Famotidine Extended Abstracts

I) <u>Primary literature Summary</u>

Ciccone, Decktor, et. al. Efficacy and tolerability of famotidine in preventing heartburn and related symptoms of upper gastrointestinal discomfort. *Am J of Therapeutics* 1995 *(*2);314-319.

<u>Study objectives</u>: To compare the efficacy of famotidine vs. placebo in preventing meal-provoked upper gastrointestinal symptoms.

<u>Methods:</u> 121 subjects between the ages of 20-61 years of age were randomly assigned to one of 4 treatments: single oral doses of placebo, famotidine 5mg, famotidine 10mg, or famotidine 20 mg spaced approximately 7 days apart. Treatment was administered 1 hour prior to ingestion of test meals (chili and wine). Rescue antacid medication (Maalox) was available for subjects who required additional interventions. Endpoints were measured using a scale immediately before each test meal and every 15 minutes thereafter for 5 hours. A global evaluation of the test medication was performed prior to rescue medication use or at the end of each treatment session.

Design: Randomized Placebo-Controlled Trial

Allocation: Allocation concealed

Blinding: Double-blinded

Follow-up period: 4 weeks

Setting: Single center

Participants: 121 subjects (58 men and 63 women) aged 20-61 years. Patients had to have a history of heartburn and acid/sour stomach occurring at least 3 times/week.

Intervention: Single oral doses of placebo vs. famotidine 5mg or famotidine 10mg or famotidine 20 mg spaced approximately 7 days apart.

Outcomes: Heartburn severity, acid/sour stomach, and overall discomfort were the main outcomes.

Patient follow-up: Out of the 121 patients that were randomized, 7 did not complete the study and were not included in the efficacy analysis. Per-protocol follow up was used.

Main results: Treatment by all three doses (5,10,and 20mg) were rated “good” or “excellent” in terms of heartburn and sour stomach by significantly more subjects (58-63%) than with placebo (38%). Rescue antacid was used significantly more in the placebo group vs. famotidine (37% vs. 17%)

Conclusions: Famotidine doses of 5, 10, and 20 mg were significantly more effective than placebo in preventing symptoms of upper gastrointestinal distress when administered 1h in advance of meal provocation

Comments:

With respect to the internal validity of this study, there are a few points worth mentioning. As this study aims to show prophylactic use of famotidine before meals it is important to distinguish what meals were being tested. For each of the sessions the participants went to they were served chilli and wine. These are two good examples of foods that should be avoided if GERD is a problem however, what triggers a person's heartburn is very variable and differs between individuals. It is there for hard to conclude that chili and wine can account for all different diets and food-triggers in the community. The study does note that 80% of the participants felt that chili and wine were equivalent to what would normally trigger their heartburn symptoms. Those lost to follow up (7 patients) were not included in the final analysis and thus per protocol follow-up was used. Although intention to treat is preferred, the low-drop out number makes the difference less significant. This is one of the only studies that account for diet and obesity as confounding factors.

In terms of external validity, this study excludes the elderly and pediatric populations. The age range is from 20-61 and thus no elderly patients were in this trial. Although this trial reported similar adverse events in the famotidine group compared to placebo, this may not be the trend the in elderly population who are more prone to H2RAs anticholinergic effects.

II) <u>Primary literature Summary</u>

Simon T, Berlin R, et al. Self-directed treatment of intermittent heartburn: a randomized, multicenter, double-blind, placebo-controlled evaluation of antacid and low doses of an H2-receptor antagonist (famotidine). ***Am J of Therapeutics*** **1995 (2);304-313.**

<u>Study objectives</u>: To compare the efficacy of self-selection agents for treatment of heartburn associated with GERD. Agents of comparison include: Famotidine at 5, 10, and 20 mg doses vs. Antacids at 11meq, vs. placebo.

<u>Methods:</u> There are 5 treatments compared in this trial: placebo, famotidine 5mg, 10mg, 20mg, and antacid (chewable 11.0mEq magnesium/aluminum hydroxide). Treatment was allowed as needed for heartburn, up to B.I.D. At each medication administration a patient took 2 tablets. One tablet was a placebo OR antacid and the other was a placebo OR famotidine. Both of the pills in the placebo group were a placebo. An open-label, backup antacid (Magnesium aluminum hydroxide = 12.3 mEq) was provided to use if the test drug did not provide adequate relief. Patients assessed heartburn relief hourly and recorded use of backup antacid. When a patient developed an episode of heartburn requiring self-medication, the patient recorded the date/time and the time of last meal, and rated the initial severity of the episode. After administration of medication, patients were instructed to observe their symptoms for 1h without additional treatment. After 1 hour the episode was considered a success if heartburn was completely relieved. If heart-burn was still there after 1 hour, patients could choose either to use open-label backup antacid or continue monitoring. If the relief occurred without taking backup antacid before the need of the 3rd hour, the episode was considered a success. The episode was considered a failure if complete relief did not occur at all of if backup antacid was taken. If they could not obtain relief by the 3rd hour they could take an additional dose of the study medication.

Design: Randomized Placebo-Controlled Trial

Allocation: Allocation concealed

Blinding: Double-blinded

Follow-up period: 4 weeks

Setting: Multi center

Participants: 29 US investigators enrolled a total of 565 outpatients, ages 18-81 years (mean 44.1 years) with heartburn self-managed at least 3 times per week with antacids

Intervention: Patients received famotidine 5mg + antacid placebo, famotidine 10mg + antacid placebo, famotidine 20mg + antacid placebo, antacid + famotidine placebo, or famotidine placebo + antacid placebo.

Outcomes: Degree of heartburn relief, time to relief, use of open-label additional antacid

Patient follow-up: 565 patients were randomized. Throughout the course of the 4 week trial 35 patients dropped out with similar rates in each group. Per protocol analysis was used to follow-up.

Main results: Relief was found in 41% of the placebo group, 59% in the famotidine 5mg group, 70% in the famotidine 10mg group, 69% in the 20mg famotidine group, and 62% in the antacid group. The median time to relief of the first heartburn episode was significantly shorter in the famotidine 5mg, famotidine 10mg, and antacid groups than placebo and 20mg famotidine group.

Famotidine 10 mg results: 70% heartburn episode relief; faster time to complete relief than placebo; 74% of subjects with treatment ratio of good or excellent (global evaluation); 26% of subjects requiring rescue antacids

Conclusions: The most efficacy came from using either the 10mg or 20mg dose of famotidine. In terms of complete alleviation of symptoms (heartburn completely not felt), the 5mg famotidine and 10mg famotidine dose take as long as the antacid. Famotidine use favors a more global relief from heartburn related to GERD. The 10mg famotidine regimen (most similar to OTC recommended regimen for heartburn) showed efficacy in all end points.

Comments:

In terms of the internal validity, there are a few noteworthy points. "Time to relief" in the study is defined as the absence of any feeling/symptom of heartburn. Using this definition, even if a person immediately feels the benefits of antacids or famotidine, their case won't be counted as "relived" until all feeling of discomfort is gone. This is why the antacid shows a similar time to "relief" as famotidine. In actuality and in other studies, antacids are generally known to provide symptom relief faster than H2RA. This study uses per-protocol analysis. Intention to treat protocol (ITT) is generally desired when following-up on patients for clinical trials. Because the dropout rate was not very high however (35/565), the use of per protocol vs. ITT may not be as important. The study design, explanation of inclusion, exclusion, and patients lost to follow-up were well documented

In terms external validity, it is important to note that this trial was made to show famotidine's role in prophylactic management of GERD associated with food-intake. The standard OTC dose of famotidine for heartburn associated with GERD is 10mg-20mg B.I.D. Because the trial did not use this dose, we cannot extrapolate the efficacy conclusion of this trial to the recommended dose.

III) <u>Primary literature Summary</u>

Berlin R, Bradstreet D, et al. Famotidine relieves symptoms of gastroesophageal reflux disease and heals erosions and ulcerations. *Archives of Internal Medicine* 1991 (153); 2394-2408.

<u>Study objectives</u>: To study the effect of famotidine compared to placebo to treat symptoms of GERD (heartburn) and heal esophageal erosions or ulcerations.

<u>Methods:</u>

Design: Randomized Controlled Trial

Allocation: Allocation unconcealed

Blinding: Double-blinded

Follow-up period: 12 weeks

Setting: Multi center

Participants: (n = 338) Criteria for inclusion in the study were those over 18 years of age with a clinical diagnosis of symptomatic GERD. The primary entry criterion was the complaint of heartburn characterized by retrosternal burning pain that occurred for 15-30 days before the study. Patients with erosive esophagitis (endoscopic grades 2-4 on the Dent Scale) and those without esophagitis were eligible to enter the clinical trial. Patients without ENDOSCOPIC esophagitis erosion had to have had experience at least 5 days of heartburn occurring during a 1-week, single-blind, placebo baseline period and a positive Bernstein Acid Infusion test.

Intervention: Patients received famotidine 40 mg H.S (135), famotidine 20mg B.I.D (137), or placebo (66). Patients were all given low-neutralizing antacids (MgOH) for as needed relief.

Outcomes: Number of daytime and nighttime heart burns, complete endoscopic healing, severity of GERD symptoms tracked by a diary/subjective severity rating scale.

Patient follow-up: 246/388 patients were followed-up on. 27.4% of the famotidine 40 mg H.S group, 24.1% of the famotidine 20mg B.I.D group, and 33.3%, of the placebo group did not finish the study. The number of patients evaluated for efficacy ranged from 201 at week 2 to 193 at week 12.

Main results: There was a significantly greater amount of patients experiencing daytime relief from heartburn in the famotidine 20mg B.I.D arm compared to placebo. This arm also showed a statistically significant total global symptom severity score, decrease in as needed low-neutralizing antacid use, and endoscopic healing. The famotidine 40mg H.S arm was superior compared to placebo in all except for complete relief of daytime heartburn. This was not an expected result. When compared to the 20mg B.I.D regimen it was inferior in each outcome.

In terms of adverse events, both arms using famotidine experienced significantly more adverse events than placebo but between the two, there was no significant difference in adverse events

Conclusions: The authors conclude that both the famotidine 20mg B.I.D and the famotidine 40mg H.S regimens are superior to placebo in the relief of symptoms associated with GERD and complete healing of erosive esophagitis. The 20mg B.I.D regimen showed better outcomes than the 40mg H.S regimen and thus the study confirms the advantage of 24 hours control of esophageal exposure time in relieving symptoms of GERD and in producing complete endoscopic healing of erosive and ulcerative lesions

Comments:

A few interval validity aspects worth mentioning include variables that may not have been accounted for. Diet, a very large factor when it comes to GERD onset, is a factor that was not mentioned and accounted for. There was no mention or control of diet for the duration of the study or of administration guidelines. 15-60minutes before eating is the recommended use of this drug for maximal efficacy. Obesity was also not accounted for which is a risk factor for onset of GERD. We are unsure if either of the groups had a higher proportion of obese individuals when compared to the others. Furthermore, in order to measure severity of symptoms, patients were given a rating scale from 0-4 (0 = no symptoms, 4 = disabling symptoms) for self-rating. This brings an element of subjectivity to the conclusions as every person experiences GERD in different severities and so severity of symptoms may not be a solid outcome to base conclusions on. Finally, a mild-antacid (MgOH was given to all subjects in the study for as needed use. Results show that 91.9% of the famotidine 40mg H.S group, 94.9% of the famotidine 20mg B.I.D group, and 93.9% of the placebo group had to use antacids at some point during the 12 week study. This may hint to a conclusion that was not mentioned by the authors that famotidine alone is not enough for controlling GERD symptoms (regardless of B.I.D vs. OD dose). Drop-out and patient follow-up was handled in a per-protocol manner which excludes 142 patients from the result analysis. Intention to treat analysis would have been more favorable in this situation.

In terms of external validity and how much we can generalize the conclusions of this study, the study only included those over the age of 18 and so we do not have any insight into the use of famotidine in the pediatric to adolescent population. The population used seemed to have moderate-severe heartburn (suffered from heartburn 15/30 days) for which PPIs are more suited to manage. Once again, the fact that diet was not controlled limits the study's validity. Because this was not controlled, we are unable to generalize the conclusions of this study to populations that may have very acidic/spicy meals vs. those that do not (vegetarians for example).

IV) <u>Primary literature Summary</u>

Kawano S, Masuda E, et al. Reflux *Esophagitis: Natural History and Treatment* "Randomized comparative study of omeprazole and famotidine in reflux esophagitis" *J of Gastroenterology ad Hepatology* 2002 (17); 955-959.

<u>Study objectives</u>: To compare the efficacy of proton pump inhibitors (omeprazole) compared to H2-receptors antagonists (famotidine)

<u>Methods:</u>

Design: Randomized Comparative study

Allocation: Allocation concealed

Blinding: None mentioned

Follow-up period: 8 weeks

Setting: Multi-center in Japan

Participants: (n = 56) Patients over the age of 20, diagnosed as having reflux esophagitis by the Los Angeles Classification Grade A-D)

Intervention: Omeprazole 20mg once daily versus famotidine 20mg B.I.D

Outcomes: Symptom severity, symptom frequency, and 'healing' defined as endoscopic observation of no mucosal breaks if there were some present at baseline

Patient follow-up: 47/56 patients had follow-up. 5 patients from the omeprazole group and 4 patients in the famotidine group were lost to follow up

Main results: Healing in the omeprazole vs. famotidine group was seen at 72% vs. 32% at week 4 and 95% vs. 53% at week 8. The symptom severity was initially relieved more frequently in the omeprazole group (67% vs. 29% at week 2 and 95% vs. 55% at week 4), but by week 8, there was no significant difference between the two groups. Symptoms include severity of heartburn, epigastralgia, acid belching, dysphagia, nausea, and vomiting.

The study did not come to conclusions comparing the two drugs in terms of adverse events, but noted that no serious adverse event occurred.

Conclusions: The authors concluded that omeprazole provides quicker healing and a greater relief from symptoms than famotidine in the context of GERD, and should be considered first choice for

Comments:

In term of internal validity, no comment was made about diet which is a major factor for experiencing symptom severity. Furthermore, there were no remarks of blinding or about the setting of this study and the study was rather small (56 patients, 9 of which were lost to follow up). The study did have equal distribution of patient demographics and dose use standard doses for each of the medication arms. For severe GERD accompanied by esophagitis, high dose famotidine is normally used and so the low, OTC-dose of 20 mg B.I.D, may not be a suitable match for the PPI.

In terms of external validity, the study only included those over the age of 20 and so extrapolating the results to the younger population may not be possible.

V) <u>Meta-analyses</u>

Tran T, Lowry A, et al. Meta-analysis: the efficacy of over-the-counter gastro-oesophageal reflux disease therapies. *Alimentary Pharmacology & Therapeutics* 2006 (25); 143-153.

Study objectives: The objective of this meta-analysis was to conduct a systematic review of trials that show the efficacy of over-the-counter (OTC) GERD therapies

Scope: The scope of the meta-analysis was to include:
1) Randomized control trials conducted in adults older than 19 years of age comparing antacids, alginate/antacid combinations, or H2RA at OTC doses to a placebo
2) Outcomes of interest including complete and adequate relief of GERD symptoms, subjective global improvement, and the use of rescue antacids

Methods: Two different investigators independently searched MEDLINE databases between 1972 and 2005 for English articles. Search terms included: GERD, or GORD, or gastro-oesophageal reflux disease or, reflux disease, or reflux and antacid, or alginate, or histamine-2 receptor antagonist and placebo (not PPI). The two researchers reviewed all potential literature independently and also abstracted data independently. A hand search of cited bibliographies was done and US manufacturers were contacted for any unpublished data. The quality of studies was measured by the Jadad scoring system from 0-5.

Through the MEDLINE search as well as contacting the U.S manufacturers for unpublished articles (which yielded 4 additional studies) there were 14 resulting studies that met the criteria and are included in the data presented by this meta-analysis. 10 randomized, placebo-controlled, double-blinded, parallel group trials were identified that compared H2RA (n=3442, placebo=2940). Of these, 2 trials focused on famotidine as the comparative H2RA.

Main results: The authors concluded that there was no significant difference in efficacy between the 4 H2RA agents captured in this meta-analysis (cimetidine, ranitidine, famotidine, and nizatidine). H2RA showed greater efficacy compared to all other OTC preparations in regards of relief of heartburn, symptomatic improvement, and episodes requiring rescue antacids. The absolute benefit increase ranged between 10-12% and relative benefit increase was 19-41%.

Conclusions: The conclusion is that over the counter medications are effective in treating symptomatic gastro-oesophageal reflux disease

Comments/critical appraisal

When it comes to internal validity there are several strengths worth mentioning. Only randomized, placebo controlled trials were included as a minimum standard of quality evidence. In terms of further evaluating the quality evidence of eligible trials, the Jaded scoring system was used to provide objectivity and avoid biases from the two authors working individually. One point that the authors note in the discussion is that the funnel plot (a scattered-plot tool used in meta-analyses to identify publication biases on the basis of treatment effect vs. study size) showed a small bias in the publications that were included in this meta-analysis. Due to the small number of trials for each clinical outcome measured, this small publication bias could not be corrected in this study.

In terms of external validity, the generalizability of the results is very good. Although no participants under the age of 19 are included in these results, the inclusion criteria and outcomes measured allow large generalizability. The authors note that their meta-analysis study addresses a current gap in literature which is a lack of systemic evidence for OTC doses to treat GERD and oesophagitis. It is therefore important to note that the results of this meta-analysis presents the efficacy for treatment of GERD at OTC doses (half that of prescription doses).

VI) <u>Clinical practice guidelines</u>

Kenneth R, Devalut, et al. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Am J of Gastroenterology* 2005 (100); 190-200.

Study objectives: The purpose of these guidelines is to update previous guidelines for diagnosing and treating gastroesophageal reflux disease (GERD). These guidelines are meant to address diagnostics methods as well as treatments including the role of lifestyle changes, patient directed (OTC) therapy, acid suppression, promotility therapy, maintenance therapy, anti-reflux surgery, and endoscopic therapy in GERD. Further insight into refractory GERD is also presented here

Scope – The scope of this review encompasses OTC preparations as well as prescription interventions for treating and diagnosing GERD. The guidelines state that the recommendations presented here are the preferred, but not only, acceptable options for treating GERD. These guidelines were created under the American College of Gastroenterology and its Practice Parameters Committee, and approved by the Board of Trustees. They apply to adult patients with the symptoms, tissue damage, or both that result from the reflux of gastric content into the esophagus

Methods – The American Journal of Gastroenterology periodically reviews previous guidelines. The guidelines were created in 1995 and updated in 1999. The original guidelines are based on an extensive world literature review and the updates (1999, and this current one) utilize the National Library of Medicine database to find any recent literature updates. When appropriate studies are reviewed a bibliographical study is also done.

In terms of how evidence is graded, the highest weight is placed on randomized clinical trials. When scientific data is lacking, recommendations are based on expert consensus obtained from both the literature and the experience of the authors. Each reviewed piece of literature was given a score as follows:

Table 1. Rating of Levels of Evidence Used for this Guideline

I	Strong evidence from at least one published systematic review of multiple well-designed randomized controlled trials
II	Strong evidence from at least one published properly designed randomized controlled trial of appropriate size and in an appropriate clinical setting
III	Evidence from published well-designed trials without randomization, single group prepost, cohort, time series or matched case-controlled studies
IV	Evidence from well-designed nonexperimental studies from more than one center or research group or opinion of respected authorities, based on clinical evidence, descriptive studies, or reports of expert consensus committees

Main results

The result of 33 randomized trials including over 3000 patients with erosive esophagitis show that symptomatic relief of GERD is achieved in 27% using placebo, 60% using H2RAs, and 83% using PPIs. (Level 1 evidence)

Conclusions

Although H2RAs are less effective than PPIs, H2RAs given in divided doses may be effective in some patients with less severe GERD. The efficacy between H2RA is generally the same and the difference between the agents lies in the different potencies, durations, and onsets. In terms of over the counter choices, H2RA are preferred in GERD due to their longer coverage/duration compared to antacids

Comments

In terms of internal validity, these guidelines do not disclose very much criteria as to the studies they included. How studies were found, searched for, or evaluated were areas that the reader does not know. This would be very hard to do mainly because there is much therapeutic material being summarized. Furthermore, how the expert panel formulated their recommendations is not described. Much of this is based on the fact that these guidelines are updates from previous guidelines and so most of the foundation has already been laid.

In terms of the external validity, the guidelines do not go into great detail in terms of how to use these agents (dose, duration, etc…). When it comes to addressing the H2RAs, these guidelines provide much insight into why a person would pick a particular agent, but when it comes to which dose to use, there is not much comment here.

VII) <u>Other literature types Patient Self-Care</u>

Co D, Patient Self Care Canadian Pharmacists Association (2010). Second Edition Chapter 33: Dyspepsia and GERD p.298-307 (Print).

Source description – Patient self-care is a comprehensive guide for health care practitioners in guiding their patients through self-care options. It is an evidence based handbook that described pathophysiology, diagnoses, non-pharmalogical options, and pharmalogical therapies as they pertain to the patient self-care context. The resource is published by the Canadian Pharmacist Association and is addressed to pharmacist practicing in Canada. The reviews and practical guidelines are made by 56 authors and 40 expert reviewers.

Summary – The use of H2RAs (famotidine) is recommended by this resource to treat mild and infrequent GERD as H2RAs may become less effective with time. All H2RA seem to have similar efficacy.

Comment – In terms of internal validity, when using this source there is no systematic explanation of how studies were found, selected, or screened for quality. Although studies are referenced at the end of each chapter, it is hard for the reader to get a picture of the type of information the author finds valuable. The author does provide information for adolescent dosing/considerations.

The handbook notes that information contained in this textbook represents the opinions and experience of individual authors. Users should be aware that the text may contain information, statements, and dosages for drugs that differ from those approved by the Therapeutic Products Directorate from Health Canada. Furthermore, the manufacturers of these drugs have not been sought for approval of this information. Thus, the text concludes that information is not meant to be all inclusive.

References

i) Ciccone, Decktor, et. al. Efficacy and tolerability of famotidine in preventing heartburn and related symptoms of upper gastrointestinal discomfort. *Am J of Therapeutics* 1995 *(*2);314-319.

ii) Simon T, Berlin R, et al. Self-directed treatment of intermittent heartburn: a randomized, multicenter, double-blind, placebo-controlled evaluation of antacid and low doses of an H2-receptor antagonist (famotidine). *Am J of Therapeutics* 1995 (2);304-313.

iii) Berlin R, Bradstreet D, et al. Famotidine relieves symptoms of gastroesophageal reflux disease and heals erosions and ulcerations. *Archives of Internal Medicine* 1991 (153); 2394-2408.

iv) Kawano S, Masuda E, et al. Reflux *Esophagitis: Natural History and Treatment* "Randomized comparative study of omeprazole and famotidine in reflux esophagitis" *J of Gastroenterology ad Hepatology* 2002 (17); 955-959.

v) Tran T, Lowry A, et al. Meta-analysis: the efficacy of over-the-counter gastro-oesophageal reflux disease therapies. *Alimentary Pharmacology & Therapeutics* 2006 (25); 143-153.

vi) Kenneth R, Devalut, et al. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Am J of Gastroenterology* 2005 (100); 190-200.

vii) Co D, Patient Self Care Canadian Pharmacists Association (2010). Second Edition Chapter 33: Dyspepsia and GERD p.298-307 (Print).