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REVIEW

Gastro-oesophageal reflux disease: extinguishing that fire

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Gastro-oesophageal reflux disease (GORD) is a highly prevalent, chronic disorder. Information regarding this disease is limited and the management of these patients changes continuously. Proton-pump inhibitors (PPIs) remain the first-choice therapy in the treatment of GORD, but a consistent proportion of these patients continue to experience symptoms despite their use. Currently, other available agents include simple antacids and acid suppression therapy, including histamine 2-receptor antagonists (H2RAs), mucosal or cytoprotective agents and pro-motility agents. Recently, several new drugs have been used to increase the defensive properties of the gastric mucosa with promising results in randomised clinical trials. Deciding on appropriate therapy will depend on the diagnosis, side-effects and cost-effectiveness of the treatment.

Keywords: GORD, proton-pump inhibitors, PPIs, histamine 2-receptor antagonists, H2RAs, potassium-competitive acid blockers, oesophageal mucosal resistance, mucosal protective agents, reflux-inhibitors

Introduction

"I would like to find a stew that will give me heartburn immediately, instead of at three o'clock in the morning." John Barrymore[1]

These symptoms of reflux disease have been known since the days of ancient Rome, with reflux symptoms associated with Falernian wine ingestion, but for hundreds of years, diseases of the oesophagus have been poorly understood, and the organ itself has received little attention.[2]

Today, gastro-oesophageal reflux disease (GORD) is a recognised medical disorder experienced by many, and typified by backflow of gastric contents into the distal part of the oesophagus (Figures 1 and 2).[3]

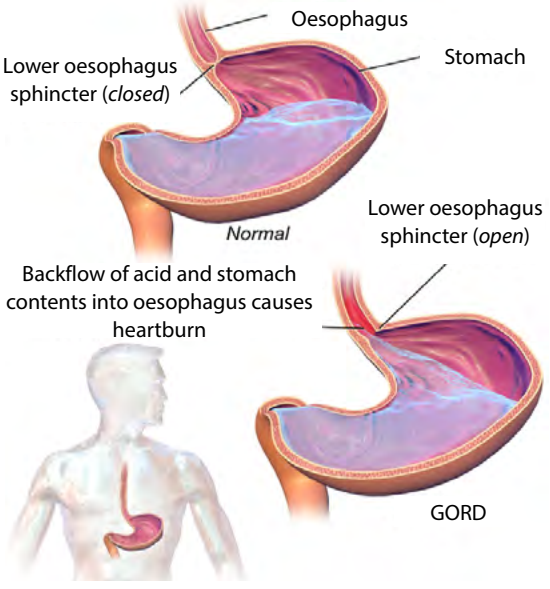

Figure 1: Gastro-oesophageal disease[3]

In Western countries, it appears that about 40–50% of the population is affected by this condition. The exact prevalence of GORD in South Africa has not been established. Dyspepsia (heartburn) and/or acid regurgitation are common symptoms.[4] GORD may be aggravated by various risk factors and co-morbidities. 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. Currently, the most useful diagnostic examinations are 24-hour impedance-pH monitoring, which allows separation of true non-erosive reflux disease (NERD) from oesophageal functional

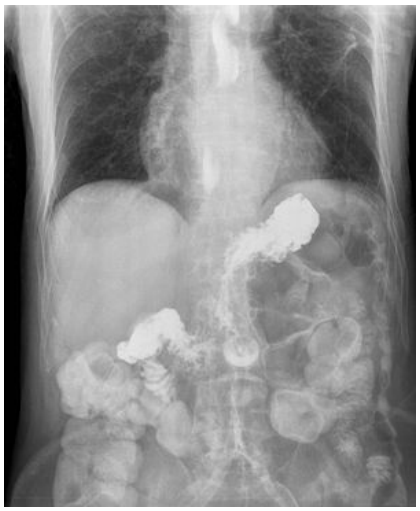

Figure 2: X-ray of the abdomen and chest in a patient with a gastrostomy. Radiocontrast was injected into the stomach and quickly seen migrating upwards through the entire oesophagus. The patient had severe reflux oesophagitis.[3]

disorders, and high-resolution manometry, which assists in excluding the existence of motility disorders sharing the same symptoms of GORD. Both, however, may require an essentially very similar pharmacotherapy treatment approach.[5-7]

Epidemiology

GORD is not age-specific but mainly occurs in people older than 40 years and men appear to be more affected. Prevalence of GORD varies, with the highest incidence in Western countries. The disease can impact on quality of life, but mortality is rare. Furthermore, it appears that gender may only play 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 are listed in Table I.[8]

Table I: Risk factors and comorbidities that may worsen or even contribute to GORD

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

Pathophysiology

The development of GORD is caused 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. Among other things, 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 are factors that can contribute to the development of GORD.[9]

Clinical presentation

The diagnoses of GORD can reasonably be entertained in the presence of typical symptoms occurring two or more times a week in patients under the age of 50 with no other symptoms. Typical symptoms include:[10]

- Heartburn: retrosternal burning sensation/discomfort occurring after meals, bending over or being supine.
- Dysphagia: roughly 30–35% of patients experience dysphagia, feeling a sensation of food stuck mainly in the retrosternal area.
- Regurgitation: the spontaneous return of gastric and/or oesophageal contents into the pharynx. Respiratory complications can arise due to the regurgitation of gastric content into the tracheobronchial tree.

Often coughing, chest pain and wheezing can represent atypical symptoms. Oesophagitis, stricture and Barrett's oesophagus (Figure 3) may occur as complications, and these patients should be referred for further diagnostic testing if they do not respond to therapy. In about 45% of cases, reflux can lead to non-cardiac chest pain and patients present to the emergency department complaining that they are experiencing a myocardial infarction.

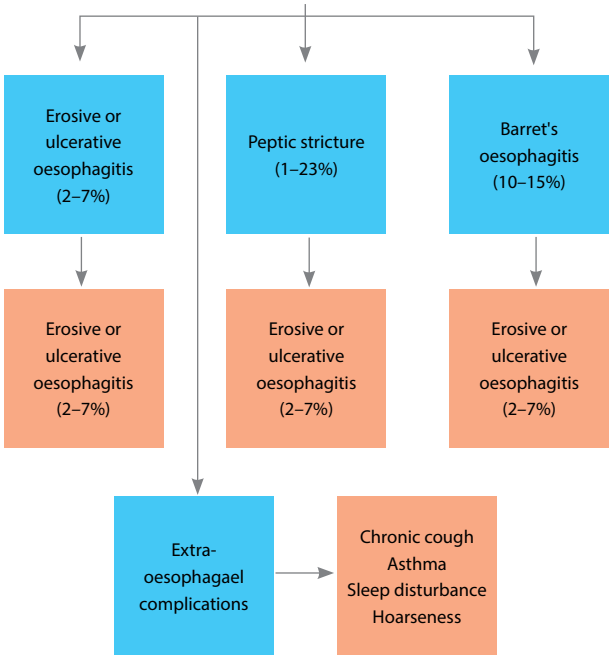

Figure 3: Complications of GORD

To rule out a cardiac cause, a 24-hour pH testing can be done or oesophageal manometry. A high-test dose of a proton-pump inhibitor (PPI) can be used alternatively[11]

Management of gastro-oesophageal reflux disease

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 is generally not necessary, unless lifestyle changes are not successful.
2. Pathological gastro-oesophageal reflux or GORD: patients who regularly experience abovementioned symptoms, requiring evaluation and treatment.
3. Secondary gastro-oesophageal reflux: where an underlying condition predisposes to gastro-oesophageal reflux.

When considering the treatment approach, it is essential to understand that GORD is characterised by inflammatory and erosive changes in the normal gut/oesophageal mucosa. Therefore, treatment for acid heartburn and GORD is aimed at:[7-12]

- decreasing the volume 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 symptomatic discomfort caused by heartburn.

The major medications used in the current practice setting are PPIs (H+/K+-ATPase inhibitors), H2RAs which target the gastric H_2-receptor and metoclopramide, the gastrointestinal 5-HT_4 receptor. These agents may be supported by simple antacids and prostaglandin analogues. The pharmacotherapy 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.[10]

Non-pharmacological management

Essentially, dietary recommendations and lifestyle modifications should be optimised for each patient. It is recommended that patients refrain from indulging in foods such as fatty foods and alcohol that could trigger the onset of dyspeptic symptoms by decreasing LESP or increasing transient lower oesophageal sphincter relaxation; orange juice, tomato juice, coffee and spicy foods have a direct irritant effect on the oesophageal mucosa. It is recommended that smaller meals should be taken more frequently to avoid unnecessary gastric distension and consequently a large volume of HCl acid production.

Patients should also be advised to avoid the use of nonsteroidal anti-inflammatory drugs (NSAIDs), e.g. aspirin, ibuprofen, diclofenac 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 or use a non-selective COX inhibitor, e.g. celecoxib, to avoid the uncomfortable dyspeptic symptoms. Furthermore, other medications which should be avoided are those that may decrease LESP and include beta-agonists, alpha-adrenergic antagonists, nitrates, calcium-channel blockers, anticholinergics, theophylline, morphine, diazepam, and barbiturates.[10,13,14,15]

Pharmacological management

The clinical presentation of the disease and symptom intensity can assist in the decision of the pharmacotherapy options in treating GORD. This may consist of one or more of the following treatment options, either alone, sequentially, or in combination:[7,10,12,13,16]

- 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 symptomatic pain relievers. The magnesium-containing antacids cause diarrhoea, while the aluminium-containing ones may cause constipation and therefore, a combination of magnesium and aluminium should be the antacid of choice. Just a reminder that divalent cations (i.e. Al_2+ and Mg_2+) can interact with chelating agents, such as certain antimicrobials, e.g. tetracycline and fluoroquinolone; calcium carbonate and sodium bicarbonate may also be used as simple antacids.[7,12] Be cautious of sodium bicarbonate in patients who require a restricted sodium intake.[7,12]

Alginates can prevent reflux through an alternative mechanism by displacing the postprandial gastric acid pocket and forming a floating gel on top of the gastric contents.

Dimethicone and simethicone may relieve a 'bloated feeling' by acting as anti-flatulents. 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.[7,10,12]

Acid-suppression therapy

Medications that increase gastric pH by suppressing acid production can be divided into two categories: the histamine 2-receptor antagonists (H2RAs) and the PPIs, with the PPIs constituting the more effective medication in this regard.[7,10,12,16]

- **Histamine 2-receptor antagonists**

Blocking the gastric H_2 receptors of parietal cells will reduce stomach acid secretion. These agents are selective inhibitors capable of suppressing both pre-prandial and food-induced acid secretion from these cells; they are less ideal for daytime acid suppression. Ulcer healing rates are significant but not as effective 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 can produce unwanted anti-androgenic side-effects in male patients and is also prone to drug interactions through its inhibition of cytochrome P450 isozymes.[7,12,16]

- **Proton-pump inhibitors**

These medications enter the parietal cells; parietal cells (also known as oxyntic cells) are epithelial cells in the stomach that secrete HCl and intrinsic factor. These cells are located in the gastric glands found in the lining of the fundus and body regions of the stomach. PPIs bind to and irreversibly inhibit the H+/K+-ATPase pump (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 into the lumen of the stomach.[7,12,16]

Thus, these medications are very effective in increasing the stomach pH rapidly and relieving symptoms and achieving good cure rates. They are administered as pro-drugs and are very widely used because of their established favourable efficacy and safety profiles. PPIs are best taken 30 minutes before breakfast as greater quantities of active pumps are available at that time of the day. Examples of PPIs include omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole. The PPIs are still the most effective agents in the management of both non-erosive and erosive GORD, as well as the complications of reflux disease.[7,10,12,16]

Mucosal or cytoprotective agents

These medications are cytoprotective because they protect the cells of the stomach and oesophagus lining against the corrosive effects of HCl.

Sucralfate forms a protective layer that covers the exposed protein surface of the ulcers and, in doing so, produces cure rates that are comparable to those obtained with the H_2-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.[7,12,16]

Misoprostol is of particular use in preventing the gastrotoxic effects of NSAIDs. It influences the ratio of acid-to-mucus secretion favourably by increasing gastric mucous secretion while decreasing acid secretion. It also promotes perfusion of the gastric mucosa because it is an analogue of prostaglandin E1 (PGE_1), a product of household cyclo-oxygenase-1. Since PGE_1 causes uterine contractions, it can be used for termination of pregnancy or the induction of labour, and should therefore be avoided during pregnancy.[7,12,16]

Bismuth compounds may also be used, and may have a variety of beneficial effects, some of which are yet to be fully understood. 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*).[16]

Pro-motility agents

Domperidone is a gastric prokinetic agent increasing the rate of gastric emptying and peristalsis; metoclopramide has a similar mechanism of action but differs from domperidone in that it crosses the blood–brain barrier. Cisapride is another 5-HT_4 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 QT-interval prolongation and thus the risk for *torsades de pointes*), 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.[7,12,16]

Parasympathomimetic medications, e.g. bethanechol, selectively stimulates muscarinic receptors. In the gastrointestinal tract (GIT) this causes smooth muscle contraction, but produces relaxation of the sphincters and therefore stimulates the functional contraction of the GIT (i.e. it increases intestinal motility).[7,16]

Table II: Main differences in the mechanisms of action between PPIs and P-CABs

Proton-pump inhibitors	Potassium-competitive acid blockers
Pro-drugs that need to be transformed to the active form	Direct action on H^+-K^+ ATP-ase
Binding covalently to H^+-K^+ ATP-ase	Binding to K^+ site of H^+-K^+ ATP-ase
Irreversible binding to the proton pump	Reversible binding to the proton pump
Full effect after 3–5 days	Full effect after the first dose
Affected by genetic polymorphism	Not affected by genetic polymorphism
Pharmacodynamic effect greater during the daytime	Pharmacodynamic effect lasting for both the daytime and nocturnal hours

The usefulness of these agents in GORD is limited, with metoclopramide and domperidone being reserved for patients with regurgitation and refractory heartburn.[16]

New pharmacological approaches on the horizon

Potassium-competitive acid blockers (P-CABs)

These novel antisecretory drugs differ from PPIs because they compete with K^+ and induce a selective and reversible inhibition of the proton pump in a dose-dependent manner.[17] They are not pro-drugs that must be activated in the parietal cells, like PPIs, and therefore their onset of action is immediate and the control of gastric acid secretion occurs after the first dose and within the first day of administration.[18] Moreover, their dissociation rate from the proton pump is slow and its retention time in the gastric mucosa is 24 hours or more; thus, the acid inhibitory activity covers both daytime and nighttime,[19] differently from PPIs which are less effective during the nocturnal period.[20] The main differences in the mechanisms of action between P-CABs and PPIs are reported in Table II.

There are many molecules pertaining to this drug category (veraprazan, linaprazan, vonoprazan, tegoprazan, etc.), but vonoprazan is certainly the most studied in the treatment of GORD. It is marketed mainly in some Asian countries and Phase III studies are in progress in Europe and the US. This drug has been shown to be effective and not inferior to PPIs in patients with mild or moderate degrees of oesophageal erosion,[21] and its healing rate was even significantly better than that of lansoprazole in patients with the grades C and D oesophagitis, a superiority maintained in CYP2C19 metabolisers.[22]

Reflux inhibitors

It is well known that TLESRs represent the most relevant mechanism in the pathophysiology of GORD, and therefore, its control has become a therapeutic target in the treatment of this disease. Baclofen, a gamma-amino-butyric acid (GABA) receptor type B agonist, has been identified as the first reflux inhibitor and, as such, is able to reduce the number of TLESRs and all types of reflux events, both acid and weakly acidic, as shown by means of impedance-pH monitoring.[23] A meta-analysis of nine studies has found that baclofen decreased the number and the length of reflux episodes as well as the incidence of TLESRs.[24] However, its clinical use is very limited because of its poor tolerability due mainly to neurological adverse events.[25]

Mucosal protectors

A new medical device containing hyaluronic acid and chondroitin-sulfate (Esoxx™, Alfasigma, Italy) has been developed as an oesophageal protective agent. The European Council classified this formulation as a Class III medical device, which should be used in human beings for the purpose of treatment or alleviation of disease. It is dispersed in a bio-adhesive carrier (poloxamer 407), which prolongs its residence time in the lumen and creates a mechanical barrier against noxious agents of refluxate over the oesophageal lining.[26] Both compounds exhibit multiple functions, such as anti-inflammatory effect, wound repair, tissue regeneration and modulation of cytokines expression.[28] A prospective, randomised clinical trial performed

in Italy in NERD patients compared Esoxx™ combined with a standard PPI dose to PPI plus placebo. The combined therapy over 14 days was significantly better than the placebo in relieving symptoms and improving the quality of life of recruited patients. The treatment was well-tolerated and no serious adverse events were registered.[27]

Visceral hypersensitivity

Even though the reduction of visceral hypersensitivity is a reasonable therapeutic target in these functional patients, the results of clinical trials using neuromodulators (Table III) have provided conflicting findings, because some studies have shown the benefit of these drugs[29,30] while others did not find any difference between anti-depressants, particularly tricyclic compounds at low dosage, and placebo.[31,32]

Table III: List of pain modulators used in randomised clinical trials for treating functional oesophageal disorders

Imipramine
Amitriptyline
Venlafaxine
Sertraline
Paroxetine
Citalopram
Gabapentin

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 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 H_2RAs 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.

Cognisance should be taken of newer pharmacological therapeutic agents being investigated that may complement the current arsenal of treatment options leading to more effective management choices.

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