A Favorable Response of Dysplastic Barrett’s Refractory to Ablation Therapy Only after Initiation of an Alginate Solution as Add-on Therapy

Mark M Brodie, Puja S Elias*, Mohamed Khalaf and Donald O Castell
Department of Gastroenterology, Medical University of South Carolina, Charleston, South Carolina, USA

*Corresponding author: Elias PS, Department of Gastroenterology, Medical University of South Carolina, Charleston, South Carolina, USA, Tel: 8438760783; E-mail: eliasps@musc.edu

Received date: September 20, 2017; Accepted date: September 27, 2017; Published date: October 05, 2017

Copyright: © 2017 Elias PS, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Alginate has been shown not only to be beneficial in their relief of symptomatic post-prandial gastroesophageal reflux, but there is also evidence that they may inhibit reflux, including bile acids and pepsin, and in turn attenuate and even prevent the activation and up-regulation of molecules associated with the development of metaplasia and cancer of the esophagus. Here we present the case of a patient with Barrett's esophagus with high-grade dysplasia (HGD) which was initially unresponsive to endoscopic radiofrequency ablation therapy and cryotherapy for high-grade dysplasia. Following initiation of therapy with an alginate solution in addition to twice daily proton pump inhibitor (PPI) therapy, the patient showed a favorable response and eventual complete eradication of his dysplastic Barrett's. The patient's course is suggestive that the alginate solution, through reflux inhibition, prevented persistent esophageal cell changes which occur secondary to gastric and bile acid exposure, thus allowing development of neosquamous epithelium. This case is intriguing with regard to the role of alginates in creating a favorable environment for esophageal healing when treating Barrett's esophagus with high-grade dysplasia.

Keywords: Gastroesophageal reflux; Endoscopy; Proton pump inhibitor; Hernia

Case Study

HPI

A.H. is a 46 year old male with history of hiatal hernia and gastroesophageal reflux disease (GERD) who presented to our tertiary referral center for management of long segment dysplastic Barrett's esophagus with high-grade dysplasia (HGD) which had been refractory to treatment with radiofrequency ablation (RFA). The patient had undergone five rounds of RFA at an outside medical center with less than 50% improvement of his dysplastic Barrett's at the time of the fifth endoscopy. His last endoscopy prior to transfer had revealed residual dysplastic Barrett's in the lower esophagus, and biopsies showed persistent HGD. On presentation to our center, the patient reported that his acid reflux was not well-controlled despite twice daily PPI. He complained of heartburn, night time regurgitation, and non-productive cough. Review of systems was otherwise negative for chest pain, shortness of breath, dysphagia, odynophagia, weight loss, abdominal pain, nausea, vomiting, or other complaints.

Past medical history: Small (2 cm) Hiatal hernia.

Past surgical history: None.

Social history: Negative for tobacco, alcohol, or illicit drug use; lives overseas, returns to the states roughly 4 times per year.

Family history: Non-contributory.

Medications: Esomeprazole 40 mg BID, Sucralfate 1 g QID.

Treatment course: After a long discussion with the therapeutic endoscopy team, options other than RFA such as endoscopic mucosal resection and cryotherapy were discussed. Given the distribution, anatomy and flat nature of his Barrett's esophagus, cryotherapy was started and he began receiving treatments every two months starting in July 2014. After the first three treatments, there was minimal endoscopic evidence of improvement in the surface area of Barrett's epithelium with less than 50% improvement, so ablation exposure times were increased from 20 to 30 seconds.

This still resulted in only mild improvement in appearance of his Barrett's after a total of six cryotherapy treatment sessions. Because of the lack of response, manometry and pH/impedance testing were completed to assess for dysmotility and ongoing acid exposure in the esophagus.

Manometry showed ineffective esophageal motility (IEM), while his pH/impedance study revealed that while acid control was good in the stomach and no abnormal acid exposure was occurring in the esophagus, there was significant persistent non-acid reflux. Due to these findings along with less than 50% improvement from initial appearance of the patient's Barrett's and persistent reflux symptoms despite twice daily PPI therapy and night-time H2 blocker therapy, the patient was tried on Bethanechol therapy in an attempt to improve his esophageal motility and possibly decrease his GERD symptoms.

He had minimal response and multiple side effects, so this was discontinued. He was then started on a twice daily alginate solution (Gaviscon Advance, EU version, 15 mL packets to be taken following meals and at night) instead of H2 blocker therapy for better attempted control of his reflux. After initiation of this therapy at 8 months, and following his 7th treatment of cryotherapy, endoscopy revealed roughly 75% improvement in his Barrett's dysplasia.

Following two additional treatments, EGD revealed full resolution of the patient's dysplastic Barrett's. Over one and a half years later, he continues to have complete resolution of BE while being maintained on twice daily PPI and twice daily alginate therapy.
Discussion

Background: Alginates are polysaccharides found most widely in the cell walls of seaweed (brown algae). They have been implicated in a variety of uses, including symptomatic relief of gastroesophageal reflux disease. They have been marketed over the past 40 years most notably as the non-prescription medication Gaviscon, which is advertised as a dual action antacid, containing both alginate and typical antacid (i.e. calcium carbonate) [1].

Mechanism: The mechanism of action of alginates involves the formation of a protective barrier on the surface of the gastric contents. The alginate itself precipitates into a gel in the presence of gastric acid. Concurrently, the bicarbonate in alginate-based solutions forms carbon dioxide in the presence of gastric acid, which converts the gel into foam which floats to the surface of the gastric contents [1]. Hence, alginate solutions form “rafts” which provide a physical barrier to acid reflux, as well as a pH-neutral substitute which refuxes into the esophagus preferentially over gastric acid [2]. Furthermore, alginates are thought to target the acid pocket, an unbuffered pool of acid that floats on top of ingested food and causes postprandial acid reflux.

In patients with hiatal hernias, scintigraphy demonstrated alginated/antacid formulations to better target the acid pocket, keep the acid pocket more often below the diaphragm, and pH impendence demonstrated fewer reflux events when compared to antacid alone [3]. Furthermore, a dorsal radiolabeled alginate to preferentially settle on the surface of gastric contents, while radiolabeled antacid was demonstrated to settle to the distal stomach [4]. Finally, supporting the “raft” model, Castell et al. demonstrated with pH monitoring that the superiority of alginates over antacids in post-prandial reflux exists primarily in the upright (as contrasted with supine) position [5].

Efficacy in relief of GERD symptoms: In addition to having been shown to be superior to placebo in relieving symptoms of GERD, alginates have also demonstrated non-inferiority to PPI in this regard, as well as superiority to placebo as add-on therapy for patients already on PPI [6-8]. Furthermore, dual action antacids (antacid with alginate) have been shown to be superior to antacids alone in reducing post-prandial esophageal acid exposure in GERD patients [9].

Bile Acid control and implications for cancerous and pre-cancerous changes: Alginates target the gastric acid pocket and provide a barrier between gastric contents and the esophagus. Since gastric contents consist of more than just gastric acid, the use of alginates has implications beyond symptomatic relief. In addition to hydrochloric acid, refluxate can include pepsin, bile acids, and pancreatic enzymes. There is good reason to believe that controlling reflux of these contents into the esophagus has health benefits as well. Specifically, the ability of alginates to form a formidable barrier between damaging and even cancer-causing molecules and the esophagus suggests deterrence of esophageal damage and oncogenesis.

Pepsin and gastric acid, and not acid alone, have been shown to lead to cell damage equivalent to esophagitis [10-13]. Bile acids have been shown to be damaging to esophageal epithelial cells by affecting membrane permeability, cell proliferation and differentiation, increasing free radicals, inducing DNA damage and up-regulating oncogenes [11,14-20]. More specifically, both gastric acid and bile acids have been shown to activate NF-kappa B, a major molecule that is up-regulated in and intrinsic to cancer development. This has been demonstrated in esophageal epithelial cells in both a dose and time-dependent manner [21,22]. There have been numerous other studies which have shown bile acids to be integral to the development of esophageal metaplasia, as well as conversion of Barrett's esophagus to esophageal adenocarcinoma [23,24]. Interestingly, Gaviscon has been shown to retard diffusion of bile acids and remove bile acids from simulated reflux events in vitro [25]. In the same study, Gaviscon also removed pepsin from the reflux event in a dose-dependent manner. A separate study exposed in vitro esophageal cell lines to deoxycholic (bile) acid in the presence and absence of alginates, and measured levels of oncogene up-regulation. It was shown that the alginate prevented induction and upstream effects of multiple oncogenes that are associated with GERD changes that lead to Barrett's esophagus and adenocarcinoma [26].

Conclusion

Alginates have been shown not only to be beneficial in their relief of symptomatic post-prandial gastroesophageal reflux, but there is also evidence that they inhibit the reflux of bile acids and pepsin into the esophagus, and in turn attenuate and even prevent the activation and up-regulation of molecules associated with the development of metaplasia and cancer of the esophagus. Here we present the case of a patient with Barrett's esophagus that was initially unresponsive to endoscopic radiofrequency ablation therapy and cryotherapy for high-grade dysplasia.

Following addition of an alginate solution, the patient showed a favorable response and eventual complete eradication of his dysplastic Barrett's. The patient's course is suggestive that the alginate solution, through additional means of reflux inhibition, prevented persistent esophageal epithelial cell changes which occur secondary to gastric and bile acid exposure, thus allowing development of neosquamous epithelium. The case of A.H. is intriguing with regard to the role of alginates in creating a favorable environment for esophageal healing post cryotherapy. Further studies are warranted to compare the response of treatment for dysplastic Barrett's with or without the addition of alginate solutions.

References

1. Daggy BP, Brodie DA, Jacoby HI (2000) Review article. Alginic-acid formulations in the treatment of heartburn and acid reflux. Aliment Pharmacol Ther 14: 669-690.
2. Charkes M, Reilley L, Rosenberg S, Fisher (1978) The mode of action of alginic acid compound in the reduction of gastroesophageal (G-E) reflux using the G-E scintiscan. Int J Nuclear Med Biol 5: 203.
3. Wout OR, Bennink RJ, Smout AJ, Thomas E, Boekxstaens GY (2013) An alginate-antacid formulation localizes to the acid pocket to reduce acid reflux in patients with gastroesophageal reflux disease. Clinical Gastroenterol Hepatol 11: 1585-1591.
4. Sweis R, Kaufman E, Anggiansah A, Wong T, Dettmar P, et al. (2013) Post-prandial reflux suppression by a raft-forming alginate (gaviscon advance) compared to a simple antacid documented by magnetic resonance imaging and pH-impedance monitoring: Mechanistic assessment in healthy volunteers and randomised, controlled, double-blind study in reflux patients. Aliment Pharmacol Ther 37: 1093-1102.
5. Donald OC, Dalton CB, Becker D, Sinclair J, Castell JA (1992) Alginic acid decreases postprandial upright gastroesophageal reflux. Digest Dis Sci 37: 589-593.
6. Sun J, Yang C, Zhao H, Zheng P, Wilkinson J, et al. (2015) Randomised clinical trial: The clinical efficacy and safety of an alginate-antacid (gaviscon double action) versus placebo, for decreasing upper gastrointestinal symptoms in symptomatic gastroesophageal reflux disease (GERD) in China. Aliment Pharmacol Ther 42: 845-854.
7. Chiu CT, Hsu CM, Wang CC, Chang JJ, Sung CM, et al. (2013) Randomised clinical trial: Sodium alginate oral suspension is non-inferior to omeprazole in the treatment of patients with non-erosive gastroesophageal disease. Aliment Pharmacol Ther 38: 1054-1064.

8. Reimer C, Lødrup AB, Smith G, Wilkinson J, Bytzer P (2016) Randomised clinical trial: Alginate (gaviscon advance) vs. placebo as add-on therapy in reflux patients with inadequate response to a once daily proton pump inhibitor. Aliment Pharmacol Ther 43: 899-909.

9. De Ruigh A, Roman S, Chen J, Pandolfino JE, Kahrilas PJ (2014) Gaviscon double action liquid (antacid & alginate) is more effective than antacid in controlling post-prandial oesophageal acid exposure in GERD patients: A double-blind crossover study. Aliment Pharmacol Ther 40: 531-537.

10. Goldberg HI (1969) Role of acid and pepsin in acute experimental esophagitis. Gastroenterol 56: 223-230.

11. Lawrence FJ, Harmon JW (1986) Experimental esophagitis in a rabbit model. J Clinical Gastroenterol 8: 26-44.

12. Salo JA, Lehto VP, Kivilaakso E (1983) Morphological alterations in experimental esophagitis. Digest Dis Sci 28: 440-448.

13. Tobey N (2001) The role of pepsin in acid injury to esophageal epithelium. Am J Gastroenterol 96: 3062-3070.

14. Roman S, Petre A, Thepot A, Hautefeuille A, Scoazec Y, et al. (2007) Downregulation of P63 upon exposure to bile salts and acid in normal and cancer esophageal cells in culture. AJP: Gastrointest Liver Physiol 293: G45-53.

15. Tao Z, Zhang F, Han Y, Gu Z, Zhou Y, et al. (2007) A rat surgical model of esophageal metaplasia and adenocarcinoma-induced by mixed reflux of gastric acid and duodenal contents. Dig Dis Sci 52: 3202-3208.

16. Boni L, Benevento A, Shimi SM, Cuschieri A (2006) Free radical production in the esophago-gastro-duodenal mucosa in response to acid and bile. Dis Esophagus 19: 99-104.

17. Dvorak K, Payne CM, Chavarria M, Ramsey L, Dvorakova B, et al. (2007) Bile acids in combination with low ph induce oxidative stress and oxidative dna damage: Relevance to the pathogenesis of barrett’s oesophagus. Gut 56: 763-771.

18. Martin F, Peters JH, Demeester TR (2007) Carcinogenesis in reflux disease-In search for bile-specific effects. Microsurg 27: 647-650.

19. Jenkins GJS, Cronin J, Alhamedani A, Rawat N, D’souza F, et al. (2008) The bile acid deoxycholic acid has a non-linear dose response for DNA damage and possibly NF-B activation in esophageal cells, with a mechanism of action involving ROS. Mutagenesis 23: 399-405.

20. Tselepis C (2003) Up-regulation of the oncogene C-myc in Barrett’s adenocarcinoma: Induction of C-myc by acidified bile acid in vitro. Gut 52: 174-180.

21. Philip RD, Witik M, Gong L, Birbe R, Chervoneva I, et al. (2006) Bile acids induce ectopic expression of intestinal guanylyl cyclase c through nuclear factor-kB and Cdx2 in human esophageal cells. Gastroenterol 130: 1191-1206.

22. Johnv R, Abdel-Latif MM, Inoue H, Kelleher D (2016) Factors regulating nuclear factor-kappa B activation in esophageal cancer cells: Role of bile acids and acid. J Cancer Res Ther 12: 364-373.

23. Attwood SE, Smyrk TC, DeMeester TR, Mirvish SS, Stein HI, et al. (1992) Duodenoesophageal reflux and the development of esophageal adenocarcinoma in rats. Surgery 111: 503-510.

24. Nehra D, Howell P, Williams CP, Pye JK, Beynon J (1999) Toxic bile acids in gastro-oesophageal reflux disease: Influence of gastric acidity. Gut 44: 598-602.

25. Vicki S, Avis J, Jolliffe IG, Johnstone LM, Dettmar PW (2009) The role of an alginate suspension on pepsin and bile acids - key aggressors in the gastric refluxate. does this have implications for the treatment of gastro-oesophageal reflux disease? J Pharm Pharmacol 61: 1021-1028.

26. Peter WD, Strugala V, Tselepis C, Jankowski JA. (2007) The effect of alginites on deoxycholic-acid-induced changes in esophageal mucosal biology at PH 4. J Biomater Sci Polym Ed 18: 317-333.