

## **Gastroesophageal reflux disease: A Review of Superior Effects of Proton Pump Inhibitors and Prokinetic agents as a Combination Therapy versus Monotherapy**

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### **Summary**

Gastroesophageal reflux disease (GERD) is chronic symptom caused by stomach acid coming up from the stomach into the esophagus. GERD is an important public health problem which is extremely common nowadays. It is associated with a huge economic burden and decreased quality of life. In industrial nations between 20 and 40 % of those experiencing common heartburn are predicted to actually have a diagnosis of GERD. The various agents currently used for treatment of GERD include proton pump inhibitors (PPIs), prokinetic agents, mucoprotective substances, antacids and H<sub>2</sub>-blockers. Of these, PPIs provide the most effective control of gastric acidity and are, therefore, the medical treatment of choice. In an effort to combat difficult cases of acid reflux, physicians are writing PPIs prescriptions in combination with prokinetic agents. Combination of PPIs and prokinetic agents is increasingly being used by medical practitioners for severe and resistant GERD. In this review we focused on the management of severe and resistant GERD, which, when treated medically, demands aggressive acid suppression, usually through the use of PPIs and prokinetic agents as a combination therapy, which seem to be the most effective treatment of control and management of acid reflux as compared to monotherapy with PPIs or prokinetic agents.

**Key words:** Gastroesophageal reflux disease (GERD), proton pump inhibitors (PPIs), prokinetic agents.

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## **Introduction**

Primary care physicians face uncertainty when making disease management decisions about patients presenting with symptoms of gastroesophageal reflux disease (GERD) without consistent terminology or a “gold standard” for diagnosis. The need for a patient-centered, symptom-driven approach to GERD assessment and diagnosis is very important as the prevalence of GERD is estimated to be 10% to 20% in Europe and North America and at least 5% in Asia<sup>1</sup>. Management of GERD includes lifestyle modifications and pharmacologic therapy. In reality, National Disease and Therapeutic Index data (U.S.A.) has revealed that physicians are writing more than 20% of omeprazole and lansoprazole prescriptions in combination with other medications, including H2RAs and prokinetic agents, or for twice-daily administration, in an effort to combat difficult cases of acid reflux<sup>2</sup>.

Worldwide, proton pump inhibitors (PPI) are being used in the treatment of GERD; in contrast, the favourable effect of prokinetic agents such as domperidone, cisapride, mosapride etc adding to the existing PPI therapy is been proved by few studies only<sup>3,4</sup>. Combination of PPI and prokinetic agent is increasingly being used in India by medical practitioners for severe and resistant GERD. Anti-secretory agents such as pantoprazole, rabeprazole etc. cause decrease in acid production and have high healing rates and rates of resolution of reflux symptoms at 4 weeks, but they do not help to improve underlying disturbance in gut motility or improve tone of cardiac sphincter; relapse is common<sup>5</sup>. In terms of symptom improvement, prokinetics noticeably have an edge over others in functional dyspepsia (46% over 20% for antisecretory agents) with superior results. On the other hand, prokinetics do not promote healing of esophagitis and so cannot be considered as an adequate treatment for GERD. Prokinetic agents act by increasing LES tone and by enhancing upper GIT motility & thus acting on one of the pathophysiological mechanisms of GERD<sup>6</sup>. Few studies have demonstrated that addition of prokinetic with antisecretory agent decreases relapse rates in GERD patients when compared to antisecretory agent alone. The combination is synergistic by decreasing acid production as well as increasing lower esophageal tone & esophageal clearance thus producing a better therapeutic response. In addition, combinations of these two agents' results in significant increase of mean C<sub>max</sub> and mean AUC which results in having a favourable effect on PPI therapy<sup>7</sup>.

The aim of this paper is to describe about the management of severe and resistant GERD through the use of PPIs and prokinetic agents as a combination therapy which seem to be the most effective treatment of control and management of acid reflux as compared to monotherapy with PPIs or prokinetic agents.

## **Clinical Studies**

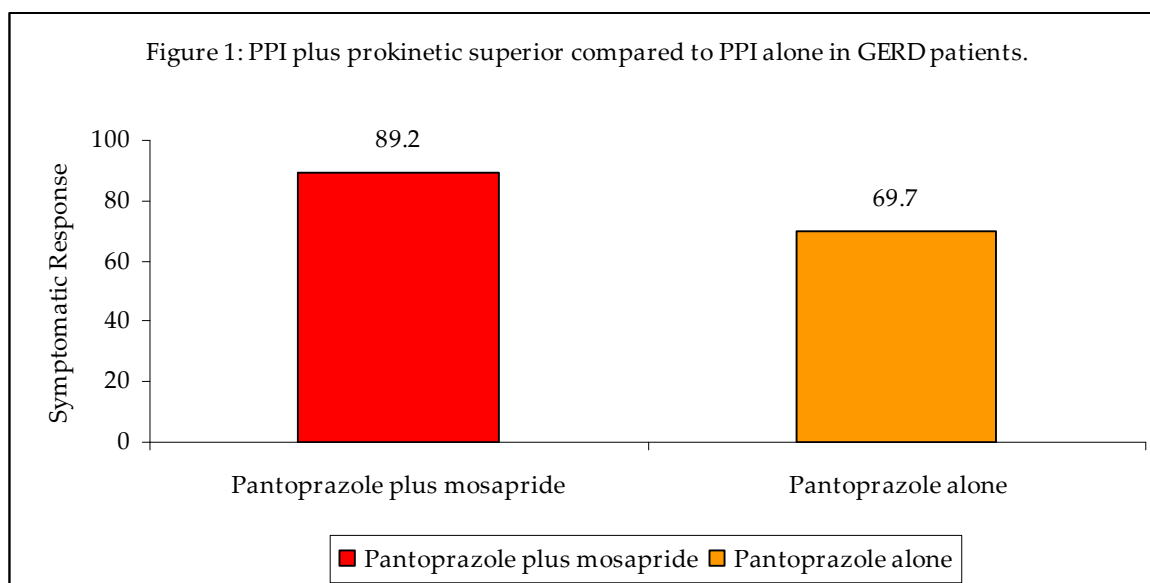
### **Combination of PPI and prokinetic superior compared to PPI alone**

Madan *et al.* conducted a prospective, randomized trial to compare the efficacy of pantoprazole and mosapride in GERD patients with pantoprazole alone. Patients (n=61) with symptoms of heartburn and/or regurgitation at least twice a week for 6 weeks were enrolled in this study<sup>3</sup>.

Patients were randomized into two groups and received treatment for 8 weeks; group A (n=33) received pantoprazole 40 mg BID and group B (n=28) received pantoprazole 40 mg BID plus mosapride 5 mg TDS. At recruitment 24-hour esophageal pH-metry and endoscopy were conducted and in all the patients endoscopy was repeated at 8 weeks.

Results of the study revealed that the symptomatic response to therapy was higher in group B when compared to group A (89.2% vs. 69.7%) and the mean symptom score after 8 weeks was significantly lower in group B(3.78±3.62 vs. 1.67±2.09) compared to group A(Fig. 1).

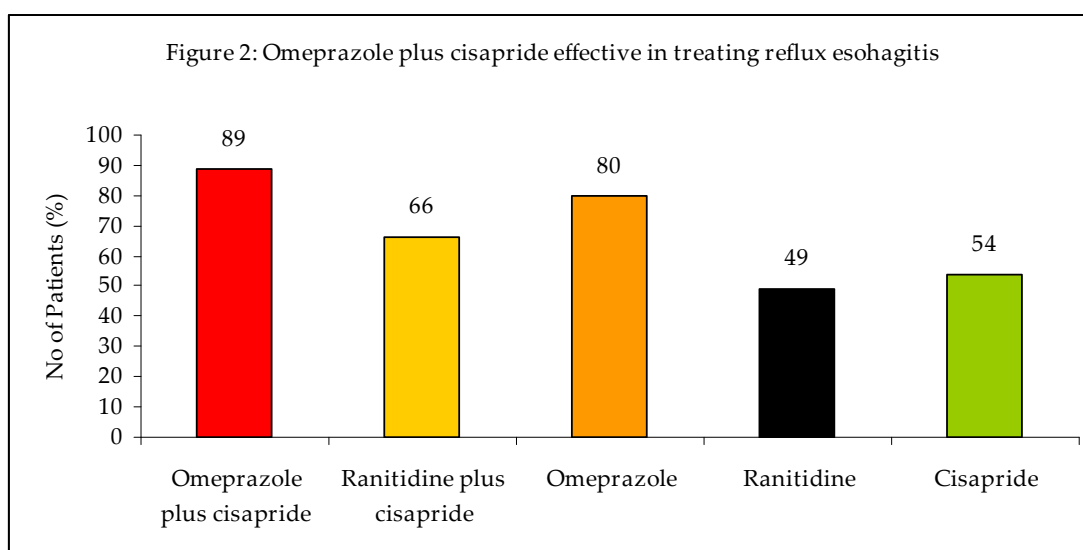
In patients with non-erosive GERD there was no significant difference in symptomatic response to either regimen (17/20 in group A and 7/9 in group B responded). However endoscopic healing of esophagitis occurred equally with either



regimen. Results from the study concluded that combination of pantoprazole and mosapride is more effective than pantoprazole alone in providing symptomatic relief to patients with erosive GERD.

### More effective than prokinetic agent alone

In another study, patients (n=175) with reflux esophagitis were enrolled and compared with 5 maintenance therapies. Results of the study revealed that the number of patients in continued remission at 12 months was found to be more in the combination of omeprazole plus cisapride group (Fig. 2). It was observed that, omeprazole was significantly more effective than cisapride or ranitidine, and



combination therapy with omeprazole plus cisapride was significantly more effective than cisapride alone, ranitidine alone, or ranitidine plus cisapride. Results from the study concluded that omeprazole in combination with cisapride is more effective than ranitidine alone or cisapride alone, and the combination of omeprazole and cisapride is more effective than ranitidine plus cisapride<sup>6</sup>.

**Effective & safe combination with high symptom improvement rates**

Singhal *et al.* conducted a study to assess the safety and efficacy of combination of PPI and prokinetic agent and the study results confirmed that the combination of pantoprazole and domperidone has comparable healing rates and high symptom improvement rates with adequate safety in cases of GERD<sup>2</sup>.

The results of the study revealed that majority of the patients were completely cured by esophagitis as evidenced by endoscopy (72.34%). Symptom improvement was measured by comparing the frequency of patients having symptom score more than 1 for a particular symptom at baseline, week 1, week 2 and week 4. With respect to resolution of symptoms, it was observed that only five patients had Epigastric pain, seven had upper abdominal bloating, one had epigastric pain before meal, and two each had nausea, belching and heart burn (symptom score > 1 for that particular symptom) at the end of therapy, while other symptoms resolved completely in the remaining patients on treatment completion according to study protocol. It was evident that, there was a significant improvement in all patients as all symptoms decreased considerably from baseline to week 4 of therapy (Table 1).

<b>Table 1: GERD symptoms: A significant improvement in all symptoms from baseline to week 4 of therapy</b>				
<b>Symptoms</b>	<b>Baseline</b>	<b>Week 1</b>	<b>Week 2</b>	<b>Week 4</b>
Upper abdominal bloating	68.5%	38.7%	28.2%	5.6%
Upper abdominal dull ache	48.4%	18.5%	12.1%	0%
Epigastric pain	70.2%	41.1%	21.8%	4%
Epigastric pain after meal	64.5%	40.3%	18.5%	0.01%
Heart burn	75%	48.3%	25%	<b>1.6%</b>
Acid regurgitation	57.3%	32.2%	10.4%	<b>0%</b>
Vomiting	40.3%	8.8%	0%	0%
Nausea	49.2%	25%	14.5%	1.6%
Loss of appetite	44%	22.6%	6.5%	<b>0%</b>
Feeling of acidity in stomach	66.9%	40.3%	19.3%	<b>0%</b>
Bleching	57.3%	29%	16.9%	1.6%

**Conclusion**

GERD has substantial adverse effects on patients’ lives. It imposes a significant health burden due to its high prevalence, as a result accurate diagnosis and appropriate management is of particular importance. It provided distinctive information on the importance of combining both PPI and prokinetic agent as it improves the healing rates and provides high symptom improvement rates compared to other agents alone.

### **Disclosure**

The authors have declared no conflicts of interest in this work.

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