Proton-pump inhibitors and the risk of antibiotic use and hospitalisation for pneumonia

Elizabeth E Roughead, Emmae N Ramsay, Nicole L Pratt, Philip Ryan and Andrew L Gilbert

ABSTRACT

Objective: To determine whether proton-pump inhibitor (PPI) use is associated with hospitalisations for pneumonia and with antibiotic use.

Design and setting: Historical cohort study in the Australian veteran population, conducted from 1 January 2002 to 30 December 2006, comparing veterans exposed to PPIs with those not exposed.

Participants: All 185 533 veterans who were Gold Card holders (ie, eligible for all health services subsidised by the Department of Veterans' Affairs) and aged 65 years and over at 1 January 2002 and had been prescribed at least one medicine in the previous 6 months.

Main outcome measures: The primary endpoint was hospitalisation for pneumonia. Secondary endpoints included hospitalisation for bacterial pneumonia and dispensings of antibiotics commonly used to treat respiratory tract infections.

Results: After adjustment for potential confounders, we found an increased risk of hospitalisation for pneumonia among those exposed to PPIs compared with the unexposed group (rate ratio [RR], 1.16; 95% CI, 1.11–1.22). The risk was not increased for bacterial pneumonia (RR, 1.13; 95% CI, 0.98–1.31), which made up 8% of pneumonia cases. An increased risk of antibiotic dispensings was observed among those exposed to PPIs (RR, 1.23; 95% CI, 1.21–1.24).

Conclusions: PPI dispensings were found to be associated with a small but significant increased risk of hospitalisation for pneumonia. While the increased risk is small, the prevalent use of PPIs means that many people could be affected.

MJA 2009; 190: 114–116

For editorial comment, see page 109

Acid-suppressant therapy represents the second leading medication therapy worldwide, with sales of $26.9 billion in 2005.[1] Proton-pump inhibitors (PPIs) are the most commonly used acid suppressants.

While PPIs are considered relatively safe, recent case–control studies suggest their use may be associated with an increased risk of respiratory tract infections[2] and community-acquired pneumonia in adults[3,4] and children.[5] Suppression of gastric acid resulting in colonisation by ingested pathogens is considered a possible causal factor.[4]

The incidence of first episode of community-acquired pneumonia has been reported to be 2.45 per 100 person-years in those exposed to PPIs compared with 0.6 per 100 person-years in those not exposed.[3] We aimed to confirm this association in the Australian veteran population by means of a retrospective cohort study, and to determine the overall incidence of community-acquired pneumonia by including multiple events (eg, all hospitalisations for pneumonia for each veteran).

METHODS

The Department of Veterans' Affairs (DVA) claims database contains details of all prescription medicines, medical and allied health services and hospitalisations subsidised by the DVA. The data file contains 80 million pharmacy records, 200 million medical and allied health service records and over six million hospital records for a treatment population of 310 000 veterans. The DVA maintain a client file, which includes data on sex, date of birth, date of death and family status. Date of death is sourced from family notifications, death notices and the Australian Government Births, Deaths and Marriages registries. Medicines are coded according to the World Health Organization anatomical and therapeutic chemical (ATC) classification[6] and the Schedule of Pharmaceutical Benefits item codes.[7] Hospitalisations are coded according to the WHO International classification of diseases, 10th revision (ICD-10).[8]

This historical cohort study included veterans aged 65 years or over at 1 January 2002, who had at least one medication prescribed in the 6 months before entry into the cohort and who were Gold Card holders (indicating they were eligible for all health services subsidised by the DVA). Veterans were excluded if they had been dispensed a histamine-2 receptor antagonist (H2RA) in the 6 months before the study. Subjects who began taking H2RAs after study entry were censored at the time of their first prescription of an H2RA.

Dosage information is not available in the dataset, so exposure to PPIs was defined as 36 days from the prescription dispensing date. This period was calculated from the data, and represents the period within which 75% of veterans return for a repeat dispensing of a PPI. During the 36 days after any dispensing of a PPI, veterans were considered exposed; at any other time they were treated as not exposed for the purpose of the analysis. Repeat dispensings within 36 days were considered as continuous exposure. Subjects not exposed to PPIs were followed from entry into the cohort until death or the end of the study on 30 December 2006.

The primary endpoint was any hospitalisation with a primary diagnosis of pneumonia (ICD-10 codes: J12–J19, inclusive). Secondary endpoints included:

- any hospitalisation with a primary diagnosis of bacterial pneumonia (ICD-10 codes: J13, J14, J15, J16);
- any dispensing of antibiotics commonly used for respiratory tract infections — amoxicillin (ATC code: J01CA04), amoxicillin with clavulanic acid (J01CR02), cefaclor (J01DC04), cefuroxime (J01DC02), erythromycin (J01FA01), roxithromycin (J01FA06), doxycycline (J01AA02), ciprofloxacin (J01MA02), oral moxifloxacin with gatifloxacin (Pharmaceutical Benefits Scheme codes: 08636M, 04329W, 04297E). Antibiotics dispensed as part of *Helicobacter pylori* eradication therapy were not included.

Hospitalisation rates were calculated as the cumulative number of hospitalisations in the exposed or unexposed period divided by the number of days at risk. Rate ratios were calculated with Poisson generalised estimating equations (GEE) to allow for clustering of patients, adjusting for age at entry into the cohort, sex, socioeconomic index of disadvantage for postcode of residence[9] at study entry, number of comorbidities (assessed annually by means of the validated RxRisk-V[10] score),

1 Antibiotic use and hospitalisation in 185 533 veterans exposed and not exposed to proton-pump inhibitors

Variable	Not exposed	Exposed	Rate ratio (95% CI)
Total person-years of follow-up	533 846	138 228	
Total admissions for pneumonia	9651	4225	
Total admissions for bacterial pneumonia	773	358	
Total prescriptions for antibiotics	513 267	229 299	
Unadjusted rate per 10 years			
Pneumonia	0.181	0.306	1.69 (1.62–1.76)
Bacterial pneumonia	0.014	0.026	1.79 (1.57–2.04)
Antibiotic use	9.61	16.59	1.72 (1.70–1.75)
Adjusted rate per 10 years*			
Pneumonia	0.28	0.33	1.16 (1.11–1.22)
Bacterial pneumonia	0.023	0.026	1.13 (0.98–1.31)
Antibiotic use	13.30	16.31	1.23 (1.21–1.24)

* Adjusted for age, sex, socioeconomic index of disadvantage, number of comorbidities, season, residential aged-care status, tiotropium as a proxy indicator of chronic obstructive pulmonary disease, renin–angiotensin system medicines concurrent with frusemide as a proxy indicator of heart failure, number of prescriptions, prescribers, pharmacies, occupational therapy visits and speech pathology services. ◆

2 Risk of hospitalisation for pneumonia for those exposed to proton-pump inhibitors compared with those not exposed, by age and socioeconomic disadvantage

Index of disadvantage	Age group	Rate ratio* (95% CI)	*P*
Low	65–74 years	1.58 (1.21–2.08)	< 0.001
Low	75–84 years	1.18 (1.06–1.31)	0.002
Low	85 + years	1.05 (0.87–1.26)	0.60
Low–medium	65–74 years	1.12 (0.86–1.45)	0.40
Low–medium	75–84 years	1.10 (1.00–1.21)	0.06
Low–medium	85 + years	1.32 (1.08–1.61)	0.007
Medium–high	65–74 years	1.25 (0.91–1.72)	0.17
Medium–high	75–84 years	1.10 (0.99–1.21)	0.07
Medium–high	85 + years	1.35 (1.14–1.59)	< 0.001
High	65–74 years	1.49 (1.06–2.10)	0.02
High	75–84 years	1.22 (1.10–1.35)	< 0.001
High	85 + years	1.02 (0.87–1.19)	0.80

* Adjusted for sex, number of comorbidities, season, residential aged-care status, tiotropium as a proxy indicator of chronic obstructive pulmonary disease, renin–angiotensin system medicines concurrent with frusemide as a proxy indicator of heart failure, number of prescriptions, prescribers, pharmacies, occupational therapy visits and speech pathology services. ◆

season, residential aged-care status, use of tiotropium as a proxy indicator of chronic obstructive pulmonary disease, use of renin–angiotensin system medicines concurrent with frusemide as a proxy indicator of heart failure, number of prescriptions, number of prescribers, number of pharmacies, occupational therapy visits and speech pathology services. These last five categories were included as additional proxy measures of frailty and health status, and updated annually. Our data tables were constructed as day-by-day events, enabling covariates to be adjusted on the date at which they were first detected. Socioeconomic index scores were categorised as low at 964.1 or below, low–medium from 964.2–1001.1, medium–high from 1001.2–1057.5, and high at 1057.6 or above. All analyses were performed using SAS, version 9.12 (SAS Institute, Cary, NC, USA).

RESULTS

The final cohort consisted of 185 533 veterans, of whom 58% were men. Their mean age was 79.4 years (SD, 5.2 years). In the year before the study, the median number of prescriptions for all medicines dispensed per year was 36. The median number of prescribers was three and the median number of pharmacies was two. At study entry 6.8% of veterans were resident in aged care.

Unadjusted risk estimates were significant for all endpoints. After adjustment, there was a small, significant increased risk of hospitalisation for pneumonia and antibiotic use among those exposed to PPIs. No increased risk was observed for bacterial pneumonia (Box 1).

Subgroup analysis by age and index of socioeconomic disadvantage found the youngest cohort, aged 65–74 years, with either a low or a high index of disadvantage score had the highest risk estimates for hospitalisation for pneumonia for those exposed to PPIs (Box 2).

DISCUSSION

Our cohort study confirms the increased risk seen in previous case–control studies of both antibiotic use and hospitalisation for pneumonia associated with use of PPIs. The overall increased rate ratio (RR) observed in our study (RR, 1.16; 95% CI, 1.11–1.22) for pneumonia is in keeping with findings observed in the Dutch population (RR, 1.9; 95% CI, 1.4–2.6)[3] and the Danish population (RR, 1.5; 95% CI, 1.3–1.7).[4] There is some evidence that the increased risk of pneumonia is highest within the first 7 days of therapy (odds ratio [OR], 5.0; 95% CI, 2.1–11.7), with risk still present but diminishing over time (OR, 1.3; 95% CI, 1.2–1.4).[4] Our study, which included ongoing exposure and repeat events, found risk levels more similar to those reported among continuous users. Only one other study assessed use of antibiotics, among a sample of 405 patients, based on patient self-report, and found a fourfold increase in risk.[2] We also found increased risk in our much larger study, although the risk estimate was more conservative. When analysed by age and index of socioeconomic disadvantage, we found the highest risk estimates among veterans aged 65–74 years who had either high or low disadvantage scores. The only other study to report risk by age group also reported higher risk estimates in the younger age groups.[4]

We included bacterial pneumonia as a secondary endpoint, because relying on administrative data assumes the diagnoses coded are correct whereas some could be misclassified, and bacterial pneumonia is potentially a more robust indicator of pneumonia cases. Unlike previously published results,[4] we did not find a significant association with this endpoint. However, only a small number of cases were coded as bacterial pneumonia; most were coded as pneumonia unspecified. Only 5.2% of people presenting to Australian general practice with pneumonia are referred to hospital,[11] which suggests our study may have under-estimated the incidence of community-acquired pneumonia.

While the overall increased risk of pneumonia and hospitalisation with the use of PPIs was small, the prevalent use of PPIs means that

many people are potentially affected. In 2005, about one million Australians were dispensed PPIs;[12] based on the incidence estimates from our study, this suggests a potential 300 000 extra antibiotic prescriptions and 4000 extra hospitalisations for pneumonia annually associated with PPI use. The estimated 30-day fatality rate among older people admitted to hospital with community-acquired pneumonia in Australia is 18%.[13]

Our study relied on administrative claims data, so we were unable to adjust for confounders such as obesity, smoking and alcohol use. However, previous studies have shown that the odds ratio did not change after adjustment for these factors.[2,4] Unmeasured confounders may have influenced the effect we observed, but one previous nested case–control study compared previous users of acid-suppressive medicines with current users to minimise the likelihood that the result was confounded, and found a level of risk[3] similar to that in our study.

In the absence of dosage information, we used 36 days as the exposure period. PPIs are supplied under the Pharmaceutical Benefits Scheme in packs to last 30 days or less. For regular users of PPIs, the exposure times are reasonable allowing for a small number of omitted doses. Veterans who used the medicines intermittently may have been misclassified, as may those who did not take the medicines. However, on average, veterans are dispensed 9.3 prescriptions per year for PPIs, suggesting that most use is continuous.

Current guidelines for PPI use recommend step-down or intermittent therapy where maintenance therapy is required.[14] Our findings in this study are only observational, but they do suggest that a more cautious approach to PPI therapy that adopts the lowest dose wherever possible may be in the best interests of patients.

ACKNOWLEDGEMENTS

This research was funded by the Australian Government Department of Veterans' Affairs as part of the delivery of the Veterans' Medicines Advice and Therapeutics Education Services (Veterans' MATES) project.

COMPETING INTERESTS

None identified.

AUTHOR DETAILS

Elizabeth E Roughead, BPharm, MAppSci, PhD, Associate Professor[1]
Emmae N Ramsay, BSc, GradDipApplStats, Statistician[2]
Nicole L Pratt, BSc(Hons), Statistician[2]
Philip Ryan, MB BS, Director[2]
Andrew L Gilbert, PhD, Professor[3]

1 School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA.
2 Data Management and Analysis Centre, Discipline of Public Health, University of Adelaide, Adelaide, SA.
3 Quality Use of Medicines and Pharmacy Research Centre, Sansom Institute, University of South Australia, Adelaide, SA.

Correspondence:
Libby.Roughead@unisa.edu.au

REFERENCES

1 Intercontinental Marketing Services. World Markets. New products and markets fuel growth in 2005. http://www.imshealth.no/web/content/0,3148,64576068_63872702_70260998_77974518,00.html (accessed Dec 2008).
2 Laheij RJ, Van Ijzendoorn MC, Janssen MJ, Jansen JB. Gastric acid-suppressive therapy and community-acquired respiratory infections. *Aliment Pharmacol Ther* 2003; 18: 847-851.
3 Laheij RJ, Sturkenboom MC, Hassing RJ, et al. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA* 2004; 292: 1955-1960.
4 Gulmez SE, Holm A, Frederiksen H, et al. Use of proton-pump inhibitors and the risk of community-acquired pneumonia: a population-based case-control study. *Arch Intern Med* 2007; 167: 950-955.
5 Canani RB, Cirillo P, Roggero P, et al. Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. *Pediatrics* 2006; 117: e817-e820.
6 World Health Organization Collaborating Centre for Drug Statistics Methodology. Anatomical therapeutic chemical code classification index with defined daily doses. http://www.whocc.no/atcddd/ (accessed Aug 2008).
7 Australian Government Department of Health and Ageing. Schedule of pharmaceutical benefits. PBS for health professionals. http://www.pbs.gov.au/html/healthpro/home (accessed Aug 2008).
8 World Health Organization. International statistical classification of diseases and related health problems. 10th revision. Geneva: WHO, 2002.
9 Australian Bureau of Statistics. Information paper: census of population and housing — socio-economic indexes for areas, Australia, 2001. Canberra: ABS, 2003. (ABS Cat No. 2039.0.) http://www.abs.gov.au/ausstats/abs@.nsf/allprimarymainfeatures/09D68973F50B8258CA2573F0000DA181?opendocument (accessed Dec 2008).
10 Sloan KL, Sales AE, Liu CF, et al. Construction and characteristics of the RxRisk-V: a VA-adapted pharmacy-based case-mix instrument. *Med Care* 2003; 41: 761-774.
11 Britt H, Miller GC, Charles J, et al. General practice activity in Australia 2006–07. Canberra: Australian Institute of Health and Welfare, 2008. http://www.aihw.gov.au/publications/index.cfm/title/10574 (accessed Dec 2008).
12 Australian Government Department of Health and Ageing. Australian statistics on medicines 2004-05. Canberra: 2007. http://www.health.gov.au/internet/main/publishing.nsf/Content/pbs-pubs-asm2004-05 (accessed Dec 2008).
13 Skull SA, Andrews RM, Byrnes GB, et al. Hospitalized community-acquired pneumonia in the elderly: an Australian case-cohort study. *Epidemiol Infect* 2008; Jun 18: 1-9. [Epub ahead of print].
14 Therapeutic Guidelines Ltd. eTG complete. Melbourne: Therapeutic Guidelines, 2008. http://www.tg.org.au/index.php?sectionid=71 (accessed Dec 2008).

(Received 29 Apr 2008, accepted 11 Sep 2008) ❑