Review

Pharmacological management of GERD: where does it stand now?

Tiberiu Hershcovici and Ronnie Fass

The Neuroenteric Clinical Research Group, Southern Arizona VA Health Care System and University of Arizona Health Sciences Center, Tucson, AZ, USA

Gastroesophageal reflux disease (GERD) is very common and advances in drug development over recent years have markedly improved GERD management. A wide range of medications are currently used in GERD treatment, including antacids, Gaviscon, sucralfate, histamine-2 receptor antagonists and prokinetics. However, proton pump inhibitors (PPIs) remain the mainstay of treatment for GERD owing to their profound and consistent inhibitory effect on acid secretion. Despite the presence of a wide armamentarium of therapeutic modalities for GERD, many areas of unmet needs remain. Drug development has focused primarily on improving PPI efficacy, reducing the transient lower esophageal sphincter relaxation rate, attenuating esophageal sensitivity and developing esophageal mucosal protectants.

Introduction

Gastroesophageal reflux disease (GERD) is the most common outpatient gastroenterological diagnosis in the USA, with a prevalence rate of 10–20% and an annual incidence of 0.38–0.45% in the Western world [1]. In the USA, 20% of the adult population experiences GERD-related symptoms weekly [2] and 7% daily [3]. GERD significantly reduces health-related quality of life and imposes a marked economic burden on the healthcare system [4]. In some patients, chronic acid reflux from GERD leads to erosion of the esophageal tissue and other complications (Box 1).

Acid suppression, most notably with proton pump inhibitors (PPIs), is currently the mainstay of therapy for GERD. Introduction of the PPI class revolutionized the management of GERD. However, resolution of esophageal mucosal inflammation seems to be much more predictable than resolution of symptoms in patients with GERD who receive PPI treatment. Consequently, failure of PPI treatment to resolve GERD-related symptoms has become the most common presentation of GERD in gastroenterological practice in the last decade. Furthermore, GERD is a chronic relapsing disorder, and thus long-term maintenance therapy with antireflux medication is typically needed. However, none of the currently available medications for GERD provides long-term cure of the disorder. Furthermore, pharmacological intervention in GERD has focused primarily on reducing acid reflux rather than targeting the direct causes of the disorder, such as transient lower esophageal sphincter relaxation (TLESR).

In this review, we summarize the data available on current pharmacological management of GERD (Table 1). Although we can celebrate the development of highly potent remedies for GERD, there are still many areas of unmet needs that will continue to require future attention.

Antacids and Gaviscon

Antacids have been around for a long period of time and have remained very popular among consumers of over-the-counter (OTC) medications. They are primarily used as needed (on demand) for episodic heartburn, commonly postprandial (following a meal). Antacids are basic compounds composed of different combinations of acid-neutralizing agents such as aluminum and magnesium hydroxide, calcium carbonate, sodium citrate and sodium bicarbonate. They provide rapid but transient symptom relief and do not contribute to healing of erosive esophagitis (EE) or prevention of GERD complications [5,6]. Side effects are dose-related and were noted more frequently in the past when these drugs were used extensively in the treatment of peptic ulcer disease. In general, magnesium-containing antacids cause diarrhea and aluminum-containing antacids can cause constipation.

Alginate-based formulations have been used for the symptomatic treatment of heartburn for decades under various brand names including Gaviscon. Alginate-based formulations usually contain sodium or potassium bicarbonate. In the presence of gastric acid, a foamy raft is created above the gastric contents. The alginate raft can preferentially move into the esophagus in place or ahead of acidic gastric contents during reflux episodes or alternatively can physically prevent reflux of gastric contents into the esophagus [7].

Sucralfate

Sucralfate, an aluminum salt of a sulfated disaccharide, is considered a mucosal protectant that binds to inflamed tissue to create a protective barrier. It is supposed to block diffusion of gastric acid and pepsin across the esophageal mucosa and inhibit the erosive action of pepsin and possibly bile. Sucralfate stimulates secretion of growth factors implicated in ulcer healing and of mucus and bicarbonate. The binding of this agent to the ulcer base is enhanced at pH below 3.5. It has been shown that sucralfate is equally effective as histamine 2 receptor antagonists (H2RAs) and alginic acid plus antacids in controlling GERD symptoms in patients with EE [8–10]. However, healing of esophageal

Corresponding author: Fass, R. (ronnie.fass@va.gov)

 0165-6147/$ – see front matter. Published by Elsevier Ltd. doi:10.1016/j.tips.2011.02.007 Trends in Pharmacological Sciences, April 2011, Vol. 32, No. 4

Box 1. Factors contributing to gastroesophageal reflux, esophageal injury and GERD-related symptoms

Esophageal factors
- Reduced or altered peristalsis
- Reduced saliva delivery to the esophagus
- Alteration in mucosal resistance (defense and repair)
- Dilated intraepithelial spaces
- Hypersensitivity

Antireflux barrier
- Transient lower esophageal sphincter (LES) relaxations
- Hypotensive LES
- Stress reflux
- Hiatal hernia

Gastroduodenal factors
- Delayed gastric emptying

Phenotypic presentation
Nonerosive reflux disease (NERD)
- Presence of troublesome reflux-associated symptoms in the absence of mucosal breaks at endoscopy

Erosive esophagitis
- Endoscopically visible breaks of the distal esophageal mucosa

Barrett's esophagus
- A change in the distal esophageal epithelium of any length that can be recognized as columnar type mucosa at endoscopy and is confirmed to have intestinal metaplasia by biopsy

Complications
- Esophageal ulceration
- Esophageal stricture
- Esophageal adenocarcinoma
- Extraesophageal manifestations
- Pharyngeal
- Laryngeal
- Pulmonary
- Sleep

Table 1. Pharmacological therapeutic options for GERD

Drug class	Dose[a]
Alginates	
Sodium alginate (Gaviscon®)	10–20 ml qid
Mucosal protectants	
Sucralfate (Carafate®)	1g po qid
Prokinetic agents	
Metoclopramide (Reglan®)	5–10 mg po q6–8 h
Domperidone (Motilium®)	10–20 mg po tid
Cisapride (Propulsid®)	5–10 mg po qid
Histamine type-2 receptor antagonists	
Cimetidine (Tagamet®)	400 mg po bid (OTC 200 mg)
Ranitidine (Zantac®)	150 mg po bid (OTC 75mg)
Famotidine (Pepcid®)	20 mg po bid (OTC 10 mg)
Nizatidine(Azid®R)	150 mg po bid
Proton pump inhibitors	
Omeprazole (Prilosec®)	20 mg po qd (OTC 20 mg)
Rabeprazole (Aciphex®)	20 mg po qd
Pantoprazole (Protonix®)	40 mg po qd
Lansoprazole (Prevacid®)	30 mg po qd
Esomeprazole (Nexium®)	40 mg po qd
Dexlansoprazole MR (Dexilant®)	30–60 mg po qd
Immediate-release omeprazole (Zegerid®)	20 mg po qd
TLESR reducers	
Baclofen	10–20 mg po tid

[a]Abbreviations: qid, *quater in die*; po, *per os*; q6–8 h, *quaque* 6–8 h; tid, *ter in die*; bid, *bis in die*; OTC, over the counter; qd, *quaque die*.

inflammation is limited to low grades of EE. Sucralfate seems to be better than placebo in improving symptoms in patients with nonerosive reflux disease (NERD) [11]. Sucralfate has minimal side effects. It can bind other drugs if taken simultaneously, although the clinical consequences are negligible.

Sucralfate is rarely prescribed today as the sole treatment for GERD, primarily because of its limited efficacy compared to PPIs and the need for multiple dosing (*quater in die*). However, the drug is commonly used for GERD treatment in pregnant women owing to a lack of maternal or fetal adverse events [12].

H2RAs

The first acid-suppressive agents developed in the 1970 s were the H2RAs. The prototype, cimetidine, was the culmination of a project at Smith, Kline & French led by James W. Black. H2RA therapy results in reliable healing of peptic ulcers and healing of mild to moderate EE. Although H2RAs improve symptoms in the majority of GERD patients, they do not reliably or completely eliminate symptoms in most patients. In addition, H2RAs perform poorly in patients with severe grades of EE.

Regardless, H2RAs are still widely used for the treatment of GERD. H2RAs reduce gastric acid output by competitive inhibition of histamine at H2-receptors on parietal cells (stomach epithelial cells). H2RAs reduce pepsin output by an unknown mechanism and reduce gastric acid volume as well [13]. As a class, the different H2RAs are considered equivalent in suppressing gastric acid output when administered in equipotent doses. The pharmacokinetic differences among the agents seem to be clinically nonsignificant [14]. Although H2RAs are effective in controlling basal acid secretion, they are less effective in suppressing postprandial acid secretion. Standard doses are effective in controlling symptoms and in healing mild to moderate EE (up to 70% of EE patients). In a meta-analysis, the efficacy of 8 weeks of H2RA treatment in healing EE was 64% for grade I and 55.5% for grade II [15]. More severe forms of EE require greater acid suppression, which H2RAs are less able to provide. Clinical trials with higher doses of H2RAs, which attempted to address this concern, have yielded conflicting results [16,17].

The potential effect of H2RAs on the nighttime histamine-driven surge in gastric acid secretion led to popular use of these drugs at bedtime by patients who continued to be symptomatic on a standard or double-dose PPI [18]. However, tachyphylaxis develops quickly with H2RAs, which limits their regular use in clinical practice [19]. The main appeal of H2RAs is their use as an on-demand therapy. Their rapid effect on GERD symptoms, which is unsurpassed by any of the currently available PPIs, makes this class of drugs a very popular OTC remedy for many GERD sufferers who never seek medical attention.