VOICE OF PRIMARY CARE GASTROENTEROLOGY

ISSUE 16. 2023 - NO 1

THE DIGEST

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The Primary Care Society for Gastroenterology
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How do you get your patients off PPIs – safely?

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Debbie Grayson is a pharmacist and expert on PPIs and their use and cessation. She explains how they work, the key problems in ceasing them, and strategies for successful weaning and cessation.

PPIs are the most widely prescribed drug class

In 2018, data from over 700 UK GP practices showed Proton Pump Inhibitor (PPI) prevalence among patients was 14.2%, equating to just over three million patients. In 2019, PPI prescribing was higher than any other drug class. These figures do not include the population regularly purchasing OTC PPIs without supervision. During the early pandemic, worldwide sales and demand for Gaviscon exceeded production capability and this may well have increased the demand for PPIs both on prescription and through self-medication.

NICE guidelines for the management of GERD is that a 4-8 week course of PPIs is recommended in the absence of a clear clinical need for maintenance therapy. Yet the 2019 data referred to above showed that 37.5% of patients using PPI medication had done so for more than a year.

After just three days of PPI use, the patient is at risk of Rebound Acid Hyper Secretion (RAHS), which may play a role in patients wrongly believing in a need for continued use. As medical professionals, we can better educate patients and manage their expectations. This is one of several important points in successful cessation.

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Common adverse effects of PPI medication [1,2]

Short-term adverse effects

IBS-like symptoms due to the effect of PPIs on digestion, constipation, diarrhoea, fatigue, cramps, headaches and more.

Long-term adverse effects

The reduction in the ability to digest and absorb nutrients can lead to many long-term health risks including increased incidence of osteoporosis, cardiovascular events, cancers and dementia.

A review of the natural process of hydrochloric acid production [3]

The cephalic phase of digestion is responsible for the start of the digestive process and the production of 20% of the required HCl. The anticipation of food – sight, smell and taste triggers – activates the hypothalamus to send messages to the medulla oblongata where the vagus nerve stimulates the parasympathetic nervous system in the stomach to trigger gastric secretions controlled by the parietal and G cells.

In the body of the stomach, the vagal nerves release acetylcholine (ACh), which stimulates the parietal cells to start hydrogen ion (H+) secretion. The ACh released from the vagal endings triggers histamine secretion from enterochromaffin-like (ECL) cells. Histamine released by these cells also stimulates H+ secretion from parietal cells.

In the antrum of the stomach, parasympathetic vagal neurons and other enteric nervous system neurons produce Gastrin Releasing Peptide (GRP), which stimulates antral G cells to produce and release gastrin. Gastrin stimulates gastric acid secretion by directly stimulating parietal cells as well as by promoting histamine secretion by ECL cells.

The gastric phase then continues the process, producing a further 50-60% of the total secretion and is a period in which swallowed food and semi-digested protein (peptides and amino acids) activate further gastric activity.

The presence of food stretches the stomach, activating reflexes in the parasympathetic and enteric nervous systems to also release ACh and stimulate the parietal cells.

The breakdown of dietary protein directly stimulates the G cells to secrete more gastrin in a positive feedback loop to accelerate protein digestion. Small peptides also act to buffer stomach acid to prevent the pH becoming excessively low.

Gastric secretions are stimulated and controlled by ACh, histamine and gastrin. All three of these stimulate parietal cells to secrete H+ into the stomach to combine with chloride ions (Cl-) to form hydrochloric acid. The chief cells secrete pepsinogen in response to gastrin and ACh. The latter also stimulates mucus secretion. When intragastric pH drops too low, D cells in the antrum release somatostatin to inhibit gastrin release from G cells, in turn reducing acid secretion.

How PPIs work in suppressing normal stomach acid production [4]

ACh binds to and activates G cells to release gastrin, which is then released into the blood and binds to CCK receptors to increase calcium to increase vesicular fusion. ECL cells, activated by gastrin, release histamine to bind to H2 receptors on the parietal cells and further increase fusion by the release of cAMP. This heightened vesicular fusion leads to increased surface area and disposition of the proton pump enzyme H+/K+ATPase, which releases H+ ions into the stomach to combine with Cl- ions to form HCl.

PPIs gain access to the enzyme when fusion has taken place and act to irreversibly bind to the enzyme, preventing the release of further H+ ions. PPIs generally have a 90-minute half-life and inhibit around 70% of the available enzymes that have been activated by food consumed 30 minutes after the drug has been taken. Failure to eat after dosing can result in reduced effectiveness of the PPI and result in higher doses being prescribed.

In any 24-hour period, 20% of pumps are destroyed and replaced. Morning-only dosing can mean that in the evening the newly made pumps can produce H+ ions and is the reason why some people get breakthrough symptoms in the evening. Taking a morning and evening dose 30 minutes before meals results in 80% inhibition of HCl production, not accounting for other factors affecting HCl output including stress etc.

In addition to reducing HCl secretion, PPIs are believed to increase the concentration of gastric-soluble mucus components and stimulate duodenal PGE2 synthesis. These effects are the rationale for their use alongside medications linked to gastric erosion.

PPIs and silent reflux or LaryngoPharyngeal Reflux (LPR) [5]

Silent reflux and LPR differ from GERD in that the contents of the stomach can travel beyond the oesophagus and into the pharynx, larynx and nasal passages. Common symptoms are globus sensation, nasal congestion, postnasal drainage and ear fullness.

When the neck of the stomach intrudes through the diaphragm, the intra-abdominal esophagus is effectively shortened, impacting esophageal motility and hindering the UES from opening properly. Patients commonly experience a non-productive cough and throat clearing but often experience no noticeable heartburn symptoms typical of GERD.

It is important to restore muscular competence around the hiatal canal to hold the esophagus taut and resolve the risk of silent reflux. A recent RCT study[5] has shown that PPIs are not more effective in treating silent reflux than placebos.

In the case of GERD, the importance of improving muscular competence around the hiatal canal is not primarily the mechanical effect of the shortening of the intra-abdominal oesophagus, but rather it is the importance of holding the neck of the stomach and the LES in the correct position beneath the diaphragm to prevent reflux occurring.

Surgery or neuromuscular training are proven methods of addressing this.

Rebound Acid Hyper Secretion (RAHS) is a problem when weaning [6]

RAHS is a common reason for failure in weaning and consequent resumption of PPI medication and reluctance to restart the cessation process.

After taking a PPI for just three days, this rebound effect is expected to occur; with long-term use this is a certainty.

When a patient takes a PPI, there is a huge reduction in gastric acidity. As a result, gastrin is produced in higher amounts in an attempt to counter the increase in pH - hypergastrinemia.

The increase in gastrin leads to increased activity of the gastrin receptor on ECL cells. Gastrin regulates the release of histamine from and the proliferation of these cells – a known risk factor for stomach and other cancers.

When PPI medication is ceased, the body makes new parietal cells that are now no longer destroyed and can respond to the increased chemical signals. The increased gastrin and histamine produced in response to the low acidity now stimulates these newly made proton pumps to release much more H+ ions and result in hypersecretion.

There is typically a 3-5 fold increase in gastrin levels with long-term use but it can be even higher in some patients.

It is often believed that gastrin levels should reduce to normal in as little as 5-7 days. However, some studies suggest that gastrin levels only do so after 10 weeks, while ECL cell and histamine levels may take as long as 20 weeks to return to normal. Until these levels normalise, rebound heartburn may continue. The length of time for rebound symptoms is therefore linked to these variations and it is difficult to predict how severely someone will suffer and for how long. Managing patients through this process is key to weaning success.

Muscle weakness around the hiatal canal

If the musculature around the hiatal canal is weak, reflux will continue with or without PPI medication. Surgical intervention is the traditional way in which these delinquent muscles are repositioned and rewrapped to restore a competent grip. Nowadays, neuromuscular training can be an easier alternative that can be introduced at an early stage.

Lifestyle complications [7,8]

In addition to muscle weakness, inappropriate relaxation of oesophageal muscles can occur with smoking, alcohol, caffeine and some foods, including chocolate, peppermint and tomatoes.

Preparing patients for PPI weaning

It is important to adequately prepare patients when attempting to successfully cease their PPI intake. This includes modifying diet and lifestyle, embedding good eating disciplines and instigating neuromuscular training as appropriate to the patient. Taking the time to explain why rebound is likely is also key to successful cessation.

Practical experience of successfully ending PPI medication

In my experience, using a range of techniques has supported the removal of PPIs in many patients whilst managing and minimising severe rebound. One such case is described here:

The patient was a successful business owner who worked long days and often grabbed food on the go whilst continuing to work on his computer. He had been diagnosed with silent reflux and later GERD, and had been taking Omeprazole 20mg twice per day for the past three years. While the medication had reduced his GERD symptoms, the silent reflux remained an issue and he also experienced a range of symptoms attributed to IBS-D which had coincided with the prescribing of the PPI.

The preparation phase is key in these cases and must be well established before total removal of the PPI is advised. As there were many factors at play here, a lot of dietary and lifestyle factors were addressed in advance of the weaning process:

- Use of the IQoro neuromuscular training device (www.iqoro.com) prior to each meal to strengthen the weakened muscles and then continued training to maintain the benefit.
- Stress management techniques were advised and discussed including breathing techniques and mindfulness – especially at mealtimes.
- Taking time to eat away from the desk and workplace distractions was also recommended.
- To improve the digestive function, the patient was encouraged to support the cephalic phase by taking time to anticipate eating instead of merely grabbing food on the go. This included consideration of the smell, taste and texture of the food.
- Taking time to eat slowly and chew thoroughly was also key as this enables better breakdown of food and can support the gastric emptying process, reducing the likelihood of stomach contents flowing backwards. Putting down the knife and fork between mouthfuls was a useful tactic here as this increased awareness of the time taken to chew each mouthful.
- Reducing coffee and alcohol intake was also encouraged to minimise relaxation of the oesophageal sphincters and this was adhered to with approximately 70% compliance.

Within three months, the patient was being compliant with the dietary and mealtime recommendations most days, with only an occasional slip dependent on work pressures. At this point, he experienced improvement in silent reflux and had no lingering symptoms of GERD.

After four months, the silent reflux symptoms had disappeared. At this point, the Omeprazole dose was reduced to 10mg twice per day. There was a minimal increase in reflux symptoms which was managed with Gaviscon as required and at bedtime.

This regime was continued for a further four weeks at which time the evening Omeprazole was discontinued and adherence to a 'no caffeine and alcohol' regime was being followed completely. To manage the potential rebound from removing the evening dose, the Gaviscon was taken routinely after the evening meal and at bedtime. Rebound symptoms were minimal at the end of these four weeks, with only the bedtime Gaviscon dose being taken to protect the oesophageal mucosa.

The final stage was to reduce the PPI to alternate day dosing for two weeks before stopping completely. Research shows that this reduces relapse rate. At this point, the Gaviscon dose was increased to being taken at the end of every meal and at bedtime to minimise oesophageal damage from RAHS which can be more severe at this juncture.

The rebound symptoms were managed well with the Gaviscon and reduced in severity over the ensuing six weeks. At this point, evening Gaviscon continued for a further two months to ensure that symptoms were completely managed and then discontinued. All lifestyle factors continue to be followed with some relaxation (occasional alcohol consumption) and the use of the IQoro continues on a twice-daily basis.

Conclusions

While PPIs have a clear therapeutic role in some patients, many could be managed much more conservatively with the measures described in the case study – reducing the PPI and using Gaviscon as needed to manage symptoms and protect the oesophageal mucosa.

Adequate education of the patient in lifestyle measures and the mechanism of RAHS, and how this can be managed, is key to successful and long-term withdrawal. Adequate preparation and prescribing of Gaviscon can reduce the risk of relapse. Neuromuscular training is crucial to strengthen the weakened muscles around the hiatal canal, without which herniation and reflux will reoccur.

A GP in primary care can easily and successfully adopt the strategies outlined above and expect the same results as have been reported. Patients should be unwilling, or unable, to continue with long-term PPI medication and willing to participate in the programme.

The GP may wish to enlist the support of other clinical colleagues – practice nurse, healthcare assistants etc – to help coach and support the patient.

I am happy to provide further support and training at https://practicewithconfidence.thinkific.com

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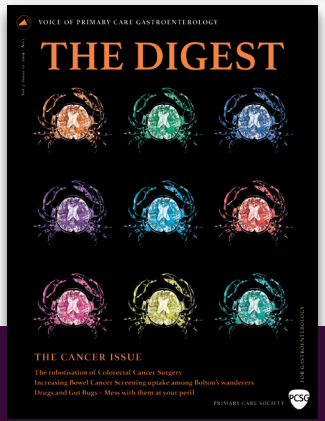

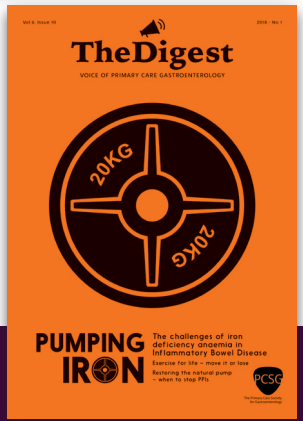

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