Commentary for Open Medicine to accompany Manzotti et al. File no. 79

Does the evidence support the effectiveness of prokinetic agents in healing of esophagitis and improvement of GERD symptoms?

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Gastroesophageal reflux disease (GERD) is common in affluent societies and its prevalence is on the rise in other areas like Southeast Asia (1). If heartburn and regurgitation are the dominant symptoms a diagnosis of GERD can be made (2). In primary care, patients are often treated empirically; such treatment is largely driven by symptoms where the aim is to decrease the patient's symptoms to the point where they either completely disappear or patients only have minimal symptoms. A considerable proportion of patients will come to endoscopy during their "GERD career". In part, endoscopy is driven by concerns about Barrett's esophagus, the development of which is associated with an increased risk of adenocarcinoma of the distal esophagus. Both Barrett esophagus and the rising prevalence of esophageal adenocarcinoma in affluent societies are clearly linked to a GERD diagnosis (3).

It is estimated that only 20%-40% of symptomatic GERD patients will have endoscopic evidence of esophagitis (4). Naturally if esophagitis is found another important aim of therapy is healing of the mucosa. There is reasonable evidence that in patients with reflux esophagitis the disappearance of symptoms is associated with endoscopic healing of the esophagitis. In summary the aims of treatment in GERD patients are symptom control and healing of esophagitis if present.

There is overwhelming evidence that acid suppression with either a proton pump inhibitor (PPI) or H_2-receptor antagonist (H_2-RA) are the mainstay of GERD treatment with PPIs clearly being superior to H_2-RAs. Over the years prokinetic agents have also been evaluated for the treatment of GERD and dyspepsia. Their mode of action includes improvement of lower esophageal sphincter function, improvement of esophageal motility, and acceleration of gastric emptying. Most of the studies were done with cisapride. The drug has been withdrawn from most markets because of rare but serious side effects of cardiac arrhythmias sometimes resulting in death(5). Prokinetics have been evaluated in the treatment of GERD, and the question is whether there indeed is evidence for their effectiveness. Studies have included a comparison of the active drug to placebo or comparison of the use of the prokinetic agents together with an acid-suppressive agent compared to use of the anti-secretory agent alone. In this issue Manzotti et al. report their systematic review, evaluating the use of prokinetic agents in the treatment of reflux esophagitis. The two main outcomes of interest were improvement of the esophageal inflammation and symptoms. The methodology was well laid out, and 18 publications fulfilled the entry criteria. Eight studies only assessed symptom improvement, five only endoscopic improvement, and six reported both outcomes **(to the editors: the numbers do not add up here nor do the 13 mentioned in the abstract as using prokinetics alone and 4 combination therapy.) AP- we need to check with authors as there are 20 studies listed in Table 1 and they indicate 17 studies in their title but they have 18 studies that fulfill entry criteria.**

The nine studies that reported symptom outcomes for which the data could be pooled used a variety of scales, which had to be transformed into improved versus not improved. One should keep in mind that any transformation of scales does run the risk of loss of information. Compared to a placebo, prokinetics (total sample size 379 patients) offered a significant benefit with regard to symptom improvement with an RR of 1.7, 95% CI, 1.37-2.12, and an absolute risk reduction of 30%. However, a funnel plot showed asymmetry,

suggesting results were not consistent from study to study. Similarly, the pooled results of the 11 studies, which reported endoscopic healing or improvement (total sample size 887 patients), showed significant heterogeneity and a small effect size with an RR of 1.26, 95% CI, 1.03-1.53, and an absolute risk difference of 16%. When the analysis was limited to complete endoscopic healing, the results were no longer statistically significant, RR 1.36, 95% CI, 0.97-1.89, again with the data demonstrating significant heterogeneity.

The authors in their evaluation did assess the quality of included studies using a modified Jadad score, which has a range from 0-8. Only two studies had a score of 7 or 8; the remainder scored 4 or 5, indicating the average study quality was moderate at best.

We believe the results and the interpretation are a lot more tentative than the authors suggest for the following reasons:

1. There is general agreement that the important outcomes in esophagitis trials are complete healing of the esophageal mucosa and complete resolution of symptoms (6).
2. Only six of the studies reported both outcomes; many of the studies were of poor quality. This is reflected by their intermediate quality scores; their low sample sizes with only three studies including more than 100 patients; and the low impact factor of the journals in which many studies were published. For a well-established clinical entity such as reflux esophagitis, high-quality studies should be the norm.
3. There are other systematic reviews, which have come to a less optimistic conclusion. A Cochrane review by Khan et al. in which only three RCTs met the inclusion criteria, involving a total of 198 patients, found a non-significant benefit for healing esophagitis by prokinetics RR 0.71, 95% CI, 0.46-1.10 (7). Another systematic review, quoted by Manzotti et al., evaluated symptomatic treatment (meaning that it was not known in these patients whether they had esophagitis) identified

only one study evaluating cisapride with a RR of 0.86, 95% CI, 0.73-1.01(8). More importantly in this study, the relative risk of symptom improvement was markedly lower than observed for PPIs (RR 0.37) and somewhat lower than H_2-blockers (RR 0.77).

4. The main analysis included not only studies that combined comparisons of the prokinetic agents versus placebo, but also trials that combined prokinetic agents with an H_2-blocker and were then compared the results to placebo. Although the direction of the results was the same in both groups of studies when they were analyzed separately we believe clinical evidence for combination therapy should not be considered as evidence for the use of the prokinetic agent alone.

Does study quality matter? It certainly does! Cisapride has also been extensively evaluated in the treatment of non-ulcer dyspepsia that is in patients who had a normal endoscopy. A systematic review clearly demonstrated that studies with a low Jadad quality score demonstrated a higher effect size than studies with a high Jadad score (9).

In summary, we believe that questions remain about proof of efficacy with regard to healing of esophagitis and symptom improvement for prokinetic agents used in the treatment of reflux esophagitis. Study methodology for such trials is well established and should report of healing of esophagitis and complete resolution of symptoms. Any future use of prokinetic agents in GERD should be subject to high-quality randomized trials with adequate sample sizes and should be compared to the current gold standard of PPI therapy.

REFERENCES

1) **Dent J**, **El-Serag HB**, **Wallander MA**, **Johansson S**. Epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut **2005;54(5):710-7.**

2) Veldhuyzen van Zanten SJO, Flook N, Chiba N, Armstrong D, Barkun A, Bradette M, Thomson A, Bursey F, Blackshaw P, Frail D, Sinclair P, for the Canadian Dyspepsia Working Group. An Evidence-Based Approach to the Management of Patients with Dyspepsia in the Era of Helicobacter pylori. CMAJ 2000;162 (Suppl 12) S3-23.

3) Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999;340(11):825-31.

4) **Sharma N**, **Donnellan C**, **Preston C**, **Delaney B**, **Duckett G**, **Moayyedi P**. A systematic review of symptomatic outcomes used in oesophagitis drug therapy trials. **Gut 2004;53 (Suppl 4):58-65.**

5) **Smalley W**, **Shatin D**, **Wysowski DK**, **Gurwitz J**, **Andrade SE**, **Goodman M**, **Chan KA**, **Platt R**, **Schech SD**, **Ray WA**. Contraindicated use of cisapride: impact of food and drug administration regulatory action. JAMA 2000 ;284(23):3036-9.

6) Vakil N, Veldhuyzen van Zanten S, Kahrilas P, Dent J, Jones R, the Global Consensus Group. The Montreal Definition and Classification of Gastroesophageal Reflux Disease: A Global Evidence-Based Consensus. Am J Gastroenterol 2006; 101(8): 1900-1920.

7) **Khan M**, **Santana J**, **Donnellan C**, **Preston C**, **Moayyedi P**. Medical treatments in the short term management of reflux oesophagitis. **Cochrane Database Syst Rev 2007;(2):CD003244.**

8) **van Pinxteren B**, **Numans ME**, **Bonis PA**, **Lau J**. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. **Cochrane Database Syst Rev 2004;(4):CD002095.**

9) Abraham N S, Moayyedi P, Daniels B, Veldhuyzen van Zanten SJO. Systematic review: the methodological quality of trials affects estimates of treatment efficacy in functional (non-ulcer) dyspepsia. Aliment Pharmacol Ther 2004; 19(6): 631-41**.**