Meta-analysis: proton pump inhibitor use and the risk of community-acquired pneumonia

Johnstone J, Nerenberg K, Loeb M

CRD summary
The authors concluded that differences between included studies precluded the interpretation of the statistical significance of the association between proton pump inhibitor use and the risk of community-acquired pneumonia. The authors’ cautious conclusions reflect evidence from potentially biased observational studies.

Authors' objectives
To evaluate the association between the use of proton pump inhibitors and community-acquired pneumonia in adults.

Searching
MEDLINE, EMBASE and CINAHL were searched from inception to January 2010 for studies published after 1988 (the year proton pump inhibitors were introduced). Search terms were reported. Reference lists of articles were screened. Reports were traced using the 'related articles' function in PubMed. An expert in the field was contacted.

Study selection
Observational studies with a control group (cohort, case-control or cross-sectional studies) were eligible if they assessed the association between the use of any regimen of out-patient proton pump inhibitors in adults (aged 18 years or over) and the first episode of community-acquired pneumonia after cohort enrolment. Control groups had to be of participants who were either not on gastric acid suppression therapy or who were using non-proton pump inhibitor acid suppression therapy. Studies were excluded if they only included immunocompromised patients, used proton pump inhibitor therapy for Helicobacter pylori or were of patients at increased risk of aspiration pneumonitis.

The primary outcome was the risk of community-acquired pneumonia.

All of the included studies were large population-based case-control studies. Most studies were conducted in Europe. Most participants were aged 60 years or over; the percentage of smokers ranged from 15 to 38% (where reported); patients with chronic obstructive pulmonary disease ranged from 6 to 38%; patients with previous stroke ranged from 5 to 7% (where reported).

Two reviewers independently selected studies and resolved disagreements by consensus. If required, authors were contacted for clarification of eligibility criteria.

Assessment of study quality
No formal validity assessment was conducted, but several potential sources of bias were discussed.

Data extraction
Two reviewers independently extracted published odds ratios (ORs) with 95% confidence intervals (CIs).

Methods of synthesis
Pooled log transformed odds ratios and 95% confidence intervals were calculated using an inverse variance random-effects model. Heterogeneity was assessed using the $X^2$ and $I^2$ statistics, with significance indicated when $p<0.10$ or $I^2>50%$.

The influence of the following three potential causes of heterogeneity was examined using subgroup analyses and tests of interaction: severity of pneumonia; duration of proton pump inhibitor therapy; and proton pump inhibitor dose. These factors were determined a priori.

Two a priori sensitivity analysis were performed by excluding studies that defined pneumonia using only database coding and by excluding studies that did not adequately adjust for potential confounders (age, gender, smoking status,
chronic obstructive pulmonary disease, previous stroke, functional status and gastro-oesophageal reflux disease). Post hoc sensitivity analysis was conducted by examining the influence of each of two studies with small degree of patient overlap.

Funnel plots were to be used to assess publication bias if more than 10 studies were included in the main analysis.

**Results of the review**

Six studies with a control group were included (n=approximately 972,827 patients). There was some overlap in patients between two studies.

Proton pump inhibitor use was associated with a statistically significant increase in the risk of community-acquired pneumonia compared with non-proton pump inhibitors use (OR 1.36, 95% CI 1.12 to 1.65). Significant heterogeneity was found ($I^2=92\%$, $p<0.001$).

A significant interaction was only found for duration of proton pump inhibitor use ($p<0.005$). A short duration of proton pump inhibitor use was associated with an increased risk of community-acquired pneumonia (OR 1.92, 95% CI 1.40 to 2.63; $I^2=75\%$; five studies), but chronic use was not (five studies; $I^2=91\%$); heterogeneity remained significant.

Significant heterogeneity remained in the analysis restricted to studies with community-acquired pneumonia plus isolation of a respiratory pathogen. Results were similar and heterogeneity remained after excluding in turn each of the two studies with patient overlap.

**Authors' conclusions**

Heterogeneity precluded interpretation of the summary estimate of the association between proton pump inhibitor use and the risk of community-acquired pneumonia. Duration of proton pump inhibitor use may influence the risk of community-acquired pneumonia and this should be examined in future studies.

**CRD commentary**

The review question was clearly stated. Inclusion criteria were appropriately defined. Several relevant sources were searched, but no attempts to minimise publication or language bias were reported. Methods were used to minimise reviewer errors and bias in the extraction of data.

Although study quality was not formally assessed, potential sources of bias were discussed including lack of adjustment for confounders and measurement bias. Data were pooled using meta-analysis and heterogeneity was assessed. Forest plots were presented. Various a priori and post hoc analyses were conducted to examine potential sources of heterogeneity.

The authors’ cautions conclusions reflected evidence from potentially biased observations studies.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that future randomised controlled trials of proton pump inhibitors should evaluate the risk of community-acquired pneumonia as an adverse event. In the interim, observational studies should be undertaken to further examine the association between community-acquired pneumonia and new use of proton pump inhibitors.

**Funding**

McMaster University, Bayer Healthcare Research Fellowship; Canadian Institute of Health Research.

**Bibliographic details**

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.