Pantoprazole, Prout and the proton pump

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Pantoprazole is a proton pump inhibitor which has recently had its clinical license extended to include maintenance therapy for the treatment of reflux oesophagitis, Helicobacter pylori eradication and short-term intravenous administration. This article reviews the history of gastric acid secretion and examines the role of proton pump inhibitors, particularly pantoprazole, in the treatment of acid-related disorders.

Until the beginning of the 19th century, the nature and content of gastric juice was poorly understood. The history of acid secretion is described in detail in Modlin (1995) but is briefly summarized below.

John Hunter, considered by many to be the father of British surgery, stated in 1786:

> **'I should not be inclined to suppose that there is any acid in the gastric juice as a component or an essential part of it'.**

Therefore, even among the most eminent physicians of the day, there was confusion as to the nature of gastric juice and whether it contained acid. It was subsequently accepted that gastric juice does contain an acid although its identity remained a matter of debate. There were proponents for the acid being lactic, phosphoric or hydrochloric acid. This point was finally resolved by William Prout (*Figure 1*) who conclusively showed that gastric juice contains hydrochloric acid.

Figure 1. Portrait of William Prout (1785–1850) by HM Paget.

At the same time as the identity of the form of acid in gastric juice was being resolved, an important series of experiments were being performed by an American army officer called William Beaumont. In 1822, a civilian called Alexis St Martin was accidentally shot in the upper abdomen and was taken to Beaumont for medical care. St Martin survived his injury but was left with a chronic gastric fistula, giving Beaumont the opportunity to perform a series of elegant experiments examining the physiological control mechanisms underlying gastric acid secretion (*Figure 2*).

The identification of the histamine-2 (H_2) receptor in the early 1970s by James Black, who was a British pharmacologist, revolutionized the treatment of acid-related disorders. In place of prolonged bed rest with milk and fish diets, or surgical intervention, there was now available a simple, orally active therapy (cimetidine) which appeared to heal most of the acid-related disor-

Figure 2. Reproduction of William Beaumont and his patient, Alexis St Martin (c1822).

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ders. Even more powerful acid suppressant therapies are now available as a result of the realization of the critical role of the proton pump (also known as H+/K+ATPase) in hydrogen ion secretion, leading to the development of proton pump inhibitors (PPIs) in the early 1980s.

The last 100 years has provided a huge body of information regarding the control of acid secretion, the main components of which are shown in *Figure 3*. Many of the factors involved in the control of acid secretion act via receptors on the enterochromaffin-like cell to cause histamine release. These effects can be blocked by administration of H_2 receptor antagonists. However, several of these same factors can also directly influence the parietal cell via H_2 receptor-independent means. PPIs are able to prevent acid secretion induced by this mechanism as they inhibit the final common pathway, i.e. the proton pump.

MECHANISM OF ACTION OF PPIS

During activation, the H+/K+ATPase moves from the cytoplasm to the microvilli. Therefore, during acid secretion, the H+/K+ATPase is located in the micro-villi lining the secretory canuliculus of the parietal cell. All of the PPIs are targeted to the extracytoplasmic luminal domain of the proton pump and must therefore reach the acidic space of the canuliculus within the parietal cell. All of the PPIs are therefore administered in a pro-drug form which become activated ('trapped') in the acidic environment of the canuliculus, resulting in covalent binding of the inhibitor to the pump. This causes an irreversible inhibition of acid secretion and a new proton pump must be manufactured by the cell to re-establish acid secretion.

Four PPIs are currently licensed for use in the UK, namely omeprazole (Losec, Astra Pharmaceuticals Ltd, Kings Langley), lansoprazole (Zoton, Wyeth Laboratories, Maidenhead), pantoprazole (Protium, Knoll Limited, Nottingham) and rabeprazole (Pariet, Janssen-Cilag Ltd, High Wycombe). Omeprazole and lansoprazole have both been available for a wide range of clinical indications for several years, whereas pantoprazole has only recently had its license extended from short-term use to being available for maintenance therapy and *Helicobacter pylori* eradication, bringing it into line with omeprazole and lansoprazole. Rabeprazole, the most recent PPI to be launched, is currently available only for short-term therapy of peptic and oesophageal ulceration. Although it is likely to gain approval for extended usage and *H. pylori* eradication in the medium-term, it will not be discussed further in this article.

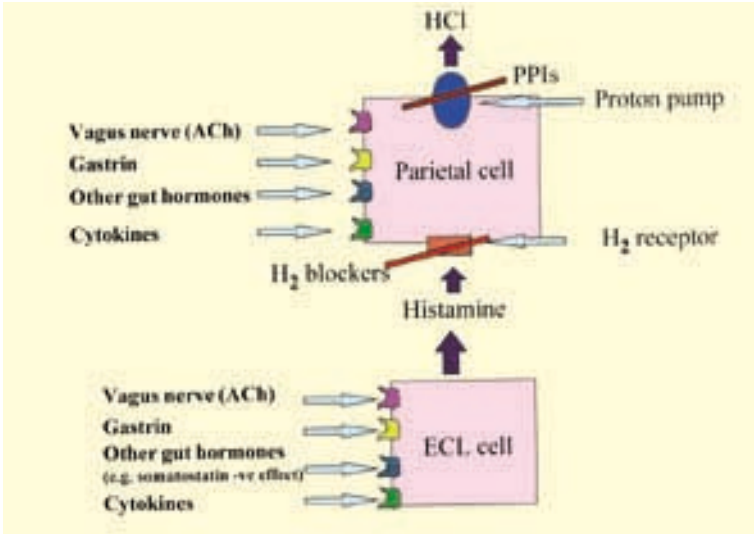

Figure 3. Control of gastric acid secretion. The parietal cell secretes hydrochloric acid (HCl) via the proton pump. Many factors influence acid secretion indirectly by causing the enterochromaffin-like cells (ECL) to release histamine which, acting via histamine-2 (H_2) receptors, stimulate the parietal cell to release acid. Factors acting via this mechanism can be inhibited by administration of H_2 receptor antagonists, such as cimetidine. However, several of these factors also directly act upon the parietal cell. H_2 receptor antagonists are relatively ineffective in influencing these pathways whereas proton pump inhibitors block the final common pathway, the proton pump itself. ACh = acetyl choline.

The chemical structures of lansoprazole, omeprazole and pantoprazole are shown in *Figure 4*. Pantoprazole is a weak base with a pKa of 3.9. This means that more than 50% of

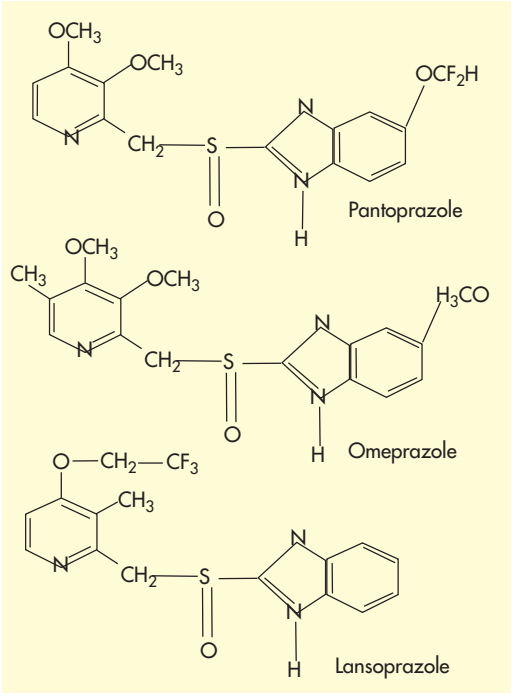

Figure 4. Structure of the proton pump inhibitors. Pantoprazole is a substituted benzimidazole derivative and has a similar overall structure to the other members of the proton pump inhibitor family.

the drug is protonated at a pH lower than 3.9, and thus virtually all of the drug is present in the protonated form in the highly acidic environment of the canaliculus. This allows it to achieve concentrations about 1 000 times higher than are found in the blood or in the cytoplasm of the parietal cell.

The protonated form of pantoprazole is a reactive species which binds to thiol groups of the proton pump, blocking the proton channel. Activation of pantoprazole at higher pH is extremely low, reducing the possibility of it reacting with thiol groups in other regions of the body, an important point when considering long-term therapy.

Although the mode of action of the different PPIs are the same, the binding of the drugs to thiol residues within the protein structure of the proton pump are not identical. Pantoprazole binds to -SH groups at residues 813 and 822 which are both integral parts of the proton channel of the pump (Shin et al, 1993), whereas omeprazole and lansoprazole also bind to thiol residues of the pump which are not important in blocking acid secretion (namely residues 892 and 321 respectively).

POTENTIAL FOR DRUG INTERACTIONS

Cytochrome p450 is the major drug metabolizing system in the liver. Co-administration of drugs which inhibit or upregulate the production of cytochrome p450 enzymes may therefore result in unwanted drug interactions as have been reported for imidazole derivatives such as cimetidine. All of the PPIs are metabolized by the same cytochrome p450 isoenzymes in the human liver, namely CYP2, C19 and A43.

Although structurally similar, the details of metabolism of the PPIs do vary; omeprazole and lansoprazole appear in the plasma as dealkylated or hydroxylated derivatives whereas pantoprazole is mainly conjugated in the cytosol, decreasing the potential for drug interactions. This difference in cytochrome p450 interaction and low risk of interactions with SH groups outside the parietal cell provide some of the data which have led the manufacturers to describe their product as 'a precise proton pump inhibitor' in their advertising literature.

TOLERABILITY

Pantoprazole has good patient tolerability with a low incidence of side-effects, diarrhoea (1.5%), headache (1.3%) and dizziness (0.7%) being the major symptoms. Similar side-effects have been reported with the other PPIs and it is probably worthwhile changing patients taking PPI who report symptoms (particularly diarrhoea) to an alternative PPI as the same symptom may not occur.

CLINICAL TRIALS OF PANTOPRAZOLE

Duodenal ulcer

Several randomized control trials have been performed examining the relative efficacy of pantoprazole *vs* ranitidine for the treatment of duodenal ulcer. Healing rates and epigastric pain relief were significantly better in a comparison of pantoprazole 40 mg *vs* ranitidine 300 mg (Schepp and Classen, 1995). Comparisons of pantoprazole (40 mg) with omeprazole (20 mg) show a similar efficacy in terms of ulcer pain and healing rates after 2 and 4 weeks. Cumulative ulcer healing rates were approximately 90% in both groups after 4 weeks therapy (Rehner et al, 1995).

Gastric ulcer

Cumulative ulcer healing rates of patients with benign gastric ulcers were significantly higher in patients taking pantoprazole (40 mg) compared with those taking ranitidine (300 mg) after 4 or 8 weeks, although epigastric pain relief was similar in both groups (Holtz et al, 1995). In a randomized controlled trial of pantoprazole (40 mg) *vs* omeprazole (20 mg) for benign gastric ulcer (Witzel et al, 1995), the cumulative healing rate was significantly greater in the pantoprazole treated group after 4 weeks (88 *vs* 77%). However, the cumulative healing rate after 8 weeks was similar in both groups (97 *vs* 96%).

Gastro-oesophageal reflux disease

PPIs are now widely used for the treatment of gastro-oesophageal reflux disease. Pantoprazole (40 mg once a day) appears to be superior to ranitidine (300 mg once a day) in its efficacy in healing oesophageal ulceration (Koop et al, 1995) and to be approximately equally as effective as omeprazole (20 mg once a day; Mossner et al, 1995).

ERADICATION OF *HELICOBACTER PYLORI*

There is now overwhelming evidence that patients with duodenal or gastric ulcers associated with colonization of *H. pylori* should receive a course of *H. pylori* eradication therapy. Present regimens, consisting of a PPI and two antibiotics for 7 days, achieve eradication rates of about 90% (Goddard and Logan, 1995).

Pantoprazole has recently obtained its license for eradication regimens and one of the

recommended regimens is pantoprazole 40 mg twice daily with clarithromycin 250 mg twice daily and metronidazole 400 mg twice daily where similar eradication rates have been reported. There are currently no data to suggest that pantoprazole is superior to the others in this regard. It is important to note, however, that whichever PPI is used, a major cause of failure to eradicate *H. pylori* is probably the patient failing to complete the course of treatment. The key element in successful eradication is emphasizing the importance of finishing the course of treatment and warning them of the possible side-effects.

INTRAVENOUS THERAPY

Pantoprazole has recently been launched for intravenous administration in patients unable to tolerate oral therapy, for conditions such as duodenal and gastric ulcer and reflux oesophagitis. The recommended dosage is the same as the oral dose (40 mg once per day by slow intravenous injection or infusion over 2–15 minutes). When administered by the intravenous route, acid suppression is rapid, occurring within 45 minutes (Simon et al, 1990). It is likely to be of use for patients in an intensive care setting or for short-term use by hospital inpatients unable to tolerate oral therapy for a short period.

CONCERNS OVER SAFETY

Although millions of scripts for PPIs have now been prescribed and there is no doubt as to their potent beneficial effects, there continues to be concern over the risks of their long-term use. Initial worries focused around the possible genotoxicity of one of the PPIs but these fears are probably unfounded. More recently, there have been some preliminary studies which suggest that patients on long-term PPIs who have *H. pylori* colonization may go on to develop atrophic gastritis, possibly increasing the risk of gastric carcinoma (Genta, 1998). Many gastroenterologists will therefore eradicate *H. pylori* in patients with oesophagitis, if found at the time of endoscopy, particualrly if long-term proton pump inhibitors are to be used, although the evidence that this is necessary is somewhat weak. Studies are presently underway to try and clarify this situation.

It has been suggested that all patients should have an endoscopy before being prescribed a PPI (Griffin and Raimes, 1998). The basis behind this advice is that treatment with PPIs might mask the symptoms of gastric cancer and partially heal the lesion, resulting in a delay to definitive treatment. Although this may be a council of perfection, the sheer number of patients who are having PPIs prescribed makes this virtually impossible within present clinical resources. It is also interesting to note that similar concerns were raised regarding the use of H_2 receptor blockers when they were first launched. It is probably more clinically important for general practitioners to take a full history from the patient and request an urgent endoscopy if sinister symptoms are detected (e.g. unexplained weight loss, iron deficiency anaemia, dysphagia).

PANTOPRAZOLE IN THE TREATMENT OF ACID-RELATED DISORDERS

The use of PPIs in clinical practice has continued to escalate and PPIs are now a major contributor to the total drug budget of the NHS. It is generally accepted that patients with *H. pylori*-related disease (peptic ulceration) should undergo a 1-week eradication course and that this is a cost-effective process to reduce peptic ulcer relapse.

The major use of PPIs, however, is probably for the treatment of long-term gastro-oesophageal reflux disease. As symptoms virtually always return on stopping therapy, it is probably appropriate to use a step-wise approach starting with lifestyle advice (lose weight, stop smoking) and treatment with H_2 receptor blockers before moving onto prescribing PPIs. In young patients (less than 50 years old), it is probably worthwhile considering referral for surgery if long-term PPIs are required and a good oesophageal surgeon is available locally.

When the decision to use PPIs has been reached, which one should the clinician use? This is a difficult area to provide definitive advice except where intravenous therapy is required when pantoprazole should be used (the only one to have a clinical license at the time of writing). If the patient is taking multiple medications, particularly drugs such as warfarin, panto-

KEY POINTS

- Pantoprazole is a potent proton pump inhibitor with high specificity and low risks of drug interactions.
- The standard dose is 40 mg once a day by the oral route (usually) or, for short periods, by the intravenous route (slow intravenous injection).
- Pantoprazole is more efficacious in healing duodenal, gastric and oesophageal ulceration than histamine-2 (H_2) receptor blockers and has a similar efficacy to omeprazole and lansoprazole.
- Proton pump inhibitors are expensive products and a step-wise approach to acid suppression is probably advisable for patients with oesophageal reflux disease.

prazole might have a slight advantage in its limited effect on the cytochrome p450 system (Duursema et al, 1995). In most patients, however, these are not major clinical concerns and there is now a large body of evidence showing that omeprazole and lansoprazole have a good safety profile. **HM**

Conflict of interest: Professor Playford has received hospitality from Astra Pharmaceuticals Ltd, Wyeth Laboratories, Knoll Ltd and Janssen-Cilag Ltd and fees for lectures from these companies. Dr Podas has received financial support to attend an overseas conference from Astra Pharmaceuticals and Wyeth Laboratories. Dr Modlin has received financial support from Byk Gulden.
Figure 2 *is reproduced from Modlin (1995) by kind permission.*

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