Print ISSN 2319-2003 | Online ISSN 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

doi: 10.5455/2319-2003.ijbcp20140604

Research Article

Comparative evaluation of itopride and domperidone in gastroesophageal reflux disease

Rahul Kumar[1]*, Balbir Singh[2], Priyamvada Sharma[3]

[1]Department of Pharmacology, King George's Medical University, Lucknow, India, [2]Department of Medicine, SN Medical College, Agra, India, [3]Department of Pharmacology, SHKM Medical College, Mewat, India

Received: 28 February 2014
Accepted: 26 March 2014

***Correspondence to:**
Dr. Rahul Kumar,
Email: rahulkgmu@gmail.com

ABSTRACT

Background: Gastroesophageal reflux disease (GERD) presents in various ways in terms of symptoms and severity. This study was conducted to assess the severity of GERD patients and to evaluate the effect of itopride and domperidone on symptoms and severity of GERD.
Methods: A single-blind study was carried out in 70 patients. Group A (n=35) patients were kept on itopride therapy, 50 mg thrice a day before meal. Group B (n=35) patients were kept on domperidone therapy, 10 mg thrice a day before meal. Patients of both groups were given rabeprazole, 20 mg once a day for hyperacidity. Patients served their own control. Each patient was followed-up at 2 weeks interval up to 8 weeks.
Results: The most common symptom was heartburn, present in 95.71% patients. Regurgitation was the next most common symptom (65.71%). The most common lesion seen endoscopically (according to Savary Miller classification) was grade I (38.57%). In 24.29% patient, only symptoms of GERD were present without any endoscopically visible mucosal injury. At the end of 2, 4, 6, and 8 weeks, relief of symptoms was more with a combination of itopride and rabeprazole in comparison to the combination of domperidane and rabeprazole, but the difference was statistically insignificant. Healing rate at the end of 4th and 8th week was slight better with a combination of itopride and rabeprazole, but the difference again was statistically insignificant.
Conclusion: Combination of itopride and rabeprazole showed insignificantly better results, both symptomatically and endoscopically in comparison to the combination of domperidone and rabeprazole.

Keywords: Itopride, Domperidone, Gastroesophageal reflux disease

INTRODUCTION

Gastroesophageal reflux disease (GERD) is defined as chronic symptoms or mucosal damage produced by the abnormal reflux in the esophagus. GERD is a common health problem in the community. Frequency of GERD in India might be increasing possibly due to modernization, change in lifestyle and diet. Prevalence of GERD (and/or its complications) differs according to gender, pregnancy, race, or geographical regions. Chances of GERD increase during pregnancy: on an average 48-79% of pregnant women complain of heartburn.[1] Though GERD is equally prevalent among men and women, there is a male preponderance of esophagitis (2:1 to 3:1) and of Barrett's metaplasia (10:1).[2] Whites are more frequently affected in comparison to other races. Prevalence is low in Africa and Asia and high in North America and Europe.[3]

Lower esophageal sphincter (LES) is the main determinant of frequency and intensity of esophageal reflux.[4] Resection of this important structure or a myotomy that destroys the circular sphincter muscle is uniformly followed by severe reflux. Therefore, it is important to examine the sphincter's role in the prevention of reflux and the events that modulate the sphincter's activity. LES pressure (LESP) is influenced by mechanical stress, hormonal and pharmacological effects[5] and it fluctuates from minute to minute and hour to hour.[6]

Management of GERD includes lifestyle modification (head of the bed elevation, avoidance of tight fitting garments, weight loss, dietary modification, restriction of alcohol use and elimination of smoking) and pharmacotherapy (prokinetic agents, mucosal protective agents, acid neutralizers, and acid suppressive agents). For the small percentage of patients who do not respond to continuous pharmacotherapy, surgical correction of the condition may

be considered. Acid suppressive agents, mainly proton-pump inhibitors, are the mainstay of the treatment of GERD. As GERD is characterized by incompetence of the anti-reflux barrier, impaired esophageal acid clearance and delayed gastric emptying, an ideal therapy would be to target these pathophysiologic abnormalities, obviating or at least decreasing the need for acid suppression.

Prokinetic agents (domperidone, cisapride, itopride, and metoclopramide) increase LESP, accelerate gastric clearance, stimulate esophageal peristalsis, increase the amplitude of esophageal contractions, or perform a combination of these actions.

Itopride is a new prokinetic agent and acts both as dopamine D_2 receptor antagonist and as an acetylcholine esterase inhibitor.[7] Dopamine D_2 receptor antagonism removes the inhibitory effect on acetylcholine release. The inhibition of enzyme acetylcholinesterase prevents degradation of acetylcholine. The net effect is an increase in acetylcholine concentration and thereby promotes gastric motility, accelerates gastric emptying, and has an anti-emetic action.[8] Main adverse effect is increased prolactin. Itopride is devoid of potential to cause prolongation of QT interval (unlike cisapride).[9] Anticholinergic agents may reduce the action of itopride.

Domperidone is a selective peripheral dopamine antagonist at the D_2 dopamine receptor.[10] The human D_2 receptor is located on chromosome 11 and belongs to the class G-protein coupled receptors.[11] Domperidone increases spontaneous gastric activity and antagonizes dopamine inhibition of gastric emptying.[12] Domperidone has been shown to increase LESP and promotes esophageal and antral peristalsis. Domperidone has no effect on gastrin release or gastric acid secretion. It increases the frequency, amplitude and duration of duodenal contractions and reduces small bowel transit time.[13] Domeperidone acts mainly on peripheral receptors and will only cross the blood-brain barrier at concentrations much higher than those achieved with therapeutic doses.[14]

However, efficacy data for these agents come from small studies. The paucity of data on the use of itopride and domperidone in patients with GERD formed the basis of the present study.

METHODS

Among all the uncomplicated GERD patients attending the out-patient gastroenterology clinic, 70 patients were selected according to inclusion and exclusion criteria and a single-blind study was carried out. Informed consent was obtained from all participants prior to enrolment in the study. The Institutional Ethics Committee has approved this study. Inclusion criteria were history of heartburn and/or regurgitation for more than 6 weeks or endoscopically proved GERD. Exclusion criteria were patients with Barretts esophagus, hiatus hernia, evidence of esophageal varices, jaundice, or post-operative stomach, pregnant women, pituitary tumor, overwhelming other physical/mental disease, history of any unusual or allergic reaction to domperidone or/and itopride.

Detailed history was obtained from each patient to determine the nature and severity of the disease with particular emphasis on the symptoms heartburn, regurgitation, water brash, dysphagia, odynophagia, globus sensation, and malena. Personal history was taken, particularly about dietary habits, smoking, alcohol intake, tobacco chewing, any previous gastrointestinal surgery and use of drugs that affect LES tone. Then each patient was subjected to routine investigations and upper gastrointestinal endoscopy to document the grade of reflux esophagitis.

Upper gastrointestinal endoscopy was done in all cases for grading the degree of esophagitis and predicting the response to therapy. The grading was done as per Miller 1995 classification.[15]

Grade 0: Normal appearing mucosa with no abnormalities
Grade 1: Mucosal edema, hyperemia, friability or a combination thereof, but no macroscopic erosions
Grade 2: One or more superficial ulcerations or erosions involving <10% of the distal 5 cm of the esophageal squamous mucosa
Grade 3: Superficial ulcerations or erosions involving 10-50% of the distal 5 cm of the esophageal squamous mucosa or an ulcer of 3-5 mm in diameter
Grade 4: Multiple erosions involving >50% of the distal 5 cm of the esophageal squamous mucosa or a single deep ulcer of >5 mm in diameter.

These patients were further grouped randomly in two Groups A and B, of 35 patients each. Group A patients were kept on itopride therapy, 50 mg thrice a day before meal. Group B patients were kept on domperidone therapy, 10 mg thrice a day before meal. Patients of both groups were given rabeprazole 20 mg once a day for hyperacidity. Patients served their own control. Each patient was followed-up at 2 weeks intervals up to 8 weeks. At each visit, an assessment for the relief of symptoms, including side-effects was done by questionnaire. A follow-up endoscopy was done in all patients at 4 weeks interval. A repeat endoscopy was done at the end of 8 weeks if no and/or lesser response obtained at 4 weeks interval. An assessment was done for the relief of symptoms by questionnaire.

RESULTS

The study enrolled 31 (44.29%) males and 39 (55.71%) females. The maximum number of cases that is, 28 (40%) were in the age group of 31-40 years followed by 22 (31.43%) cases in the age group of 21-30 years. The

mean age of the cases was 32.014 ± 10.035 years. The mean age of the cases in Group A was 32.23 ± 9.493 years and in Group B was 31.80 ± 10.684 years. Table 1 shows the age and sex distribution of selected GERD patients.

Table 2 illustrates the incidence of various symptoms. Among both the group the most common symptom was heartburn, present in 67 (95.71%) patients. Regurgitation was the next most common symptom, present in 46 (65.71%) patients. The least common symptom was malena present in 3 (4.29%).

As shown in Table 3, maximum number of patients, 20 (28.57%) were present with duration of symptoms <12 months. Sixteen (22.86%) patients presented whose duration of symptoms lie between 25 and 36 months, were the second largest group. Four (5.71%) patients whose symptoms were present for >60 months, constituted the smallest group.

Table 4 shows the endoscopic appearance of the esophagus at the start of enrolment of patients in the study. Grading was done according to Miller classification. According to endoscopic appearance, Grade 1 was the most common in both Groups A and B and in overall present in 27 (38.57%) patients. Next common endoscopic finding was the Grade 0 as it was present in 17 (24.29%) patients. Grade II was not much behind and constituted overall a set of 16 (22.86%) patients. Grade III was present in 9 (12.86%) patients. Grade IV was present only in one patient in Group A and no patients in Group B, with an overall presentation of 1.43%.

Table 5 shows improvement in due course of therapy. After 2 weeks of treatment, relief in symptoms was almost same in both groups. In Group A, there was an improvement in 20 (57.14%) patients, out of these 20 patients, 10 got marked relief, and 10 got moderate relief. In group B, there was an improvement in 19 (54.29%) patients, out of which 8 got marked relief and 11 got moderate relief. The difference was statistically insignificant (x^2=0.0578, p>0.05). After 4 weeks of treatment, there was an improvement in 23 (65.71%) patients in Group A. Of these 23 patients, 13 got marked relief, and 10 got moderate relief. In Group B, there was an improvement in 21 (60.00%) patients, out of which 11 got marked relief and 10 got moderate relief. The difference was statistically insignificant (x^2=0.244, p>0.05). After 6 weeks of treatment, in Group A, there was an improvement in 28 (80%) patients. Of these 28 patients, 19 got marked relief, and 9 got moderate relief. In Group B, there was an improvement in 25 (71.43%) patients, out of which 16 got marked relief, and 9 got moderate relief. The difference was statistically insignificant (x^2=0.70, p>0.05). After 8 weeks of treatment, in Group A there was an improvement in 32 (91.43%) patients out of these 32 patients, 29 got marked relief and 3 got moderate relief. In Group B, there was an improvement in 29 (82.86%) patients, out of which 25 got marked relief and 4 got moderate relief. The difference was statistically insignificant (x^2=1.148, p>0.05).

Table 6 shows healing (as observed by endoscopy) after 4 and 8 weeks of treatment. After 4 weeks of treatment, healing was seen in 24 (68.57%) patients in Group A and 21 (60%) patients in Group B. The difference was statistically insignificant (x^2=0.56, p>0.05). After 8 weeks of treatment, healing was seen in 31 (88.57%) patients in Group A and 30 (85.71%) patients in Group B. The difference was statistically insignificant (x^2=0.128, p>0.05). No patient of either group reported any serious adverse effect.

DISCUSSION

Pharmacotherapy is considered first line treatment for patients with gastroesophageal reflux disease. Instituting lifestyle changes may be helpful, but evidences in their favor are not enough. Domperidone and itopride, both are the prokinetic agents and while domperidone is commonly used in most of the countries, the use of itopride is restricted to Asian countries.

In the present study, the mean age of patients was 32.014 years. The maximum number of cases, that is, 28 (40%) were in the age group of 31-40 years. In a study by Kim et al., the mean age of GERD patients was 45 years.[8] According to another study, there is an increase in number of GERD patients aged between 18 and 34.[16] This concludes that there is a decrease in mean age for GERD patients.

Among both groups, the most common symptom was heartburn, present in 67 (95.71%) patients. Regurgitation was the next most common symptom present in 46 (65.71%)

Table 1: Age and sex distribution of GERD patients (M=male, F=female).

Age groups (years)	Group-A (n=35)				Group-B (n=35)				Total A+B (n=70)			
	M	F	Total	% of total	M	F	Total	% of total	M	F	Total	% of total
<20	1	3	4	11.43	2	4	6	17.14	3	7	10	14.29
21-30	6	5	11	31.42	4	7	11	31.43	10	12	22	31.43
31-40	6	9	15	42.86	6	7	13	37.14	12	16	28	40.00
41-50	1	2	3	8.57	2	0	2	5.71	3	2	5	7.14
>51	1	1	2	5.71	2	1	3	8.53	3	2	5	7.14
Total	15	20	35	100	16	19	35	100	31	39	70	100

GERD: Gastroesophapeal reflux disease

patients. The least common symptom was malena present in 3 (4.29%) patients. Earlier studies also found the heartburn to be the most common symptom.[4,17]

Table 2: Incidence of various symptoms.

Symptom	Group A (n=35)		Group B (n=35)		Total A+B (n=70)	
	No.	%	No.	%	No.	%
Heartburn	33	94.29	34	97.14	67	95.71
Regurgitation	21	60.00	25	71.43	46	65.71
Waterbrash	15	42.86	7	20.00	22	31.43
Dysphagia	6	17.14	5	14.29	11	15.711
Odynophagia	2	5.71	3	8.57	5	7.14
Globus sensation	5	14.29	3	8.57	8	11.43
Malena	1	2.86	2	5.71	3	4.29

Table 3: Duration of symptoms.

Duration of symptom (months)	Group A (n=35)		Group B (n=35)		Total A+B (n=70)	
	No.	%	No.	%	No.	%
<12	9	25.71	11	31.43	20	28.57
13-24	8	22.86	6	17.14	14	20.00
25-36	8	22.86	8	22.86	16	22.86
37-48	4	11.43	7	20.00	11	15.71
49-60	4	11.43	1	2.86	5	7.14
>61	2	5.71	2	5.71	4	5.71
Total	35	100	35	100	70	100

Table 4: Endoscopically grading of GERD patients.

Endoscopic grade	Group A (n=35)		Group B (n=35)		Total A+B (n=70)	
	No.	%	No.	%	No.	%
Grade 0	8	22.86	9	25.71	17	24.29
Grade I	15	42.86	12	34.29	27	38.57
Grade II	7	20.00	9	25.71	16	22.86
Grade III	4	11.43	5	14.29	9	12.86
Grade IV	1	2.86	0	0	1	1.43
Total	35	100	35	100	70	100

GERD: Gastroesophapeal reflux disease

Maximum number of patients that is, 20 (28.57%) were presented with duration of symptoms <12 months. The second largest group of 16 (22.86%) was of those patients whose duration of symptoms lie between 25 and 36 months. Four (5.71%) patients presented with duration of symptoms more than 60 months. A previous study also suggests that half of all patients with reflux symptoms visit their physician within 3 years of symptom onset.[18]

A study showed that itopride 50 mg three times a day provided marked improvement in GERD symptoms in about 57% patients.[19] Another study showed the effect of itopride in comparison with cisapride in 225 patients and observed marked to moderate improvement in 79.3% of those receiving itopride and 71.9% of those receiving cisapride.[20] A trial in 26 GERD patients found significant symptomatic improvement without significant changes in the mean level of prolactin with the 4 weeks treatment of 150 mg itopride.[8]

According to a study, rabeprazole provided relief in about 73% of patients after 8 weeks treatment.[21] When rabeprazole alone provided relief in 73% patients and 57-79% patients got benefited by itopride alone, it might be assumed that their combination will provide more benefit than each alone. Similarly, our study shows a benefit in 91.43% patients. A study states that there is a good response in 86% GERD patients by combination of domperidone and rabeprazole.[22] This is in accordance of our study, which shows good effect in 82.86% patients.

After 4 weeks of treatment as demonstrated by endoscopy, the healing rate was 68.57% (24 patients) in Group A and 60% (21 patients) in Group B. The difference was statistically insignificant (x^2=0.56, p>0.05). After 8 weeks of treatment, the healing rate as demonstrated by endoscopy was 88.57% in Group A and 85.71% in Group B. The difference was again statistically insignificant (x^2=0.128, p>0.05). A study found that an 8 weeks course of rabeprazole 20 mg daily healed 92% of patients with erosive esophagitis.[21] Data of our study lie close to this study.

So to conclude, relief of symptoms and healing rate, both were more with combination of itopride and rabeprazole in comparison to combination of domperidane and rabeprazole, but the difference was statistically insignificant. Further larger studies of longer duration and larger groups are needed to establish this fact.

Table 5: Improvement in due course of therapy.

Follow-up duration	Group A (n=35)				Group B (n=35)			
	Improved		Not Improved		Improved		Not Improved	
	No.	%	No.	%	No.	%	No.	%
After 2 weeks	20	57.14	15	42.86	19	54.29	16	45.71
After 4 weeks	23	65.71	12	34.29	21	60.00	14	40.00
After 6 weeks	28	80.00	7	20.00	25	71.43	10	28.57
After 8 weeks	32	91.43	3	8.57	29	82.86	6	17.14

Table 6: Healing (as observed by endoscopy) after 4 and 8 weeks.

Follow-up duration	Group A (n=35)				Group B (n=35)			
	Endoscopically Healed		Endoscopically not healed		Endoscopically Healed		Endoscopically not healed	
	No.	%	No.	%	No.	%	No.	%
After 4 weeks	24	68.57	11	31.43	21	60.00	14	40.00
After 8 weeks	31	88.57	4	11.43	30	85.71	5	14.29

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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doi: 10.5455/2319-2003.ijbcp20140604
Cite this article as: Kumar R, Singh B, Sharma P. Comparative evaluation of itopride and domperidone in gastroesophageal reflux disease. Int J Basic Clin Pharmacol 2014;3:437-41.