

Gastro-oesophageal reflux: an overview of the pharmacotherapeutic treatment options

L Malan,¹ Q Labuschagne,¹ N Schellack,¹ G Schellack,² JC Meyer¹

¹Sefako Makgatho Health Sciences University (SMU)

²Pharmaceutical Industry (Clinical Research)

Corresponding author, email: natalie.schellack@smu.ac.za

Abstract

Gastro-oesophageal reflux disease (GORD) produces symptoms that cause great irritation to the patient. Pharmacotherapeutic management is directed at minimising these symptoms and reducing the causative factors, e.g. acid production, thereby providing relief. Currently available agents include simple antacids and acid suppression therapy, including histamine 2-receptor antagonists, proton pump inhibitors, mucosal or cytoprotective agents and pro-motility agents. Deciding on appropriate therapy will depend on the diagnosis, side-effects and cost-effectiveness of the treatment.

Keywords: GORD, gastro-oesophageal reflux, PPIs, proton-pump inhibitors

Introduction

Gastro-oesophageal reflux disease (GORD) is a medical disorder known and experienced by many, where gastric contents of the stomach return backwards into the distal part of the oesophagus. Up to 40% of the Western population is affected. The exact prevalence of GORD in South Africa is uncertain. Heartburn (dyspepsia) and/or acid regurgitation are common symptoms.¹ GORD may be aggravated by various comorbidities and risk factors. GORD can be classified into three different categories namely physiological gastro-oesophageal reflux, pathological gastro-oesophageal reflux and secondary gastro-oesophageal reflux. Management of GORD is aimed at decreasing the amount of stomach acid that enters the distal oesophagus usually by increasing the rate at which the stomach empties into the duodenum, and relieving the discomfort caused by heartburn. From a treatment perspective, however, the distinction between the management of GORD and peptic ulceration is purely arbitrary. Both are acid peptic diseases that are characterised by inflammatory and erosive changes in the normal gut mucosa. Both require an essentially similar pharmacotherapeutic treatment approach (refer to Figure 1).²⁻⁴

Epidemiology

GORD is not age specific but mainly occurs in people older than 40 years. Prevalence of GORD varies, with the highest incidence in Western countries. Mortality is rare but the disease can impact on the quality of life. Gender only plays a significant role in the development of Barrett's oesophagus but not of GORD. Risk factors and comorbidities that may worsen or even contribute to GORD include the following⁵:

- Family history
- Obesity
- Smoking
- Alcohol consumption
- Certain medication and foods
- Respiratory diseases
- Reflux chest pain syndrome

Pathophysiology

GORD develops when there is abnormal reflux of gastric contents from the stomach into the oesophagus. A defective lower oesophageal sphincter pressure (LESP) is the main pathophysiological mechanism. Other normal mucosal defence mechanisms contributing to GORD include abnormal oesophageal anatomy, improper oesophageal clearance of gastric fluids, reduced mucosal resistance to acid, delayed or ineffective gastric emptying, inadequate production of epidermal growth factor and reduced salivary buffering of acid.⁶

Clinical presentation

The presumptive diagnosis of GORD is made in the presence of typical symptoms (heartburn, regurgitation and dysphagia) occurring two or more times a week in patients under the age of 50 with no other symptoms.⁷

Other atypical symptoms include coughing, chest pain and wheezing. Complications such as oesophagitis, stricture and Barrett's oesophagus may occur and these patients should be

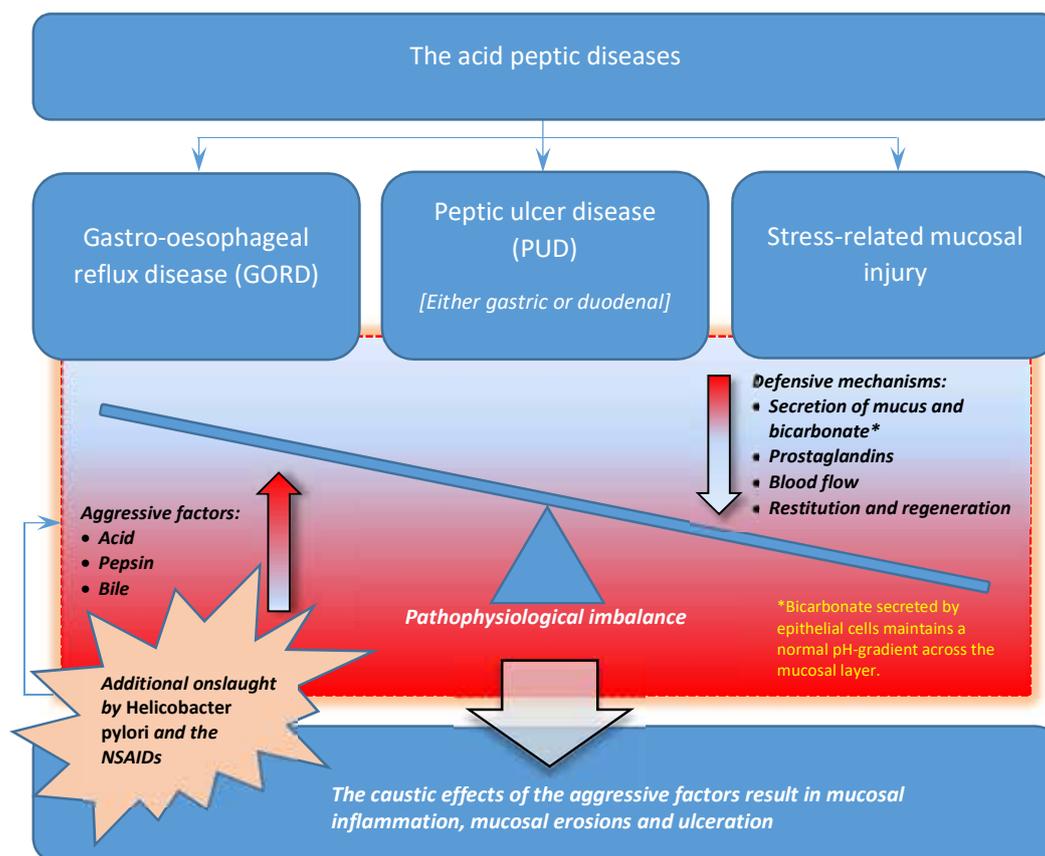


Figure 1: The acid peptic diseases and their resultant mucosal injury. (Common contributors to the pathological imbalance between the aggressive factors and the normal defence mechanisms are infections with *Helicobacter pylori* and the use of non-steroidal anti-inflammatory drugs (NSAIDs). The latter two aggravating factors contribute to nine in 10 cases of peptic ulceration).²

Heartburn: retrosternal burning sensation/discomfort occurring after meals, bending over or lying supine.

Regurgitation: spontaneous return of gastric and/or oesophageal contents into the pharynx. Respiratory complications can arise due to regurgitation of gastric content into the tracheobronchial tree.

Dysphagia: One third of patients experience dysphagia, feeling a sensation of food stuck mainly in the retrosternal area.

referred for further diagnostic testing if they do not respond to therapy.⁸

In 50% of cases reflux causes non-cardiac chest pain and patients present to the emergency department thinking that they are having a myocardial infarction. To rule out a cardiac cause, a 24-hour pH testing can be done or oesophageal manometry. A high dose of a proton-pump inhibitor (PPI) can be used alternatively.⁸

GORD is classified into three categories:

1. Physiological (or functional) gastro-oesophageal reflux: no underlying factors or conditions are present with normal growth and development. Pharmacological treatment generally not necessary, unless lifestyle changes are not successful.
2. Pathological gastro-oesophageal reflux or GORD: patients who regularly experience above-mentioned symptoms, requiring evaluation and treatment.
3. Secondary gastro-oesophageal reflux: where an underlying condition predisposes gastro-oesophageal reflux.

Management of GORD

GORD is characterised by inflammatory and erosive changes in the normal gut mucosa. The treatment approach to patients with dyspeptic symptoms, as for acid heartburn and GORD, is aimed at^{4,9}:

- Decreasing the amount of stomach acid that enters the distal oesophagus, usually by neutralising stomach acid, decreasing the production of hydrochloric acid (HCl), increasing the rate at which the stomach empties into the duodenum, and
- Relieving the discomfort caused by heartburn.

The major drug used in the current practice setting is the so-called proton pump inhibitors (H⁺/K⁺-ATPase inhibitors), which targets the gastric H₂-receptor and the gastrointestinal 5-HT₄-receptor. These targets may be supported by simple antacids and prostaglandin analogues. The pharmacotherapeutical measures may be supported by basic, non-pharmacological intervention strategies.

The treatment of GORD should be individualised, with the goal being the alleviation of symptoms, decreasing the frequency of

recurrent disease, promoting the healing of mucosal injury and the prevention of complications.⁷

Non-pharmacological management

Dietary recommendations and lifestyle modifications should be individualised for each patient. It is recommended that patients refrain from indulging in foods that could trigger the onset of dyspeptic symptoms, such as fats, alcohol, peppermint and spearmint. These foods may decrease LES or increase transient lower oesophageal sphincter relaxation whereas spicy foods, orange juice, tomato juice and coffee have a direct irritant effect on the oesophageal mucosa. Smaller meals should preferably be taken more frequently so as to avoid unnecessary gastric distension.

Patients should also be advised to avoid the use of NSAIDs and other medications linked to the occurrence of dyspepsia, whenever possible. If an NSAID must be used, then the patient should be given preventative therapy to avoid the uncomfortable dyspeptic symptoms.^{7,10,11,12}

Other non-pharmacological measures can include:

- Elevating the head end of the bed, which increases oesophageal clearance as well as the pH. This may be done using 15–20 cm blocks underneath the head side of the bed
- Weight loss in obese patients (reduces symptoms)
- Adding protein-rich meals to the diet (augments LES)
- Avoiding food intake at least two hours before sleeping, especially when nocturnal symptoms are present
- Cessation of smoking
- Always taking drugs when in the upright sitting position and with enough liquid

Pharmacological management

The pharmacological management of GORD should be dictated by the clinical presentation of the disease and symptom intensity. It may consist of one or more of the following treatment options, either alone, sequentially, or in combination^{4,7,9,10,13}:

- Simple antacids
- Acid-suppression therapy
- Mucosal or cytoprotective agents
- Pro-motility agents

Simple antacids

Simple antacids, such as those containing aluminium and magnesium, neutralise the HCl in the stomach and are quite effective as pain relievers. The magnesium-containing antacids cause diarrhoea, while the aluminium-containing ones cause constipation. The combination of magnesium and aluminium will therefore constitute the antacid of choice (e.g. a combination of aluminium hydroxide and magnesium trisilicate). The divalent cations (i.e. Al₃⁺ and Mg₂⁺), however, would interact with chelating agents, such as the tetracycline and fluoroquinolone antimicrobials, and several other drug interactions are possible.^{4,9}

Combining an antacid with an alginate may actually prevent reflux, in that the alginate literally forms a floating gel on top of the gastric contents. Calcium carbonate and sodium bicarbonate may also be used as simple antacids. However, care should be taken with these agents, since calcium carbonate may interfere with normal acid-base balance and cause metabolic alkalosis, or it may elicit rebound gastric acid secretion, making it suitable for short-term use only. Meanwhile sodium bicarbonate should be used with caution in patients who require a restricted sodium intake.^{4,9}

Dimethicone and simethicone may relieve a 'bloating feeling' by acting as antifoaming or defoaming agents. They may also be of benefit in the management of intestinal colic in infants and children. However, they do not contribute to the efficacy of the acid neutralisation brought about by the antacids and there is no evidence supporting their chronic use.^{4,7,9}

Acid-suppression therapy

Drugs that increase gastric pH fall into two categories, namely the histamine 2-receptor antagonists (H₂RAs) and the PPIs, with the latter group constituting the most effective drugs by far.^{4,7,9,13}

- *Histamine 2-receptor antagonists (H₂RAs)*

Blocking the gastric H₂ receptors of parietal cells will reduce stomach acid secretion. These agents are highly selective inhibitors capable of suppressing both basal and food-induced acid secretion from these cells, albeit more modestly for the latter and making them less ideal for day-time acid suppression. Ulcer healing rates are significant but not nearly as good as those obtained through the use of the PPIs. In patients with erosive oesophagitis, the H₂RAs are only effective in fewer than 50% of cases. Cimetidine, ranitidine, famotidine and nizatidine are examples of these selective histaminergic-receptor blockers. Cimetidine has the disadvantage of sometimes producing unwanted antiandrogenic side-effects in male patients (it has a fairly small affinity for androgen receptors).

It also has a higher likelihood of multiple drug interactions through its inhibition of cytochrome P450 isozymes. These agents are especially useful in the suppression of nocturnal acid secretion, which largely depends on the physiological actions of histamine.^{4,9,13}

- *Proton-pump inhibitors (PPIs)*

These drugs enter the parietal cells of the gastric glands, found in the gastric pits of the stomach lining, where they subsequently and irreversibly inhibit the H⁺/K⁺-ATPase pump (i.e. the proton pump that is specifically responsible for the H⁺-secretion into the lumen of the gastric pits where these cations combine with the secreted Cl⁻ from a separate pump to form HCl). This effectively prevents the secretion of gastric acid from the gastric pits into the lumen of the stomach.^{4,9,13}

Therefore, these drugs are highly effective in increasing the stomach pH, rapidly relieving symptoms and achieving good cure rates. They are administered as prodrugs and are very widely used because of their established favourable efficacy and safety profiles. PPIs are best taken 30 minutes before breakfast

as a greater quantity of active pumps are available at that time of the day. Currently available examples of PPIs are omeprazole, esomeprazole (the S-isomer of omeprazole), lansoprazole, pantoprazole and rabeprazole. The PPIs are still the most effective agents in the management of both nonerosive and erosive GORD, as well as the complications of reflux disease.^{4,7,9,13}

Mucosal or cytoprotective agents

These drugs are referred to as cytoprotective because they protect the cells of the stomach lining against the corrosive effects of stomach acid. In addition, misoprostol also promotes perfusion of the gastric mucosa because it is an analogue of prostaglandin E1 (PGE₁).

Sucralfate forms a protective layer that covers the exposed surface of the ulcer and, in doing so, produces cure rates that are comparable to those obtained with the H₂ receptor antagonists. It should preferably be taken one hour before meals, since it is activated by stomach acid. The viscous paste will cover exposed ulcer or erosive surfaces for up to six hours. Wherever sucralfate is combined with any of the simple antacids, the antacid should be taken half an hour after taking the sucralfate (i.e. on an empty stomach as well).^{4,9,13}

Misoprostol is of particular use in preventing the gastrototoxic effects of NSAIDs. It influences the ratio of acid-to-mucus secretion favourably by increasing gastric mucus secretion while decreasing acid secretion. Care should be taken with this drug, however, since PGE₁ causes uterine contractions. It can be used for termination of pregnancy or the induction of labour, and should therefore be avoided during pregnancy.^{4,9,13}

Bismuth compounds may also be used, and may have a variety of beneficial effects, some of which are yet to be fully elucidated. These include the formation of a protective barrier by coating ulcers and erosions in the mucosal lining, stimulating the secretion of mucus, bicarbonate and prostaglandins, as well as its ability to act as an antimicrobial and to bind enterotoxins (hence its usefulness in the management of traveller's diarrhoea and to help eradicate *Helicobacter pylori*).¹³

Pro-motility agents

Metoclopramide acts as an agonist at gastrointestinal 5-HT₄ receptors, thus increasing the rate of gastric emptying and peristalsis. Domperidone has a similar mechanism of action, but differs from metoclopramide in that it does not cross the blood-brain barrier. Cisapride is another 5-HT₄ receptor agonist which is unrelated to the abovementioned two drugs. It has the disadvantage of causing potentially serious cardiac side-effects, such as ventricular dysrhythmias (by causing QTc-interval prolongation), especially when its own metabolism is inhibited (through various drug interactions, for instance). Access to this drug has been restricted and it should be used with extreme caution.^{4,9,13}

Bethanechol is a parasympathomimetic drug which selectively stimulates muscarinic receptors (of the M₃-subtype). In the gastrointestinal tract (GIT) this causes smooth muscle contraction, but produces relaxation of the sphincters. Bethanechol therefore stimulates the functional contraction of the GIT (i.e. it increases intestinal motility). A different approach with a similar outcome on the motility of the GIT would be to use neostigmine. Erythromycin also has pro-kinetic properties. It acts as a direct stimulator of the motilin receptors.^{4,13}

The usefulness of these agents in GORD is limited, with metoclopramide and domperidone being reserved for patients with regurgitation and refractory heartburn.¹³

Conclusion

Physicians and other healthcare professionals should be aware of GORD and its treatment strategies, since it constitutes a significant disease burden worldwide. In the management of GORD various agents and classes of agents are available, either for management of symptoms, or for the treatment thereof. It has been shown that the PPIs are more effective than the H₂RAs in managing GORD, and are also superior to placebo in patients with GORD symptoms. Specific drug selection within the PPI group, should be based on individual adverse effects profiles and the expected onset of action.

References

1. Van Rensburg CJ, Kulich KR, Carlsson J, Wiklund IK. 2005. What is the burden of illness in patients with reflux disease in South Africa? The South African gastroenterology review.
2. Katzung BG, Masters SB, Trevor AJ. Basic and Clinical Pharmacology. 11th edition. 2009. The McGraw-Hill Companies, Inc. China.
3. Dipiro JT, Talbert RL, Yee GC, et al. Pharmacotherapy – A Pathophysiologic Approach. 8th Edition. P555. 2011. The McGraw-Hill Companies, Inc. China.
4. Schellack G, editor. Pharmacology in clinical practice: application made easy for nurses and allied health professionals. 2nd ed. Claremont: Juta and Company, Ltd; 2010.
5. Dent J, El-Serag HB, Wallander MA, Johansson S. 2005. Epidemiology of gastro-oesophageal reflux disease: A systematic review. Gut. 54:710–717.
6. DeVault KR, Castell DO. 2005. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. American Journal of Gastroenterology. 100:190–200.
7. Huerta-Iga F, Bielsa-Fernandez MV, Remes-Troche JM, et al, on behalf of the 2015 GERD Study Group. Diagnosis and treatment of gastroesophageal reflux disease: recommendations of the Asociacion Mexicana de Gastroenterologia. Revista de Gastroenterologia de Mexico. 2016;81:208–222.
8. Patti MG, Anand BS. 2016. Gastroesophageal reflux disease differential diagnosis. <http://emedicine.medscape.com/article/176595-differential> Date of access: 13 Jan 2017.
9. Brenner GM, Stevens CW. Pharmacology. Fourth Edition. China: Elsevier Saunders. 2013.
10. Fong S, Dunn J. Dyspepsia: alarm symptoms, investigation and management. The journal of prescribing and medicines management. 2013;24:13–26.
11. Harmon C, Peura DA. Evaluation and management of dyspepsia. Therapeutic Advances in Gastroenterology. 2010;2:87–98.
12. Tuskey A, Peura D. The use of H₂ antagonists in treating and preventing NSAID-induced mucosal damage. Arthritis Research and Therapy 2013;15 (Suppl 3): S6.
13. Mearin F, Calleja JL. Defining functional dyspepsia. Revista Espanola de Enfermedades Digestivas. 2011;103:640–647.