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Review

Evidence that changes the way you practise: the pharmacological management of gastro-oesophageal reflux disease

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Abstract

Gastro-oesophageal reflux disease (GORD) is defined as a chronic symptom-based disease that affects the upper gastrointestinal tract, resulting in mucosal damage caused by the retrograde flow of gastric acid from the stomach through an incompetent cardiac sphincter into the lower oesophagus. Typically, symptoms include dyspepsia, epigastric pain, heartburn, belching, bloating, nausea, early satiation and postprandial fullness. Several risk factors have been identified, which mainly include alcohol (15%), aspirin and nonsteroidal anti-inflammatory drugs (25%), corticosteroids, obesity and pregnancy (10%), hiatal hernias (60-80%), hypercalcaemia, *Helicobacter pylori* infection (40-90%) and hypersecretory states (Zollinger-Ellison syndrome). Complications of GORD include non-oesophageal reflux disease, erosive oesophagitis, Barrett's oesophagus and adenocarcinoma. A study in the USA showed that GORD was responsible for the greatest direct cost of any gastrointestinal disease, and most of that expenditure was on pharmacotherapy. The pharmacological management of GORD will be the focus of this article.

Keywords: gastro-oeosophageal reflux disease, gastric secretion, dyspepsia, proton-pump inhibitor, histamine-2-receptor antagonists

Introduction

Gastro-oesophageal reflux disease (GORD) is defined as a chronic symptom-based disease that affects the upper gastrointestinal tract, resulting in mucosal damage caused by the retrograde flow of gastric acid from the stomach through an incompetent cardiac sphincter into the lower oesophagus.[1] Typically, symptoms include dyspepsia, epigastric pain, heartburn, belching, bloating, nausea, early satiation and postprandial fullness.[2] Several risk factors have been identified, which mainly include alcohol (15%), aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) (25%), corticosteroids, obesity and pregnancy (10%), hiatal hernias (60-80%), hypercalcaemia, *Helicobacter pylori* infection (40-90%) and hypersecretory states (Zollinger-Ellison syndrome).[3] Complications of GORD include non-oesophageal reflux disease (NORD), erosive oesophagitis (EO), Barrett's oesophagus and adenocarcinoma. A study in the USA showed that GORD was responsible for the greatest direct cost of any gastrointestinal disease, and most of that expenditure was on pharmacotherapy.[4]

GORD is a major cause of ill health and debility if not managed properly, and is a common worldwide phenomenon, with an estimated 20-40% incidence in the global adult population. Statistics published by the American Gastroenterological Association revealed that only 5% of patients with symptoms of dyspepsia present to their general practitioner, of whom approximately 1% are referred for endoscopy.[5] Many patients self-medicate with over-the-counter (OTC) medications, such as antacids, low-dose histamine-2-receptor antagonists (H_2RAs) and low-dose proton-pump inhibitors (PPIs) to relieve the episodic or food-related symptoms of GORD. Typically, these patients do not seek medical advice unless their symptoms persist or worsen. The advantage of self-treatment with OTC drugs is the provision of effective and rapid symptomatic relief for approximately 25% of patients with GORD. It is reported in South Africa that nearly 20% of patients first present to their pharmacist,[6] and that 27% seek treatment from a traditional healer or herbalist before consulting a physician.[7]

GORD is no longer a condition that is only treated by doctors. Various treatment options exist, and numerous treatment guidelines are published and updated regularly. Adequate control of acid secretion is key to the successful management of GORD. This ranges from lifestyle modification, antacid and acid secretion modifiers (H_2RAs and PPIs) to anti-reflux surgery.[8] Psychological therapeutic interventions and alternative medicine techniques, such as acupuncture, are controversial, but show some benefit, especially in NORD patients who have failed anti-reflux treatment.[9] Allied healthcare professionals, including nurses and pharmacists, are encouraged to treat GORD in the absence of danger signs (weight loss, haematemesis, melaenia and dysphagia) for a two-week period with either an antacid or a PPI, according to the latest *Standard treatment guidelines and essential medicines list for South Africa: 2012 edition.*[10] This might be seen as a cost-saving method as most of these PPIs were previously only available as a prescription Schedule 4 substance. Recently, some formulations of pantoprazole and lansoprazole were reclassified as Schedule 2 drugs, and therefore don't require a prescription. However, a limitation has been imposed, and the supply may not exceed a treatment period of 14 days, after which referral to a physician is mandatory.[6]

Table I: Clinical comparison between the selected end-points of available proton-pump inhibitors

	Esomeprazole	Omeprazole	Rabeprazole	Lansoprazole	Pantoprazole
Mean *Helicobacter pylori* eradication after triple therapy	86%	84%	87%	85%	71%
Reduction in acute gastrointestinal bleeding	94%	83%	96%	94%	84%
Time to adequate GORD symptom relief	6 days	2 days	2 days	4 days	4 days

GORD: gastro-oesophageal reflux disease

H_2RAs have always been available as either a Schedule 2 or 3 substance, depending on the quantity and strength of the active ingredient. They provide quick and effective symptomatic relief, particularly in patients with mild GORD, but become less effective over time. Currently, cimetidine and ranitidine are the only drugs from this class that are still available in South Africa. Cimetidine is the least expensive, but the high incidence of drug interactions [the inhibition of cytochrome P450 (CYP450] and endocrinological side-effects (gynaecomastia and loss of libido) make it unsuitable for long-term use, especially in male patients. First-line monotherapy with an H_2RA has largely been replaced by a PPI, and its only justifiable indication may be in combination therapy with omeprazole for conditions characterised by excessive nocturnal gastric acid secretion that has not adequately responded to a PPI alone.[11]

When compared to H_2RAs, PPIs provide faster and more significant symptomatic relief and show better healing of ulcers, including the prevention of EO.[8] They also represent pharmacological superiority in the inhibition of acid secretion, and provide reliable, single daily-dose efficacy, including the risk reduction of ulcers in patients taking NSAIDs.[12] Studies have also shown that patients who are given prescriptions for PPIs tend to be more satisfied than those who are given H_2RAs.[13]

Choice of proton-pump inhibitor

PPIs have a similar mechanism of action in the suppression of gastric acid secretion. They cause irreversible inhibition of the H^+/K^+ ATPase enzyme (proton pump) in the gastric parietal cells. The restoration of acid production only recurs after *de novo* re-synthesis of the proton pump, which takes approximately 50 hours. This is the reason for the prolonged antisecretory clinical effect, in spite of an average plasma half-life ranging from 1-3 hours.[14] Many studies have been published that favour one PPI over another, but when the therapeutic end-point in clinical effectiveness is considered, it has to be concluded that the choice of PPI mainly resides in variables such as patient or prescriber preference, cost, availability, adverse effects, onset of action and drug interactions.[15] With the exception of omeprazole, these drugs have a limited propensity for drug-drug interactions, although metabolism occurs via the CYP450 system. This is illustrated by a few examples from the published literature. The reviews are summarised in Table I.

Refractory gastro-oesophageal reflux disease and noncompliance

On-demand therapy with currently available PPIs appears to be effective in the long-term management of approximately 70% of patients with NORD or mild and uninvestigated forms of GORD. However, PPIs are not as effective as monotherapy in patients with severe EO.[16] Therefore, PPI failure may occur in up to 30-40% of patients. Some mechanisms that may contribute to this unfortunate occurrence include residual acid reflux, weakly acidic and weakly alkaline reflux, oesophageal hypersensitivity, psychological co-morbidity and an incorrect diagnosis. Lack of patient compliance may be as high as 50%, and should be cautiously observed and include proper patient education. Upper endoscopy and pH testing seem to have limited diagnostic value in elucidating the reasons for failed PPI treatment.[17] Increasing the dose or switching to another PPI should then be considered, followed by transient lower oesophageal sphincter relaxation reducers, endoscopic treatment, anti-reflux surgery and pain modulators.

Helicobacter pylori and non-malignant diseases

Triple therapy, consisting of a PPI with a combination of two antibiotics, remains the mainstay of *H. pylori* eradication. However, with increasing resistance to clarithromycin; tetracyclines and levofloxacin, in combination with amoxicillin, have been the focus of recent prescribing trends in first-line treatment failure.[18] *H. pylori* eradication results in a decreased incidence of recurrent peptic ulcer bleeding, and newer guidelines advocate a test-and-treat approach in patients with a previous history of ulcer bleeding and NSAID use. It has also been shown that there may be an inverse relationship between *H. pylori* infection and asthma or allergy.[19]

Proton-pump inhibitors in the elderly

PPIs are regarded as being relatively safe in the elderly, although there have been reports of various adverse effects, the most important being pneumonia, osteoporosis and bone fractures, bacterial infections *(Clostridium)* and a decrease in vitamin D and magnesium, which might be problematic in elderly patients on prolonged therapy. Therefore, it is relevant to consider the risk to benefit ratio in this age group.[20]

Proton-pump inhibitors in children

Peptic conditions in the paediatric population have long been managed with PPIs, achieving significant success in conditions including gastric ulcers, established *H. pylori* infections and GORD. Safety data on children younger than one year of age are not readily available, except for the recent approval of esomeprazole in the management of EO in infants. Although these drugs are regarded as safe, they are cleared by the CP450 enzyme system, which only functions effectively from approximately 5-6 months after birth. Therefore, this immature functionality may cause a decrease in the clearance and elimination of PPIs in infants, exposing them to potential adverse effects. However,

the treatment of paediatric patients with PPIs has not been associated with significant abnormalities or unwanted serious side-effects.[21]

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