficacy is judged for public subsidy. Arguments have been advanced about revisiting the public subsidy for current medicines as a new evidence base develops. This opens the whole debate on how long-term adverse effects, often unknown at the time of original drug approval and application for subsidy, can later be considered when determining public purchase of ‘health outcomes’ for an ever pressured public prescription funding scheme.

At the time that AUS and NS were making their formulary reimbursement decisions about PPIs, judgements were made in the context of the health care systems, financial resources available, the ability to negotiate price (purchasing power), concordance with practice guidelines and other relevant considerations. There have been some data published previously about gastroprotective medication utilisation. Our previous publication investigated relationships between prescribing of NSAIDs and increasing utilisation of NSAIDs with reportedly less gastrotoxicity in AUS. However, there was no decrease in use of gastroprotection with the introduction of the new class of COX-2 selective inhibitors. The utilisation of PPIs in the total population of AUS has been reported previously as about 55 DDD/1000/day. This is comparable with PPI use reported in Scotland, again for their whole population, of approximately 70 DDD/
1000/day in 2006 (rising from about 60 DDD/1000/day in 2005).\textsuperscript{53} Again, these data for the whole population appear consistent with Austria, which reported PPIs use in 2005 of 35 DDD/1000/day rising to 42 in 2006. UK data have been reported for one Primary Care Trust, again for their whole population, for PPI use of 48–55 DDD/1000/day in 2005–2006.\textsuperscript{54} There are some data available for Canada at the country level, but these do not show actual DDD/1000/day to enable comparison to the present study\textsuperscript{55}

These data suggest that NS had very low use of PPIs in seniors and social security beneficiaries (about 20% of the whole population but known to account for about 80% of prescription medicine use). AUS on the other hand seems to have very high use of PPIs in this beneficiary group. Therefore, these two would appear to be good comparator jurisdictions to detect any population health differences in outcomes due to PPI use. Importantly, overall use of the gastroprotective agents was similar suggesting that there was no difference in GI conditions in the two populations, just differences in the treatments chosen.

**Future research**

It would be very interesting to conduct research to evaluate differences now apparent in beneficial and adverse events attributable to gastroprotective agents between the two jurisdictions, NS and AUS. The differences in utilisation during this 2001–2005 time window could lead to differences in current (2012) health outcomes, for example, in benefits such as reduced GI bleeds in people receiving concomitant NSAIDs, or from resultant adverse effects of PPIs. For example, more fractures, or at least increased use of antiresorptive agents, in AUS could be apparent. Such large differences in utilisation of the PPIs and H2RAs should lead to different population health outcomes. It would be useful to start with GI bleeding as a potential benefit of PPIs over H2RAs and osteoporosis as a risk as there is evidence that there is a larger risk of this adverse effect with PPI use, compared with H2RAs. This can now be tested in a research context.

A previous study, based on administrative dispensing data from Ireland, has found an association between prescribing of bisphosphonates following the use of PPIs.\textsuperscript{56} An odds ratio of 2.09 (95%CI 2.04–2.13) for the prescribing of a bisphosphonate following over 2 years of PPI therapy was reported.\textsuperscript{56} Even for an adverse event of low prevalence, such as bone fracture, this is a greatly increased relative risk that could lead to clinically detectable differences between populations with historically low use of PPIs compared with those with historically high use. The population in this Irish study was demographically comparable with the NS and AUS populations included in the current investigation.

**Limitations**

The limited populations included in this study (eligible seniors and social security recipients) could represent a limitation to our study. However, it is well documented that this group accounts for about 80–85% of medication use.\textsuperscript{57} Therefore, the majority of relevant medication use data are captured. Our previous pharmacoepidemiological studies also show that these populations are comparable in demographics across NS and AUS, and provide very useful data for investigating effects of differences in pharmaceutical policy.\textsuperscript{26–29} AUS also does not collect complete data for all PBS medications reimbursed for general beneficiaries, omitting those falling under the general copayment ($28.60 in 2005), which would include many H2RAs. This is not an issue for concession beneficiaries as all these drugs are above their lower

| Table 1. The drug utilisation 90% (DU\textsubscript{90%}) between 2001 and 2005 for gastroprotective agents in (a) Australia concession beneficiaries and (b) Nova Scotia Pharmacare populations |
|---|---|---|---|---|
| 2001 | 2002 | 2003 | 2004 | 2005 |
| (a) | Ranitidine (40%) | Omeprazole (40%) | Omeprazole (36%) | Omeprazole (33%) | Omeprazole (31%) |
| | Omeprazole (31%) | Ranitidine (25%) | Ranitidine (19%) | Pantoprazole (18%) | Esomeprazole (20%) |
| | Pantoprazole (11%) | Pantoprazole (17%) | Pantoprazole (17%) | Esomeprazole (17%) | Pantoprazole (19%) |
| | Famotidine (7%) | Lansoprazole (7%) | Esomeprazole (12%) | Lansoprazole (7%) | Rabeprazole (7%) |
| (b) | Ranitidine (70%) | Ranitidine (69%) | Ranitidine (66%) | Ranitidine (64%) | Ranitidine (62%) |
| | Omeprazole (16%) | Omeprazole (17%) | Omeprazole (17%) | Omeprazole (15%) | Omeprazole (16%) |
| | Pantoprazole (4%) | Pantoprazole (5%) | Pantoprazole (5%) | Rabeprazole (9%) | Rabeprazole (13%) |

copayment. NS only collects data for those insured by the Pharmacare programmes and not for patients outside these groups who may pay privately or be covered by private drug insurance programmes. By only investigating eligible beneficiaries, these problems of missing undercopayment data and missing private prescriptions are minimised. The databases also do not record medicines obtained over-the-counter, and again, by reporting on groups receiving the highest subsidy, these groups are least likely able to afford to purchase gastroprotective medications over-the-counter at the retail prices. There are also limitations with using administrative prescription data as these are not linked to other health records. Outcomes cannot be followed up for specific cohorts, either beneficial or adverse; however, this may change as administrative database linkages ensue and/or with the advent of electronic health records. There are also limitations with using a dispensing database as there is no assurance that the recipient actually took the medication.

CONCLUSIONS

While the total use of gastroprotective agents (PPIs and H2RAs combined) was similar in seniors and social security beneficiaries in both NS and in AUS, the proportion over this use accounted for by PPIs, over the period 2001–2005, was significantly higher in the AUS population. Almost 90% of the use of gastroprotective agents was accounted for by PPIs in AUS by 2005, compared with just over a third of that in NS in comparable populations. There is a growing opinion that changing evidence should be incorporated into public subsidy decisions for medications, and more rigor is evolving about obtaining such data from ‘real life’ use. Such large differences in utilisation of these two classes of medication could lead to attributable differences in effects by now, more than 7 years on from the period of differing exposure. Future research would be useful to investigate any population differences in beneficial and adverse effects of PPIs, given that we now have two populations with quite different exposure to these agents.

CONFLICT OF INTEREST

N. B. was recently employed by Novartis Pharma AG. I. S. has received financial reimbursement from Health Canada and Green Shield Canada, and held a Chair funded by CHSRF/CIHR cosponsored by NSHRF. In the past 3 years, S. V. Z. has received speaking fees from AstraZeneca, Nycomed (now Takeda) and Abbott Laboratories who market omeprazole, esomeprazole, lansoprazole and dexilant in Canada, and has served as member of advisory boards of AstraZeneca, Takeda and Abbott Laboratories.

KEY POINTS

- Use of PPIs and H2RAs increased between 2001-2005 in Australia (AUS) and Nova Scotia, Canada (NS)
- AUS used a far higher proportion of PPIs than NS, with PPIs almost 90% of use in AUS by 2005
- NS used a far higher proportion of H2RAs than AUS, with ranitidine accounting for 60-70%
- Real life differences in utilisation between AUS and NS, now 7-12 years ago, may lead to differences in either benefits or adverse effects of long term PPI use

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