How the prescribing of omeprazole took off — and never looked back

In The Journal's latest article on landmark drugs, Jenny Bryan looks at how the use of omeprazole rose once safety concerns were resolved.

A product that spent its early life with cancer scare stories hanging around its neck, the first proton pump inhibitor (PPI), omeprazole, has not done badly. Licensed for the treatment of duodenal ulcer and other acid-related disorders, omeprazole hovered at or near the top of the world's best seller charts through much of the 1990s. It then took on a new lease of life in 2000 with the approval of its S-enatiomer, esomeprazole, which, last year, had the third highest global sales behind Lipitor and Plavix.

However, omeprazole's early history was a different story. Discovered in 1977 by Swedish pharmaceutical company Astra, omeprazole is a substituted benzimidazole that prevents release of hydrogen ions from the parietal cells of the stomach by blocking H⁺, K⁺-ATPase — the so-called proton pump. An early clinical study showed that a daily 30mg dose of omeprazole could all but eliminate gastric acid and provide 24-hour suppression far greater than that achievable with the H₂ antagonists cimetidine 1g daily or ranitidine 300mg daily. This was good news for ulcer sufferers and those with acid reflux disease but, almost immediately, there were concerns that such extreme acid suppression could have adverse effects on the stomach environment.

"Gastric acid is nature's disinfectant, so we were worried that, by virtually removing it, we could allow bacteria to grow which were capable of converting nitrates in the diet to nitrites and then to potentially cancer-causing N-nitroso compounds. Sure enough, when we did the experiments, that's exactly what we saw," recalls Roy Pounder, emeritus professor of medicine, London University.

Not good for rats

Despite the ominous data, omeprazole development continued — only to be dealt a further blow when long-term rat carcinogenicity studies showed development of gastric carcinoids — tumours arising from enterochromaffin-like (ECL) cells in the gastric mucosa.

"All human studies were immediately suspended while people discussed what was happening," explains Professor Pounder. "The rats had been given lifetime doses of omeprazole, but the tumours weren't just bumps, they were growths that occurred with all doses that were tested."

Prolonged inhibition of gastric acid is associated with increased production of gastrin, the stomach hormone that stimulates gastric acid production and also ECL cells. So, it was suggested that the hypergastrinaemia arising from omeprazole's powerful effects on acid production could be responsible for the appearance of the gastric carcinoids.

But carcinoids were not found in mice studies, and the rise in gastrin levels seen with omeprazole in humans was well below that associated with pernicious anaemia — a condition with a recognised link to gastric carcinoids and cancer in man.

Launched to a cautious world

Omeprazole was duly launched in the UK in 1989, but in a lower, 20mg daily dose than that identified in the original dose-finding study.

"The 20mg dose worked in two-thirds of people and, although it wasn't the best dose, it was a compromise because it was seen to be at the safest dose," explains Professor Pounder. However, nagging doubts about omeprazole’s safety and the natural conservatism of Britain's doctors meant that early take-up was variable. The situation was not helped when Glaxo researchers published data showing that omeprazole stimulated cell growth in superficial gastric epithelial cells, initiating a bitter long-running feud between Glaxo and Astra, which spilled over into other therapy areas where the two companies were rivals.

Meanwhile, adverse event reporting showed increased levels of headache, rash and diarrhoea — the latter linked to a possible effect of omeprazole's acid-suppressing effects on stomach bacteria.

To omeprazole's rescue came an apparent epidemic of reflux oesophagitis in the 1990s for which the drug had clear advantages over H₂ antagonist treatment with faster and higher healing rates.

As Professor Pounder explains, the increase in oesophagitis was related to a more sedentary lifestyle and rising obesity, with a falling prevalence of Helicobacter pylori. At the same time, doctors could see what they were treating more easily as endoscopy became readily available.

"Helicobacter eradication therapy soon got rid of the cause of most peptic ulcers, so there was a gradual migration away from treating ulcer disease and towards treating oesophagitis. When patients started omeprazole, they felt so much better that they didn't want to stop treatment," says Professor Pounder.

Once GPs were sufficiently reassured that PPI treatment was a safe and effective option for all their acid disease needs, omeprazole prescribing took off — and never looked back. Recognising the huge potential market once the safety concerns were resolved, other pharmaceutical companies launched a new generation of PPIs.

The next generation

First to market was lansoprazole in 1994 with the promise of greater binding at proton pump receptors than omeprazole and greater bioavailability, bringing with it greater efficacy at a lower price. Next came pantoprazole, which had lansoprazole's superior bioavailability,

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ity, but with lower potential for drug interactions than the other drugs. In 1998 came the slightly more potent rabeprazole and, finally, esomeprazole — launched by AstraZeneca — as omeprazole neared the end of its patent life.

Although omeprazole is a racemic mixture of the R- and S-isomers, esomeprazole is the S-isomer alone, and demonstrates greater bioavailability, higher plasma levels and greater acid suppression than the earlier drug. In clinical trials of reflux oesophagitis, esomeprazole 40mg has demonstrated superior healing rates to omeprazole 20mg at four and eight weeks, although some doubt whether esomeprazole would have proved superior at equivalent dosing.

**NICE steps in**

With PPIs consistently among the most commonly prescribed drugs in primary care, a number of efforts have been made to rein back their use. NICE published guidance on appropriate use of PPIs in 2000, which was updated in 2004. But studies in the UK, Europe, the US and Australia have shown widespread inappropriate use.

In the year to December 2008, PPI prescribing in England alone rose 12.2 per cent to over 32 million items. But, thanks to the fact that generic omeprazole and lansoprazole are responsible for nearly nine out of 10 prescriptions, the overall cost decreased by £25m in 2008.

With AstraZeneca’s patents on omeprazole expired, a new brand of the drug has taken on a new lease of life in the past five years as an over-the-counter product marketed ironically — considering its earlier spat with AstraZeneca — by GlaxoSmithKline.

The old concerns about cancer appear to have largely disappeared although, as Professor Pounder points out, the safety of long-term, continued acid suppression has yet to be proven in man, and the rise in gastrointestinal infections, such as **Clostridium difficile**, has been linked to excessive PPI use. Professor Pounder questions whether every patient needs such complete acid suppression and supports more individualised treatment with intermittent treatment for more patients: “It isn’t too late to educate new heartburn patients to try losing weight or to use an H₂ blocker to see if that works rather than going straight to PPI. There’s no doubt that PPIs have been a huge step forward for people with really bad oesophageal disease. But, for a lot of patients, we’re using a sledgehammer to crack a nut.”

**References**