Does the evidence show that prokinetic agents are effective in healing esophagitis and improving symptoms of GERD?

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Gastroesophageal reflux disease (GERD) is common in affluent societies, and its prevalence is also on the rise in developing regions such as Southeast Asia.[1] When heartburn and regurgitation are the dominant symptoms, a diagnosis of GERD can be made.[2] In primary care, patients are often treated empirically; treatment choices are driven largely by symptoms, with the aim of reducing those symptoms to the point where they become minimal or disappear. A considerable proportion of patients undergo endoscopy during their "GERD career." In part, the use of endoscopy is motivated by concerns about Barrett's esophagus, a condition associated with an increased risk of adenocarcinoma of the distal esophagus. Both Barrett's esophagus and the rising prevalence of esophageal adenocarcinoma in affluent societies are clearly associated with GERD.[3]

It is estimated that only 20%–40% of symptomatic patients with GERD will have endoscopic evidence of esophagitis.[4] Naturally, when 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 endoscopically demonstrated healing of the esophagitis. Thus, the aims of treatment in patients with GERD are symptom control and the healing of esophagitis where it occurs.

There is overwhelming evidence that acid suppression with either a proton pump inhibitor (PPI) or a histamine-2 (H_2) receptor antagonist should be used as the mainstay of GERD treatment, and that PPIs are clearly superior to H_2-receptor antagonists. 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 Most studies were conducted with cisapride, a drug that has been withdrawn from most markets because of the rare but serious side effect of cardiac arrhythmias sometimes resulting in death.[5] Prokinetics have been evaluated in the treatment of GERD, and the question is whether there is indeed sufficient evidence of their effectiveness. Studies have included a comparison of the active drug to placebo, and comparison of the use of prokinetic agents with an acid-suppressive agent versus use of the anti-secretory agent alone.

Manzotti and colleagues[6] report in *Open Medicine* the findings of a systematic review in which they evaluate the use of prokinetic agents in the treatment of reflux esophagitis. The two main outcomes of interest were improvement of symptoms and healing of esophageal inflammation. The methodology is well laid out, and the authors report that 18 publications fulfilled their criteria for review. Of these, 8 studies assessed only symptom improvement, 5 assessed only endoscopic improvement, and 6 reported both outcomes.

The 9 studies reporting symptom outcomes for which data could be pooled used a variety of scales, which for the systematic review had to be transformed into a measure of "improved" versus "not improved." It is important to keep in mind that any transformation of scales runs the risk of losing information.

Compared with placebo, prokinetic agents (total sample size 379 patients) offered a significant benefit with regard to symptom improvement, with a relative risk (RR) of 1.7 (95% confidence interval [CI] 1.37–2.12) and an absolute risk reduction of 30%. However, a funnel plot shows asymmetry, suggesting that the results were not consistent from study to study. Similarly, the pooled results of the 11 studies that 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, the data demonstrated significant heterogeneity.

The authors assessed the quality of the studies included in their systematic review 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 that the average study quality was moderate at best. We suggest that the results of the analysis should be viewed far more tentatively 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.[7]

2. Only six of the studies reported both outcomes, and many of the studies were of poor quality. This is reflected by their intermediate quality scores; their low sample sizes (only 3 studies including more than 100 patients); and the low impact factor of the journals in which many of the studies were published. For a well-established clinical entity such as reflux esophagitis, high-quality studies should be the norm.

3. Other systematic reviews have come to a less optimistic conclusion that that drawn by Manzotti and colleagues. A Cochrane review by Khan and colleagues, in which only 3 randomized controlled trials, involving a total of 198 patients, met the inclusion criteria, found a non-significant benefit of prokinetic agents in healing esophagitis (RR 0.71, 95% CI 0.46–1.10).[8] Another systematic review, cited by Manzotti and colleagues, evaluated symptomatic treatment (meaning that it is not known whether these patients had esophagitis) and identified only 1 study that evaluated cisapride (RR 0.86, 95% CI 0.73–1.01).[9] More importantly, in this review the relative risk of symptom improvement was markedly lower than observed for PPIs (RR 0.37) and somewhat lower than for 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 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 that 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 whose endoscopic findings were normal. A systematic review clearly demonstrated that studies with a low Jadad quality score showed a higher effect size than studies with a high Jadad score.[10]

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. The 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 subjected to high-quality randomized trials with adequate sample sizes and should be compared against 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):710-717.
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):825-831.

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):3036-3039.

6. Manzotti ME, Catalano HN, Serrano FA, Di Stilio G, Koch MF, Guyatt G. Prokinetic drug utility in the treatment of gastroesophageal reflux esophagitis: a systematic review of randomized controlled trials. *Open Med* 2007;1(3):e170-180.

7. 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.

8. 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.

9. 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.

10. 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): 631-641.

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