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Are Sodium Alginate Solutions Effective in Reducing Postprandial Symptoms in Adults with Gastroesophageal Reflux?

Kristi L. Hackman
Philadelphia College of Osteopathic Medicine, kristiha@pcom.edu

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Kristi L. Hackman, PA-S

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not sodium alginate solutions are effective in reducing postprandial symptoms in adults with gastroesophageal reflux?

STUDY DESIGN: A review of three English language studies published from 2006-2011. Includes two randomized, double-blind, controlled trials and one controlled case series.

DATA SOURCES: Randomized, placebo-controlled studies evaluating the effectiveness and safety of sodium alginate solutions (Gaviscon) for managing gastroesophageal reflux disease (GERD) symptoms in adults were located using the PubMed, CINAHL, and Cochrane Library databases.

OUTCOMES MEASURED: The primary measures of effectiveness used were the Reflux Severity Index Questionnaire and Reflux Disease Questionnaire. The secondary measures of effectiveness were the incidence of symptoms with time of onset and time until resolution. The measures of symptom reduction included heartburn (epigastric, substernal pain), acid taste in mouth, regurgitation, nausea, flatulence, hoarseness, excess mucous and throat clearing, and cough.

RESULTS: Two randomized, controlled studies and one controlled case series comparing sodium alginate solutions to a placebo, proton pump inhibitor and H_2 receptor antagonist were reviewed. Dettmar et al. noted a statistically significant decrease in incidence of esophageal symptoms compared to control and omeprazole. McGlashan and colleagues noted a mean reduction in severity of symptoms at two and six months after Gaviscon treatment compared with control. Kwiatek et al. noted a statistically significant reduction in an acid taste in patients' mouths after Gaviscon treatment. All three studies also found sodium alginate solutions to be well tolerated. The majority of adverse events were mild; the most common events included mild nausea and headache.

CONCLUSIONS: The results of all three studies in this review support a similar conclusion, that sodium alginate solutions are both effective and safe in the treatment of adults over 18 years of age diagnosed with GERD. Liquid alginate suspensions like Gaviscon formulations provide an alternative, non-systemic, barrier mode of action in the treatment of GERD. Further research regarding specific formulations available and the role in prevention of Barrett's esophagus is warranted.

KEY WORDS: Alginates, gastroesophageal reflux

INTRODUCTION

Gastroesophageal reflux disease is a common digestive system dysfunction associated with a spectrum of various symptoms of indigestion in patients of all backgrounds. Lower esophageal sphincter dysfunction causes gastric contents, including hydrochloric acid, to reflux into the esophagus causing an array of symptoms in a large proportion of American adults.[3] This paper evaluates two double blind, randomized controlled clinical trials and one controlled case series comparing the efficacy of alginates as an alternative oral medication to PPI's, H_2RA's and antacids for improving postprandial symptoms of acid reflux in adult patients.

GERD is a very common disorder that is encountered in various types of medical practices and settings. Nationally, 25-40% of Americans experience symptomatic GERD at some point in their lives.[3] This issue proves to be persistent and difficult to alleviate as 7-10% of Americans experience symptoms of reflux on a daily basis.[3] Managing GERD is well within the scope of practice for physician assistants as many PAs advise patients in use of OTC medications for GERD, while many more prescribe proton pump inhibitors or H_2 blocker medications. An exact number for total healthcare costs of GERD has not been identified; however, prescription medications cost an average of over $200 per month wholesale.[3] Many healthcare visits per year are dedicated to GERD management; for instance, 4 to 5 million office visits in the USA occurred in 1985 for "GERD and related esophageal disorders".[3]

Acid reflux is more commonly found in pregnant, obese, and smoking patients; although, the exact cause of reflux is not known in all patients. Pregnant patients are more likely to experience symptoms of GERD as the pregnancy progresses, with about 72% of women having symptoms in the third trimester.[6] This condition often causes heartburn, a burning feeling in the chest and throat, especially after eating or at night. Additionally, GERD can cause cough or

asthma symptoms. As stomach contents ascend from the esophagus and reach the larynx, it can make a patient's voice sound hoarse, cause chronic throat clearing, or even leave a bitter taste in patients' mouths.[2] Studies have shown that a state of chronic GERD can cause changes or metaplasia of the cells of the esophagus, causing Barrett's esophagus.[4] In rare cases, Barrett's esophagus can lead to esophageal cancer, which is typically deadly and occurs more commonly in Caucasian men over 50 years of age.[4]

Usual methods used to treat this condition include proton pump inhibitors as the "gold standard treatment" such as omeprazole (OTC), lansoprazole (OTC), pantoprazole, rabeprazole, esomeprazole, and dexlansoprazole.[2] These medications suppress acid secretion by the parietal cells of the stomach. H_2 blockers (receptor antagonists) such as famotidine (OTC), nizatidine (OTC), ranitidine (OTC), cimetidine (OTC) are used to control excess acid production as well.[2] Over-the-counter antacids such as Mylanta®, Rolaids®, or Tums® are useful in neutralizing gastric acid.[2] In refractory cases, surgery can be done to alter the anatomy of the GI tract via total or partial fundoplication. Endoscopic treatments such as EndoCinch™, Stretta®, and EsophyX™ have also been used in more troublesome cases.[2]

Proton pump inhibitors are the most recommended treatment for GERD, as they reduce the amount of acid produced by the stomach; however, these medications are absorbed systemically. The use of oral sodium alginate solutions (Gaviscon) may provide an alternative method of relief by creating a protective layer over gastric contents without absorption into the bloodstream.[2] This type of medication is classified as a reflux suppressant because the effect is not on the gastric acid itself, but rather forming a viscous mechanical block of the reflux episode. This protective layer in the stomach, formed by the floating and foaming mechanism, may improve incidence, duration, and severity of postprandial symptoms from GERD in adults.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not sodium alginate solutions are effective in reducing postprandial symptoms in adults with gastroesophageal reflux?

METHODS

Criteria used for selection of studies included a population of adults experiencing gastroesophageal reflux and an intervention of sodium alginate treatments (Gaviscon). Comparisons that were used included a proton pump inhibitor, an H_2 receptor antagonist, or no treatment. Outcomes that were measured included reduction in symptoms such as heartburn (epigastric, substernal pain), acid taste in mouth, regurgitation, nausea, flatulence, hoarseness, excess mucous and throat clearing, and cough. The studies included were two randomized controlled trials and one controlled case series.

All articles were written in English, published in peer reviewed journals, and searched for via key words including: alginates and gastroesophageal reflux. The three studies in this review were researched via Medline, CINAHL, and Cochrane library databases. Articles were selected based on relevance, utility, and importance of outcomes to patients. Inclusion criteria maintained that studies included were randomized, controlled, double blind clinical trials of patient oriented outcomes. Exclusion criteria annulled data of patients who were pregnant or breastfeeding, less than 18 years of age, or diagnosed clinically with another underlying significant disease. Statistics reported by the studies included p values, mean differences, mean VAS scores, ANOVA, paired T test, and confidence intervals. Demographics and characteristics of the specific studies are found in Table 1.

Table 1: **Demographics & Characteristics of included studies**

Study	Type	# Pts	Age	Inclusion criteria	Exclusion criteria	W/D	Interventions
Dettmar, 2006	Double blind RCT	19	Ages 18–70 years	body mass index of 19–32; normal medical history and physical examination	pregnant, breast feeding, evidence of another clinically significant disease; food or drug allergies, consumed alcohol within 24 h of each dosing day	3	1. Sodium Alginate 20 mL (Liquid Gaviscon) 2. Omeprazole 10 mg (Losec) 3. Ranitidine 75 mg (Zantac 75) 4. Water control (50 mL tap water)
Kwiatek, 2011	Controlled cases series	10	Ages 26-46 years	remained off acid-suppressive medications for at least 1 week prior; experiencing typical GERD symptoms	history of upper gastrointestinal surgery	0	20 mL oral dose of an alginate-antacid formulation (Gaviscon Double Action Liquid)
McGlashan, 2009	Double blind RCT	49	> 18 years old	patients with laryngopharyngeal reflux from any race	recent history of H2 receptor blockers, PPIs, and salt restricted diets; underlying medical conditions	20	Gaviscon advance suspension 10mL after meals and at bedtime

OUTCOMES MEASURED

Each trial investigated patient-oriented evidence that matters by attaining information from participants about their symptoms. The outcomes that were focused on in this review are reduction in symptoms (incidence, severity and length of time) of GERD including heartburn (epigastric, substernal pain), acid taste in mouth, regurgitation, nausea, flatulence, voice hoarseness, dysphagia, excess mucous and throat clearing, and cough. These outcomes were measured in each study via three means such as the Reflux Severity Index Questionnaire, a visual analogue scale of severity, and by incidence of symptoms with time of onset, time until resolution, and severity in a diary of symptoms by subjects.

RESULTS

This review includes one randomized controlled trial comparing Gaviscon to water control, a second randomized controlled trial comparing Gaviscon to omeprazole, ranitidine and water control, and lastly, a controlled case series of Gaviscon without control. Each of the trials included only adult patients over the age of 18 and both randomized controlled trials excluded participants with other clinically significant medical conditions. The randomized control trial by Dettmar, et al. also excluded pregnant or breastfeeding women and subjects consuming alcohol within 24 hours of the study, while the McGlashan, et al. trial excluded subjects with a recent history of H_2RA's, PPI's, or salt restricted diets. The presentation of patients in each trial was patients with upper digestive tract symptoms experiencing occasional gastroesophageal reflux and the setting for the data collection was a hospital or medical center in each of the trials.

Although one author, Dettmar, et al. did not explicitly state that an intention to treat analysis was used, it can be implied that all three studies utilized intention to treat analysis. Compliance to follow up in the Dettmar, et al. randomized control trial and the Kwiatek, et al. controlled case series was good with only 3 and 0 withdrawn participants respectively.[1,5] The randomized control trial by McGlashan, et al. however, lost 20 of the original 49 subjects.[7] Therefore, loss to follow up is a limiting factor of the study.

The data analysis varied in each study. The randomized controlled trial by McGlashan et al. focused more on laryngeal vs. esophageal symptoms such as hoarseness, throat clearing, excess mucous, globus pharyngeus, dysphagia, and cough along with the classic symptom of heartburn via the RSI (Reflux Severity Index) at months 0, 2, and 6.[7] The reduction in symptoms via the RSI is compared between Gaviscon Advance group and a no treatment control group. This study showed a mean reduction in symptoms, on the RSI questionnaire, of 12.6 points in the

Gaviscon group and 7.8 points in the control group at month 2 ($p<0.001$ paired t-test).[7] In month 6, the mean reduction in RSI was 12.7 points for the Gaviscon group ($p<0.001$) and 6.3 points for the control group ($p=0.002$), as demonstrated by Table 2.[7]

Table 2: **Reduction in symptom RSI (Reflux Severity Index)** from McGlashan et. al. (2009)

	Gaviscon Advance	**No treatment (control)**
Mean reduction from month 0 to 2	12.6 ($p<0.001$)	7.8 ($p<0.001$)
Mean reduction from month 0 to 6	12.7 ($p<0.001$)	6.3 ($p= 0.002$)

The treatment effects in the Dettmar et al. randomized controlled trial were measured by symptom incidence by treatment. The study found that 6% of the sodium alginate group experienced esophageal symptoms while 22% experienced gastric symptoms.[1] Even in the control group, 16% experience esophageal symptoms and 20% experienced gastric symptoms, as seen in Table 3.[1] Therefore, esophageal symptoms were relieved by sodium alginate compared to placebo, while gastric symptoms were not. In contrast, 12% of the omeprazole group experienced esophageal symptoms, while 18% experienced gastric symptoms.[1] Only 3% of the ranitidine group experienced esophageal symptoms, however, 27% experienced gastric symptoms.[1]

Table 3: **Symptom incidence by treatment** in Dettmar et. al. 2006

	Sodium alginate n= 67	**Omeprazole** n= 68	**Ranitidine** n= 67	**Control** n= 64
Esophageal symptoms incidence	6%	12%	3%	16%
Gastric symptoms incidence	22%	18%	27%	20%

Treatment effects in the Kwiatek et al. controlled case series were recorded by a visual analogue scale of symptom severity with a score range of 0-100 for each symptom. Four symptoms were scored from 0 to 100 while fasting, postprandial, and again post-Gaviscon. A total VAS score was then computed at each interval surveyed (fasting, postprandial, post-

Gaviscon) for all symptoms combined. The scores for the incidence of the first symptom, burning behind the breastbone, were 3 while fasting, 12 at the postprandial measurement, and 6 post-Gaviscon intervention.[5] The scores for pain behind the breastbone were 5 while fasting, 9 postprandially, and only 4 post-Gaviscon.[5] The scores for acid taste in mouth were only 1 during the fasting period, 12 at the postprandial interval, and 6 post-treatment with Gaviscon Advance.[5] The scores for the final symptom of an unpleasant movement of material upwards from the stomach were 13 while fasting, 19 postprandially, and 14 post-Gaviscon.[5] The only symptom that showed a statistically significant reduction after Gaviscon, compared with fasting, was an acid taste in subjects' mouths with a p-value of 0.04, as shown by Table 4.[5]

Table 4: **Symptom severity by VAS from 0-100** from Kwiatek et. al. (2011)

	Fasting	**Postprandial**	**Post-Gaviscon**
Burning behind breastbone	3	12	6
Pain behind breastbone	5	9	4
Acid taste in mouth	1	12	6
Unpleasant movement of material upwards from stomach	13	19	14
Total VAS score (0-400)	32	69	41

Safety and tolerability of each intervention was measured via number of adverse events during the trial. The Dettmar et al. randomized controlled trial noted five adverse events in 4 of 17 subjects, only one of which (mild nausea) was considered to be related to a study intervention, ranitidine, yielding 6 as the number needed to harm.[1] The randomized controlled trial by McGlashan et al. found the most common adverse event to be headache in 46% of treatment group and 32% of control group. However, only 7% of events in the treatment group are considered possibly related to Gaviscon and the calculated number needed to harm is 8.[7] Within the controlled case series by Kwiatek, et al. there is no mention of adverse events, tolerability or safety of the intervention.

DISCUSSION

This review supports the use of sodium alginate solutions as a safe and effective treatment choice for adults over 18 years of age diagnosed with gastroesophageal reflux disease. The articles on sodium alginate solutions specifically studied adults; however, many studies have shown considerable benefit to the use of sodium alginates in infants with gastroesophageal reflux. The formulation of Gaviscon for infants contains solely sodium alginate and does not include any antacid agents. This gel-like agent works similarly in infants with reflux problems who often spit up after feeding, a concern which is typically outgrown by age one.[4]

Various formulations of this medication are widely available in the United States and sold over the counter, with no prescription necessary, at reasonable costs varying from $6 to $16.[2] Gaviscon Advance and Gaviscon Double Action are the suspensions that contain sodium alginate as the main ingredient, and are distributed more widely in the UK. The original and extra strength formulations sold primarily in the U.S. contain aluminum hydroxide and magnesium carbonate, both antacids, as the main ingredients, but also contain sodium alginate.[2] Although, Gaviscon leads the market in raft-forming system medications, there are alternative preparations available.

Side effects of the medication include gas, constipation, belching, and a laxative effect if the maximum dose is exceeded. Allergic reactions are rare, but patients who have known hypercalcemia or chronic kidney disease should avoid the formulations that include calcium carbonate as an active antacid. Patients using formulations with antacids should also be advised that they can affect the absorption of other medications in the gastrointestinal tract. There are no black box warnings listed for this medication.[4]

A limitation of the selection of articles is that it only includes studies that examine adults. Although GERD is most commonly found in adults, a second population of infants is also affected by gastroesophageal reflux that is typically transient, but at times requires medical treatment with these types of suspensions. An additional limitation of the studies inclusively is the small sample size. For the study by Dettmar et al, the generalizability of the results to the population described is not strong due to a follow up time that is not sufficiently long, the loss of more than 20% of the subjects, and the methods which were not double blinded.[1] These factors weaken the validity of the study because the subjects themselves were not kept blind to the treatments received, and the follow up time was only four hours.

For the controlled case series by Kwiatek, et al. a significant limitation is the short follow up time of twenty minutes after Gaviscon treatment, in addition to the small sample size of 10.[5] The validity of this study is also limited purely by design due to the fact that it is not a randomized controlled trial. Furthermore, the study by McGlashan et al. is limited because there was a pronounced placebo effect of perceived symptoms by patients, which may have resulted from vocal hygiene and dietary advice received by all patients, even those in the control group.[7] However, in this article the follow up time was sufficiently long enough at 6 months so that the results may be generalizable to the population analyzed.

CONCLUSION

This review of two randomized, controlled trials and one case controlled series determined sodium alginate solutions to be safe and effective for managing GERD symptoms in adults over 18 years of age. Gaviscon and other sodium alginate suspensions provide adults diagnosed with GERD or Barrett's esophagus, and their medical providers, with an additional treatment option with an alternative mode of action. Although many studies regarding GERD

include analysis of esophageal pH, additional research evaluating which specific formulation and dose of Gaviscon is most effective in symptom reduction is warranted. Pregnant women, whom are stereotypically plagued with gastroesophageal reflux, are a specific population that has been studied in the past. Future research should be designed to examine the effects of sodium alginate treatments in young patients, as well as how its efficacy compares to PPI or H_2RA medications for gastroesophageal reflux.

A study that also includes patients who have had surgical or endoscopic correction of GERD compared to medical therapy would be beneficiary. Additionally, future studies that compare all medical therapy options to lifestyle modifications alone should be done to determine the efficacy of avoiding medical management in GERD patients. It would be informative and useful to conduct further research to determine whether or not sodium alginates serve a role in patients with Barrett's esophagus to stop or slow the progression of metaplasia in the esophagus. Because sodium alginate solutions are reasonably priced, generally harmless, and universally accessible, studies should continue in order to provide the increasing number of GERD sufferers with safe and efficacious treatment and prevention options.

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