

# Risks of proton-pump inhibitors: what every doctor should know

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*No drug is completely safe and, while the risks seem small, some side effects can be serious*

When I went to medical school, the mantra “know thy drugs” was pounded into me repeatedly, and it has served me well. Among the most commonly prescribed drugs in Australia are the proton-pump inhibitors (PPIs). In 2005, one million Australians were dispensed drugs in this class.<sup>1</sup> There is no doubt that PPIs are safe relative to most other medications we prescribe, but suppressing gastric acid is not physiological.<sup>2</sup>

A low level of gastric acid promotes the growth of swallowed and enteric flora in the proximal gut, and these bacteria may be aspirated during episodes of physiological reflux. In this issue of the Journal, Roughead and colleagues assess the risk of pneumonia in Australian veterans taking PPIs (*page 114*); they identified a 16% increase in risk, equating to four extra hospitalisations for pneumonia each year for every 1000 people prescribed a PPI.<sup>1</sup> A study from Denmark found current use of PPIs was associated with a 1.5-fold (or 50%) increase in the risk of community-acquired pneumonia (95% CI, 1.3–1.7); the attributable proportion (ie, the fraction of pneumonia potentially caused by PPIs) was calculated to be 4%.<sup>3</sup> Similarly, a Netherlands study reported an adjusted relative risk for pneumonia among those using PPIs versus those who stopped using the drugs of 1.89 (95% CI, 1.36–2.62).<sup>4</sup> There is, therefore, a small increased risk of pneumonia, and this may be further increased in those who have recently begun taking PPIs. However, no preventive strategies are available to reduce this risk, and a causal association has not been established. Indeed, the increase could still be caused by unidentified confounders. For example, many patients in these studies had multiple comorbid conditions that might have given rise to an increased risk of pneumonia in the first place, such as alcoholism, previous stroke, or immune compromise secondary to chronic disease.<sup>3,4</sup>

A case-control study reported a significantly increased risk of *Clostridium difficile* infection in those who were exposed to PPIs in the 90 days before the infection, with an odds ratio (OR) of 3.5 (95% CI, 2.3–5.2).<sup>5</sup> As expected, previous exposure to antibiotics was also a significant risk factor for *C. difficile* infection in this study. An association with H<sub>2</sub>-receptor antagonists, as well as non-steroidal anti-inflammatory drugs (but not aspirin), was also reported.<sup>5</sup> An increased risk of other enteric infections has similarly been observed with PPI use (OR, 2.55; 95% CI, 1.53–4.26), although combining data in this meta-analysis was problematic because of significant study heterogeneity.<sup>6</sup> Whether other comorbid conditions in patients taking these drugs account for the association remains to be clarified, and any causal link is still speculative.

An acid environment is needed for insoluble calcium absorption, but the effects of PPI on dietary calcium absorption are uncertain. Increasing dietary calcium intake and taking calcium citrate as a supplement (which does not require gastric acid for absorption) is not established practice for patients who are prescribed acid-suppressing medications. A large retrospective study from the United Kingdom General Practice Research Database suggested that there was an increased risk of hip fracture in

patients taking PPIs, with an adjusted odds ratio of 1.44 (95% CI, 1.30–1.59).<sup>7</sup> Importantly, the calculated excess risk was small (about 1263 patients over the age of 50 would need to be treated with PPIs for a year to identify one excess hip fracture). A weaker effect was seen with H<sub>2</sub>-receptor antagonists. A recent Canadian case-control study in an administrative claims database examined longer-term PPI use and osteoporosis-related fractures; exposure of 7 years or more was modestly associated with an increased fracture risk (OR, 1.92; 95% CI, 1.16–3.18).<sup>8</sup> A causal association has not been established, but it may be worth considering increasing calcium intake for prevention and assessing bone mineral density in those requiring a daily PPI for more than 5 years.<sup>9</sup> Carpopedal spasm secondary to low serum magnesium and calcium levels that reversed with withdrawal of PPI therapy in two patients has also been reported.<sup>10</sup>

Iron absorption does not appear to be affected by PPI use, but long-term acid suppression has been linked to malabsorption of vitamin B<sub>12</sub>, especially in older people.<sup>11</sup> Therefore, it may be reasonable to assess vitamin B<sub>12</sub> levels annually in older patients requiring maintenance PPI therapy, but this is not routine practice, as the cost versus the benefit is unknown.

Patients infected with *Helicobacter pylori* and who are taking long-term PPI therapy are at increased risk of developing gastric atrophy, but the exact clinical significance remains uncertain.<sup>12,13</sup> Gastrin release increases with PPI therapy because of acid suppression, but there is no evidence this leads to neoplastic changes in the stomach. One study reported that 30% of patients taking omeprazole developed gastric atrophy, although this appeared to occur primarily in those concurrently infected with *H. pylori*.<sup>13</sup> However, the development of gastric body intestinal metaplasia is rare, and there is no definite evidence that long-term maintenance PPI therapy in the setting of *H. pylori* induces dysplasia or gastric cancer. Despite this, some authorities do recommend screening for *H. pylori* infection if long-term PPI use is contemplated, and offering eradication therapy to those infected, and this is my practice too.<sup>14</sup> There appears to be no increased risk of colon cancer in PPI users, which some have speculated could occur secondarily to hypergastrinaemia.<sup>15</sup>

Finally, an increasing number of cases of acute interstitial nephritis are being reported in association with PPI therapy, and this appears to be an idiosyncratic class effect; sadly, not all patients recover kidney function when they stop taking the drug.<sup>16</sup>

The bottom line is that no drug is completely safe, and this applies to acid suppression therapy. Fortunately, the risks, if causal, seem small, although preventive strategies are largely unavailable and identifying those at particularly high risk of serious side effects (eg, based on pharmacogenomics to individualise therapy) is not yet an established strategy. However, it is prudent and best practice to warn patients about the potential serious (albeit rare) side effects of PPIs, to prescribe the lowest possible dose of PPI (when indicated) for as short a time as possible, and to consider alternative management options if these are available.

### Competing interests

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