THE DEVELOPMENT AND SAFETY OF PROTON PUMP INHIBITORS

Since the discovery of omeprazole in 1979, dispensing of proton pump inhibitors (PPIs) in England has increased more than 100-fold, and several products are now available without prescription. Although PPIs are effective and generally well tolerated, observational studies suggest an association with several adverse effects. Further trials are needed to establish causal relationships.

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INFOGRAPHIC

1979 Omeprazole, a PPI that blocks gastric hydrogen potassium ATPase and inhibits gastric acid secretion, is discovered by Swedish pharmaceutical company Astra Hålsén. Human trials begin the following year.

1985 Long-term rat carcinogenicity studies show development of slow-growing gastric tumours and human studies are suspended. But it is found that the tumours are caused by total inhibition of acid secretion and not related to omeprazole’s safety, so human trials resume.


2003 Retrospective case-control study finds PPI use associated with increased risk of community-acquired pneumonia (adjusted relative risk 1.89, 95% CI 1.33–2.67) (JAMA 2003;289:971). Observational studies in 2007 and 2008 confirm this link, especially when PPIs have been recently started (OR 1.52, 95% CI 1.21–1.97) (Lancet Infect Dis 2007;7:550 and Ann Intern Med 2008;149:51).

2004 Population-based cohort study finds current use of PPIs associated with increased risk of community-acquired pneumonia (adjusted relative risk 1.89, 95% CI 1.33–2.67), (JAMA 2003;289:971). In 2009, a double-blind randomized controlled trial does not show any significant increase in risk of cardiovascular events (Lancet 2008;372:900). However, in 2012, the FDA advises that concomitant use of esomeprazole and omeprazole with clopidogrel should be avoided because it reduces the pharmacological activity of clopidogrel.

2005 Large observational study reports concomitant use of diaphragm and PPIs in people aged >65 years may increase risk of death from recurrent heart attack (adjusted OR 1.37, 95% CI 1.03–1.57) (CMAJ 2005;172:719). In 2010, a large French study confirms the link between PPIs and increased risk of heart attack, renal failure and dementia (CMAJ 2010;182:1853).

2006 Hypomagnesaemia reported as potential side effect of PPIs. The US Food and Drug Administration (FDA) warns in 2011 that long-term PPI use is linked with low magnesium and associated risk for cardiac arrhythmias, but little risk with short courses. In 2015, a systematic review of observational studies suggests PPI use for 1–2 years associated with increased risk of vitamin B12 deficiency (HR 1.15, 95% CI 1.12–1.28) (Hum Nutr 2015;69:286).

2006 Observational study reports that long-term, high-dose PPI use in people aged >65 years is associated with increased risk of hip fracture (adjusted OR 1.28, 95% CI 1.10–1.46) (Hum Nutr 2015;69:286).

2007 Further study in 2008 confirms link and finds short-term use does not increase risk (CMAJ 2008;179:1351). In 2010, the FDA warns of possible increased risk of hip, wrist and spine fractures with PPIs.

2008 Significant increase in risk of cardiovascular events is reported (OR 1.27, 95% CI 1.03–1.57) (CMAJ 2008;179:1351). Risk for cardiac arrest, heart failure and dementia is increased (CMAJ 2010;182:1853).

2009 US approval desesomeprazole (Pradaxal, later changed to Donavant; Takeda) dual-daylightrelease formulation that relieves GERD for up to 24 hours. Approved in EU countries 2007 but not yet launched in UK.

2009 Pantoprazole reclassified in Europe and can be sold in pharmacies for short-term relief of reflux. Launched as over-the-counter product in UK pharmacies 2010 (Pantocid Control GIK).

2010 Omeprazole most widely prescribed PPI in community. In 2015, and the second most commonly dispensed medicine overall (acarbose came first with 244M items).

2013 Observational study finds patients with renal disease nearly twice as likely to have been exposed to PPIs than those without it (OR 1.72, 95% CI 1.27–2.31) (JASN 2013;34:1569). Two studies in 2015 confirm the link (JASN 2015;36:738 and JASN, online, 14 April 2016).

2015 Omeprazole reclassified as pharmacy medicine in England for short-term treatment of reflux; never launched in UK. Becomes first PPI to be sold outside of pharmacies in UK (Nurse Control). PPI launches after further reclassification in 2015.