

Evaluation Of Safety And Efficacy Of Pantoprazole And Domperidone Combination In Patients With Gastroesophageal Reflux Disease

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Citation

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Abstract

Background: Gastro-esophageal reflux disease (GERD) and non ulcer dyspepsia (NUD) are overlapping disorders with common symptomatology. The combination is synergistic by decreasing acid production as well as increasing lower esophageal tone & esophageal clearance thus producing a better therapeutic response.

Objective: To evaluate the safety and efficacy of the combination

Methods: In patients satisfying the inclusion and exclusion criteria for GERD (Group A, n=105) and Non Erosive GERD (Group B, n=19) baseline symptomatology, endoscopy & laboratory investigations were done followed by test medication once daily for 28 days & monitored for symptom improvement at week 1, 2, & 4 and endoscopy and laboratory investigations at week 4.

Results: Of Group A patients having erosive GERD 68/94 (72.34%) were completely cured, 19/94 (20.21%) partially cured, 7/94 (7.44%) not cured. All patients having Non-Erosive GERD had significant improvement in symptoms at 4 week from baseline.

Conclusion: Combination of pantoprazole and domperidone is a effective & safe combination with high symptom improvement rates.

INTRODUCTION

GERD is one of the commonest esophageal disorder, with overlapping symptomatology with NUD. Erosive GERD is differentiated from functional dyspepsia by positive endoscopic findings but there is a considerable overlap between functional dyspepsia & non-erosive reflux disease. There is a controversy with regard to whether symptoms of heartburn & acid regurgitation should be considered as a part of NUD or not. Rome II definition considers them to be indicative of GERD whereas others believe them to be a part of dyspepsia¹. We believe these to be a spectrum of disease with some patients having erosive esophagitis and others not but most having common symptoms. The basic mechanisms underline the spectrum are –increased acid production, decreased tone of lower esophageal sphincter (LES) & disturbances in gut motility.

In fact, National Disease and Therapeutic Index data

(U.S.A.) has shown 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.² With respect to reports with combination of anti-secretory with prokinetics in GERD & NUD from India, study by Madan et al. has shown that combination of pantoprazole and mosapride has better symptomatic relief than pantoprazole alone in cases of GERD whereas healing rates are similar.³ Another such study comparing ranitidine and domperidone with ranitidine alone has found better symptom improvement with the combination.⁴ We designed the study with an objective to evaluate the therapeutic efficacy and safety of combination of pantoprazole with domperidone in management of GERD.

MATERIALS AND METHODS

The study was an open-label, non-comparative, non-randomized study carried out in 3 large medical college hospitals and one specialist digestive disease hospital in India during September 2003 to march 2004. Informed consent was obtained from the patients & the study was in accordance with the clinical principles laid down in declaration of Helsinki. A minimum of 100 subjects were to be enrolled at 4 centers to account for dropouts a total of 124 patients were recruited for the study.

INCLUSION CRITERIA

Patients of either sex 18 yrs or more willing to give informed consent

Patients endoscopically classified according to modified Hetzel-Dent grade 1-3 esophagitis₅.

Grade 0- no mucosal abnormality; Grade 1- no macroscopic erosions but erythema, hyperemia/mucosal friability; Grade 2- superficial erosion involving < 10% of mucosal surface of last 5cm of esophageal squamous mucosa; Grade 3- superficial erosions or ulcerations involving 10-50% of mucosal surface of last 5cm of esophageal squamous mucosa; Grade 4- Deep mucosal ulceration anywhere in esophagus or confluent erosion or ulceration of more than 50% of the mucosal surface of distal 5cm of esophageal mucosa.

3. Patients having a score ≥ 16 on Dyspepsia Questionnaire₆ were considered

Symptoms of all the patients were graded on a 5 point Linkert scale using Dyspepsia Questionnaire₆

(i) Epigastric pain. (ii) Upper abdominal bloating. (iii) Upper abdominal dull ache. (iv) Epigastric pain before meal. (v) Epigastric pain when anxious. (vi) Vomiting. (vii) Nausea. (viii) Bleching. (ix) Acid regurgitation. (x) Heart burn. (xi) Feeling of acidity in stomach. (xii) Loss of appetite.

SCORE 1. (None) no symptoms: 2. (mild) symptoms can be easily ignored: 3. (mod) awareness of symptoms but easily tolerated: 4. (severe) symptoms sufficient enough to cause interference with normal activities: 5. (incapacitating) inability to perform daily activities and/or require days off work. The questionnaire when used for dyspepsia had good test-retest reproducibility and internal consistency with an intraclass correlation coefficient of 0.89 & Cronbachs alpha coefficient of 0.90₆.

Patients who were enrolled in the study were finally classified into: 1- Erosive GERD- having endoscopic evidence of esophagitis. 2- Non Erosive GERD- no esophagitis but having symptoms considered typical of GERD ie. Heartburn & acid regurgitation on >4 of the past 7 days before enrolment and a score of >16 on dyspepsia questionnaire.

Patients having any of the following were excluded from study: History of esophageal/gastric/definitive acid lowering surgery or patients having active ulceration other than primary study condition. Barrets esophagus ≥ 3 cm,₇ high grade dysplasia, peptic ulcers or gastroparesis. Patients taking other anti GERD medication within two weeks or PPIs within previous 1 month of participation. Pyloric stenosis or concurrent serious systemic disorder. Regular intake of steroids or any ulcerogenic medication e.g. NSAIDS. H/O Allergic drug reactions or drug addicts. Pregnant or lactating women.

The study drug comprised of pantoprazole 40mg and domperidone 20mg (10mg immediate release form and rest 10mg in delayed release form) tablets which were given half hour before breakfast to the patient everyday.

The response of cases recruited for the drug trial evaluated on the basis of:

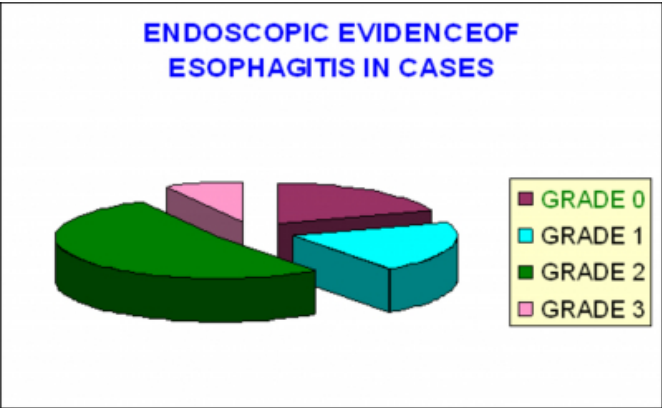
- Endoscopic healing of esophagitis at week 4 in patients of erosive GERD.
- Evaluation of symptom score at week 1, 2 and 4.
- During the clinical trial, the patients were monitored at week 1, 2, and 4 weeks for the occurrence of any adverse effects and laboratory parameters were repeated at end of therapy.

RESULTS

According to Hetzel-Dent grading scale, at baseline, 30 out of 124 (24.2%) of study patients had Grade 0 esophagitis, therefore only 94 of 124 patients had esophageal lesions of grade 1 to 3. Out of 94, 24 patients (25.53%) had Grade 1, majority 61 (64.9%) had Grade 2 & only 9 (9.57%) had Grade 3 esophagitis. (Figure: 1)

Figure 1

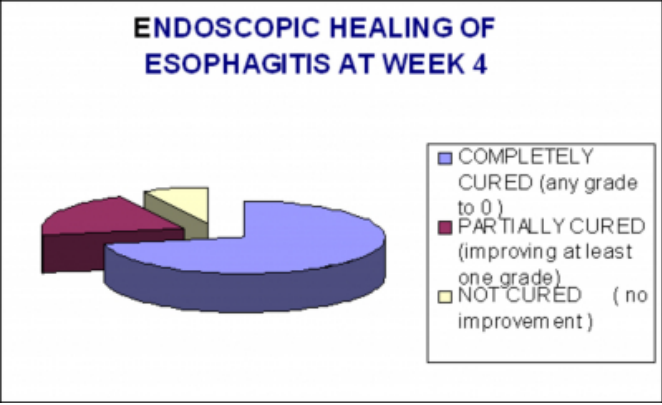
Figure 1:



Endoscopic evidence of healing of esophagitis: 1. Completely cured- any grade esophagitis improving to grade 0, (68/94) 72.34% [grade 3 to 0 : 3 patients, grade 2 to 0 : 45 patients and grade 1 to 0 : 20 patients]. 2. Partially cured- improving at least one grade lower from baseline (19/94) 20.21% [grade 3 to 2 : none, grade 3 to 1 : 13 patients and grade 2 to 1 : 6 patients]. 3. Not cured- remaining at the same grade as baseline (7/94) 7.44% [grade 3: none, grade 2: 3 patients and grade 1: 4 patients]. (Figure: 2)

Figure 2

Figure 2:



Symptom improvement was measured by comparing the frequency of patients having symptom score > 1 for a particular symptom at baseline, week 1, week 2 and week 4. (Figures 3, 4 & 5)

Figure 3

Figure 3:

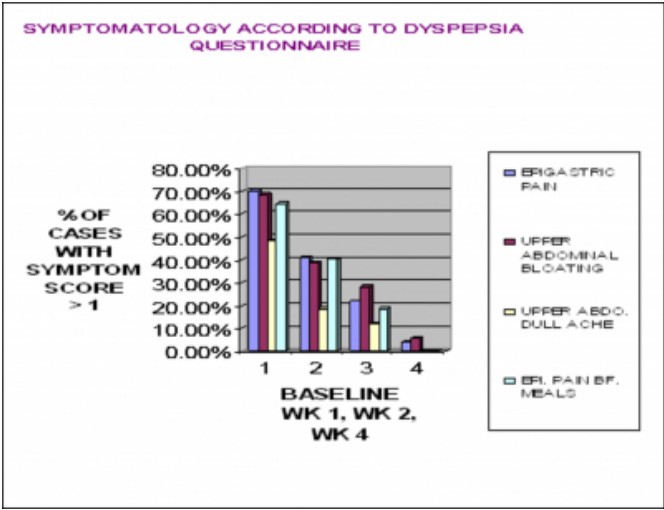


Figure 4

Figure 4:

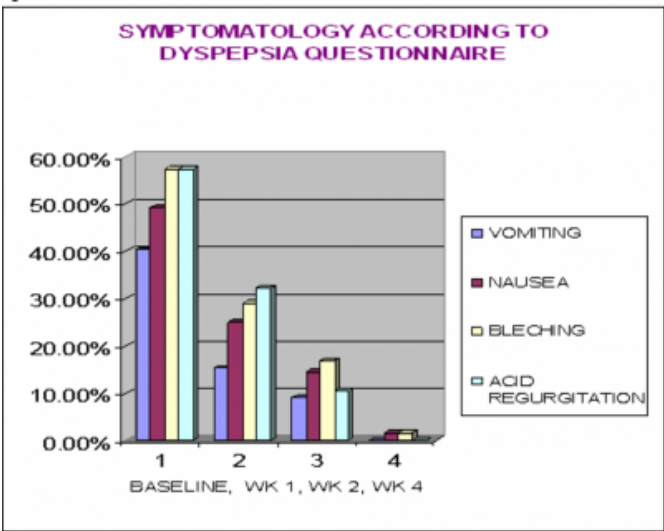
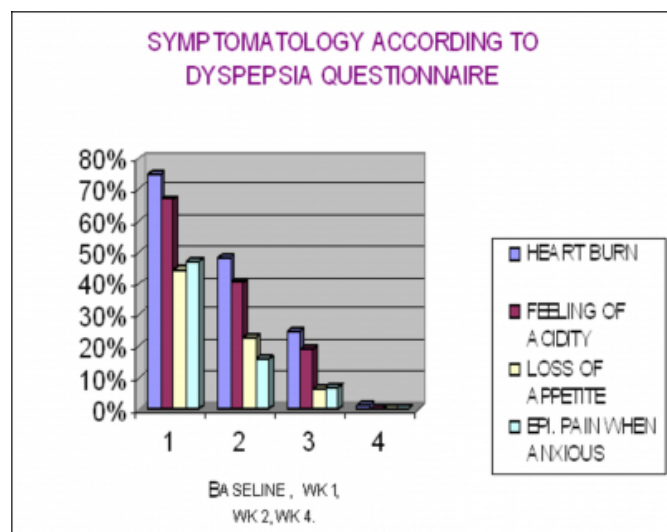


Figure 5

Figure 5:



1. Epigastric pain was reported in 87/124 (70.2%) of study patients at start of therapy ie. baseline reduced to 51/124 (41.1%) at week 1, 27/124 (21.8%) at week 2 and 5/124 (4%) at week 4. 2. Upper abdominal bloating was present in 85/124 (68.5%) at start, 48/124 (38.7%) at week 1, 35/124 (28.2%) at week 2 and only 7/124 (5.6%) at end ie. week 4. 3. Upper abdominal dull ache in 690/124 (48.4%) at start, 23/124 (18.5%) at week 1, 15/124 (12.1%) at week 2 and none at week 4. 4. Epigastric pain before meal in 80/124(64.51%) at baseline, 50/124 (40.32%) at week 1, 23/124 (18.55%) at week 2 and 1/124 (0.01%) at week 4. 5. Epigastric pain when anxious in 58/124 (46.77%) at baseline, 20/124 (16.13%) at week 1, 9/124 (7.26%) at week 2 and none at week 4. 6. Vomiting was found in 50/124 (40.3%) at baseline, 19/124 (15.3%) at week 1, 11/124 at week 2 and none at week 4. 7. Nausea was present in 61/124 (49.2%) at start, 31/124 (25%) at week 1, 18/124 (14.5%) at week 2 and only 2/124 (1.6%) at week 4. 8. Bleching was found in 71/124 (57.3%) at start, 36/1254 (29%) at week 1, 21/124 (16.9%) at week 2 and 2/124 (1.6%) at week 4. 9. Acid regurgitation was complained by 71/124 (57.3%) at start, 40/124 (32.23%) at week 1, 13/124 (110.48) at week 2 and none at week 4 had reflux. 10. Heart burn was found in 93/124 (75%) at start, remained in 60/124 (48.38) at week 1, 31/124 (25%) at week 2 and 2/124 (1.6%) at end. 11. Feeling of acidity in stomach in 83/124 (66.94%) at start, 50/124 (40.32%) at week 1, 24/124 (19.35%) at week 2 and none at end. 12. Loss of appetite was present in 55/124 (44.4%) at start, 28/124 (22.6%) at week 1, 8/124 (6.5%) at week 2 and none at end.

When analyzed statistically it was observed that at each assessment period ie. Week 1, 2 and 4 respectively the reduction in symptoms of GERD were all highly significant $p < 0.001$ when compared to baseline. No significant effect was observed in symptoms of vomiting, nausea, upper abdominal dull ache and bloating sensation between week 1 & 2 only.

Thus in cases of erosive GERD high healing rates were observed with the combination as evidenced by healing of endoscopic esophagitis. All patients of non erosive GERD had significant improvement of in symptoms from baseline to week 4 of therapy.

SAFETY PARAMETERS Out of 124 patients 2 patients reported diarrhea at week 1. 1 patient complained of dyspepsia at week 1 and one at week 2. Metallic taste was reported in 2 patients one at week 1 and other at week 2. However all the adverse events were mild in nature and did not warrant any discontinuation of therapy.

The other laboratory parameters ie. hematological (Hb, TLC, DLC, ESR) and biochemical (SGOT, SGPT, S. Creatinine, S Uric acid, Alkaline phosphatase) and fasting blood sugar did not show any clinically relevant changes on completion of protocol therapy as compared to baseline. No relevant change was seen in vitals of patients at the end of therapy.

A noticeable increase in Hb value was observed at the end of therapy when compared with baseline values ie. 12.89 (at week 4) vs. 12.65 (at baseline), which was clinically insignificant.

DISCUSSION

Worldwide, treatment of gastroesophageal reflux disease involves use of proton pump inhibitors however; the beneficial effect of addition of prokinetics such as domperidone, cisapride, mosapride etc has been proved by limited studies only^{3,4}. Pantoprazole and Domperidone is increasingly being used in India as a combination by medical practitioners for severe and resistant GERD but no study till date has studied the safety and efficacy of the combination. Anti-secretory agents such as Pantoprazole, Lansoprazole, Omiprazole, Ranitidine cause decrease in acid production and have high healing rates and rates of resolution of reflux symptoms (74 to 79% and 83 to 85% respectively with pantoprazole) ⁸ at 4 weeks, but they do not help to improve underlying disturbance in gut motility or improve tone of

cardiac sphincter; relapse is common₉ (17.5% with pantoprazole)₁₀. Prokinetics which clearly have an edge over others in functional dyspepsia (46% over 20% for antisecretory agents) bring out superior results in terms of symptom improvement₁₁. They do not promote healing of esophagitis and so cannot be considered adequate for treating GERD (only 65.2% healing rates)₁₀. Domperidone and cisapride have almost same success rates in NUD whereas the former has a much favorable adverse effect profile. Domperidone acts by increasing LES tone and by enhancing upper GIT motility & thus acting on one of the pathophysiological mechanisms of GERD. A study comparing different maintenance therapies for reflux esophagitis has concluded that addition of prokinetic with antisecretory agent decreases relapse (Relapse rate 20% with omeprazole and only 11% with combination of omeprazole and cisapride).₁₂

The natural history of condition is that of relapsing and remitting symptoms that are multifactorial in origin and also placebo response rates are variable and high, for these reasons valid comparisons between study groups comparing one drug with other are not practical and much meaningful.₁₁ By involving a patient population of significant size in a multicentric study we aimed at determining the therapeutic success rate and safety of combination. All of the patients included in the study had either erosive or non-erosive GERD with severe symptoms. According to our past clinical experience it was thought that it is not justified to treat these patients with PPI's alone as this subset of patients remained symptomatic on PPI's, though the rates of healing of esophagitis might be adequate.

The drug combination of pantoprazole and domperidone achieved high endoscopic esophageal healing rates, 72.34% of patients completely cured while 20.21% patients had partial healing. Our results compare favorably with previous study by Madan et al. (2004), who reported 70.5% esophageal healing rates with pantoprazole and mosapride in a comparative trial. With respect to resolution of symptoms in our study 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.

Our study emphasizes that, addition of domperidone with

pantoprazole is helpful by acting on multiple pathophysiological mechanisms of the disease. Further long-term studies are needed to evaluate the effect of combining the drugs in preventing relapse. The data generated from our study leads us to believe that the combination of pantoprazole and domperidone has comparable healing rates and high symptom improvement rates with adequate safety in cases of GERD.

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