Taking the 'sauer' out of sauerkraut: a rapid update on the pathophysiology and treatment of gastro-oesophageal reflux disease

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Gastro-oesophageal reflux disease: a brief pathophysiological background

Gastro-oesophageal reflux disease (GERD), in layman's terms known as heartburn, is a condition characterised by frequent oesophageal contact with gastric acid. Contrary to what is generally accepted, GERD is *not* caused by excessive quantities of gastric acid. Rather, symptoms result from any combination of a number of contributing factors, including decreased lower oesophageal sphincter pressure, hiatus hernia (where the stomach protrudes through the diaphragm), reduced oesophageal and gastric clearance and compromised oesophageal mucosa barrier integrity.¹ Although most patients are able to manage GERD symptoms by means of lifestyle changes, chronic and recurrent episodes of reflux may result in erosive oesophagitis, nasal inflammation, dysphagia, i.e. difficulty in swallowing, and even pulmonary complications, e.g. asthma.²

Decreased lower oesophageal sphincter pressure can be caused by a number of factors, including diets rich in fats, cigarette smoking, and medication use. Further, apart from fatty meals, certain foods can have a direct influence on lower oesophageal sphincter pressure. These include citrus and tomato juice, coffee and overly spicy ingredients.¹ Considering the oesophageal and gastric clearance rate, a frequent construct underlying the manifestation of GERD is increased contact time between the oesophageal epithelium and gastric content. As such, rapid clearance rates result in briefer periods of contact, which ultimately prevents reflux symptomology. Patient cohorts that are especially susceptible to reduced oesophageal clearance rates are overweight and obese individuals and those following a sedentary lifestyle, pregnant women, and the elderly.¹ Although the oesophageal epithelium is not nearly as well protected against the erosive effects of gastric acid as the gastric epithelium itself, it does possess some innate protective mechanisms to prevent damage to especially the lower extremities of the oesophagus during brief periods of acidic exposure. These include acid-neutralising bicarbonate secretion, mucus production and epithelial cell contact via tight junctions.

Due to the brief nature of this review, a more detailed dissection of GERD and its anatomical and physiological correlates is beyond the scope of the current work. Instead, we will focus on the therapeutic interventions as they are founded on the abovementioned aetiopathological mechanisms underlying the condition.

The treatment of GERD

Lifestyle modification

As alluded to earlier, a number of lifestyle factors can contribute to the manifestation of GERD-related symptoms. As such, patients, especially those presenting with infrequent symptom episodes only, may benefit from improvements in lifestyle. Interventions that can often be made without significant effort include moderate weight loss, changing sleeping posture so that the head is elevated relative to the position of the abdomen, avoiding tight fitting clothes and, if possible, smoking cessation.^{3,4} That said, since patients often resist engaging in substantial and significant lifestyle modification, the majority of individuals will need pharmacotherapy to ensure adequate symptom prevention and resolution.

Pharmacotherapy

The main objectives in the treatment of GERD are symptom relief, prevention of symptom relapse, healing of erosive oesophagitis and prevention of complications.⁵ Conventional pharmacological treatment strategies for GERD do not focus on the pathophysiology of GERD, but rather on establishing a less acidic reflux content to improve heartburn symptoms and provide the eroded mucosa in the distal oesophagus, if present, sufficient time to heal.² As such, acid-suppressing therapy is currently the mainstay of GERD treatment, with proton pump inhibitors (PPI) being superior to histamine-2 (H₂) antagonists in this regard.^{6,7} Alternative pharmacological therapies include prokinetics, transient lower oesophageal sphincter relaxation inhibitors (TLESR), and oesophageal mucosal nociceptor blockers.⁶

The proton pump inhibitors (PPIs)

Since their first introduction in the 1980s, PPIs have gradually become the backbone of acid reduction therapy. The PPIs act as irreversible blockers of the activated H^+/K^+ -ATPase proton pump in the gastric parietal cells.^{8,9} Due to its relatively short half-life of 1–2 hours and considering that PPIs only bind to the activated form of the proton pumps in gastric parietal cells (in response to a meal), optimal acid suppression occurs when PPIs are administered 30–60 minutes prior to breakfast. However, once bound, the drug remains attached to the proton pump and is only cleared following the normal cell-specific degradation and replacement of the pump. This ensures a long-lasting effect, irrespective of their short half-life. That said, not all the parietal proton pumps are active during a single meal. As such, the efficacy of PPIs improves with subsequent dosing.¹⁰ Omeprazole was the first in its class, with esomeprazole, lansoprazole, pantoprazole and rabeprazole currently on the South African market. Similar therapeutic efficacy (healing of erosive oesophagitis and achieving symptom control) is a shared characteristic among the different conventional PPIs.^{11,12} In patients who do not present with severe symptoms, e.g. signs of gastro-intestinal bleeding, weight loss, and dysphagia, an empiric PPI-trial is currently considered not only to be a cost-effective diagnostic tool, but also an efficient initial intervention for GERD.¹³ In both erosive GERD (ERD) and non-erosive reflux disease (NERD), complete symptom relief is reported in 72% of patients, whereas this number decreases to more or less 50% if there is no objective evidence of abnormal oesophageal acid exposure.¹⁴ In the event where patients experience extra-oesophageal manifestations of GERD (hoarseness, non-cardiac chest pain, coughing and asthma) as well as nocturnal GERD, symptoms may require twice daily PPI treatment⁴ as superior intragastric pH control is achieved with a twice daily omeprazole 20 mg regimen compared to a once daily 40 mg omeprazole dose.¹⁵ For the approximately one third of patients that fail to respond to an eight-week trial of a standard PPI dose, switching to another PPI or doubling the dose (given twice daily) are common therapeutic strategies. Further, PPI therapy can be combined with alginates and H_2 antagonists for symptom relief; however, considering that PPIs are activated in an acidic environment, such strategies are to be used as a final resort only. Moreover, to overcome the concern of tolerance against the H_2 antagonists, it is recommended that they are given on demand and/or intermittently.¹⁶ Prokinetics (see below), TLESRs and neuromodulators may also be used as add-on therapy, but the additional benefits are usually limited to subgroups of the population.¹⁷ The efficacy of PPIs, their low incidence of side-effects and good tolerability has led to their widespread long-term use (even without an appropriate indication), raising concerns regarding the consequences thereof.¹⁸ These concerns, including ischaemic heart and chronic kidney disease, bone fractures, community-acquired pneumonia, *Clostridium difficile* intestinal infection and dementia, are however, essentially founded on data from large association studies, rather than causal studies.^{19,20} To date, the evidence of serious adverse effects resulting from long-term PPI use is lacking. Indeed, appropriate use of PPIs is more important than the risk of side-effects and it is

therefore recommended that physicians should keep prescribing these drugs in clinical conditions for which they are indicated.²⁰ Some patients may benefit from intermittently administered, brief PPI courses (at least five days), given on demand if symptoms recur,⁹ but continuous long-term treatment is usually the standard of care for appropriately diagnosed and confirmed GERD.^{8,21} Importantly, as no tolerance with regard to the acid suppression effects of PPIs develops – as opposed to what is seen with histamine H_2 receptor antagonists^{22,23} – patients that present with symptom exacerbation while being treated with PPIs should be referred to their medical practitioners for follow-up investigation.

Histamine H_2 receptor antagonists

Cimetidine and ranitidine are competitive antagonists of the parietal H_2 receptors that primarily inhibit nocturnal gastric acid secretion.²⁴ Post-prandial gastrin- or acetylcholine-induced gastric acid secretion is not effectively inhibited and attenuation of their antisecretory effects (tolerance) develops within two weeks of continuous twice daily administration.^{22,24,25} Consequently, the H_2 antagonists are not very effective in the treatment of GERD associated with postprandial reflux.²¹ Although bedtime H_2 antagonists are sometimes used to treat nocturnal gastric acid breakthrough in patients already on a twice daily PPI regimen,^{26,27} controversy exists over its long-term efficacy due to the development of tolerance.^{17,28,29} H_2 antagonists are usually well tolerated, but may increase the risk of infections because of acid suppression.³⁰ Recently, ranitidine was the focus of intense clinical scrutiny, due to carcinogenic concerns related to one of the ingredients in ranitidine formulations, i.e. N-nitrosodimethylamine (NDMA). As such, from 1 October 2019, the South African Health Products Regulatory Authority (SAHPRA) has advised South Africans to return any heartburn medicines that contain ranitidine to their pharmacies, while the marketing of ranitidine-containing products was banned with immediate effect.

Antacids and alginates

Antacids neutralise gastric acid after it is secreted and are useful for rapid and temporary symptom relief of mild, occasional heartburn; however, they are not effective in healing erosive oesophagitis.^{4,31} Most antacids consist of combinations of aluminium and magnesium hydroxide, while some effervescent antacids also contain sodium bicarbonate. Calcium carbonate is the most potent antacid available.⁴ However, carbonate-containing antacids are not recommended due to their carbon dioxide-generating effect, which results in flatulence and relaxation of the oesophageal sphincter. Although being cost-effective and relatively safe, they are not free from risks and side-effects (diarrhoea with magnesium-containing and constipation with aluminium-containing formulations). Alginate, an insoluble substance that increases the surface tension of the gastric liquid content, is sometimes included in antacid preparations to form a protective layer against oesophageal acid exposure³² and to displace the postprandial gastric acid pocket.³³ Such

combinations were found to be more effective in improving GERD symptoms than antacids alone.³⁴

Prokinetics

The objective of prokinetic agents in the treatment of GERD is to enhance lower oesophageal sphincter tone, improving oesophageal clearance and increasing gastric motility, thereby increasing the emptying rate of gastric contents³⁵ and decreasing oesophageal exposure to gastric content. Examples of prokinetics include metoclopramide (lipophilic dopamine/serotonin receptor antagonist), domperidone (hydrophilic dopamine receptor antagonist), bethanechol (muscarinic receptor agonist), erythromycin (macrolide with motilin receptor agonist effects) and baclofen (GABA_B receptor agonist).³⁶ Of these, baclofen is associated with the most favourable side-effect profile, especially in paediatric patients.³⁶ Nevertheless, baclofen therapy used in combination with a PPI, could in fact result in greater side-effect risk.³⁷ In turn, the central nervous system activity of metoclopramide limits its use, with the peripheral dopaminergic agonist, domperidone, considered as alternative. Importantly, domperidone is currently not FDA-approved for the treatment of GERD,³⁸ probably because of its limited efficacy.³⁹ The increasing awareness of antimicrobial resistance also limits the use of erythromycin (and other macrolides) in the treatment of GERD. Regardless, the combination of a prokinetic agent with a PPI does not appear to have any significant clinical advantage over PPI monotherapy.^{9,37} Finally, although also being able to induce prokinetic effects, cisapride is no longer available because of its potential to induce heart rhythm abnormalities.³⁶

Potassium-competitive acid blocker

Vonoprazan is a potassium-competitive acid blocker (P-CAB) that was approved for clinical use in Japan in 2014.⁴⁰ Its mechanism of action involves competing with K⁺ at the H⁺/K⁺-ATPase proton pump, thereby blocking H⁺ secretion.⁴¹ The main advantages of vonoprazan over commonly-used PPIs include it being stable in an acidic environment, binding *reversibly to both the active and resting phase of H⁺/K⁺-ATPase*, and its slower dissociation rate from the binding site. As such, vonoprazan has a longer half-life than the PPIs in general and can be taken before or after a meal. Further, it demonstrates therapeutic benefit after a single dose.^{40,41} Vonoprazan has produced comparable therapeutic outcome to PPI monotherapy,⁴² yet its efficacy in PPI-resistant GERD^{43,44} is what makes it an attractive treatment alternative to PPI-augmented therapy. Finally, the side-effect profile of vonoprazan is also considered acceptable (pending larger and future studies), with mild to moderate gastrointestinal-related side-effects, nasopharyngitis and headache most commonly reported,⁴⁵ while a four to eight-week treatment period does not induce any significant liver function alterations.⁴⁵

Mucosal protectants

Mucosal protectants can be used in severe cases of erosive esophagitis. These include misoprostol, sucralfate and bismuth. However, they present with minimal therapeutic benefit in uncomplicated GERD or isolated heartburn episodes.¹ Further,

with respect to misoprostol, which is prescribed in South African abortion drug regimens, its use for non-abortion-related indications is not advised due to the significant risk it poses to women of reproductive age.

Conclusion

In this review, we provided a rapid review of current literature pertaining to GERD. Although the mainstay of treatment for GERD in South Africa is still founded on PPIs, alternatives include lifestyle change, H₂ antagonists and novel drugs, i.e. vonoprazan (not yet registered in South Africa). Although the widespread use of PPIs raised some concern in terms of safety, large-scale, retrospective meta-analyses failed to reveal any significant risk to patient safety.

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