Use of proton pump inhibitors (PPIs) on discharge from hospital and 1-year mortality in older patients

An observational study notes that prescription of high-dose PPIs in older patients discharged from acute care hospitals may be associated with increased 1-year mortality.

Overview: Recent studies and case reports have raised potential safety concerns associated with the use of PPIs. The Medicines and Healthcare Products Regulatory Agency’s April 2012 Drug Safety Update reported cases of hypomagnesaemia associated with prolonged use of PPIs and that epidemiological studies suggested an association between long-term use and increased risk of bone fracture. Increased risk of Clostridium difficile infection has also been noted.

Current advice: NICE guidance on low back pain (which is currently being updated), osteoarthritis (also being updated) and rheumatoid arthritis advises that in these conditions oral non-steroidal anti-inflammatory drugs or COX-2 inhibitors should be co-prescribed with a PPI (only if aged over 45 years for low back pain) to reduce the risk of gastrointestinal side-effects.

NICE guidance on dyspepsia (which is currently being updated) recommends that patients presenting in primary care with dyspepsia for whom urgent referral for endoscopy is not indicated should initially have their medication reviewed and be offered lifestyle advice. If this is not successful, they should be offered either empirical full-dose PPI therapy for 1 month, or testing for Helicobacter pylori infection and eradication treatment. If the option tried is not successful, the alternative should be offered.

If patients still experience symptoms, NICE advises that low-dose treatment with a limited number of repeat prescriptions should be offered. The use of treatment on an as-required basis should be discussed with patients. Similarly, after initial treatment, patients with endoscopically-determined gastro-oesophageal reflux disease or peptic ulceration should continue on low-dose treatment, as required, only if necessary and with a limited number of repeat prescriptions. Patients should be reviewed at least annually.

New evidence: An observational study reported by Maggio et al. (2013) investigated the association between use of PPIs and mortality or the combined end point of death or rehospitalisation in patients aged 65 years or older discharged from acute care hospitals. The study used data from an Italian pharmacosurveillance study including 491 patients with a mean age of 80 years. The study compared outcomes for patients prescribed PPIs on discharge from hospital (n=174) with those for patients not prescribed PPIs (n=317).

The prescription of PPIs on discharge was associated with increased mortality at 1 year (18.4% versus 10.4%; adjusted hazard ratio [HR]=1.51, 95% confidence interval [CI] 1.03 to 2.77; p=0.03). After adjusting for confounding factors there was no such association for the combined end point of death or rehospitalisation (adjusted HR=1.49, 95% CI 0.98 to 2.17; p=0.11). Prescription of high-dose
PPIs at discharge was associated with an increased risk of 1-year mortality (adjusted HR=2.59, 95% CI 1.22 to 7.16; p=0.007), but low-dose PPIs were not (adjusted HR=1.34, 95% CI 0.73 to 2.69; p=0.77). High-dose PPIs were classed as daily doses of: omeprazole 40 mg, pantoprazole 40 mg, lansoprazole 30 mg, rabeprazole 20 mg and esomeprazole 40 mg. Low-dose PPIs were classed as daily doses of: omeprazole 10–20 mg, pantoprazole 10–20 mg, lansoprazole 15 mg, rabeprazole 10 mg and esomeprazole 20 mg.

Commentary: “It is a common perception that PPIs are relatively harmless drugs, with their use having increased over the last decade. Despite the NICE guideline on dyspepsia discouraging long-term use of PPIs, medication review of PPIs does not always happen as frequently or as widely as it should. This study shows that in addition to known risks associated with long-term use, such as increased susceptibility to community acquired pneumonia, *C difficile* diarrhea, malnutrition, bone fractures and electrolyte abnormalities, there may be an association between long-term PPI use and higher mortality in older patients. Furthermore, this risk appears to increase with higher doses.

“Observational studies such as this one can only suggest an association, not establish causation, and are prone to confounding. Unlike in the setting of an RCT, in ‘real life’, treatment plans are chosen, changed, or actively not chosen in the light of individual patients’ risk factors, preferences and tolerability or response to other drugs. Thus observed differences in outcomes may be due to differences among the patients, not only the different treatments.

“In this study, efforts were made to reduce confounding and to adjust for known risk factors. However, as acknowledged by the authors, cardiovascular disease, gastroesophageal reflux disease and peptic ulcers were more prevalent in the PPI group and confounding by indication is a concern. Residual confounding due to unmeasured factors may also have affected the results.

“The duration of exposure to PPIs before hospitalisation was not available and the authors were not able to investigate whether associations existed between the use of PPIs and specific causes of death. However, consistent with the NICE guideline on the management of dyspepsia in primary care, we should be vigilant in the review of long term PPI use, especially in older people, making sure that unnecessary prescriptions are avoided.” – Dr Vinod Kumar Gowda, Clinical Director and Consultant Physician, Honorary Lecturer, University of Liverpool and Department of Medicine for Older People, St Helens and Knowsley Teaching Hospitals NHS Trust

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