EXTENDED ABSTRACT

I) <u>Primary literature</u> (ex. RCTs, observational studies, etc.)

7) Khanna MU, Abraham P, Nair NG, et al. Colloidal bismuth subcitrate in non-ulcer dyspepsia. J Postgrad Med 1992; 38(3): 106-8.

Study design: open label trial

Study objective: To determine the effect of colloidal bismuth citrate on symptoms, Helicobacter pylori status and histological features of patients with non-ulcer dyspepsia.

Methods:

Design: Open label trial
Allocation: Unconcealed, all participants received same treatment
Blinding: Not blinded
Follow-up period: 4 weeks
Setting: Not defined
Participants: n=35 (18 males, 17 females), aged 19-60 years, 26 subjects H.pylori positive at study start
Inclusion criteria: Patients with non-ulcer dyspepsia (defined as meal-related gastrointestinal symptoms lasting for a minimum of 4 weeks, without focal lesion or systemic disease)
Exclusion criteria: Previous gastric surgery, ingestion of any drug including: NSAIDs and any other drugs likely to modify upper gastrointestinal symptoms (eg. Anti-ulcer or prokinetic drugs) in the previous month and pregnancy
Intervention: 240mg of colloidal bismuth citrate given twice daily for 4 weeks
Outcomes: Changes in H. pylori status and histology as per Whitehead classification for gastritis and duodenitis, effect on bloating, pain and gastritis
Patient follow-up: 35 of the 35 patients recruited completed the study
19/26 of H.pylori positive subjects at start reassessed at study end

Main results: Symptom/ condition distribution was as follows (note n=32 for gastritis as only 32 had follow-up histological samples available): pain 34/35, gas bloat 18/35, gastritis 29/32, duodenitis 22/31; distribution was equal across H. pylori positive and negative groups. Symptomatic improvement of greater than 50% was seen in 29/35 (82.8%) patients. No statistical difference between gas bloat and pain response to treatment. Out of the 19 subjects retested for H.pylori status, 14 (73.7%) cleared the organism. Improvement in gastritis was seen in 14/23 (60.8%) patients with 8 having a normal diagnosis at study end. Improvement in

duodenitis was seen in 10/17 patients. Symptomatic responses of neither gastritis nor duodenitis were related to H.pylori status, its clearance or the presence of gastritis or duodenitis at study start. No adverse effects noted with colloidal bismuth citrate therapy.

Conclusions: Colloidal bismuth citrate is not associated with adverse effects at doses of 240mg twice daily and is effective at alleviating pain, gastritis, duodenitis and gas bloating secondary to non-ulcer dyspepsia, regardless of H.pylori status. As well, this treatment may also assist in clearing H.pylori from the gastrointestinal system.

Comments/critical appraisal:

In the assessment of the internal validity of the study a few limitations were identified. Firstly, patient demographics were not provided for test subjects and comorbidities that may reflect study biases that could affect the overall study outcome. As well, the study was conducted as an open-label trial, which could have introduced subject bias in that participants were aware that they were being administered bismuth, a common agent for dyspepsia for their symptoms. Therefore it is hard to draw a causal relationship between the alleviation of symptoms with the use of bismuth due to potential user bias. Additionally, no explanation was provided for the decrease in subjects who had histological samples taken to assess gastritis or duodenitis calling into question whether no adverse effects truly occurred with colloidal bismuth citrate therapy. As well, it appears that the inclusion criteria selected for patients with mild symptoms. In this case, a placebo control would have been useful in determining if the symptoms would spontaneously resolve or if the placebo effect was a factor in the alleviation gas bloat and pain.

In regards to the external validity the criteria used are broad enough that it may be useful in its application to the general public, most of whom, suffer from mild to moderate dyspepsia. However, despite the wide age range used as selection criteria the population size (n=35) appears to be too small to concretely determine how the use of colloidal bismuth citrate will affect the non-ulcer dyspepsia on a population level and limits its external validity.

8) Borkent MV, Beker MA. Treatment of ulcerative reflux oesophagitis with colloidal bismuth subcitrate in combination with cimetidine. Gut 1988; 29: 385-389.

Study objectives: To compare colloidal bismuth subcitrate in combination with cimetidine vs cimetidine monotherapy in the treatment of reflux esophagitis.
Methods:

Design: randomly assigned, double-blind trial
Allocation: Random assignment to cimetidine monotherapy or combination therapy groups
Blinding: double blinding
Follow-up period: 6 weeks
Setting: Hospital
Participants: n=28 (8 men, 12 women), ages 56-79

Inclusion criteria: Patients with endoscopically and histologically proven grade 3-4a reflux esophagitis who had been previously treated with H_2 receptor antagonists with or without antacids for at least 3 months.

Exclusion criteria: Patients with grade 4b reflux esophagitis, complications and Zollinger-Ellison disease, those receiving drugs known to interfere with peptic ulcer disease (eg. NSAIDs), those with cardiovascular, liver and renal diseases, malignancies and pregnancy.

Intervention: Cimetidine 800mg at night + placebo vs Colloidal bismuth subcitrate 120mg four times a day + cimetidine 800mg at night administered via intraesophageal tubing.

Outcomes: Histological changes in esophageal tissue

Patient follow-up: 6 weeks

Main results: In the 10 patients on cimetidine and bismuth therapy, 6 had no endoscopic signs of esophagitis after 2 weeks, one was considered cured and 3 continued to have grade I reflux esophagitis but required no further therapy. In the 10 patients on cimetidine monotherapy, 1 had grade I esophagitis at week 1, 3 were grade II at week 3 and 6 showed no improvement. The difference in healing was significant between the groups ($p=0.001$). At week 3 the 9 patients with grades II- III esophagitis in the cimetidine group received bismuth. In this case, 3 were cured after 2 weeks, 3 at week 3 and 3 continued to have grade I esophagitis. An additional finding was that 9 confirmed cases of campylobacter were found amongst patients at test start. Five of the 9 were treated with the combination therapy and were cured within a week. Conversely, the remaining 4 were in the cimetidine only arm and 2 remained campylobacter positive at test end.

Conclusions: This study suggests that the treatment of ulcerative reflux esophagitis with colloidal bismuth and cimetidine provides better treatment than cimetidine alone. At this time, no conclusion can be drawn as to whether colloidal bismuth should be considered a curative treatment alternative for campylobacter; more study is needed. However, the authors suggest the following indications for colloidal bismuth therapy in reflux esophagitis: 1) persistent reflux esophagitis 2) the need for rapid healing before surgical interventions and potentially 3) for treatment of reflux esophagitis in the presence of campylobacter.

Comments/critical appraisal

In this study, a limitation which threatens the internal validity of this trial is the failure of the experimenters to provide patient demographics or more specific information on the distribution of grade 3-4a ulcerations between arms of the study. Therefore, despite reporting

blind assignment it is unclear as to whether the allocation was such that subject selection did not occur and reflect results in favor of the combination therapy arm.

The external validity of this trial is low due to the small size of its population (n=20) and its short patient follow-up period. The brevity of the follow-up is of importance in this case in that dyspepsia and reflux esophagitis are defined as recurrent, chronic conditions. Considering this, a period of symptom remission of greater than 6 weeks should be used to determine if treatment is successful as these conditions often recur at variable intervals. Furthermore, this trial delivered medications in a manner that is impractical in day to day life and using a methodology induce healing or treatment responses that are not reproducible in real life. In this trial medications were applied directly to the areas of esophagitis via an intraesophageal tube. Subjects were then instructed to avoid food and drink for at least 30 minutes after treatment which is highly impractical in that subjects in the cimetidine+ bismuth arm were given medications four times daily. Therefore, it is questionable whether combination therapy would be as beneficial in a community population. Additionally, bismuth is intended for use for short periods of time as prior studies have implicated prolonged exposure to nephrotoxicity and should therefore be used with caution in this regimen.

II) Systematic reviews and meta-analyses

9) Moayyedi P, Soo S, Deeks J, et al. Systematic review: antacids, H_2 antagonists, prokinetics, bismuth and sucralfate therapy for non-ulcer dyspepsia. Aliment Pharmcol Ther 2003; 17: 1215-1227.

Study objectives: To conduct a review assessing therapeutic alternatives in non-ulcer dyspepsia

Scope: A total of 44 papers consisting of parallel-group randomized controlled trials and the first period of cross-over randomized controlled trials fulfilling inclusion criteria were used. Randomized trials had to include adult patients with dyspepsia and had to have the following criteria: negative barium and endoscopic studies, hiatal hernias, less than five gastric erosions or mild duodenitis. Studies were excluded if they contained the following: outcome assessments done after less than a week of follow-up, patient populations of >20% taking NSAIDs and studies with patients that only had GERD symptoms.

Methods: An electronic search was done using the Cochrane Controlled Trials Register, Medline, EMBASE, Cinahl and SIGLE until September 2002. Dyspepsia outcomes were categorized as being cured/improved or same/worse. Experts in the field of dyspepsia in 15 countries were contacted for relevant unpublished materials.

Main results: Prokinetics (14 trials, n=1053, RRR= 48%, CI= 27-63%) and histamine-2 receptor antagonists (11 trials, n=2164, RRR= 22%, CI=7-35%) were significantly more effective than placebo. Conversely, bismuth salts (RRR=40%, CI=-3-65%) were found to be marginally better than placebo whereas antacids and sucralfate were not.

Conclusions: The meta-analysis conducted suggests that prokinetic and H2 receptor antagonists are superior to both bismuth salts and placebo for the treatment of non-ulcer dyspepsia.

Comments/critical appraisal:

In the assessment of internal validity it is important to note a bias that was brought forward by the assessors post-analysis. Using funnel plot analysis it was determined that the magnitude of the effect favoring H2 receptor antagonists and prokinetic agents over placebo may be exaggerated due to publication bias. However, this publication bias does not affect the results obtained for bismuth, which, suggest that this alternative performs better if not similarly to placebo.

As with most clinical reviews, this review has low external validity in that the assessors used broad inclusion criteria in order to increase the number of papers accepted for analysis. In this review, no restrictions were placed on patient age other than being adult and no patient demographics or criterion per trial were listed. Therefore, it is unknown exactly what population this data can be accurately applied to since the criteria were not very stringent. Therefore, though clinical reviews are useful for providing general guidance in therapeutics practitioners should be cognizant that these reviews should not replace more individualized care especially in high-risk populations. Overall the data suggest little benefit from bismuth therapy, however, this opinion may change with increased study.

III) <u>Other literature types</u> (ex. narrative reviews, databases, textbooks, web-based resources, etc.)

10) Locke RG, Talley NJ. Current Clinical Practice: Management of non-ulcer dyspepsia. J Gastroenterology and Hepatology 1993; 8: 279-286.
Date published: Jan 12,1993
Type of resource: Clinical review
Bismuth salt used: Unspecified

Summary: Dyspepsia, also known as non-ulcer dyspepsia (NUD) is defined in this clinical review as a persistent or recurrent abdominal pain or discomfort centered in the upper abdomen. Here, the discomfort can include: early satiety, post-prandial fullness, nausea, vomiting, or upper abdominal bloating.

Recommendations for the empiric treatment of NUD are separated into 4 subgroups: ulcer-like dyspepsia, dysmotility-like dyspepsia, unspecified dyspepsia and GERD associated dyspepsia. For dysmotility-like and unspecified dyspepsias, the prokinetic drugs cisapride and domeperidone are recommended as well as H_2 receptor blockers. In GERD associated dyspepsia experts recommended anti-reflux advise (non-pharmacological alternatives) and H_2 receptor blockers. Finally for ulcer-like dyspepsia, H_2 receptor blockers, sucralfate and triple therapy for the eradication of H.pylori were suggested. In this case, bismuth was

mostly indicated for the treatment of NUD as part of the triple treatment and not as a single therapeutic agent for the treatment of NUD.

There is evidence suggesting a role for H.pylori in chronic gastritis, NUD and peptic ulcer disease. A reported 50% of NUD patients are infected with H.pylori with a higher suggested prevalence of infected patients with dyspepsia as compared to controls. Treatment of H.pylori infection in NUD with bismuth is controversial. In studies examining this relationship experimenters found that symptoms improved but that the observed improvement did not necessarily correlate with histology or H.pylori status. Furthermore, many of these trials use bismuth as monotherapy for H.pylori, which is now known to be ineffective. Additionally, in a trial using triple therapy consisting of bismuth, metronidazole and amoxicillin 49% of patients successfully cleared their H.pylori infections. Again, symptoms improved regardless of whether H.pylori was eradicated.
Therefore, treatment for H.pylori may be considered when symptoms persist despite antisecretory or prokinetic therapy. Routine eradication or screening for the bacteria is not recommended.

Comments/appraisal:
This paper further documents the evidence available for the use of bismuth salts in the treatment of H.pylori and its effects on the manifestations of chronic gastritis, peptic ulcer disease and non-ulcer dyspepsia. In this document, the author states that the treatment of H.pylori with bismuth was controversial in that there was no definitive correlation between symptom improvement or changes in histology with eradication. Furthermore, the author continues to suggest H.pylori treatment should only be attempted in patients with intractable symptoms unresponsive to antisecretory or prokinetic therapy.

However, the external validity of the paper is low in that “intractable symptoms” were not defined nor was the degree of change required to warrant H.pylori eradication. Though meant to be used as a general therapeutic overview the lack of definition of patient parameters limits the use of this document as a therapeutic tool for initiating or modifying treatment.

11) Bernstein RK. Bismuth subsalicylate- an aid to the diagnosis and treatment of reflux esophagitis. Diabetes Care 1984; 7(4): 404-405.
Date Published: July-August 1984
Type of resource: Case study
Bismuth salt used: Bismuth subsalicylate

Summary: A case study featuring a 50 year-old diabetic women experiencing occasional, severe, retrosternal burning pain that was increasing in severity and frequency. She experienced minimal or transient to no relief from antacid tablets or liquid preparations (Mylanta) at the time of attacks. Gastroparesis diabeticorum (GD) with secondary esophageal reflux was suspected despite the absence of symptoms 3 hours post meals and while supine. Upon diagnosis of moderate retardation of gastric emptying she was prescribed metoclopramide twice daily.

This caused diarrhea and had a 1-hour delay of onset during which the patient reported "intolerable" pain. A half-cup of bismuth subsalicylate was recommended to alleviate the pain during this lag period and was successful at doing so instantaneously. Symptoms of pain did not return on the days where bismuth was taken and the metoclopramide was stopped. The patient is now taking bismuth as needed and experiencing total relief each time that lasts several hours. Therefore the author suggests adding bismuth subsalicylate as a diagnostic and alternative for the general treatment and differentiation of GD pain in diabetics.

Comments/ Critical Appraisal:
There were many limitations in regards to the internal validity of this article as the author failed to define many of the therapeutic interventions used. In this case study the type and dose of antacid tablets and metaclopramide were not reported. Though bismuth is presented as being an effective diagnostic and therapeutic alternative for the diagnosis of reflux esophagitis the lack of data on medications used makes it difficult to determine if all drugs were used a therapeutic levels to sufficiently eliminate them as choices.

In regards to external validity, since the study consisted of only one patient it may be assumed that its applicability to the general population is low. However, the occurrence of moderate retardation of gastric emptying and secondary reflux due to diabetes is not entirely uncommon especially in uncontrolled diabetics with comorbidities this finding does contribute somewhat to their therapeutic alternatives and should be considered despite the weak evidence.

12) Up to Date – Pharmacology of antiulcer medications
Author: Andrew H Soll, MD
Section Editor: Mark Feldman, MD
Deputy Editor: Shilpa Grover, MD
Type of resource: Tertiary, peer-reviewed web-resource
Last update: Jan 19, 2011
Literature current through: Jan 2012

Summary:

Recently, the treatment of peptic ulcers has changed over the past couple of decades. Agents such as bismuth were once shown to heal peptic ulcers prior to the discovery of the bacteria H. pylori's role in its etiology; but it is suspected upon retrospective analysis that many of the peptic ulcer subjects were H. pylori positive. Several forms of bismuth were used for ulcer treatment, which included: colloidal bismuth subcitrate (CBS) also known as tri-potassium di-citrato bismuthate (De-Nol) and bismuth subsalicylate (BSS, pepto-bismol). To date, the efficacy of bismuth in the treatment of NSAID, non-NSAID and non-H.pylori ulcers has not been established and therefore is not recommended in the treatment of peptic ulcers. However, an exception to this rule is the use of bismuth as part of a combination antibiotic regimen for H.pylori elimination. It is suggested that Bismuth be combined with a twice-daily proton pump

inhibitor to ensure ulcer healing and effectively cure existent H.pylori infections. However, it should be made clear that bismuth does not inhibit or neutralize gastric acid and in the treatment of ulcers that blackened stools may be the result of bismuth reacting with hydrogen sulfide in the colon as opposed to a new bleed.

The most important therapeutic contribution of the bismuth salts is the suppression of H.pylori allowing for ulcer healing. Thus, explaining its lack of efficacy in healing H.pylori negative ulcerations. However, prior studies from the pre-H.pylori era suggest that bismuth may aid ulcer healing through the following actions: inhibition of peptic activity (with no effect on pepsin secretion), protective CBS bismuth binding to ulcer craters, increased mucosal prostaglandin, mucous and bicarbonate production and possibly macrophage recruitment to ulcer crater edges stimulating ulcer healing as shown in rat models.

Comments/ Appraisal

At this time, there is not enough evidence on bismuth subsalicylate to determine is antiulcer properties and therefore its role in treatment beyond its inclusion into H.pylori elimination therapy. Extensive research has been conducted with bismuth as an agent in triple and quadruple antibiotic therapy for H.pylori eradication and can be safely recommended for this use. However, a controversy exists as to whether eradication produces a clinical effect as studies have shown both positive and no effect on symptom presentation post-eradication therapy. As stated its effect on NSAID, non-NSAID and non-H.pylori ulcers has not been clearly established and should not be recommended for these indications. This review accurately reflects the current therapeutic opinion on bismuth salts.

REFERENCES

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2) Johnson PC, Ericsson CD, DuPont HL, et al. Comparison of loperamide with bismuth subsalicylate for the treatment of acute travelers' diarrhea. JAMA 1986; 255(6): 757-760.
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4) https://www.e-therapeutics.ca/tc.showChapter.action?documentId=c0046#c0046n00237 (Accessed Mar 10, 2012)
5) http://www.canadadrugs.com/search.php?keyword=Pepto+Bismol+Chewables (accessed Mar 10, 2012)
6) http://www.uptodate.com.proxy1.lib.uwo.ca:2048/contents/treatment-regimens-for-helicobacter-pylori?source=search_result&search=bismuth&selectedTitle=10%7E82 (Accessed Mar 10, 2012)
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