Gastric acid suppressants—too much of a good thing?

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Gastric acid suppressants, in the form of histamine-2 receptor antagonists (H2RAs) and subsequently proton pump inhibitors (PPIs), have transformed the management of dyspepsia, peptic ulceration and gastro-oesophageal reflux disease. PPIs are now among the most commonly prescribed medications worldwide. In the United Kingdom, PPIs accounted for 34 million prescriptions worth £192 million in the year to June 2009 [1], and $26.5 billion was spent globally on PPIs in 2008 [2]. A large number of patients—as many as 90% in one study [3]—are taking these drugs with no appropriate guideline-based indication. Whilst PPIs and H2RAs are considered by most prescribers to be both effective and safe, their side-effect profile may be less benign in older people than has been hitherto realised.

Several of the adverse effects of gastric acid suppressants that have been documented are pertinent to older people. Observational studies show an association between the use of gastric acid suppressants and community-acquired pneumonia (CAP). Several studies have shown that current PPI use, particularly if started recently, is associated with an increased risk of CAP [4, 5]. The studies did not consistently observe an association with H2RAs, perhaps because of their weaker acid suppressant activity. One study examining cardiothoracic surgery patients taking stress ulcer prophylaxis found pantoprazole, but not ranitidine, was associated with an increased risk of hospital-acquired pneumonia [6]. It has been suggested that losing the non-specific defence of a gastric pH below 4 results in more gut flora residing in the upper gastrointestinal (GI) tract [4], and the more powerful acid suppressant effects of PPIs would therefore be expected to be more strongly linked with pneumonia, as is observed.

There is also a significant body of observational evidence linking gastric acid suppression to enteric infection. A systematic review published in 2007 [7] reported an increased risk of *Salmonella* and *Campylobacter* infection in those using gastric acid suppressants (odds ratio, OR 2.55; 95% confidence interval, 95% CI 1.53–4.26). The association was greater with PPIs (OR 3.33, 95% CI 1.84–6.02) than H2RAs, but remained significant for H2RAs (OR 2.03, 95% CI 1.05–3.92). Gastric acid suppression is associated with colonisation of the normally sterile upper GI tract [8]; acid suppression may therefore remove an important physiological barrier, allowing orally ingested enteric pathogens to reach the gut.

Perhaps most importantly for older people, acid suppression may also be associated with an increased risk of *Clostridium difficile*-associated disease (CDAD). Although some studies did not find an association between PPIs and CDAD, a number of other studies have demonstrated that PPI use increases the risk of developing CDAD in both hospitalised and community-dwelling patients, with a meta-analysis [7] reporting a significant increase in risk (OR 1.96, 95% CI 1.28–3.00). A weaker association appears to exist for H2RA use [9]. Patients treated for CDAD are more likely to have a recurrence if they remain on PPI therapy [8].

There are other potentially adverse effects of gastric acid suppressants that are relevant to the health of older people. A number of case reports have suggested a relationship between PPIs and microscopic colitis, a condition now increasingly recognised as a cause of chronic watery diarrhoea in older people. Severe hypomagnesaemia resistant to magnesium replacement but resolving on withdrawal of PPI has been reported, especially in older people [10]. This can be partially corrected by high-dose oral magnesium supplement, suggesting that PPIs inhibit the active transport mechanism of intestinal magnesium absorption [10]. Low serum magnesium levels have been shown to be associated with adverse prognosis and increased mortality in various settings [11] and have been found to independently correlate with muscle performance in older people [12].

The change in gastric acidity with consequent changes in drug absorption has been blamed for malabsorption of nutrients including iron, vitamin B12 and many of the drug interactions with PPIs. Although this has not been of major clinical concern, the recent controversy surrounding concomitant use of PPIs and clopidogrel serves as a reminder that this class of drugs is not without the risk of interactions [13]. Finally, some recent studies have suggested an association between PPI use and increased risk of osteoporotic fracture [14], although this association does not appear to be consistent across all populations.

What should we do about these observations? There is no doubt that gastric acid suppressants are important drugs with a crucial role in the management of a number of GI diseases, and care is needed to ensure that patients taking these agents for good indications do not have their prescriptions stopped. However, there is good evidence that they are frequently being prescribed for non-specific and inappropriate reasons, and that a large number of patients are taking these agents for much longer than necessary [15]. It is unlikely that large randomised controlled trials in older people will be performed to give definitive evidence on the risk-benefit ratio in older people taking these agents, but it would seem sensible to redouble our efforts to stop these agents in patients with previous dyspepsia but no endoscopic disease or gastric irritant use. By reducing the dose gradually over a period of a few weeks any impact of rebound acid secretion, and hence symptoms, should be minimised. Not only would this reduce the burden of medication and potentially protect against major infective illnesses, it would also free up significant amounts of money in these straitened times to be reinvested in health interventions of proven benefit to older people.

Key points

- Considerable resources are spent on inappropriately prescribed gastric acid suppressants.
- PPIs are associated with an increased risk of CAP.
- Gastric acid suppression is associated with an increased risk of enteric infection.
- PPIs are associated with a variety of other forms of ill health in older people.

Conflicts of interest

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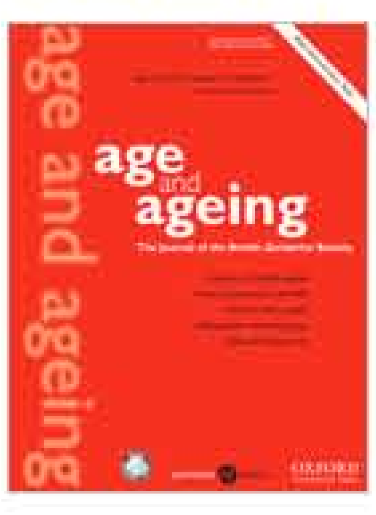

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