REVIEW ARTICLE

Role of Sodium Alginate in Gastroesophageal Reflux Disease: An Overview

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ABSTRACT

Sodium alginate helps manage and treat heartburn and gastroesophageal reflux disease (GERD). This article discusses the structure, mechanism of action and clinical application. A brief review of the literature is carried out.

Keywords: Gastroesophageal reflux disease, sodium alginate

Gastroesophageal reflux disease (GERD) is a digestive disorder that occurs when gastric contents, which are acidic stomach juices or food and fluids, reflux from the stomach into the esophagus. This irritates the stomach lining, leading to heartburn and regurgitation occurring two or more times a week[1]. The symptoms can occur in the daytime but have a higher impact at night due to loss of usual physiological function associated with sleep and supine position[2]. In India, 22.2% of people suffer from heartburn[3]. The prevalence of GERD ranges from 7.6% to 30%, and less than 10% of GERD patients in India have erosive esophagitis[4].

The typical symptoms of GERD are heartburn, regurgitation and water brash/hypersalivation, while the atypical symptoms are nausea, eructation/belching, bloating, slow digestion, early satiety, vomiting, epigastric pain, precordial chest pain, early and nocturnal awakening and nightmares, hoarseness, pharyngeal pain, cough, wheeze and chronic rhinosinusitis. The alarming symptoms of GERD include dysphagia, odynophagia, epigastric mass, gastrointestinal tract bleeding and lymphadenopathy[5]. Patients with GERD have significantly poor health-related quality of life (HRQoL). The rate and intensity of acid complaints or gastrointestinal symptoms significantly influence the quality of life. The presence of gastrointestinal symptoms is associated with reduced work productivity[6].

Treatment goals and strategies of GERD are based on (a) effective and rapid relief of symptoms and improvement in HRQoL for patients; (b) healing of esophageal mucosal damage, preventing the relapse of erosive esophagitis and reducing the development of other serious complications; (c) preventing the repeated reflux of gastric contents into the esophagus and reduce the damaging effect of gastric acid[6,7].

MECHANISMS OF ACTION OF VARIOUS DRUGS FOR TREATMENT OF GERD

Antacids

Antacids reduce the acid reaching the duodenum by neutralizing the acid present in the stomach[8]. They also offer rapid and short-term relief[9]. The easily available antacids and serotonergic or dopaminergic receptor activators offer only short-term relief of symptoms[9].

Proton Pump Inhibitors

Proton pump inhibitors (PPIs) bind and inactivate the hydrogen potassium ATPase in the parietal cells of gastric mucosa. They are rapid-acting and produce a considerable but dose-dependent elevation of gastric pH[4]. PPIs do not significantly change the size and position of acid pockets, nor do they displace them to a more distal location. Acid pockets persist even after treatment with PPIs[10]. The long-term continuous use of PPIs and prokinetics is associated with chronic side effects, which limit their use. Safety implications with PPIs include increased risk of diseases, such

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as hospital- and community-acquired pneumonia, *Campylobacter enteritis*, *Clostridium difficile*-associated disease and fractures[11]. Despite high efficacy, failure to respond to PPIs has now become the most common presentation in gastrointestinal practice[12].

Prokinetics

Since it is a known fact that the pathogenesis of GERD is a disordered function of the lower esophageal sphincter, the use of a prokinetic agent in such patients seems logical[13]. Prokinetics activate serotonergic or dopaminergic receptors to increase esophageal and gastric peristalsis, which aids in esophageal clearance[9,14]. This is particularly crucial for individuals with GERD characterized by transient lower esophageal sphincter relaxation (TLESR), which refers to spontaneous lower esophageal sphincter relaxation unrelated to swallowing and plays a pivotal role in GERD patients.

In GERD patients, symptom relief through acid-suppressive therapy usually obviates the need for additional treatments or diagnostic procedures. Acid-suppressive therapy, such as proton pump inhibitors (PPIs), alleviates symptoms, fosters esophageal healing and mitigates potential complications. However, addressing the underlying cause of TLESR may become necessary to sustain remission and deter relapses. In situations where acid-suppressive therapy falls short of yielding a complete response, including a prokinetic agent may be advantageous[15].

Additionally, prokinetics alone may not be sufficient for significant relief in GERD patients. When used in conjunction with PPIs, prokinetics reduce the frequency of reflux episodes, resulting in more substantial improvements in symptom scores[16].

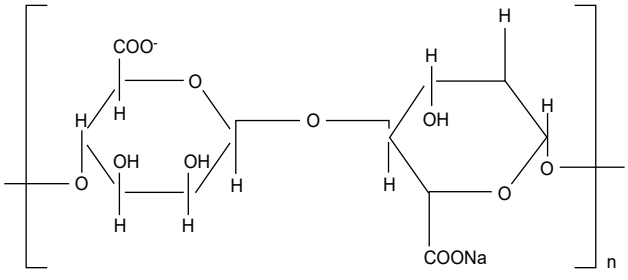
Histamine Receptor Antagonists

The histamine receptor antagonists competitively and reversibly block histamine type 2 (H_2) receptors, thereby decreasing gastric acid secretion. They are safe and significantly more effective than antacids. Acid suppression therapy with histamine receptor antagonists, though effective, has slower onset of action and is relatively ineffective in most patients[6]. Patients continue to use acid-reducing medications regularly and have no significant differences in grade of esophagitis and impact on quality of life[9,13].

Alginates

Alginates precipitate to form a gel, which then floats in the stomach and displaces postprandial gastric acid pocket, thus physically blocking the refluxate from entering the esophagus. It may also coat and protect the esophageal mucosa[9]. The acid pocket is a phenomenon that occurs in both healthy individuals and in patients suffering from esophageal hypersensitivity after a meal. Acid pockets are unbuffered acidic regions formed near the gastroesophageal squamocolumnar junction during postprandial period. This region escapes the buffering effect of meals, remaining highly acidic (median pH 1.6) compared with the body of stomach (pH 4.7) and thus is termed acid pocket. It plays an important role in causing acid reflux by shortening the lower esophageal sphincter after a meal or during transient hiatus herniation[17].

Structure of sodium alginate



Sodium alginate is a basic polysaccharide derived from alginic acid. It is composed of 1,4-β-D-mannuronic and L-guluronic acid. It is obtained from brown algae and contains 30% to 60% alginic acid. The conversion of alginic acid to sodium alginate allows its solubility in water, which assists in its extraction[18]. The floating ability of alginate depends on the amount of carbon dioxide generated, amount of carbon dioxide entrapped in gel and the molecular properties of alginate, i.e., molecular weight and the ratio of D-mannuronic and L-guluronic acid. The addition of calcium to the alginate crosslinks with an alginate-containing acid polymer, that aids in floating with greater viscoelastic strength. On the other hand, the combination of aluminum and alginate reduces floating ability. The magnesium-alginate antacid formulation also remains floating in the stomach for only 1 hour[19].

Modes of action

Alginates act by the following modes.

Prevention of gastric reflux: Alginates prevent gastric reflux by suppressing gastric reflux, and preventing postprandial reflux. The G-block structure of sodium alginate reacts with the acid in the stomach, thus producing a low-density gel that floats on top of stomach contents. This forms a physical barrier that suppresses gastric reflux. The physical barrier formed by alginate eliminates or displaces the acid pocket, preventing postprandial acid reflux[20].

Inhibition of pepsin and bile acids: Alginates inhibit pepsin and bile acids by reflux of pepsin and bile acids and by relieving symptoms, such as regurgitation and heartburn. Pepsin and bile acids are believed to be a major etiological factors associated with the development of gastroesophageal complications, i.e., Barrett's esophagus and esophageal adenocarcinoma. Alginate relieves symptoms by removing both pepsin and bile acids from gastric refluxate, thus limiting their diffusion and aiding relief[18,20].

Mucosal protection: Alginates protect the mucosa firstly by reflux prevention and secondly by their bioadhesive potential. They play a major role in protecting esophageal mucosa by reducing risk of inflammation via prevention of reflux of gastric contents. Alginates form an adherent viscous layer when it comes in contact with the esophageal mucosa and demonstrate bioadhesive potential[20].

Sodium alginate has a rapid onset of action, within 1 hour of administration, when compared to other antacids[21]. The mode of action of alginate is physical and does not depend on absorption into the systemic circulation. On ingestion, alginate reacts rapidly with gastric acid to form an alginic acid gel, which has a near neutral pH and floats on the stomach contents and thus quickly and effectively prevents the impending gastroesophageal reflux. Alginate formulations require three chemical reactions to take place simultaneously: transformation to alginic acid, sodium bicarbonate reacting to form carbon dioxide and calcium carbonate releasing free calcium ions to bind with alginic acid providing strength to float. In severe cases, the float itself may be refluxed into the esophagus, in preference to the stomach contents, and exert a demulcent effect. The sodium alginate was found to be retained in the stomach for up to 4 hours, thus preventing acid reflux for a longer duration[22].

Alginate-containing formulations are safe, well-tolerated and comparable to the other antireflux medications such as omeprazole, ranitidine and other nonalginate antacids. Additionally, there have been no reports of any significant adverse events associated with alginate antacids. Alginate very rarely causes immune system disorders in the form of anaphylactic and anaphylactoid reactions and hypersensitivity reactions such as urticaria and respiratory effects like bronchospasm[23-26].

Uses of alginate

The floating ability of sodium alginate above the acid pocket aids in preventing acid reflux. Alginate therapy successfully led to a reduction in regurgitation compared to patients in the placebo group[23]. A randomized, double-blind placebo control trial suggested that the alginate-antacid combination (n = 212) compared to placebo (n = 212), is an effective treatment option in patients with reflux symptoms[7].

In obese patients, the alginate-antacid combination was more effective than control in suppressing gastric reflux after a late-night supper[23]. Sodium alginate was effective in patients suffering from heartburn and epigastric pain due to its faster onset of action, thus providing long-term relief of symptoms[27]. Sodium alginate, compared with anhydrous magaldrate was found to be quick in relieving heartburn symptoms and/or acid regurgitation[28].

Due to its localizing and acid neutralizing effect, the alginate-antacid combination was significantly more effective in reducing gastric reflux events[29]. The alginate-antacid combination is also effective in reducing postprandial esophageal acid exposure[30].

Adding sodium alginate to PPI therapy was significantly more effective in attaining a complete resolution of heartburn and heartburn-free days compared to PPI therapy alone[31]. Alginates were also effective in step-down or cessation of PPI therapy[11,20].

In patients, the addition of alginate with H_2 receptor antagonists was observed to be more effective in alleviating gastric acid reflux. Gastric reflux events were significantly reduced with sodium alginates compared to cimetidine[32].

Need of Alginate-antacid Combination

PPIs are considered the first-line approach for endoscopic healing and symptomatic relief in patients with GERD. Still, a substantial subgroup of patients, around 30%, continue to experience reflux symptoms despite adequate dosing[12,20]. Either because of general unease with open-ended pharmacotherapy or because of the intermittent nature of reflux symptoms, prefer to address reflux symptoms with PRN medication. The problem has been the limited efficacy of this approach; antacids neutralize gastric acid in a short time frame after ingestion, but the effect is soon overcome by meal-stimulated acid secretion[30].

On the other hand, treatment with the combination of alginate and antacid decreases the severity and frequency of heartburn, leading to complete resolution of symptoms[20]. The combination potentially targets postprandial symptoms because of its localized acid-neutralizing action in the proximal stomach, while maintaining effective alginate float[7]. The alginate-antacid

combination decreases burden of reflux symptoms, especially in PPI-unresponsive patients. The oral suspension of alginate that contains antacids, such as calcium carbonate, sodium bicarbonate and magnesium hydroxide, is used[20].

It should be given only on medical advice in children under 12 years of age. In adults and children over 12 years, 10-20 mL after meals and at bedtime is given. No dosage modification is required in elderly persons and patients with hepatic impairment, and can be safely administered. Alginate should be cautiously administered in renal insufficiency patients if a highly restricted salt diet is necessary. In patients with diabetes, sugar-free formula can be administered. Alginate is considered a safe treatment of choice for GERD during pregnancy[12,20].

CONCLUSION

Sodium alginate is useful in treating GERD, more so when combined with antacids and PPIs.

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