Important New Evidence Service

In Partnership with The Centre for Medicines Optimisation at Keele University

ScriptSwitch™ Rapid Update 1 – January 2017

Gastrointestinal disorders: proton pump inhibitors and community acquired pneumonia

A large observational study has found that although evidence of an increased risk of community acquired pneumonia among proton pump inhibitor (PPI) users exists, this association may be due entirely to confounding factors present before PPI use, rather than PPI use itself. Whilst this study may provide some reassurance for people who require PPIs, given the concerns that their use is associated with a number of other adverse outcomes (e.g. hip fracture, *Clostridium difficile* infection, hypomagnesemia, kidney disease), they should be prescribed only if clearly indicated and for the shortest possible time.

Reference: Othman F, Crooks CJ, Card TR. Community acquired pneumonia incidence before and after proton pump inhibitor prescription: population based study. BMJ 2016;355:i5813

What do we know already?

- PPIs are commonly used in the management of dyspepsia and gastrooesophageal reflux disease (GORD) and for the prevention and treatment of NSAID-associated ulcers.
- NICE guidance on GORD and dyspepsia in adults (CG184, 2014) and children (NG1, 2015) provides advice on the use of PPIs in gastrointestinal (GI) disorders. NICE also recommend PPIs for people using oral NSAIDs for rheumatoid arthritis (CG79, 2009) or osteoarthritis (CG177, 2014).
- Whilst PPIs are generally well-tolerated, there is evidence, mostly from observational studies, of an association with a number of potentially serious adverse effects including osteoporotic fracture, *C.difficile* infections, hypomagnesemia, acute interstitial nephritis and acute kidney injury.[1]
- There has also been concern that PPIs may increase in the risk of pneumonia, possibly due to a reduction in the acidity of the stomach leading to bacterial overgrowth of the stomach and oesophagus, increasing the risk of bacterial aspiration. Although several observational studies have examined the association between PPI treatment and community acquired pneumonia, results have been inconsistent and the studies have been criticised for a lack of control for unmeasured confounding.[2]

What does this evidence add?

- This study used three complementary analyses to examine the association between PPI use and community acquired pneumonia. A multivariable COX regression analysis indicated that the risk for community acquired pneumonia was higher among PPI users than non-users (adjusted hazard ratio [HR] 1.67). However a self-controlled case series analysis found that the incidence rate ratio of pneumonia was higher in the 30 days *before* PPI prescription than in the 30 days *after* prescription (1.92 *vs.* 1.19). In another analysis, which adjusted for patients' underlying pneumonia risk and changes in pneumonia incidence over time, the relative risk for pneumonia decreased in the year after starting PPIs.
- The authors of the study concluded that while a crude association existed between PPI prescriptions and an increased rate of community acquired pneumonia, the link could be explained by an underlying increased risk of pneumonia in patients preceding a PPI prescription. The confounding factors present before PPI use (e.g. patient traits and comorbidities), rather than PPI use itself, were the main contributors to the increased rate of pneumonia observed among PPI users.
- An accompanying editorial noted that many previous studies had reported increases in risk of pneumonia after a relatively short period of exposure and concluded that "It is not biologically plausible for PPIs to increase the risk of community acquired pneumonia within such a short timeframe, suggesting the presence of protopathic bias or reverse causality (that is, PPIs were prescribed to treat the early symptoms of pneumonia, such as chest pain, mistakenly attributed to reflux)."

Important New Evidence is produced by Optum as part of the ScriptSwitch Medicines Management Bulletin in partnership with The Centre for Medicines Optimisation at Keele University.The views expressed are Keele's and may not reflect local prescribing guidance. External hyperlinks are provided as a convenience to users but are out of Keele's and Optum's control and do not constitute an endorsement by Optum or Keele.

Study details

Participants:

- The study analysed data from the Clinical Practice Research Datalink (CPRD) (a large UK-based electronic database of primary care records) from January 1990 to August 2013. A total of 160,000 adults (mean age 56 years, 55% women) newly treated with a PPI were matched one to one (by age [within 5 years], sex and year of prescription) with an unexposed cohort who had never received a PPI prescription. Most patients used PPIs for a short period, with a median duration of 28 (interquartile range 28-76) days.
- Hospital Episode Statistic (HES)/Office for National Statistics (ONS) linked information was available for 257,886 patients within the study population.

Intervention and comparison:

- The association between community acquired pneumonia and PPI prescription was estimated using three methods:
  - a traditional cohort analyses - a multivariable COX model comparing risk in PPI exposed patients with controls, corrected for potential confounders (e.g. smoking status, Charlson comorbidity index score, number of GP visits in the previous year, systemic corticosteroid or opioid use, and immunosuppression).
  - a self-controlled case series analysis - a within subject approach that compared the rate of pneumonia before and after the start of PPI.
  - a prior event rate analysis – a before and after analysis that adjusted for differences in the underlying event rate between exposure groups to minimise time-fixed confounding.
- The authors used a "broad primary care" definition of community acquired pneumonia, including CPRD read codes for chest infection and lower respiratory tract infection, to ensure that all cases of pneumonia were captured. A narrow primary care definition eliminated codes not specific for pneumonia.

Outcomes and results:

- Compared with unexposed patients, those prescribed PPIs were more likely to have a history of smoking (42.9% *vs.* 33.7% of their matched controls); they also had a higher burden of comorbidity and were more likely to use corticosteroids or opioids.

COX Regression analysis

- The COX regression analysis found that patients exposed to PPIs had an increased risk of community acquired pneumonia compared with controls. After adjustment for confounders, the analysis found people exposed to a PPI had a 1.67 (95% confidence interval [CI], 1.55 to 1.79) higher risk of community acquired pneumonia (by the broad primary care definition) than controls.
- Hazard ratios for PPI-associated community acquired pneumonia were greater when pneumonia was defined more narrowly with adjusted hazard ratios of 3.73 (95% CI, 2.69 to 5.16) using narrow primary care definition and 3.55 (95% CI, 3.03 to 4.16) using definitions based on hospital and mortality records.

Self-controlled case series

- This analysis included 48,451 PPI exposed patients in CPRD with a record of at least one community acquired pneumonia (broad primary care definition) and 5582 patients with hospital episode statistics linked data who had a record of pneumonia related to hospital admission or death.
- The incidence rate ratio for community acquired pneumonia (broad definition) among PPI users was found to be higher in the 30 days *before* starting PPIs (incidence rate ratio 1.92, 95% CI 1.84 to 2.00) than in the 30 days *after* starting (1.19, 95% CI 1.14 to 1.25).
- As for the COX regression analysis, differences in ratios were higher if the more narrow definition of pneumonia.

Prior event ratio analysis

- This analysis found the incidence of community acquired pneumonia was higher in the year before than the year after PPI prescription, such that the analysis showed a reduced relative risk of pneumonia (broad definition) associated with PPI use (prior event rate ratio 0.91, 95% CI 0.83 to 0.99).
- The prior event rate ratio for pneumonia in the HES/ONS subset was 0.74 (95% CI 0.69 to 0.97).

Level of evidence: Level 2 (limited quality patient-oriented evidence) according to the SORT criteria.

Study funding: The lead study author received a scholarship award from King Saud bin Abdulaziz University for Health Sciences (KSAU-HS), Saudi Arabia. The funding source had no role in the design or conduct of the study.

Important New Evidence is produced by Optum as part of the ScriptSwitch Medicines Management Bulletin in partnership with The Centre for Medicines Optimisation at Keele University.The views expressed are Keele's and may not reflect local prescribing guidance. External hyperlinks are provided as a convenience to users but are out of Keele's and Optum's control and do not constitute an endorsement by Optum or Keele.