Calming the acid: Pharmacotherapeutic approaches to gastro-oesophageal reflux disorder

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Abstract

Gastro-oesophageal reflux disease (GORD) is a chronic disorder where gastric contents, inclusive of gastric acid, pepsin and foodstuff, enter the oesophagus which leads to irritation and potential erosion. While refluxate regurgitation is a physiological process, pathophysiological levels of reflux may manifest as heartburn, regurgitation, and non-cardiac chest pain. Management should be approached from a non-pharmacotherapeutic vantage, where pharmacotherapy is included where justified to support treatment outcomes. In this review, the broad medication classes used for GORD treatment in South Africa are discussed, including the first-line proton pump inhibitors, histamine-2-receptor antagonists, antacids, and alginate-based treatments.

Keywords: antacid; alginate; gastro-oesophageal reflux disease; H2-receptor antagonist; proton pump inhibitor

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Introduction

Refluxate regurgitation, where gastric content moves into the oesophagus and oral cavity, is a natural physiological process that occurs throughout the day, however, does not necessarily incur pathological implications.[1] However, when frequency increases or removal from the oesophagus is not adequate, gastro-oesophageal reflux disease (GORD) may occur.[1-4] GORD is generally classified as either erosive oesophagitis or non-erosive oesophagitis, or may include premalignant Barrett's oesophagus.[1,5,6] Erosion is thus not necessarily present in all cases, which leaves non-erosive oesophagitis as the more commonly found presentation.[1-4,6] Symptomatically, GORD may present as per Table I.

Table I: Symptoms of gastro-oesophageal reflux disease[1-7]

Typical symptoms
Burning sensation in the chest and oral cavity
Refluxate regurgitation
Non-cardiac chest pain and discomfort
Extraoesophageal symptoms
Ear, nose and throat symptoms, such as asthma, sore throat, wheezing, pharyngitis, and sinusitis
Tooth erosion
Alarm symptoms
Dysphagia and odynophagia
Vomiting, including potential haematemesis
Unexplained weight loss
Iron-deficiency anaemia

A global prevalence systematic review by Nirwan et al. highlighted an overall GORD burden of 13.98%.[8] From the limited data available from Africa (n = 2) in their study, no prevalence could be determined, though other regions ranged from 12.88% (Latin America and The Caribbean) to 19.55% (North America).[8] Li et al. reported in their systematic review an incidence of 4 524.95 per 100 000 population in sub-Saharan Africa.[9] As such, GORD levels remain notable across the globe. GORD, as a chronic lifestyle disorder, is increasing and has significant impact on the quality of life of individuals. As such a common disorder, pharmacotherapeutic approaches have been well described and are, in general, not a cost-intensive management. However, it does not undermine the importance of non-pharmacotherapeutic approaches that should underpin health considerations.

Pathophysiology

GORD is a multifactorial disease, and thus various factors may contribute to its pathological development. Most commonly, loss of the anti-reflux barrier results in GORD, where the combined structural properties of the lower oesophageal sphincter, diaphragmatic crural sling, phreno-oesophageal ligament, angle of His, and intra-abdominal oesophageal length cannot prevent regurgitation.[6,10] As such, sphincter relaxation due to transient postprandial relaxation or due to lower oesophageal sphincter dysfunction promotes regurgitation of refluxate into the oesophagus.[1,2,4,6,11] Meal-induced lower oesophageal sphincter relaxation invariably contributes to a high acid burden within the oesophagus.[2,4] Increased abdominal pressure, hiatal hernias and delayed gastric emptying further contributes to reflux, as well as a supine position, thus potentiating the release of contents into the oesophagus.[2,4,11]

The refluxate contains a variety of potential irritants and eroding factors, such as gastric acid, pepsin, bile and biliary acids, pancreatic enzymes, and duodenal contents which may result in acidic or enzymatic oesophageal erosion and irritation.[12,13] The acid

pocket that forms post-meals is a challenge in GORD, particularly when coupled to reflux barrier dysfunction.[13] Furthermore, should the oesophagus not adequately clear contents, it contributes to localised damage.[2,4,6] Oesophageal mucosal health further determines the susceptibility of the lining to such damage.[2]

Risk factors

Various factors, ranging from the person and the environment, may predispose one to GORD, though it's important to acknowledge the multifactorial nature of the disease[2] which includes modifiable and non-modifiable factors.[1,5] Non-modifiable factors include advanced age, sex, genetics and anatomical concerns (e.g. hiatus hernias).[1,2,6] Increased body weight and adiposity, diet (including caffeinated drinks, alcohol, aerated drinks, acidic foods such as citrus and tomatoes, and chocolates), smoking and certain medication (such as certain nonsteroidal anti-inflammatory drugs, anticholinergics and antibiotics) are modifiable risk factors that increase the risk to develop GORD.[1,2,4,6]

Non-pharmacotherapeutic approaches

Lifestyle modifications are considered an important first step in resolving GORD, however, some contention is noted of their efficacy, given limited trial data.[2,4,10] Given the multifactorial nature of GORD, lifestyle changes are a cost-effective strategy to mitigate some of the underlying risk factors.[4] Alteration to diet and eating patterns allows for lower production of acid or disruption of the stomach contents, thus also reducing the potential for regurgitation or the acidity of refluxate.[2,4] These changes may include eating smaller, but more frequent meals; not eating within two hours of sleeping; and eliminating or reducing intake of GORD-sensitising foods and drinks, such as caffeinated or aerated drinks and acidic foods.[2,4] Postural alterations after eating, such as not reclining after meals or elevating the head while sleeping reduce potential refluxate regurgitation.[2,4] Smoking cessation and decreasing body weight if obese may also reduce the prevalence of GORD.[2,4] Under certain circumstances, such as the continued worsening or GORD, inefficacy of pharmacotherapy, high adverse effects burden or additional comorbidities or complexities may justify a surgical treatment, such as surgical fundoplications.[1,3,4,14]

Pharmacotherapeutic approaches

Pharmacotherapeutic management to GORD aims to reduce refluxate regurgitation and the acidity of the gastric contents, which in turn reduces the presence of irritants in the oesophagus and the severity of damage they may cause. Symptomatic severity and associated factors help designate the most appropriate treatment. Importantly, given potential overuse of pharmacotherapy, rationale clinical decision-making is needed to ensure that lifestyle changes underpin supportive pharmacotherapeutic use as needed.[15]

Proton pump inhibitor

Proton pump inhibitors (PPIs) are considered the primary pharmacotherapeutic option for GORD as they reduce the acidity of the gastric contents, thus mitigating their erosive and irritant properties.[10,15] PPIs are prodrugs which require bioactivation via protonation in the gastric parietal cell secretory canaliculi.[6] PPIs bind covalently and irreversibly to the gastric proton pump (H^+-K^+-ATPase), thus potently reducing acid secretion over an extended period of time, regardless of their short biological half-life.[6,15] Given the regeneration of proton pumps, continuous administration is needed to maintain efficacy during the active stages of the disease administration.[6] Given the need for an acidic environment, it rationalises their administration between 30 to 60 minutes prior to meals to ensure sufficient gastric acid production occurs.[6] Furthermore, as *de novo* synthesis of proton pumps occurs to a greater degree with overnight fasting, it supports recommendations for morning administration.[6]

A list of commonly prescribed PPIs is provided in Table II. PPIs should be prescribed at the lowest recommended dose and duration, with regular review to avoid overuse.[16] Given its potential for overuse or irrational prescription, use should also be considered cautiously or avoided in cases where isolated throat symptoms, undifferentiated or isolated gastrointestinal symptoms that are unlikely to be associated with GORD.[15,17,18] For less complex or severe cases of GORD, short-term therapy of four to eight weeks is considered, while longer treatments are considered with higher severity (such as erosive oesophagitis at a Los Angeles classification of Grade C and D).[15,17] Refractory GORD is defined when non-responsive or partial response to PPIs

Table II: Proton pump inhibitors available in South Africa (as obtained from mobiMIMS[19])

Proton pump inhibitor	Examples	Formulations	Available dose
Omeprazole	Lokit, Losec, Omez, Omiflux, Probitor, Rapacid, Sandoz Omeprazole	Capsules	10 mg, 20 mg, 40 mg
Lansoprazole	Adco-Roznal, Burnloc, Conoran, Lancap, Lasoloc, Lansoprazole Unicorn, Roznal OTC	Capsules	15 mg, 20, mg 30 mg, 40 mg
Dexlansoprazole	Dexilant	Capsules	30 mg, 60 mg
Esemoprazole	Esomeprazole Cipla, Fluxtrin, Fluxtrin OTC, Nexiam, Nexipraz, Nexomep, Truloc, Trusfluks	Tablets	20 mg, 40 mg
Pantroprazole	Pantocid, Pantoloc, Pantor, Pentoz, Peploc, Peploc OTC, Prazoloc, Prazoloc OTC, Praztek, Topzole	Tablets	20 mg, 40 mg
Rabeprazole	Rabemed, Ulcopraz	Tablets	10 mg, 20 mg

is observed after eight weeks of treatment,[7] which may justify approaching alternative management formats, such as surgery subject to diagnosis.[3,4,14]

Due to the potential for rebound acid hypersecretion, weaning off is recommended during deprescribing to avoid unnecessary complications.[6,17] Patients should be advised that an initial resurgence of symptoms may not suggest GORD itself, but rather a transient acid hypersecretion that should resolve.[15] To support deprescribing, PPI dose tapering can be done or transitioned to as-needed, or alternative treatment can be used, such as H2-receptor antagonists or alginates.[15,17] However, contention remains about how much or whether such replacements may reduce deprescribing-related effects, such as reoccurrence of GORD.[18]

Although PPIs are generally tolerated well in the short term, some adverse effects may occur, including abdominal pain, diarrhoea, dizziness, headaches and nausea.[6,15,17] Less common side-effects may include mineral imbalances (such as hypomagnesaemia, hypokalaemia and hypocalcaemia), potential for enteric bacterial infections (e.g. *Clostridium difficile*), rebound acid hypersecretion, nutrient malabsorption, and bone density concerns,[6,15,17] though many of these are considered with chronic use or have associated confounding factors complicating their causality.[6,10,15,17] Some concerns have also been raised regarding potential cardiovascular and gastric cancer associations with chronic use.[6]

H2-receptor antagonists

Histamine (H)-2 receptor antagonists can be considered as an alternative or adjunct to PPIs when symptoms are mild or intermittent.[16,20] H2-receptor antagonists selectively and reversibly inhibit H2 receptors on gastric parietal cells, thus reducing the secretion of gastric acid into the gastric lumen.[21,20] In South Africa, cimetidine is the H2-receptor antagonist of choice following the removal of ranitidine due to concerns of carcinogenic contaminants.[22,23] Cimetidine is available as tablets (200 or 400 mg; Bio Cimetidine, Lenamet OTC) or an intravenous/intramuscular injectable (200 mg/2 mL; Pharma-Q Cimetidine).[19] Tablet administrations are taken with meals, typically as 400 mg four times per day for four to eight weeks (with a maximum dose of 2.4 g per day) for Bio Cimeditine, or three times daily for a maximum of two weeks and not exceeding 800 for Lenamet OTC.[19] Tolerance may develop with use, thus limiting the efficacy of H2-receptor antagonists.[20]

Cimetidine may incur altered bowel movement, including diarrhoea and constipation, and fatigue, though it is rare.[24] Cimetidine, due to anti-androgenic activity, may predispose male patients to unwanted side-effects, such as gynocomastia, which is not present in other H2-receptor antagonists.[21,24,25] Furthermore, it is a cytochrome P450 inhibitor, which increases the risk of associated drug-drug interactions.[21,25] Relative contraindications include cases of QT prolongation, urinary retention, hepatotoxicity and glaucoma.[24]

Antacids and alginate-based treatments

Antacids may be an alternative or adjunct to PPIs in mild or intermittent cases, but should only be considered for immediate relief.[16,26] Antacids neutralise acid via buffering systems which further reduces pepsin activity.[21,26,27] However, antacids only work acutely and for a short duration, thus limiting their efficacy in management.[20,21] Various antacids can be used throughout the day to help reduce gastric acidity before or after meals depending on their formulations.[19] Although safe, notable side-effects may include diarrhoea (magnesium hydroxide), constipation (aluminium hydroxide), bloating and flatulence.[26,27] Common combinations of aluminium and magnesium hydroxide may leverage the counteracting gastrointestinal disturbances to prevent altered bowel movements.[27] Furthermore, inappropriate use may mask underlying conditions leading to the concern, thus preventing appropriate treatment.[26]

Alginate-based treatments, such as those combined with antacids, can be considered to reduce post-prandial-mediated refluxate regurgitation[16] due to their ability to form a physical barrier on top of the gastric contents which perturbs the acid pocket and protects mucosa.[20,26,28] Combinations include: sodium bicarbonate, sodium alginate and calcium carbonate (suspensions such as Gelacid and Gelusil Plus; 10 to 20 mL four times daily); aluminium hydroxide, magnesium hydroxide and simethicone (tablets such as Gelusil-S; 1 to 2 tablets up to eight times per day); and oxethazaine, aluminium hydroxide and magnesium hydroxide (suspensions such as Mucaine; 5 to 10 mL four times daily).[19] Adverse effects may include self-limiting bloating or gastrointestinal distress, with rare hypersensitivity reaction.[28]

Conclusion

GORD remains a chronic and increasing concern in the community that may reduce the quality of life of individuals. While PPIs are considered the first pharmacotherapeutic option for treatment, rational use is needed to ensure it does not mask potential underlying triggering factors or potentiate medication burden or unnecessary use. Appropriate medication and disease review is needed to ensure continued treatment is justified and works to the benefit of the patient. As a multifactorial disease, management should be considered carefully to ensure that underlying reasons for the occurrence thereof be mitigated, with pharmacotherapy affording support to resolve symptoms and underlying pathophysiological concerns.

Conflict of interest

The author has no conflict of interest to disclose.

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