

Alginates Extended Abstract

III) Clinical practice guidelines: DeVault KR, Castell DO; American College of Gastroenterology. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Am J Gastroenterol. 2005 Jan;100(1):190-200.

Study objectives: These guidelines were published by the American College of Gastroenterology first in 1995, and again in 1999. These guidelines are revised as continual advancements are made in gastroesophageal reflux disease (GERD). The guidelines are intended for all practitioners who address GERD and indicate the preferred approach. The guidelines were developed under the guidance of the American College of Gastroenterology and its Practice Parameters Committee and approved by the Board of Trustees.

Scope: These guidelines are applicable to adult patients with symptoms, tissue damage, or both that result from the reflux of gastric content into the esophagus. In these guidelines, GERD is defined as symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus. The scope of the guidelines includes both diagnosis and treatment.

Methods: World literature was reviewed for each revision of the guidelines using the National Library of Medicine database. Appropriate studies were analyzed and relevant studies in the reference lists were obtained and reviewed. To evaluate evidence, a hierarchy was used and for each guideline a score was given for the strength of evidence, ranging from I – IV.

Design: Expert Opinion/Guideline, Review Article

Allocation: Not applicable

Blinding: Not applicable

Follow-up Period: Not applicable

Setting: Not applicable

Patients: Not applicable

Patient Follow up: Not applicable

Outcomes / Results: Not applicable

Conclusions: The treatment guidelines covered patient directed therapy, acid suppression, promotility therapy, maintenance therapy, surgery, endoscopic therapy, and refractory GERD. Patient directed therapy and in particular alginic acid had a minor, but definite place in the guidelines for treatment of mild forms of GERD with a level of evidence rating of IV.

Comments:

When assessing internal validity, there are few issues to address. The authors of the guidelines did not include how studies were reviewed or selected for inclusion in the guidelines, which leaves room for bias in the selection process and decreases credibility.

In terms of the external validity of the study, there was no definition given for the different severities of GERD symptoms. For example, although the guidelines state that anti-refluxants are useful in the treatment of milder forms of GERD, it does not specify what would be classified as mild. This leaves ambiguity regarding the symptoms to be treated with alginate therapy. There is also no mention of the patient population that was studied, or any trial details for the products that may be self-selected. Although this is effective in keeping the guidelines to a manageable length, in order to apply the guidelines to a specific group of patients more research must be conducted. This review is applicable to the self care algorithm as it provides a baseline place in therapy for OTC (over the counter) products and alginate use in GERD.

IV) Other literature types: Therapeutic Research Faculty. Algin Monograph. Natural Medicines Comprehensive Database.

<http://naturaldatabase.therapeuticresearch.com/nd/Search.aspx?cs=&s=ND&pt=100&id=275&fs=ND&searchid=32463826> Accessed Online Feb 1, 2011.

Source description: Natural Medicines Comprehensive Database is an objective, evidence-based resource for health care professionals. The database was released in 1999, and is updated daily. It contains almost 1, 100 monographs on individual natural ingredients, with references detailing where their information is obtained. To assign efficacy and safety ratings a team analyzes medical literature and determines ratings based on preset criteria. The monograph on Algin, also known as alginate or sodium alginate is referenced as the medical ingredient in Gaviscon Liquid®.

Summary: The database recommends that there is insufficient reliable information available regarding the effectiveness of this product, but that it is likely safe when used in typical amounts. The database also warns that the fiber may impair the absorption of oral drugs and that caution is recommended.

Comments:

The internal validity of this particular monograph is questionable. Although the monograph deemed that there was insufficient reliable information regarding algin's effectiveness, both Gaviscon® and Maalox® received a brand evidence-based rating of 5/10. It is therefore questionable how this rating was determined. While there is a note detailing when the site was last updated, I could not determine when the last update of the individual monographs occurred, which could mean the information is outdated.

In terms of external validity, the database does not even include GERD or dyspepsia in the normal uses of algin, although it is linked to both Gaviscon® and Maalox® in the database as either a main active ingredient or the only active ingredient. Therefore, it is hard to apply the efficacy or safety findings in the Algin monograph to GERD and dyspepsia patients. Although the active ingredient is the same, there may be different dosages and patient considerations and therefore, this monograph does not have much application to the treatment algorithm.

II) Systematic reviews and meta-analyses: Tran T, Lowry AM, El-Serag HB. Meta-analysis: the efficacy of over-the-counter gastro-oesophageal reflux disease therapies. *Aliment Pharmacol Ther.* 2007 Jan 15;25(2):143-53.

Study objectives: Over the counter histamine-2 receptor antagonists (H2RA), antacids and alginates are commonly used for GERD. This Meta-analysis attempted to conduct a systematic review of related treatment trials.

Scope: The included studies were all randomized controlled trials (RCTs) published in English. The inclusion criteria stipulated that the RCT should compare an antacid, alginate/antacid combination, or H2RA at OTC doses to placebo, and that the trials should include outcomes such as adequate relief of GERD symptoms, subjective global improvement, and use of rescue antacids. Trials were excluded if they included prescription strength or high dose GERD agents, or had no well defined outcomes. The duration of the studies varied, and the patient population in the studies was not specified.

Methods: A systematic search was performed by two investigators for randomized, placebo-controlled trials between 1972-2005. Fourteen trials were included in the meta-analysis. Quality was measured by the Jadad score, and rated from 0 to 5. Results were pooled using a random effects model. The absolute benefit increase, relative benefit increase, and number needed to treat (NNT) for treatment compared to placebo was calculated for each study included in the meta-analysis. Heterogeneity was evaluated, as was publication bias.

Main results: Ten trials looked at H2RAs, four trials examined antacids, and four trials examined the combination of alginates with antacids (Gaviscon®). The majority of the trials for alginate/antacids had endpoints of subjective improvements, and lasted two weeks. The absolute benefit increase versus placebo was 26%. The relative benefit increase was 0.6 and the number needed to treat was 4. There

was no significant heterogeneity found in these trials. The absolute benefit increase was greater, and the NNT smaller in the alginate/antacid combination than H2RAs or antacids alone.

Conclusions: OTC medications are effective for GERD symptoms. The relative benefit increase was greatest with alginate and antacid combinations, followed by OTC dose histamine-2 receptor antagonists (H2RAs) and lastly antacid-only products. The efficacy of alginates was shown in prevention and treatment of GERD following meals, and therefore seems to have a place in therapy treating individuals with infrequent postcibal episodes or breakthrough symptoms on other treatments.

Comments

The internal validity of this meta-analysis is fairly solid, as it included only RCTs, ensuring good quality studies. Furthermore, they assigned a rating regarding the quality of each study included. This ensures the reader is aware of the strength of the evidence on which the analysis is based. Tests for heterogeneity and publication biases were also performed. A “small” study effect was found, implying that there could be some publication bias. However, the authors did actively seek non published literature from manufacturers.

The external validity is less robust. The patient population was only described as “over 19”, and trial durations were generally not included, leading to a deficiency of information on how long patients should use these treatments. Patients on prescription medications, such as proton pump inhibitors (PPIs), were also excluded, so the extrapolation of the efficacy of these anti-refluxants for patients who take PPIs and have breakthrough symptoms at meals may not be accurate. Finally, due to study limitations the meta-analysis did not measure the efficacy of treatment over a long period of time, and safety was not examined. However, this meta analysis is applicable to the algorithm. It gives a perspective on the efficacy and NNT of different OTC products, and can help stagger products along the algorithm.

II) Systematic reviews and meta-analyses: Mandel KG, Daggy BP, Brodie DA, Jacoby HI. Review article: alginate-raft formulations in the treatment of heartburn and acid reflux. Aliment Pharmacol Ther. 2000 Jun;14(6):669-90. Review.

Study objectives: The aim of this paper is to review alginate-based, raft forming formulations, and other products for the treatment of heartburn and acid reflux.

Scope: There were multiple studies considered in this review. In vitro and in vivo studies were included. The number of subjects in the studies ranged from 16 to close to 3000. Alginate products were compared to placebo, antacids, H2RAs, PPIs, sucralfate, and others. Some studies included were done in infants and pregnancy. Studies ran anywhere from 2 weeks to 2 years.

Methods: The review did not specify how studies were identified. It included in vitro and in vivo studies, with many open label and parallel studies. In total, 106 references were used, approximately 30 of which were studies on the efficacy of alginate formulations.

Main results: In vitro studies show the ability of alginates to form “rafts” in dilute acid, and to sustain a layer of high pH on top of an acid solution in modified Rossett and Rice tests. They also show that the addition of antacids can increase the neutralization profile of the raft, but simultaneously reduce the raft strength. In vivo studies have shown the presence of floating rafts after administration using imaging techniques, which lasts up to 4 hours. They have also demonstrated that alginate/antacid products may not work by neutralizing the gastric contents, but by improving the performance of the raft. Approximately 30 trials evaluating efficacy were included, which show superiority of alginates to placebo, and superiority or equal efficacy when compared to antacids. The trials show alginate based products are effective for meal induced heartburn symptoms, while PPIs are superior for long term severe GERD symptoms. One study also indicated that Gaviscon® is more effective than cisapride for the symptomatic relief of dyspepsia.

Conclusions: Both tablet and liquid formulations of alginate products are able to form a raft that floats on gastric contents. This acts as a barrier to acid and food reflux. These products have a rapid onset similar to that of antacids, but a longer duration of action. They are effective for heartburn, and may be more effective than conventional antacids. They also have a good safety profile, as their mechanism of action is not dependant on systemic absorption. However, night time efficacy is still questionable, as the raft may not be efficacious in stopping reflux when the patient is in the supine position.

Comments

For the internal validity, this review covered a large amount of material and studies, and was well laid out and informative. However, there was no indication of how the studies included in the review were identified, or if the review just included every study on alginates performed. There is also no indication for the reader on the level of evidence for certain conclusions, or a grading for studies to indicate the quality. This would have improved the review.

The external validity of this review is high, because it covers many topics with multiple patient populations. Therefore a reader can identify a useful study and determine the bottom line before delving into more depth as to the internal and external validity of that particular study. This review is becoming outdated, as it was published in 2000. This study applies to the algorithm as it draws many conclusions on the usefulness of alginates in self medication.

1) Primary literature: Dettmar PW, Hampson FC, Taubel J, Lorch U, Johnstone LM, Sykes J, Berry PJ.

The suppression of gastro-oesophageal reflux by alginates. Int J Clin Pract. 2007 Oct;61(10):1654-62.

Study objectives: The objective of this study was to compare alginate products with the same amounts of active ingredients in different dosage forms. The suppression of reflux after a standard meal was determined using ambulatory esophageal pH monitoring. The study was designed as a non-inferiority trial to show that gastroesophageal reflux was no worse after treatment with the tablet formulation compared to liquid formulation.

Methods

Design: Single centre, randomized, three period cross-over, controlled study

Allocation: Each volunteer received a single dose of all three treatments in a computer generated randomized order.

Blinding: Not blinded

Follow-up period: Oesophageal pH was recorded for 4h after ingestion of treatment or control doses, and a record was made of any adverse events. This was done three times for each patient. There was no additional follow-up done.

Setting: St. George's University of London, London, UK

Participants: 35 healthy volunteers ages 18-65 years, who were shown to have oesophageal pH<4 for more than 2% of the 4 hour measurement period at a reflux screening visit. Participants were excluded if they had any of a variety of health problems, or if they had used medication recently.

Intervention: The three treatments studied were 10mL of Gaviscon Advance® suspension, two Gaviscon Advance® chewable tablets with 10mL unchilled water and 10mL of water as a control. The two alginate treatments both contained 1000mg sodium alginate and 200mg potassium bicarbonate.

Outcome: The primary parameter was the percentage of time esophageal pH fell below 4 over the 4 hour period that was recorded for analysis after the ingestion of the standardized meal. Other outcomes included the percentage of time and number of occasions that the esophageal pH fell below 4 and 5.

Patient follow-up: 36 volunteers were randomized into the study, and results for 35 volunteers were included in the efficacy evaluable analysis.

Main results: The non-inferiority of the tablet treatment in comparison to the suspension treatment of alginate reflux suppressant preparations in suppressing acid reflux was demonstrated. For the primary

parameter of percentage of time that the esophageal pH fell below 4, the results (-0.0121 to 0.0501) were all below the non-inferiority margin previously laid out (0.056), demonstrating the non-inferiority. The method was also able to determine statistically significant differences between the active and control groups demonstrating that the method was sensitive enough to discern variations.

Conclusions: Both the suspension and tablet formulations were shown to be statistically superior to control for the percentage time and number of occasions esophageal pH fell below 4 and 5. There was no statistically significant difference between the alginate suspension and alginate tablets in any of these parameters.

Comments:

When assessing the internal validity of a study both strengths and weaknesses must be considered. Strengths included the authors' outline of the method for predetermining the non-inferiority margin value, and outline for the rationale of the number of volunteers needed. Additionally, they had the foresight to increase enrollment to account for potential dropouts. Weaknesses of the trial include the lack of blinding in the evaluators and presumably patients. This may be less of a concern as symptoms were not an outcome followed by the study.

The downfall of this trial is in the external validity. Symptoms of GERD were not evaluated, as the outcomes analysed were esophageal pH levels. However, some patients may experience GERD at differing levels of esophageal pH, and therefore the outcomes in this study are not directly applicable to our GERD patients. In addition, many patients were excluded based on health, and inclusion did not mean the patient had GERD symptoms. The patient population was mainly young caucasians who were not overweight, which is not the typical patient likely to need GERD treatment. All of these factors decrease the external validity of the study. This study is applicable to the algorithm because it suggests that different alginate products are equally efficacious.

I) Primary literature: Dettmar PW, Sykes J, Little SL, Bryan J. Rapid onset of effect of sodium alginate on gastro-oesophageal reflux compared with ranitidine and omeprazole, and relationship between symptoms and reflux episodes. Int J Clin Pract. 2006 Mar;60(3):275-83.

Study objectives: The objective was to compare the time of onset of effect of sodium alginate 20mL, omeprazole 10mg, ranitidine 75mg, and control based on esophageal and intrinsic pH and to determine any correlation between reflux symptoms and reflux episodes in volunteers suffering from occasional gastro-oesophageal reflux.

Methods

Design: single-centre, open, randomised, four-period crossover study

Allocation: Patients were randomized to receive a single dose of each treatment according to a Williams Squared randomisation list.

Blinding: Not blinded.

Follow-up period: participant's gastric and esophageal pH was measured for 4.5 hours after each treatment. A post study medical examination was also performed.

Setting: Nottingham University Medical School, UK.

Participants: 19 individuals age 18-70 with a BMI of 19-32. Patients had occasional gastroesophageal reflux symptoms associated with a particular food or drink. Exclusion criteria included pregnancy, lactation, under medical care for GERD, and abnormal diet, and a list of clinically significant medical conditions.

Intervention: The treatments were SA 20 ml, omeprazole 10 mg, ranitidine 75 mg, and 50mL water control. Omeprazole and ranitidine were taken with 50mL of tap water. The pH was recorded at 6 second intervals for 4.5 hours after ingestion of a meal. The treatment was administered 30 minutes after the meal.

Outcomes: The outcomes evaluated include the time to onset of action of SA 20 ml, omeprazole 10 mg, ranitidine 75 mg and a water control based on changes in esophageal, fundal, corporeal, and antral pH data. Secondary outcomes were the association between reflux symptoms and episodes.

Patient follow-up: Out of the 19 subjects recruited, 16 were included in the efficacy evaluation, and 17 were included in the safety evaluation.

Main results: sodium alginate showed significantly better prevention of acid exposure in the oesophagus during the first hour than the other three treatment groups. This supports its physical mechanism of action versus ranitidine's pharmacological mechanism, which began to demonstrate effectiveness at two hours. Over the entire 4 hours, SA was more effective than control or omeprazole and comparable with ranitidine. Omeprazole had little effect on esophageal pH during the study, possibly due to the formulation. Omeprazole is enteric coated and requires several doses to obtain the maximum effect. There was little evidence of association between 'oesophageal' symptoms and reflux episodes but associations between 'gastric' symptoms and acidity in the oesophagus, fundus and corpus were apparent.

Conclusions: sodium alginate was superior to omeprazole, ranitidine, and water in reducing reflux and gastric acidity within one hour. It was also superior to omeprazole and water for the full four hours of the study. There was little insight provided on the relationship between symptoms and reflux episodes defined on the basis of pH changes.

Comments:

The internal validity of the study was well thought out and presented despite the small sample size. The sample size did meet the needs for 80% power. The data analysis seemed thorough including graphs and area under the curve calculations. This study was not blinded.

The external validity of the study starts out strong, with a population that frequently experiences heartburn and self medicates with OTC products. However, there is an abundance of exclusion criteria, and the data cannot be extrapolated to individuals who use anti reflux therapy frequently, as only one dose of each agent was given in the study. This could have impacted the omeprazole outcomes, as increased efficacy is seen with continual dosing. Additionally, most of the studies' conclusions are based on results from pH measurements rather than reported symptoms. The introduction acknowledges that 30% of asymptomatic people have acid reflux and 30% of people with symptoms have no abnormal acid reflux, however the conclusions are still based mainly on pH values rather than symptoms. Therefore this study may not be as applicable to our algorithm as it only identifies a theoretical earlier onset of sodium alginate effect for GERD symptoms, rather than drawing conclusions based on symptom resolution.

I) Primary literature: Lai IR, Wu MS, Lin JT. Prospective, randomized, and active controlled study of the efficacy of alginic acid and antacid in the treatment of patients with endoscopy-negative reflux disease. World J Gastroenterol. 2006 Feb 7;12(5):747-54.

Study objectives: This study aims to assess the efficacy and safety of a combination product containing alginic acid plus antacid compared to equal strength antacid in patients with endoscopy negative reflux disease (ENRD).

Methods

Design: This was a prospective, randomized, open-label and active-controlled study.

Allocation: Patients received the therapy based on a random number sheet generated by SAS.

Blinding: Not blinded

Follow-up period: Patients were followed for 6 weeks.

Setting: Taiwan, not further specified.

Participants: The study included 134 patients, with 69 patients randomized to alginic acid plus antacid and 65 randomized to antacid only. Individuals age 18-75 years with diagnosed ENRD were included.

Patients were asked to discontinue other anti-reflux therapies at least 3 days before the study. Exclusion criteria included: patients who had a history of intolerance or allergies to the product, endoscopic evidence of esophagitis, history of partial or total gastrectomy, or had esophageal stricture, pregnancy or lactation.

Intervention: A baseline endoscopy was performed, and randomization occurred within 7 days. ENRD patients were randomized to receive alginic acid and antacid (200mg alginic acid, 30mg aluminum hydroxide and 40 mg magnesium hydrocarbonate per tablet), or antacid only (500mg $\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O}$ per tablet) for 6 weeks with an assessment at 3 and 6 weeks. The dose for both groups was 2 chewable tablets, 4 times daily.

Outcomes: The primary endpoint for efficacy was a change in severity of heartburn based on a visual analog scale (VAS) at the 6th week of treatment. Secondary efficacy endpoints included change in the severity of multiple symptoms associated with reflux at the 3rd week of treatment, change in the frequency of symptoms, and change in the quality of life from a doctor's point of view. The primary outcome for safety was the incidence of adverse drug reactions.

Patient follow-up: The study ran from June 2003 – December 2004. 112 patients out of the 134 patients randomized completed the study (84%).

Main results: No statistically significant difference in demographics between the patients in the treatment groups was detected. For the primary efficacy endpoint, the study found a statistically significant greater improvement in patients treated with the alginic acid/antacid combination versus patients treated with antacids alone. There were statistically significant improvements in the alginic acid/antacid group versus the antacid group alone in some of the symptoms associated with reflux at 3 weeks, but not all. The results also suggest differences in the severity of reflux symptoms and the quality of life from the doctor's point of view favouring the alginic acid/antacid combination. No statistical significant difference was found between the two groups in the incidence of adverse events, and only mild to moderate adverse events were reported.

Conclusions: The alginic acid/antacid treatment was found to be more effective in reducing symptoms including heartburn, regurgitation, vomiting, and belching in patients with ENRD. It also reduced heartburn and regurgitation in the first week of the study, while the antacid only group had a delayed onset, at approximately 2 weeks. The authors concluded that the alginic acid/antacid combination is more effective than antacids in the symptomatic control of ENRD, and that the safety profiles were comparable.

Comments

Some points that could affect the internal validity of the study include the lack of blinding and the lack of a placebo controlled arm. The study did include an intention to treat population with baseline assessments. Discontinuation of other anti-reflux medications such as PPIs 3 days before entering the study could have lead to rebound acid secretion and affected study results.

The applicability of this study to Canadians is questionable, as it was conducted in Taiwan. Race was not mentioned in the demographics section. In addition, products unavailable in Canada were used (Topaal[®] and Nacid[®]), so it is unclear if these results can be extrapolated to Canadian alginic acid/antacid products such as Gaviscon[®] Heartburn & Acid Reflux Relief Formula Tablets which contain alginic acid and magnesium carbonate. This trial was based on symptomatic analysis which is a good endpoint to evaluate in ENRD patients using OTC products. Two thirds of patients with GERD symptoms may not have esophageal or mucosal erosion, and would be classified as having ENRD. Therefore this subset of patients is still applicable to the algorithm if race is not taken into account. This study suggests that alginate/antacid combination products should be considered before antacids, as they may be more effective.

References:

DeVault KR, Castell DO; American College of Gastroenterology. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Am J Gastroenterol*. 2005 Jan;100(1):190-200.

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Canadian Pharmacists Association. Gaviscon® Monograph. Compendium of Pharmaceuticals and Specialties, online version (e-CPS).