EBSCR Expanded Abstracts: Calcium Carbonate

A. Tertiary Literature

1) Williams D, Schade R. Gastroesophageal Reflux Disease. Pharmacotherapy: A Pathophysiological Approach, 8th Edition. Chapter 29.

Source description: A thorough review of primary and secondary literature. Many experts have contributed to the textbook to discuss the pathophysiology, epidemiology, clinical presentation, and treatment of a wide range of disease states. Information is well referenced and strongly supported. This is the most recent edition, being updated in 2011.

Summary:

The use of OTC antacids is given level IV evidence for use in mild, infrequent heartburn or regurgitation. If continuous use is needed for 2 weeks or longer, assessment by a physician is needed. It is noted that superiority of antacids over placebo for treating even mild GERD is not well documented. However, patients and practitioners typically consider them effective for immediate relief of symptoms. Combination with other GERD therapies is quite common.

Comments/critical appraisal: Internal validity is not a concern with this publication. Applying the information directly to clinical practice is difficult. Many references have been included and the conclusions may have been over-simplified. This information should be used more for an introduction to a topic rather than a guideline to treatment. The large amount of references provides an excellent source of additional material to read through and critically appraise.

2) Fennerty M, Finke K, Kushner P et al. Short and Long-Term Management of Heatburn and Other Acid-Related Disorders: Development of An Algorithm For Primary Care Providers. The Journal of Family Practice (2009): 58(7); S1-212.

Study objectives: Develop a comprehensive 2-part algorithm for short and long-term management of heartburn to help health care providers select the most appropriate treatment options.

Scope: Patients ranged from those presenting with their first occurrence of acute heartburn of unknown cause, to management of patients suffering from chronic heartburn related to GERD or use of NSAIDs. Interventions included various antacid preparations, H2RAs, and PPIs. Outcomes focused on symptomatic resolution of heartburn. The duration of treatment was indefinite as long as the patient remained symptomatic.

Methods: An expert workgroup of nurse practitioners, physician assistants, primary care physicians, gastroenterologists, and a pharmacist developed the guidelines. No information is available to describe how studies were identified or for the grading of recommendations. Studies cited are generally reviews without primary literature. Product monographs are also widely referenced.

Main results: The workgroup produced treatment algorithms for both acute and long-term management of heartburn. In the acute setting, a good patient history is required, as well as exclusion of several red flags which may indicate more serious conditions. The long-term treatment requires previous diagnosis of the cause of the patient's heartburn symptoms. Both algorithms include appropriate follow-up therapy and periodic re-assessment of need for therapy.

Conclusions: Antacids have a rapid onset but short duration of action. They are therefore only recommended for episodic (≤ 1 time per week) treatment or meal-related heartburn. Tablets should be chewed to maximize efficacy. Adverse effects include constipation, belching, and flatulence. Drug interactions should be considered.
Comments/critical appraisal: No critical appraisal of the cited references is given. As no selection criteria are given, it makes it difficult to address the internal validity of this guideline. This also makes it hard to consider the external validity. No information is given regarding the effect these algorithms have on patient outcomes. It seems unlikely that a single guideline would be thorough enough to apply to all patients of all etiologies of heartburn. As the methods and selection criteria are not given, this guideline should not be recommended for routine care of patients.

B. Primary and Secondary Literature

3) Pettit M. Treatment of Gastroesophageal Reflux Disease. Pharmacy World & Science (2005) 27: 432-435.

Study objectives: Bring together information on the treatment of GERD.
Scope: All patients involved had a previous diagnosis of GERD. Interventions included anatacids, alginates, H2RAs, PPIs, sucralfate, prokinetics, and surgical interventions. Outcomes included symptomatic relief, quality of life, rate of complications, gastric pH control, and speed/completeness of erosion healing. Duration of follow-up ranged from five days to thirteen years.
Methods: A Medline search was done using the search term "gastroesophageal refluc disease". Multiple sub-searches where then done to select manuscripts relevant to treatment of GERD. Data was taken from published manuscripts and their citations. A total of 27 references were used.
Main results: High-dose PPIs were found to be the most effective choice for symtptomatic GERD. Standard-dose was more effective than half-dose, and all three choices were more effective than standard doses of H2RAs. Acid control is the focus of treatment. There is high correlation between absence of symptoms and remission.
Conclusions: Antacids act locally to provide rapid, short-term relief of symptoms. They may be effective for mild GERD, but only 25% of patients have relief of symptoms. They have no effect on healing of esophagitis. Frequent dosing limits convenience.
Comments/critical appraisal: For the most part the research is thorough and well-done. While the initial search method is given, the criteria of the sub-searches are not given. This makes it impossible to determine why the listed references were chosen. A large patient population of various backgrounds supports the external validity. Various outcomes were used, including objective ones. There was a large range in follow-up times which may have an impact on the conclusions of the study. Overall, this study is well done but should not be the lone resource for choosing therapy.

4) Hershcovici T and Fass R. Pharmacological Mangement of GERD: Where Does It Stand Now? Trends In Pharmacological Sciences (2001): 32(4); 258-264.

Study objectives: Summarize the available data on current pharmacological management of GERD and identify unmet needs for data that can be addressed in the future.
Scope: The evaluated patients suffered from symptomatic GERD. Interventions included antacids, Gaviscon, sucralfate, H2RAs, PPIs, potassium-competitive acid blockers, transient lower esophageal sphincter relaxation (TLESR) reducers, visceral pain modulators, and prokinetic agents. Interventions examined include symptomatic relief, esophageal erosion healing, prevention of complications. Duration was not specified.

Methods: A total of 63 studies were included, but no criteria for inclusion or exclusion were given. Trials were generally RCT s, but some reviews and population-based studies were also cited.
Main results: Further investigation is needed for the treatment of refractory GERD, NERD, postprandial heartburn,atypical GERD, extraesophageal manifestations of GERD, and Barrett's esophagus.
Conclusions: Antacids see frequent use for treatment of symptoms of episodic or postprandial heartburn. The symptomatic relief is rapid but transient. Antacids have no benefit for healing esophageal erosion or preventing complications.
Comments/critical appraisal: A large number of studies were cited in the creation of this review. The majority of them are primary literature, most being RCTs. There is no search method or criteria given though, so it is impossible to determine if they were the best studies to be included. Many therapies are addressed and the information is superficial. No information is given to help select a therapy in a patient-centered process. A general place in therapy is given instead.

5) Earnest D, Robinson M, Rodriquez-Stanley S et al. Managing Heartburn At The 'Base' of The GERD 'iceberg': Effervescent Ranitidine 150mg B.D. Provides Faster and Better Heartburn Relief Than Antacids. Alimentary Pharmacology & Therapeutics (2000): 14(7); 911-918.

Study objectives: Compare the efficacy if effervescent ranitidine to as-needed calcium carbonate for patient self-treatment of heartburn.
Methods:
Design: randomised control trial
Allocation: Concealed
Blinding: Unblinded
Follow-up period: 12 weeks
Setting: University of Arizona Health Sciences Center
Participants: 155 subjects with frequent antacid-responsive heartburn
Intervention: Effervescent ranitidine 150mg tablets twice daily versus calcium carbonate 750mg as-needed. Patients in either group were allowed to have additional doses of calcium carbonate as needed for symptomatic relief.
Outcomes: The number of tablets of rescue antacid used per day as well as heartburn frequency and severity were recorded as part of the study. Esophageal healing was measured with grade ≤ 1 considered healed. Quality of life was assessed using various indices such as pain.
Patient follow-up: 100%
Main results: Ranitidine significantly reduced heartburn frequency and severity after a single day ($P < 0.02$). At week 6, ranitidine significantly reduced the daily use of rescue antacid (7.3 tablets/day vs. 14.1 tablets/day, $P<0.001$). Ranitidine produced better rates of esophagitis healing (55% vs. 29%, $P=0.022$). By the end of the study ranitidine was superior in all quality of life indices ($P < 0.05$).
Conclusions: Ranitidine 150mg BID is more effective than calcium carbonate in reducing heartburn, healing erosive esophagitis, alleviating pain, and improving quality of life in patients suffering from chronic heartburn.
Comments/critical appraisal: No objective way of assessing heartburn severity or frequency was outlined in the trial. This makes it difficult to eliminate any bias the researchers may have had in determining the effects of the treatments. The patients also reported their daily consumption of rescue antacid which may not be reliable. A 12 week treatment course is fairly short in a chronic condition. It may be possible that over a greater length of time calcium carbonate would produce results more similar to ranitidine. There was also no placebo comparison so the size of the placebo effect is not accounted for.

The information gained from this study supports that ranitidine is likely superior to calcium carbonate in treating the symptoms and complications of GERD. Some factors may have overestimated the superiority of ranitidine, but the objective measurement of esophageal healing helps to support the claim that ranitidine is superior.

6) Rayburn W, Liles E, Christensen H, Robinson M. Anatacids vs. Antacids Plus Non-Prescription Ranitidine For Heartburn During Pregnancy. International Journal of Gynecology & Obstetrics (1999): 66; 35-37.

Study objectives: To determine if the non-prescription 75mg strength of ranitidine in combination with calcium carbonate was more effective than calcium carbonate alone in treating heartburn among pregnant women.

Methods:

Design: randomised control trial
Allocation: Concealed
Blinding: Double blinded
Follow-up period: 3 weeks
Setting: The University of New Mexico Health Sciences Center
Participants: 50 women suffering from heartburn who were at 20 weeks gestation or more. Patients first received one week of open-label treatment with up to eight tablets of calcium carbonate per day. If the patient still experienced four or more episodes of moderate to severe heartburn after this period, they were blindly randomized to one of the experimental groups
Intervention: Following the lead-in, patients were randomized to ranitidine 75mg or placebo twice daily. Both groups continued to be allowed use of calcium carbonate tablets which was provided by the researchers.
Outcomes: 10-point visual analog scale for heartburn intensity.
Patient follow-up: (60%) 30 (ranitidine = 15, placebo = 15)
Main results: The baseline heartburn intensity was 7.9. Treatment with calcium carbonate reduced this score to 6.5 ($P < 0.05$). By the end of the trial, the overall heartburn intensity score was 4.4 ($p<0.01$) but the ranitidine-calcium carbonate group reached a score of 3.7 (vs. 7.7 at baseline, $P<0.001$). All birth outcomes were favorable.
Conclusions: Heartburn associated with pregnancy may respond to calcium carbonate but ranitidine 75mg may be warranted in heartburn that does not respond.
Comments/critical appraisal: The internal validity suffers due to low patient follow-up. Of the original 50 women selected, 20 did not complete the study. Of these, 10 withdrew after the initial lead-in because they received adequate relief of symptoms with calcium carbonate. Had they been included, the evidence may find that calcium carbonate was superior. Also, seven patients (47%) of patients in the placebo-calcium carbonate group dropped out of the study due to lack of efficacy in relieving symptoms. In comparison, none of the ranitidine-calcium carbonate patients dropped out.

The external validity is also questionable. The sample size is quite small, with only 15 patients in the ranitidine group and 8 patients in the placebo group finishing. The heartburn severity scale was also not well explained so it is hard to judge exactly what the effect was. There is a safety concern as treatment only lasted two weeks, and only women of at least 20 weeks gestation were included. If treatment lasted longer or began earlier important safety differences between the two treatments may have emerged. Of note, the manufacturer of ranitidine provided funding for the study.

This trial should be expected to have minimal impact on clinical practice. The data is simply too small to approximate the difference. It is likely the effect of calcium carbonate was underestimated. At best, this study shows that either option may be effective and safe and further research is needed.