Gastro-oesophageal reflux disease and its management

Gastro-oesophageal reflux is a normal physiological phenomenon occurring during brief periods of gastro-oesophageal sphincter relaxation. However, when refluxed acid exceeds normal limits this can affect quality of life and expose sufferers to risks of complications. Gareth Nickless and Paula Morgan give an overview of the management of gastro-oesophageal reflux disease.

Identify knowledge gaps

1. What is gastro-oesophageal reflux disease (GORD)?
2. What role does Helicobacter pylori play in GORD?
3. What are the options for treating GORD?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society’s areas of competence for pharmacists are listed in “Plan and record”, (available at: www.uptodate.org.uk). This article relates to “common disease states and their drug therapies” (see appendix 4 of “Plan and record”).

GASTRO-OESOPHAGEAL reflux disease (GORD) is a term often used interchangeably with dyspepsia, which is one of its features. Dyspepsia (“bad digestion”) represents a complex of symptoms. There is no universally accepted definition but a working party in 1988 referred to any symptoms of the upper gastrointestinal tract that are present over at least four weeks, including upper abdominal pain, heartburn, acid reflux, nausea and vomiting. If this broad definition is used, dyspepsia occurs in 40 per cent of the population annually and is responsible for
Panel 1 describes the regulation of acid production in the stomach. When refluxed acid repeatedly exceeds normal limits it affects quality of life, causing dyspepsia, chest pain, belching, bloating and cough — symptoms of GORD. In addition to abnormal acid reflux, some patients with GORD also experience reflux of pepsin and bile. GORD affects 7 per cent of people on a daily basis and 30 per cent occasionally, with one in 10 people seeking medical help at some time in their lives. Prevalence increases with age and is slightly higher in females.

A variety of lifestyle factors have been implicated in GORD despite a lack of evidence. Reported factors and suggested mechanisms include:

- Caffeine, chocolate, alcohol, spicy food and cigarette smoking could decrease lower oesophageal sphincter tone
- Fatty foods could delay gastric emptying (seen in up to 40 per cent of patients with GORD)
- Over-eating, obesity, poor posture and wearing tight-fitting clothing could increase intra-abdominal pressure (This may help to explain why symptoms of GORD are commonly experienced during pregnancy.)

A variety of medicines have been implicated in GORD (and oesophagitis; see below). Non-steroidal anti-inflammatory drugs inhibit the production of prostaglandins that protect the gastric and oesophageal mucosa. Oral bisphosphonates are direct irritants of the oesophageal mucosa (although symptoms can be prevented in many cases by patients taking these medicines with a tumeful of water then remaining upright for at least 30 minutes). Nitrates, calcium channel blockers and theophyllines can also contribute to GORD by reducing lower oesophageal sphincter tone. Although avoiding medicines that can trigger or worsen GORD forms part of the management of strategy, this may not always be possible if a patient relies on such medicines to achieve good control of other conditions (eg, nitrates for angina).

Despite its well recognised role in the pathophysiology of peptic ulcer disease, there is no evidence that *Helicobacter pylori* infection contributes to GORD.

### Complications

Symptoms of GORD (and dyspepsia) are often recurrent and repeated exposure of the lower oesophagus to refluxed gastric contents can result in oesophageal mucosal damage. This can be identified in patients undergoing upper gastrointestinal endoscopy either as oesophagitis (which may progress to benign narrowing of the oesophagus), oesophageal ulceration or Barrett’s oesophagus. The severity of oesophagitis can be graded using the Los Angeles classification (see Panel 2, p36). Severe oesophagitis and oesophageal ulcers can result in acute or chronic bleeding and patients can become anaemic as a result.

Barrett’s oesophagus (also known as columnar-lined oesophagus) is a pre-malignant condition where any portion of the normal squamous lining of the oesophagus has been replaced with macroscopically visible metaplastic columnar epithelium. The condition is identified in 1.4 per cent of all endoscopies and is seen in about 12 per cent of patients with GORD symptoms who undergo upper gastrointestinal endoscopy and 36 per cent of those with endoscopic evidence of oesophagitis. Barrett’s oesophagus is more common in patients who have long-standing reflux symptoms and becomes prevalent in patients over the age of 40 years. The main concern with Barrett’s oesophagus is that the occurrence of
osophageal cancer (especially adenocarcinoma) is increased 10-fold compared with the general population. Adenocarcinoma of the oesophagus is believed to originate from columnar metaplasia so patients with Barrett’s oesophagus are enrolled on a surveillance endoscopy programme in order to detect adenocarcinoma at the earliest possible stage. The prevalence of oesophageal cancer is increasing and it has been suggested that this correlates with the increasing prevalence of GORD.

Investigation of symptoms

Symptoms of dyspepsia are a poor predictor of upper gastrointestinal disease and most patients can be managed without a formal diagnosis. In addition, symptom severity does not always correlate with mucosal damage and in over half of all patients undergoing upper gastrointestinal endoscopy for the investigation of reflux-like symptoms no damage is seen (such patients are described as having endoscopy-negative reflux disease).

Endoscopy will establish whether or not the patient has developed oesophagitis and exclude any differential diagnoses, such as gastric or duodenal ulceration. The procedure can be performed with or without sedation (patients who require sedation should be advised not to drive, drink alcohol, operate machinery or sign binding documents for 24 hours afterwards). Barium swallows are rarely used these days — they can be used to show a hiatus hernia (when part of the stomach radiates into the chest through a diaphragmatic defect, which can result in lower oesophageal sphincter weakness and increased reflux of gastric contents) but so can upper gastrointestinal endoscopy. Monitoring pH over 24 hours is an accurate procedure that can help to establish the severity of reflux and correlation with symptoms but this is not commonly used because it is cumbersome and invasive. However, the test may be useful for symptomatic patients with endoscopy-negative disease.

National Institute for Health and Clinical Excellence guidelines on the management of dyspepsia state that routine endoscopy is not necessary for all patients presenting with symptoms of GORD. However, people with signs of a significant upper gastrointestinal bleed (eg, vomiting blood) should undergo upper gastrointestinal endoscopy on the same day, and those (of any age) presenting with chronic gastrointestinal bleeding, progressive unintentional weight loss, progressive difficulty swallowing, persistent vomiting, iron deficiency anaemia or epigastric mass (“alarm” signs), or with a suspicious barium meal result, should be referred for urgent endoscopy (ie, within two weeks). Referral for endoscopy should be considered in those over 55 years of age with unexplained and persistent recent onset dyspepsia. It should also be considered in these patients if they have had a gastric ulcer, gastric surgery, pernicious anaemia, continued need for NSAID use or a family history of gastric cancer.

Management strategies

The management of GORD involves identification and removal of precipitating factors, lifestyle changes and drug therapy, with the overall aim being to reduce or prevent symptoms and achieve healing of any oesophagitis. A small number of patients may need surgery.

Lifestyle factors

Although, as already stated, there is no evidence from randomised controlled trials supporting the role of lifestyle factors in GORD, some patients report a reduction in symptoms when lifestyle changes are made. For example, patients who have previously identified specific precipitants of reflux symptoms (eg, caffeine and fatty or spicy foods) can be advised to try to eliminate these from their routine. Raising a bed head 10–20cm can prevent nocturnal symptoms. Lifestyle advice is safe and inexpensive and can promote patient participation, control and choice in the management of the disease. Patients are also likely to gain general benefits when adhering to lifestyle advice, which should include information relating to healthy eating, smoking cessation, weight loss and moderating alcohol intake (including avoiding binge drinking).

Pharmacological treatments

Pharmacological treatments include proton pump inhibitors, histamine (H2) receptor antagonists and antacids.

Proton pump inhibitors

Proton pump inhibitors (PPIs) inhibit the secretion of gastric acid by blocking K+/H+-ATPase pumps on the surface of parietal cells and have been found to be most effective in the treatment of GORD. There are currently five PPIs available in the UK: omeprazole,esomeprazole (the S-isomer of omeprazole), lansoprazole, pantoprazole and rabeprazole. PPIs improve gastro-oesophageal reflux symptoms in most cases and should be considered first-line treatment for patients with severe symptoms of GORD or where there is a proven or severe disease (ie, oesophagitis, oesophageal ulceration or Barrett’s oesophagus). Studies have shown PPIs to be more effective than H2 receptor antagonists and placebo at healing oesophagitis1 and in reducing symptoms in endoscopy negative reflux disease.
Evidence shows that there is no significant difference between “equivalent” doses of PPIs. Choice should be based primarily on cost and subsequent individual patient response. One meta-analysis identified a double-blind randomised controlled trial where esomeprazole 40mg was found to be superior to omeprazole 20mg in achieving healing. However, this is not a fair comparison and a study of equivalent doses of esomeprazole (20mg) and omeprazole (20mg) revealed no difference in healing. Furthermore, results from other studies would suggest that omeprazole 40mg would be similar in effectiveness to esomeprazole 40mg, despite this comparison having never been made directly.

Generally, PPIs are well tolerated. The most commonly observed side effects include gastrointestinal disturbances (including nausea, vomiting, abdominal pain, flatulence, diarrhoea, constipation), headache and dizziness. There has been speculation that PPIs might cause gastric cancer as a result of long-term acid suppression although studies suggest that long-term therapy is not harmful in this way. However, continued acid suppression can affect the sterility of the stomach, predisposing patients to gastrointestinal infections. For example, PPI use is associated with Clostridium difficile toxin diarrhoea. Current advice is, therefore, to review PPI therapy in any patient who develops this type of diarrhoea.

Another recent concern surrounds a study that showed that PPIs increase hip fracture risk, probably as a result of reduced calcium absorption due to no or low production of gastric acid (hypochlorhydria). However, the authors believe that further studies are needed to confirm their findings. Finally, there has been a lot of recent publicity about PPIs reducing the efficacy of clopidogrel by preventing activation. There is some controversy surrounding this interaction in that it is not clear if all PPIs cause this effect and a recent paper demonstrated that PPIs did not reduce the efficacy of clopidogrel in patients being treated for acute coronary syndrome.

H2 receptor antagonists H2 receptor antagonists reduce acid production by blocking the action of histamine at H2 receptors found on parietal cells. In addition to treating the less severe symptoms of GORD effectively, H2 receptor antagonists have been shown to be superior to placebo in healing oesophagitis, although significance varies between studies. Ranitidine and nizatidine have superseded cimetidine as the most widely used H2 receptor antagonists, mainly due to the lower potential for drug-drug interactions. Some H2 receptor antagonists are also licensed to be sold OTC for the short-term treatment of heartburn and hyperacidity and for the prevention of these symptoms when associated with the consumption of food or drink. These drugs are generally well tolerated but side effects include diarrhoea and other gastrointestinal disturbances, altered liver function tests (rarely liver damage), headaches, dizziness, rash and tiredness.

Current NICE guidelines recommend following the step-down approach

Antacids and alginate Antacids and antacids with alginate are commonly used (both on prescription and OTC) by people with symptoms of GORD but there is a lack of evidence for their efficacy — antacid and alginate combinations are superior to placebo in relieving reflux symptoms but there are no trials comparing these to placebo in the healing of oesophagitis.

Simple antacids usually contain aluminium or magnesium, which neutralise stomach acid. Alginates, such as sodium alginate, form a protective coating over the walls of the stomach and oesophagus. Alginates and alginate preparations increase the viscosity of stomach contents (often described as “forming a raft”) and can protect the oesophageal mucosa from acid reflux.

Patients can be encouraged to take antacid-containing medicines when symptoms occur or are expected (ie, usually about an hour after a meal and at bedtime). Antacids should not be taken at the same time as other drugs because they can impair absorption (eg, by chelation or affecting enteric coating). The sodium content of antacid-alginate preparations varies and this should be borne in mind when selecting such preparations for patients with heart failure, hypertension, chronic kidney disease or ascites, and for those who are pregnant.

Side effects of antacids and alginites are usually mild and temporary, including diarrhoea (especially magnesium-containing preparations), constipation (aluminium-containing preparations) and belching.

Prokinetic agents Prokinetic agents may improve gastro-oesophageal sphincter function and accelerate gastric emptying. They can be added to therapy when patients show an inadequate response to PPIs. Although the evidence for metoclopramide and domperidone is sparse, they may be useful for patients who have motility disorders, such as diabetic gastroparesis (patients with gastroparesis are prone to symptoms of GORD). Cisapride is no longer licensed in the UK because of concerns regarding its potential to cause cardiac arrhythmias.

Previously, prescribers chose between a “step-up” (starting with antacids then stepping up to an H2 receptor antagonist or PPI if needed) or “step-down” approach (starting with a PPI then decreasing the dose, switching to an H2 receptor antagonist or antacid, or stopping treatment altogether when symptoms are controlled) when managing GORD. Current NICE guidelines recommend following the step-down approach, whereby patients with GORD should be offered a full dose PPI (eg, lansoprazole 30mg daily) for one or two months. The guidelines also recommend that patients who have severe...
Panel 3: Role of the pharmacist in GORD

- Identifying alarm signs and recommending urgent GP referral
- Identifying medicines that may cause symptoms of dyspepsia
- Giving lifestyle advice
- Giving advice on the range of pharmacy-only and over-the-counter medicines (reflecting symptoms and previous usage) and providing help with prescribed medicines
- Referring patients gaining inadequate symptomatic relief from medicines or requiring medicines for long periods

Oesophagitis and remain symptomatic should have their PPI dose doubled for one month because this can improve healing rates. Although PPIs are more effective than H2 receptor antagonists and prokinetics at reducing symptoms of dyspepsia, a small number of patients will remain symptomatic and may respond to the addition of an H2 receptor antagonist at night or proton pump inhibitor for one month. Patients who have needed endoscopic dilation of an oesophageal stricture should remain on long-term full dose PPI therapy — one large RCT demonstrated PPIs to be more effective than H2 receptor antagonists for this purpose.

If patients respond to initial PPI therapy, on demand therapy (where treatment is only taken when symptoms occur) can be promoted to encourage patient involvement. Although there are concerns that if this practice were widely adopted some patients with grade C or D oesophagitis might be exposed to it, there is no evidence that they will be harmed by this approach because they are likely to take PPI therapy more often, in line with their symptom recurrence.

Most patients will experience symptom recurrence within one year and if this happens they should be offered a PPI at the lowest possible dose needed to control symptoms, with a limited number of repeat prescriptions. Patients requiring long-term symptom management should be offered an annual review of their condition and encouraged to “step down” or stop treatment where appropriate. In some cases a return to self-management using antacids (with or without alginate) when required may be appropriate.

Pharmacists should also be aware of the difference in PPI therapy for GORD and for ulcers. The recommended treatment duration for duodenal and gastric ulcers is four and eight weeks, respectively.

Surgical interventions Anti-reflux surgery is not routinely recommended for the management of persistent GORD although individual patients whose quality of life is significantly impaired may benefit from such an intervention. Studies have shown that surgery is no more effective than medication at achieving long-term remission and laparoscopic surgery is no better than open surgery. The post-operative mortality rate associated with anti-reflux surgery is 0.1–0.5 per cent.

Role for pharmacists Pharmacists can play a significant role in the ongoing management of patients with GORD (see Panel 3). There may also be a role for pharmacists following up patients prescribed treatments for GORD in outpatient clinics or in the community. This could easily be part of a medicines use review, clinical review or as part of a consultation with a pharmacist prescriber.

Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist’s CPD portfolio.

1. Make sure your patients know why they are being prescribed a proton pump inhibitor or H2 antagonist.
2. Check that those receiving repeat prescriptions for PPIs have had their treatment reviewed.
3. Train your staff to recognise the symptoms of GORD, including alarm symptoms that require referral.

Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions: What have you learnt? How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?

Gareth Nickless, ClinDip, MRPharmS, is lead clinical liaison tutor at Wirral University Teaching Hospitals NHS Foundation trust and Liverpool John Moores University, and Paula Morgan, MPharm, MRPharmS, is preregistration manager at Wirral University Teaching Hospitals NHS Foundation Trust.

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