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EVALUATION OF THE EFFICACY, TOLERABILITY AND SAFETY OF A COMBINATION OF ESOMEPRAZOLE AND DOMPERIDONE IN GERD.

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ABSTRACT

Background: Gastroesophageal reflux disease (GERD) represents spectra of symptoms and of reflux damage to the esophagus. The burden of GERD results from its widespread prevalence and the unfavorable impact of its symptoms on well-being and quality-of –life. **Aim of the study**: To evaluate the clinical efficacy, tolerability and safety of a fixed – dose combination of Esomeprazole 20 mg + sustained release (SR) Domperdone 30mg administered once daily in adult Indian patients for the symptomatic relief of dyspepsia associated with GERD. **Material and methods:** This prospective studywas conducted between JUNE 2015 and JUNE 2016 in 137 patients in department of medicine, Sree Balaji Medical College & Hospital, Chennai, India with dyspepsia associated with GERD. Patients were treated with a fixed – dose combination on Esomeprazole 20 mg + sustained release (SR) Domperidone 30 mg administered once daily for a period of 2 weeks. Efficacy was assessed on the basis of improvement in the symptoms and patients' satisfaction with the treatment. Tolerability and safety was assessed by physical examination, laboratory parameters and monitoring of treatment – emergent adverse events. **Results:** Of the 137 patients enrolled in the study, 6 patients were lost to follow – up. Thus, the data of 131 patients was available for evaluation of efficacy. As per the patient's assessment of treatment response, 92.4% of the total cases expressed extreme – to-good satisfaction with the treatment. **Conclusion:** The present study suggests that a fixed – dose

combination of Esomeprazole 20 mg and sustained release (SR) Domperidone 30 mg is an effective and well tolerated therapeutic option in the management of symptomatic relief of dyspepsia associated with GERD in adult Indian patients.

KEYWORDS: Gastroesophageal reflux disease (GERD), Domperidone.

INTRODUCTION

GERD represents a spectrum of symptoms and of reflux damage to the esophagus. The burden of GERD results from its widespread prevalence and the unfavorable impact of its symptoms on well-being and quality-of-life'. The current clinical practice involves prescription of a combination of prokinetic drug with an acid suppressant to provide Overall symptomatic relief.

The disease has an estimated incidence of 10-40% in the general population; however, the true incidenceof GERD may be considerably higher since many patients self-medicate with over-the-counter antacids and never seek medical advice'.

The reflux damage in GERD is due to a prolonged acid exposure of the esophagus arising from an imbalance between protective motility factors and aggressive acid secretory factors'. The key factor in the pathogenesis of GERD is disordered function of the lower esophageal sphincter. Other factors include delayed gastric emptying and decreased peristalsis in the body of the esophagus. GERD ranges from episodic symptomatic reflux without esophagitis to severe esophageal mucosal damage, such as Barrett's metaplasia or peptic stricture'.

The various therapeutic approaches for GERD are to increase the competence of the antireflux barrier, to enhance esophageal clearance, to improve gastric emptying and pyloric sphincter competence, to coat damaged tissue, and especially, to reduce the volume and pH of gastric contents. These medical goals of therapy can be achieved with prokinetic agents, antacids, sucralfate suspension, histamine2 receptor antagonists (H_2RAs) and proton pump inhibitors $(PPls)_2$.

Since the introduction of omeprazole in 1989, PPls have consistently been shown to be far more effective than H_2RAs (e.g., ranitidine, cimetidine) in terms of healing of esophagitis and resolution of GERD symptoms. PPls have become the drugs of first choice in healing of all patients with more severe forms of reflux esophagitis, and increasingly also for patients with milder forms of esophagitis, certainly those who fail to respond to other drugs. In

maintenance treatment of GERD, PPls are the most effective drugs, offering the possibility of keeping nearly all patients in remission with adjusted doses. As a class, these drugs are extremely safe.[2-4]

Esomeprazole, the S-isomer of omeprazole, is the first PPl to be developed as a single optical isomer. It provides better acid.

MATERIAL AND METHODS

This prospective studywas conducted between JUNE 2015 and JUNE 2016 in 137 patients in department of medicine, Sree Balaji Medical College & Hospital, Chennai, India with dyspepsia associated with GERD (diagnosed as per the Rome II criteria). Patients were treated with a fixed – dose combination on Esomeprazole 20 mg + sustained release (SR) Domperidone 30 mg administered once daily for a period of 2 weeks. Efficacy was assessed on the basis of improvement in the symptoms and patients' satisfaction with the treatment. Tolerability and safety was assessed by physical examination, laboratory parameters and monitoring of treatment – emergent adverse events.

RESULTS

A statistically signaificant reduction was observed in the mean scores of heartburn (87-9%), epigastric pain (81.7%), belching (93.1%) and acid regurgitation (86.2%) at the end of treatment. Of the 31.3% patients who complained of dysphagia at baseline, only 4.6% reported it at the end of the study. Of the 41% patients reporting nausea at baseline, only 3.2% reported it at the end of the treatment.

A total of six patients were lost to follow – up and were considered as drop-outs. Thus, the data of 131 patients was available for evaluation of efficacy. As per the patient's assessment of treatment response, 92.4% of the total cases expressed extreme – to-good satisfaction with the treatment. There were no discontinuations from the study due to treatment failure. There were no alterations in laboratory parameters following therapy with Esomeprazole 20 mg + sustained release (sK) Domperidone 30 mg fixed – dose combination. Only 10.09% of total study cases had mild adverse events after treatment of which the most common events were headache and dry month. The adverse events did not result in discontinuation of therapy.

Table 1 depicts the baseline demographic data of the patients.

Table 1 Baseline demographic data	
Patameters	Mean SD
No. of patients	137
Age (yrs) Range	42.46± 7.71 25-60 yrs
Weight (kg) Range	53.09 ± 7.34 43-67 kg
Height (cm) Range	165-70 ± 3.54 161-172 cm
Sex Male (%) Female (%)	 81 (59) 56 (41)

Efficacy outcomes

The effect of therapy with fixed –dose combination of Esomeprazole 20 mg+ sustained release (SR) Domperidone 30 mg on various symptoms associated with GERD is depicted in Table 2.

At baseline, the mean score of heartburn was 2.39. After treatment with the study drug, the mean score was significantly reduced by 52.7% and 89.1% at the end of the 7^{th} and 14^{th} day, respectively. The mean score of acid regurgitation was 1.89 at baseline. After the treatment at the end of 7^{th} day the mean score of acid regurgitation was significantly reduced by 56.6%. At the end of treatment, on day 14, reduction was 86.2%. Mean score of belching were 1.82 at baseline. Following treatment with the study drug, at the end of the 7^{th} day the mean score of belching reduced significantly by 64.3% and further by 93.1% at the end of the study. At baseline the mean score of epigastric pain was 2.19. After therapy, the mean score was reduced by 52.5% from baseline which was statistically significant. At the end of treatment on day 14 the values reduced further by 81.7% from baseline.

The number of patients with dysphagia before and after treatment with the study drug is shown in Table 3. At baseline, 31.3% of total study cases had dysphagia. After treatment, at the end of 14^{th} day, only 4.6% of study cases had dysphagia, which was statistically significant ($p<0.05$).

At baseline, 41% of the patients had nausea, but at the end of the treatment only 3.2% patients reported it.

The global assessment of efficacy of therapy with Esomeprazole 20 mg+sustained release (SR) Domperidone 30 mg by the patients is presented in

Table: 2 Effect of therapy with fixed dose combination of Esomeprazole 20mg+Sustained Release (SR) Domperidone 30 mg on symptoms of Dyspepsia associated with GERD

Duration in days	Mean score of Heartburn (Mean % ±SD) change	Man score of Regurgitation (Mean % ±SD) change	Mean score of Belching (Mean % ±SD) change	Mean score of Epigastric Pain (Mean % ±SD) change
Basal	2.39-±1.07	1.89 -±0.80	1.82-±0.67	2.19 -±0.89
7	*1.13 52.7±0.90	*0.82 56.6±0.69	*0.65 64.3±0.47	*1.04 52.5±0.75
14	*0.26 89.1±0.44	*0.26 86.2±0.34	*0.13 93.1±0.24	*0.40 81.7±0.48

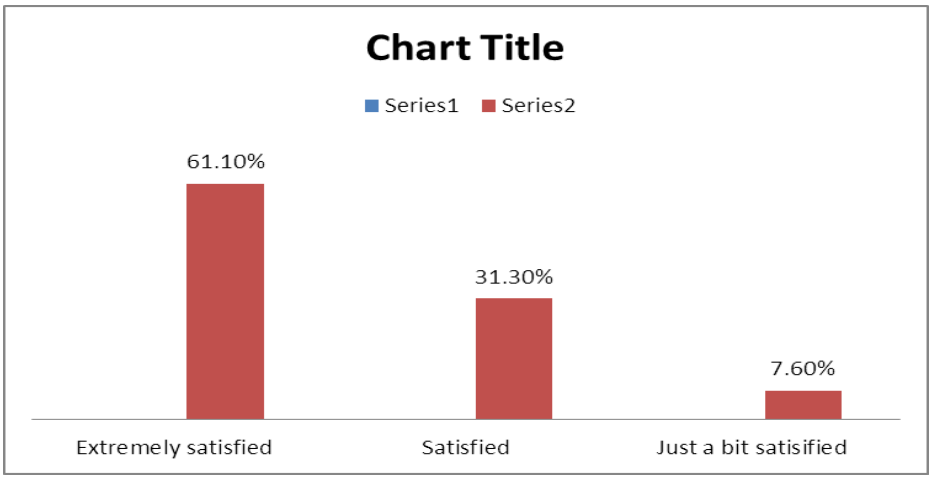

Fig. 1. It was observed that as per patients' assessment, 92.4% of the total cases were extremely satisfied or satisfied with the therapy and only 7.6% were just a bit satisfied.

Safety outcomes

The vital paramenters such as the temperature, pulse rate, respiratory rate and systolic and diastolic blood pressure values. Were within normal limits at baseline.

The adverse event profile is shown in Table 4.A total of 10.09% of the study cases had an adverse even after the treatment. The most common adverse events were headache, dry mouth followed by drowsiness, nausea, constipation and flatulence. The adverse events were mild and transient in all the cases.

Table 3 Effect of therapy with Esomeprazole 20mg + sustained Release (SR) domperidone 30mg on daysphagia

Duration in days	No. of cases with dysphagia	
	No. of cases (n=131)	Percentage
Basal	41	31.3
7	18	13.7
14	06	4.6*

By Chi-square test. *p <0.05 significant.

Table 4 Profile of adverse events

Events	No. of patients (n=137)	Percentage
Headache	04	2.9
Drowsiness	02	1.5
Dry mouth	04	2.9
Nausea	03	2.2
Flatulence	01	0.7
Constipation	03	2.2
No. of patients	15	10.9

DISCUSSION

GERD is a common, usually lifelong, disorder resulting from chronic abnormal exposure of the lower esophagus to gastric contents. Motor dysfunction of the lower esophageal sphincter is the primary cause of this disease. Although the principal symptoms of GERD are heartburn and regurgitation, studies have demonstrated that up to 50% of patients may have other symptoms of dysmotility including epigastric discomfort or fullness, nausea and early satiety. Resolution of symptoms is pivotal to improving the patient's quality-of-life and reducing costs associated with acid-related disorders.[1-2]

Monotherapy is usually insufficient for optimal management of GERD. Clinical trials of combination therapy H_2RAs/PPl plus sucralfate plus cisapride) in GERD have documented that combination therapy is superior to monotherapy in effective management of GERD symptoms.[2-3]

A combination of 150 mg ranitidine twice daily and 20 mg cisapride twice daily was a safe and effective treatment for moderate –to-severe reflux.

Esophagitis in 344 symptomatic patients with endoscopically confirmed reflux resophagitis. A statistically significant difference (p=0.015) in the cumulative healing rate was observed between patients given ranitidine, plus cisapride (82%) and those given ranitidine alone (71%).[17] In 175 patients with endoscopically confirmed reflux esophagitis, omeprazole alone or in combination with endoscopically confirmed reflux esophagitis, omeprazole alone

or in combination with cisapride was more effective than ranitidine alone or cisapride alone, and the combination of omeprazole and cisapride was more effective than ranitidine plus cisapride in maintaining remission at 12 months of therapy.[19]

The comparison of cimetidine alone with cimetidine plus metoclopramide also showed that combined therapy was better in management of symptomatic GERD.[20] Another study documented that a combination of omeprazole 20mg once daily plus cisapride 5mg thrice daily was more efficacious than omeprazole 20mg once daily in healing grade II esophagitis when administered for a period of 8 weeks.[21]

Results of the present study confirm the above data. A significant reduction of 87.9% in the mean score of heartburn and an 81.7% reduction in the mean score of epigastric pain were observed at the end of treatment. There was also a significant decrease in the mean score of acid regurgitation at the end of the study (86.2%). Similarly, a statistically significant decrease of 93.1% in mean score of belching was noted following treatment. Of the 31.3% of the patients who complained of dysphagia at baseline, only 4.6% reported it at the end of the study. Nausea was present in 41% of the patients at baseline in the present study. Following therapy with the study drug, the number of patient reporting nausea at the end of combination two potent drugs, viz, an anti-emetic and gastroprokinetic agent, domperidone with a proton pump inhibitor, Esomeprazole in the symptomatic relief of dyspepsia associated with GERD. As per the patients' assessment of treatment response, 92.4% of the total cases were extremely satisfied or satisfied with the treatment. There were no discontinuations from the study due to treatment failure.

Therapy with the fixed –dose combination of Esomeprazole 20mg+ sustained release (SR) Domperidone 30mg was well tolerated and only 10.09% of the total cases had mild adverse events. The most common events included headache and dry mouth. No abnormalities were detected in the laboratory variables at the end of therapy. None of the patients discontinued the therapy on account of adverse events.

CONCLUSION

The results of the present study suggests that a fixed – dose combination of Esomeprazole 20mg and sustained release (SR) Domperidone 30 mg is an effective and well tolerated therapeutic option in the management of symptomatic relief of dyspepsia associated with GERD in adult Indian patients.

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