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The role of alginate-based therapy in gastroesophageal reflux disease

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Abstract

Gastroesophageal reflux disease (GERD) is one of the most common digestive pathologies, with worldwide spread and increasing incidence. Due to the chronic nature of this condition, the dreaded complications that can occur during evolution and the negative impact on patients' quality of life, it is imperative to administer symptomatic treatment to eliminate or improve symptoms, cure erosive esophagitis and prevent recurrences and complications. Alginic acid formulations have a unique, particular mechanism of action, acting as a long-lasting physical barrier floating on the surface of the gastric pool, displacing the postprandial gastric acid pocket and protecting esophagus mucosa during reflux episodes. Numerous studies evaluated the efficacy of alginate treatment in GERD, by comparison to antacids, proton pump inhibitors (PPIs), histamine 2 receptor antagonists (H2RAs), or placebo. While most studies found superiority of alginate treatment when compared to antacids or to placebo, PPIs treatment was overall more effective than alginate in controlling GERD symptoms. There were some trials that reported alginate non-inferiority when compared to PPIs, especially in the setting of NERD. Thus, alginate could represent a therapeutic alternative to PPIs in this category of patients. The current trends according to the current guidelines promote as the first recommendation in GERD management the treatment with PPIs. However, alginate/antacid therapy has a well-established place as additional therapy for PPIs or in mild forms with less than two episodes of heartburn per week as the first administration therapy.

Keywords: gastroesophageal reflux disease, gastric acid pocket, alginate-based therapy

INTRODUCTION

The burden of the gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) is one of the most common digestive pathologies, with worldwide spread and increasing incidence, consisting of all clinical symptoms, with or without lesions of the esophageal mucosa, caused by reflux of gastric contents into the esophagus (1). Typical symptoms include acid regurgitation – perception of flow of refluxed stomach content into the mouth or hypopharynx, heartburn – a retrosternal burning sensation and chest pain. The condition can also present with extra-esophageal symptoms, including laryngitis, asthma, chronic cough and dental erosions (2,3).

GERD is one of the most common diseases in Western countries, with an estimated global prevalence of 10-20%, with considerable geographical variation. In addition, the occurrence of GERD has been increasing during the past two decades (4). Recent studies have determined that GERD is the most frequently diagnos-

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tic between gastrointestinal diseases in USA (8.9 million of visits) (5). The geographical distribution of GERD varies in different regions of the world, being more common in developed countries and much rarer in developing countries. Epidemiological studies have shown an increased prevalence of GERD in South Asia and South-Eastern Europe (over 25%) and a lower prevalence in South-East Asia, Canada and France (below 10%) (6). There are no data on the prevalence of GERD in Africa. Population studies conducted in the US have estimated GERD prevalence rates of up to 30%, with a weekly prevalence of symptoms of about 20% (6). The prevalence of GERD in North America, Asia and Europe has increased by about 50% since the early 1990s (7). In Romania, the prevalence of GERD is not specified; conclusive statistics are lacking, but there is certainty that the condition is more common than reported.

The main cause of GERD is insufficient contraction of the lower esophageal sphincter and transient pathological relaxation of the SEI triggered outside swallowing. The most common pathology associated with GERD is hiatal sliding hernia, but any increase in intra-abdominal pressure or surgery in the esogastric region can cause GERD (8). The pathogenesis of GERD is multifactorial, the lesions being secondary to the imbalance between the aggression factors contained in the reflux fluid and the defense factors of the esophageal mucosa (9). Reflux components other than acid, such as bile from duodenogastroesophageal reflux and the proteolytic enzyme pepsin, may also contribute to symptom perception in patients with GERD (10).

Clinical implications

The main complications that may occur in the evolution of GERD due to excessive exposure to gastric reflux are esophagitis, benign esophageal stenosis (peptic), esophageal ulcer, upper digestive hemorrhage, Barrett's esophagus (EB) and finally, the most unwanted complication, esophageal adenocarcinoma (11,12).

The chronicity of GERD disrupts many aspects of the patients of everyday lives, through interference with normal daily activities, such as eating and drinking, work, sleep, and enjoyment of social life thus resulting in a reduced quality of life. Although almost half of adults have their symptoms for 10 years or more, consultation rates are low (13). Only 5% - 30% of individuals with GERD consult a physician about their symptoms each year. It has been shown that GERD accounts for around 5% of a primary care physician's workload (14). Patients' perceptions of their condition, comorbidity factors and external reasons such as work and social factors are mainly related to consultation rates for GERD.

Thus, GERD represent a real public health problem, with a significant socio-economic and psychological impact and increased morbidity. GERD is thought to affect the patient's quality of life to the same extent as coronary events or rheumatic conditions (15). The considerable economic impact of the disease is determined by the costs of consultations, investigations, prescription drugs, costs of surgical therapies and treatment of complications of gastroesophageal reflux.

Due to the chronic nature of this condition, the dreaded complications that can occur in the evolution of this condition and the negative impact on patients' quality of life, it is imperative to administer symptomatic treatment to eliminate or improve symptoms, cure erosive esophagitis and prevent recurrences and complications.

Importance of treatment optimization

Although PPIs have emerged as the most effective therapy for symptom relief, healing and long-term maintenance in the treatment of GERD patients, in 30-40% of patients PPIs therapy fails to completely resolve symptoms (16). Therefore, there is certainly room for improvement when complete resolution of symptoms is considered as end- point.

Recent studies have tried to find different explanations for these PPIs noncomplete respondents, including the presence of postprandial reflux episodes related to the newly secreted acid layered on top of the ingested table, proximal to squamocolumnar junction ("pocket acid"), weakly acid reflux, high volume reflux, esophageal hypersensitivity, reduced efficacy of PPIs in controlling the progression of nocturnal acid, poor adherence to prolonged treatment with PPIs and alkaline reflux given by the presence of bile in the component of duodenogastric reflux. Also, PPIs provides a more modest therapeutic gain in patients with non-erosive reflux disease as compared with those with erosive esophagitis (17). There is a clear need for GERD therapies beyond the PPIs.

Recently, alginate formulations have shown greater potential for gastric reflux and have been given a more important role as adjuvant therapies in patients with GERD (9).

ALGINATES – ACTION OVERVIEW

Alginic acid formulations, also called alginates, naturally occur as structural polysaccharides in brown algae (18). They have a unique, particular mechanism of action. They act differently from antacids in the treatment of dyspepsia and reflux disease, through a physical, rather than pharmacological mechanism. Alginic acid reacts with sodium bicarbonate in the presence of human saliva, to form sodium alginate. Further, in

the gastric lumen, due to the acid environment, sodium alginate precipitate rapidly, having as result the formation of a low-density viscous gel of near-neutral pH, which will float on the surface of the gastric pool (19). It is like a mechanical barrier has formed, blocking by physical means the reflux. Both in healthy volunteers and in patients with GERD, scintigraphic studies showed that the ingested alginate stays in the upper part of the stomach, while during reflux episodes, the viscous compound will come first in contact with the esophagus, protecting esophageal mucosa from being irritated and damaged (20). The floating property of alginates explain why they are selectively retained in the fundus, unlike antacids. Additionally, resonance magnetic studies demonstrated the same behavior of the alginate rafts, having as targeted location the region close to the esophagogastric junction, where the acid pocket develops (21). Thus, the physical barrier displaces the postprandial gastric acid pocket, acting like a strong raft. Apart this pure contact effect, alginate has the capacity of removing pepsin and also the bile acids from the gastric refluxate, with negative influence on the enzymatic role of pepsin (22).

The alginate-based products are recommended to be administrated after meals, fact explained by their mechanism of action. Studies have shown that the intragastric precipitation takes place into minutes, thus the therapeutic effect is immediately noticed, practically within one hour after administration, faster that antisecretory drugs (23). The fact that alginates are rapidly ready-to-act is important, taking into account that most gastro-esophageal reflux events occur in the first postprandial hour (24).

Alginate may be administered alone, or, more often, it is used in combination with antacids – the so-called alginate-based products. Thus, the effect will be reinforced by adding the specific action of the antacid, consisting in neutralizing gastric acid. The most frequent and known combination is with sodium carbonate and calcium carbonate. However, there are also alternative alginate-antacids formulations, including potassium bicarbonate, aluminum hydroxide, magnesium trisilicate or magnesium carbonate (25).

Several decades have already passed since alginate-based compounds are available. In the United States as well as in Europe, they are typically sold under the brand name of Gaviscon; other commercial products are Algicon and Pyrogastrone.

Alginate-based products are administered orally, having as presentation pharmaceutical forms the tablets (swallowable or chewable) and the oral viscous suspension (presented in bottles or pre-dosed sachets). For all types, administration of the compound has to be after meals, and it is also efficient before bedtime, systematically or as needed, until four times a day. Examples of pharmaceutical forms of presentation are shown in Table 1 (25-27).

The adverse events of alginate-antacid formulations are uncommon. Exceptionally, otherwise as for any drug, there may be an intolerance manifested as hypersensitivity or anaphylactoid reactions. In clinical practice, precaution is needed in patients with congestive cardiac failure or renal insufficiency, due to the sodium content (28). In the case of moderate or severe renal disfunction, alginate should not be used. Similarly, for products containing calcium, there is an accumulation risk for the patients with hypercalcemia, nephrocalcinosis or recurrent renal lithiasis. Other possible adverse events are alkalosis, milk-alkali syndrome, or constipation. However, these last adverse events tend to appear specifically in overdosage situations (29).

Alginate-based formulations were successfully studied in pregnancy-associated heartburn; effectiveness and lack of safety concerns were noted for several products, as liquid Gaviscon (30) and Algicon suspension (31).

CLINICAL EFFICACY OF ALGINATE-BASED THERAPY IN GERD

Numerous studies evaluated the efficacy of alginate treatment in GERD, by comparison to antacids (32,33), PPIs (34-37), histamine 2 receptor antagonists (H2RAs) (38), or placebo (32,39,40).

TABLE 1. *Examples of commercial alginate-antacid formulations*

Product	Pharmaceutical form	Qualitative and quantitative composition per dose
Gaviscon Double Action Tablets, Reckitt Benckiser Healthcare (UK) Ltd (26)	Tablets	Sodium alginate 250 mg, sodium bicarbonate 106.5 mg, calcium carbonate 187.5 mg/tablet
Gaviscon Peppermint Liquid Relief, Reckitt Benckiser Healthcare (UK) Ltd (26)	Oral suspension	Sodium alginate 250 mg, sodium bicarbonate 133.5 mg, calcium carbonate 80 mg/5 ml
Gaviscon Double Action Mint, Reckitt Benckiser Healthcare (UK) Ltd (26)	Oral suspension	Sodium alginate 500 mg, sodium bicarbonate 213 mg, calcium carbonate 325 mg/10 ml
Pyrogastrone, *Winthrop* Laboratories, UK (27)	Tablets	Carbenoxolone 20 mg, magnesium trisilicate 60 mg, aluminum hydroxide gel 240 mg, sodium bicarbonate 210 mg, alginic acid 600 mg
Algicon, W.H. Rorer Inc., USA (25)	Oral suspension	Sodium alginate 500 mg, potassium bicarbonate 100 mg/5 ml

When compared to placebo or antacid therapy alginate treatment presented superior efficacy in the control of symptoms. Stanciu et al. conducted in 1974 one of the first trials analyzing the effect of alginate treatment on gastro-esophageal reflux. The authors included 60 patients divided randomly into three groups, receiving alginate and antacid combined therapy, antacid therapy, and placebo, respectively. Reflux episodes were documented using 15-hours recordings of lower esophageal pH. The authors concluded that most of the patients from the alginate and antacid group showed global improvement of symptoms (89.3%), but less patients from the antacid alone and placebo groups presented a favorable outcome (67.8%, 42.8%, respectively) (32). During the following year, Barnardo et al. carried out a double-blind trial including 26 patients with GERD symptoms that were randomized to receiving either alginate and antacid therapy or placebo. The results suggested that alginate and antacid therapy would provide reduction of postprandial retrosternal pain that continued for many weeks after the discontinuation of the treatment (40). More recently, Thomas et al., in a randomized, double-blind, parallel group single center study analyzed the efficacy of alginate and antacid treatment versus placebo in 110 patients with symptoms of GERD and found a significant overall treatment response in the therapeutic group compared to the placebo group (83.9% versus 62.9%) (8). In 2006, Giannini et al. conducted a randomized, open-label, parallel group multicenter study analyzing the effects of alginate and antacid versus antacid alone therapy. The authors concluded that alginate and antacid provided a more rapid response concerning symptom relief and had a prolonged duration compared to antacid alone (33).

However, when PPIs were used as comparators, most authors concluded that alginate therapy was not superior. Goves et al. described the superiority of omeprazole versus antacid/alginate in a randomized, single-blind, parallel group multicenter trial conducted in 1998. The authors reported significant relief from symptoms in 64% of patients from the omeprazole group versus in 30% of patients from the alginate/antacid group (37). In 2012, Manabe et al. investigated the benefit of adding alginate to omeprazole therapy in patients with non-erosive reflux disease (NERD). The authors conducted a randomized, open-label, parallel group multicenter study, including 76 patients, randomly assigned into two groups, receiving either alginate and omeprazole, or omeprazole alone. They reported that that 56% of patients from the first group presented resolution of symptoms compared to only 25.7% of the ones from the second group, and concluded that combined PPI and alginate therapy was superior to PPI therapy alone (36). However, during the same year, Pouchain et al. investigated the effect of alginate versus omeprazole in a multicenter randomized double-blind double-dummy non-inferiority trial including 278 patients. The authors reported a significantly lower mean number of symptom-free days by day 7 in the omeprazole group compared to the alginate group but no significant difference in the reduction in pain intensity between groups by day 7 or day 14, suggesting that alginate was non-inferior to omeprazole for patients with moderate symptoms (35). Moreover, the following year, Chiu et al., in a double-blind parallel randomized trial comprising 195 patients diagnosed with NERD, reported non-inferiority of sodium alginate therapy to omeprazole (34).

Even though these were randomized-controlled trials, there were some differences concerning several aspects of the used methodologies, which could account for the disparities between the conclusions of the studies. Although there were several double-blind trials (39,40), some studies were single-blind (32,37). There was considerable heterogeneity between studies in regard to the diagnosis of GERD. While most studies considered that typical symptoms were sufficient for defining GERD (32,33,39), one study included in the definition the presence of reflux on barium swallow (40). These variations are explainable by the lack of a universally accepted definition for GERD up to 2006. Moreover, there were differences in the defined outcomes of the studies. While the majority of the authors considered the end-point to be the significant improvement of GERD symptoms (32,34,40), some randomized controlled trials only accepted as outcome the complete resolution of symptoms (33,36,37).

The chronology of these studies provides evidence of a shifting trend favoring alginate-based therapy in patients with GERD. This trend is explained by the recent refining of the diagnostic criteria for GERD, and the identification of a category of patients suffering from GERD symptoms without findings of esophagitis at endoscopic evaluation entitled NERD (41). This condition associates a lower response to PPIs (42), thus adding alginate therapy could prove to be beneficial in this subset of patients (34).

PLACE OF ALGINATE-BASED THERAPY IN CONSENSUS AND CLINICAL PRACTICE GUIDELINES

Although PPIs are the first strong recommendations in GERD in many guidelines, use of alginate-based therapy has showed to be a good choice in battling the reflux displaced from the acidic pocket (43). The usage of alginate -antacids combo therapy is described in many guidelines according to the severity of the GERD and the frequency of the symptoms weekly. According to the World Gastroenterology Organization (WGO) 2015 guidelines, patients with less than two episodes of heartburn weekly, will respond to dietary care, and

administrations of alginate-antacids therapy (44). In patients with mild symptoms, and non- erosive findings at endoscopic examination, "on-demand therapy" with PPIs, may be an effective strategy in some patients. Another statement of the guideline is referring to the higher efficacity of combinations of drugs in GERD treatment. For patients with GERD with incipient symptomatology, a combination of PPIs and alginate or antacids is recommended, the effect being superior than using antisecretory drugs as a single therapy (45). This opinion stated in the guidelines using alginate – antacid therapy alone in battling the first symptoms of GERD is not shared with many others guidelines, where the superiority of the antisecretory drugs are stated as first line recommendations after additional lifestyle changes.

In patients with symptomatic disease, life style changes and antisecretory drugs are the first line recommendations. According to the American Gastroenterological Association (AGA) guidelines a strong recommendation for patients with symptomatic disease are the antisecretory drugs, PPI being the most effective. A single dose or twice a day dose of PPIs is recommended in patients with heartburn symptoms or extraesophageal GERD symptoms (46). Another perspective is seen in the guidelines of the Japanese Gastroenterological society. Although PPIs is hard to be overtaken by other classes of drugs, in this guideline the 8-week treatment with PPIs is considered first stage in this disease management, although this period can be accompanied by alginate or antacids for symptoms relief (47). As a partial conclusion in the Japanese guideline, monotherapy with alginate-antacid medication is not recommended in favor of PPIs.

Another perspective regarding GERD management is observed in National Institute for Health and Care Excellence (NICE) 2014 guideline. In cases of association of GERD and dyspeptic syndrome, a clear recommendation for long term, is to encourage patients to take lower doses of PPIs when needed and to take antacid-alginate therapy as self-treatment. Even if in this guideline the first line treatment is antisecretory therapy, we can notice that, in some situations, patients are having the choice to self-treat the symptomatology with alginate/antacid therapy (48).

It is clear that according to guidelines recommendations using alginate or antacid therapy alone in management of GERD is less effective compared to PPIs or H2 receptor antagonist. We have to acknowledge that some patients have only intermittent or mild forms, situations that may not necessary require an antisecretory drug as first line treatment. According to a recent metanalysis, Leiman et al. highlights that alginate therapy is more effective compared to antacid therapy in these mild and intermittent GERD forms, these findings being observed in many studies (43).

GERD management involves the use of various therapeutic methods that are recommended by the clinician depending on the severity of the symptoms. Although there are minor differences between various guidelines for medical treatment of GERD, in Table 2 are presented the most common therapeutic "weapons" used to relieve symptomatology and create barriers against the acid reflux (9).

TABLE 2. *Current options in GERD management*

Type of treatment	Subtype
Lifestyle and dietary changes	– Head position in bed – Avoid meals within 3 hours before bedtime – Losing weight
Medical management	– Antacids – Alginates – PPIs – H2 receptor antagonist – Prokinetics – Baclofen – Sucralfate
Surgical management	– Fundoplication – Linx magnetic ring
Endoscopic procedures	– Transoral incisionless fundoplication – Stretta procedure

To summarize the place of alginate/antacid therapy according to frequently used guidelines, we present the main first-line recommendations in GERD in Table 3.

TABLE 3. *First line recommendations regarding treatment in GERD according to international guidelines*

Guidelines for GERD diagnosis and management	Recommendations for treatment
WGO 2015 Guidelines (44)	Alginate and antacid therapy after dietary changes in patients with less than 2 episodes of reflux/week Short-term treatment with a once-daily PPIs in patients with more frequent and severe episodes of heartburn
AGA 2008 Guidelines (46)	PPIs daily for 8 weeks
NICE 2014 Guidelines (48)	PPIs + alginate/ antacid as self-treatment
Japanese Gastroenterological Society 2016 Guidelines (47)	PPIs for 8 weeks ± alginate and antacid therapy for symptoms relief
American College of Gastroenterology 2013 Guidelines (49)	Dietary regime and life style changes 8-week course of PPIs
Consensus of Gastroesophageal Reflux Disease in Taiwan 2015 (50)	Double dosage of PPIs Prokinetics and alginate therapy as additional drugs for patients with non-erosive esophagitis

CONCLUSIONS

GERD, as one of the most common digestive pathologies, with worldwide spread, increasing incidence, and with negative consequences on the quality of life and/or on the clinical evolution to complications, needs imperatively an optimal treatment. Apart PPIs, which are undoubtedly a therapeutic cornerstone, alginate-based therapy plays a unique and well-defined role in GERD treatment, as showed by various studies. Current consensus and evidence-based clinical practice guidelines are endorsing the benefit of alginate-based formulations, as part of a tailored, clinically-guided therapy.

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