

COMPARISON OF SAFETY AND EFFICACY OF LEVOSULPIRIDE AND ITOPRIDE IN TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE

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ABSTRACT

BACKGROUND

Gastroesophageal Reflux Disease (GERD) is a common condition caused by reflux of the liquid acidic contents of the stomach into the oesophagus. Prokinetic medications can be used to treat or control the disease. Such medications can have mild-to-serious adverse effects. Levosulpiride and itopride are two such medications, which are used for treating GERD.

The aim of the study is to assess the safety and efficacy of levosulpiride and itopride in the management of GERD and to study the side effects and treatment outcome.

MATERIALS AND METHODS

A total 210 patients aged 18 to 90 years, 99 males and 111 females (male:female ratio of 1:1.1) with reflux oesophagitis were divided into three groups and an endoscopy test was done before starting treatment. The control group received rabeprazole and the two test groups received levosulpiride and itopride. Clinical adverse events were recorded at the end of week 1 and week 2. Following treatment, relief of symptoms was assessed at the end of 2 weeks.

RESULTS

There were total 210 patients (99 males and 111 females). The male-to-female ratio was 1:1.1. GERD was more common in the 31-50 year age group. Most common symptoms were of dyspepsia, regurgitation, vomiting and heartburn. Improvement of symptoms during the treatment was seen in 53% levosulpiride and 41% itopride patients, respectively. The main adverse effects were abdominal pain and nausea. The percentage of nausea was high with itopride than levosulpiride.

CONCLUSION

Gastroesophageal reflux disease is a common problem frequently seen in both genders and in younger people. Symptomatic relief and endoscopic recovery is early with levosulpiride than itopride. Levosulpiride gives better quality of life earlier in the treatment than itopride and has lesser side effects and better healing outcome.

KEYWORDS

Gastroesophageal Reflux Disease, Levosulpiride, Itopride.

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BACKGROUND

Gastroesophageal Reflux Disease (GERD) is caused due to the liquid acidic contents of the stomach regurgitating into the oesophagus and causing mucosal damage of the oesophageal lining.¹ Based on the Los Angeles Classification, it is graded into four categories A to D having increasingly severe disease.² The aetiology of GERD is complex and has multiple causes. It is associated with various risk factors and also complications. It has varied clinical presentation, dyspepsia being the most common symptom.

Prokinetic medications help control acid reflux by strengthening the Lower Oesophageal Sphincter (LES), so

that the contents of the stomach empty faster, thereby preventing the acid reflux. Levosulpiride and itopride are two such prokinetic drugs.

MATERIALS AND METHODS

This was a single centre, observational, non-interventional prospective study done in the Departments of General Medicine and Gastroenterology, at Princess Esra Hospital, Shah Ali Banda, Hyderabad, over a period of six months.

Inclusion Criteria

1. Patient age 18-90 years.
2. Patients who are willing to give verbal informed consent for the study.
3. Inpatients and outpatients of both genders.
4. Non-pregnant females.
5. Patients with no severe co-morbid diseases.
6. Patients with no complications of acid peptic disease at the time of entry into the study.

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Exclusion Criteria

1. Patients in intensive care and critical care units and other non-selected departments.
2. Pregnant females.

Treatment chart or case sheets and patient data collection form having demographic details, complete medical, surgical and drug history, laboratory data, endoscopy and imaging results.

A total 210 patients aged 18 to 90 years, 99 males and 111 females (male:female ratio of 1:1.1) with reflux oesophagitis as determined by endoscopy and presenting symptoms of dyspepsia like epigastric distension or pain, nausea, heartburn, anorexia, haematemesis, dysphagia and regurgitation were considered. Patients with endoscopic evidence of oesophagitis and symptomatically diagnosed patients were taken under study.

Patients were enrolled in a randomised manner. First of all, patient consultation was done, data was collected and an endoscopy test was done before starting treatment. Then, treatment was initiated with levosulpiride or itopride twice daily before meals. Follow up was done and any adverse drug reactions were noted and finally at the end of two weeks outcome was assessed.

Patients were randomly categorised into 3 groups.

Group 1 (n=10) marked as control group (C) received rabeprazole (Rabium) without any prokinetic drug twice a day 30 minutes before meals for 2 weeks.

Group 2 (n=140) marked as levosulpiride group (L) received levosulpiride (Rekool-L) 150 mg, Levazeo 25 mg twice a day before meals and Inj. Levazeo.

Group 3 (n=60) marked as itopride group (I) received itopride (Ganaton 25 mg) twice a day before meals and Inj. Itopride hydrochloride.

Concomitant medication with any other prokinetic drug, antacids, enzyme preparations, H2-blockers or proton pump inhibitors was not permitted during the study period.

They were instructed to avoid alcohol and smoking during the study period and to come for follow up during the treatment. Clinical adverse events were recorded at the end of week 1 and week 2 along with their nature, intensity, action taken and outcome. Following treatment, relief of symptoms was assessed at the end of 2 weeks.

RESULTS

Group I (C) had 10 patients (4.7%), Group II (L) had 140 patients (66.6%) and Group III (I) had 60 patients (28.5%). There were 99 males and 111 females. The male-to-female ratio was 1:1.1. Group I control group (10 patients) had 4 (40%) male and 6 (60%) female patients. The male:female ratio was 2:3. Group II levosulpiride group (140 patients) had 65 (46%) male and 75 (54%) female patients. The ratio was 4.3:5. Group III itopride group (60 patients) had 28 (47%) male and 32 (53%) female patients. The ratio was 4.7:5.3.

Age (Years)	Levosulpiride			Itopride			Total
	Males	Females	Total	Males	Females	Total	
18-30	22	22	44	5	12	17	61
31-50	22	33	55	15	15	30	85
51-70	23	14	37	7	4	11	48
71-90	1	3	4	-	2	2	6
Total	68	72	140	27	33	60	200

Table 1. Results Based on Age Groups

The group 1 (control) had 2 patients of 18-30 years, 6 patients of 31-50 years, 1 patient of 51-70 years and 1 patient of 71-90 years. Both the test groups had more number of patients in the 31-50 year age group.

Symptoms	Before (%)			During (%)			After (%)		
	C	L	I	C	L	I	C	L	I
Heartburn	60	37.1	60	40	20.7	45	50	4.2	31.6
Chest pain	50	48.5	31.6	50	17.8	16.6	40	7.1	16.6
Dysphagia	50	42.1	40	30	22.1	28.3	30	14.2	15
Regurgitation of food	70	70	61.6	70	25	35	80	10	25
Dyspepsia	80	72	70	60	37.8	31.6	50	16.4	36.6
Loss of appetite	40	27.1	26.6	40	15	16.6	40	7.1	11.6
Vomiting	80	50.7	35	60	18.14	71.4	70	4.2	33.3
Haematemesis	20	15	18.3	20	7.1	15	10	0	5

Table 2. Symptoms in the Study Group Before, During and After Treatment

C - Control group, L - Levosulpiride, I - Itopride group.

The most common lesion seen endoscopically was Grade A with hiatal hernia (36%).

Alcohol consumption was recorded in 28% (56 patients), smoking in 24.5% (49 patients), diabetes in 67.5% (135 patients), addictions 32.5% (67 patients), hypothyroidism 27.5% (55 patients), obesity 31.5% (63 patients), hypertension and previous surgery unrelated to the current diagnosis were found in less than 2% of patients.

The most common symptom was dyspepsia present in 74% patients and regurgitation was the next common symptom (67.21%) and other symptoms included vomiting

(55.2%), heartburn (52.3%), dysphagia (44%), chest pain (43.3%), loss of appetite (31.2%) and haematemesis (17.7%).

The percentage of symptoms in control group before treatment was heartburn (60%), chest pain (50%), dysphagia (50%), regurgitation of food (70%), loss of appetite (40%), vomiting (80%) and haematemesis (20%).

Adverse Effects of the Drugs After and Before Treatment

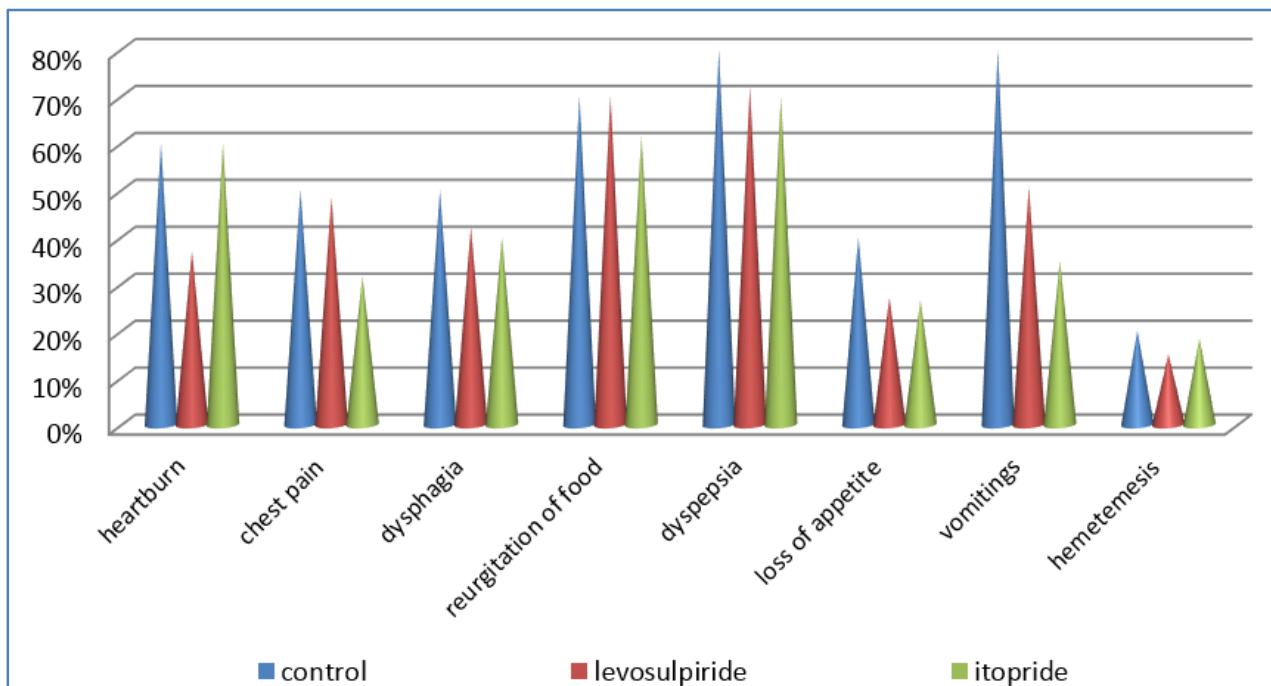


Figure 1

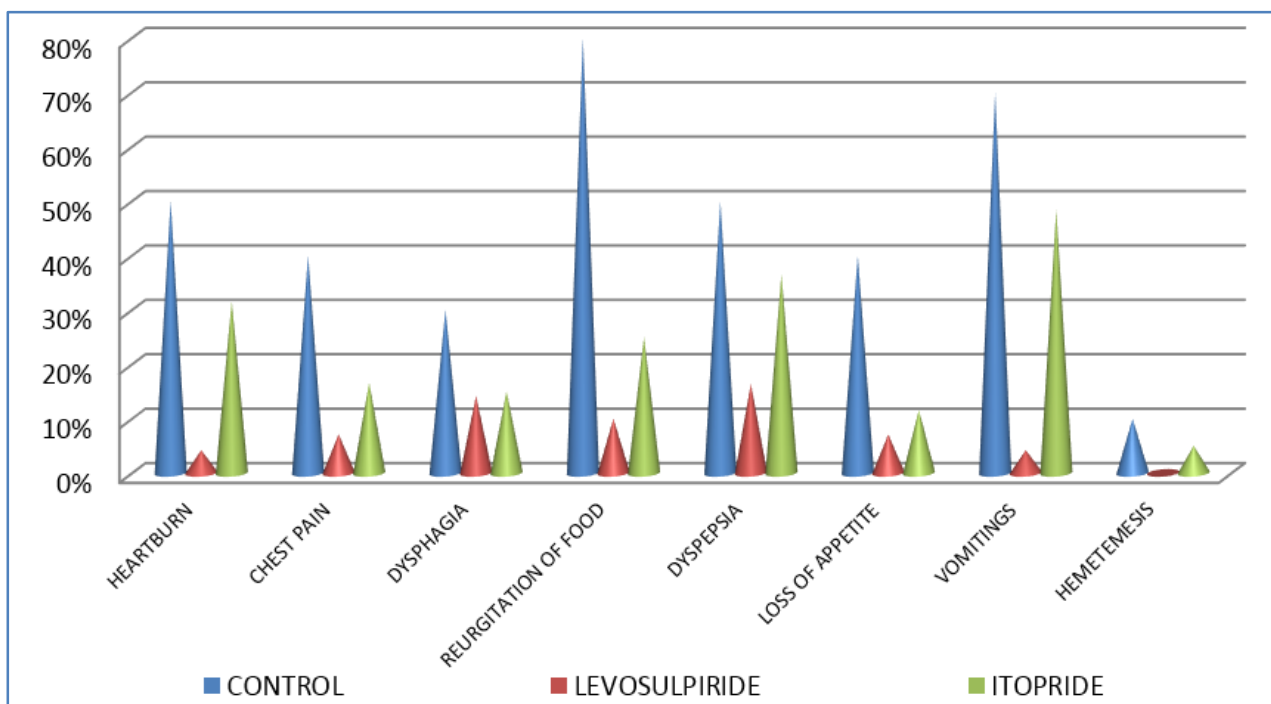


Figure 2

During the treatment, the adverse drug effects were recorded and the levosulpiride and itopride groups reported adverse effects in 37.2% and 73.4% patients, respectively.

Both groups recorded abdominal pain, nausea, constipation and diarrhoea. The itopride group in addition reported were dizziness, rashes, sleeping disorders, agranulocytosis and galactorrhoea.

The adverse effects seen with levosulpiride were abdominal pain (26.4%), nausea (17.80%), constipation (10%) and diarrhoea (5.7%).

The complaints of constipation and diarrhoea reverted to normal immediately after specific treatment, whereas nausea persisted before and during treatment.

No adverse effects were seen in 62.8% cases in group 2 and in 26.6% in group 3.

The adverse effects observed during itopride treatment were abdominal pain (50%), nausea (35%), dizziness (21.6%), constipation (16.6%), rashes (10%), diarrhoea

(10%), sleeping disorders (3.30%), agranulocytosis (3.3) and galactorrhoea (1.60%).

The main adverse effects seen were abdominal pain and nausea.

The abdominal pain was due to the disease. The percentage of nausea before and after treatment was calculated to check the safety of drug and was 50.70% before treatment and 18.14% during treatment with levosulpiride. With itopride, it was 35% before and 71.40% during the treatment.

The percentage of nausea was high with itopride than levosulpiride. When compared to before and during treatment, itopride showed increase in the percentage of nausea than levosulpiride. Levosulpiride had less adverse effect of nausea than itopride. At the end of therapy, percentage of reduced symptoms was seen in all categories.

Symptoms	Levosulpiride				Itopride			
	Symptoms (%)		Recovery (%)		Symptoms (%)		Recovery (%)	
	Before	After	Before	After	Before	After	Before	After
Heartburn	37.1%	4.2%	44.2%	88.7%	60%	31.6%	25%	47.4%
Chest pain	48.5%	7.1%	63.3%	85.4%	31.6%	16.6%	47.5%	47.4%
Dysphagia	42.1%	14.2%	47.6%	66.2%	40%	15%	29.2%	62.5%
Regurgitation	70%	10%	64.3%	85.8%	61.6%	25%	43.2%	59.5%
Dyspepsia	72%	16.4%	47.5%	77.3%	70%	36.6%	54.9%	47.8%
Loss of appetite	27.1%	7.1%	44.7%	73.9%	26.6%	11.6%	37.6%	56.4%
Vomiting	50.7%	4.2%	64.3%	91.8%	35%	33.3%	30.6%	42.9%
Haematemesis	15%	0%	52.7%	100%	18.3%	5%	18.1%	72.7%

Table 3. Percentage of Symptoms in Levosulpiride and Itopride Group Before and After Treatment

The percentage of recovery of symptoms with controlled drug treatment was found to be heartburn (16.7%), chest pain (20%), dysphagia (40%), regurgitation (0%), dyspepsia (37.5%), loss of appetite (0%), vomiting (12.5%) and haematemesis (50%).

Improvement in oesophagitis grades from baseline to end line was observed in 83.6% of patients in levosulpiride group in comparison to 54.5% in itopride group.

Hence, at the end of therapy, decrease in the number of symptoms was significantly higher in the group of patients receiving levosulpiride (83.6%) with lesser adverse effects.

DISCUSSION

Study was designed to compare levosulpiride and itopride at standard recommended doses as healing and prophylactic treatment for patients having GERD.

In the present study, patients in 31-50 year age group were found more prone to disease and the overall prevalence was almost equal in males and females. Wang et al³ have reported a high prevalence (22.2%) of GERD in south Indian population and found the disease more common in older men. Locke et al⁴ in 1997 and 1999 reported a prevalence of 19.8% and 20% for GERD, respectively. The individuals in their study were in the age group 25-75 years. Mantynen et al⁵ in a study of 2,60,000

Finnish individuals found that GERD was present in 1.3% individuals with the mean age being 58.1 years and had an almost equal male:female ratio of 1:1.3. In a study of 1,482 healthy persons by Rai et al,⁶ the prevalence of GERD was 22% in the age range 20-40 years.

Sharma et al⁷ in an interview-based questionnaire amongst hospital employees reported the mean age of individuals with GERD to be 34.8±10.2 years and two thirds men had a BMI of 23.2±3.9. In our study, also obesity was seen in 31.5% cases. Our findings are similar to the observations of above studies.

In the present study, most common symptoms were of dyspepsia followed by regurgitation, vomiting, heartburn, dysphagia, chest pain, loss of appetite and haematemesis. A wide range of dyspeptic symptoms reflect the high prevalence of functional disorders of the GI tract.

Rai et al⁶ have also observed heartburn in 88% and regurgitation in 80% of individuals in their study. A study on GERD⁸ from Finland (n=2,500) showed an equal prevalence of heartburn and acid regurgitation of 15%. In an Italian study⁹ (n=700) between the ages 21-68 years, heartburn was present in 7.7% and almost a similar number, 6.6% had regurgitation. Richa et al¹⁰ in a study (n=32) found heartburn in 53%, regurgitation in 43% and oesophagitis in 40% patients. In the present study, on endoscopy, Grade A

oesophagitis was the most common type. An endoscopic study¹¹ from southern China (n=16,606) also showed a low frequency of 4% of endoscopic oesophagitis with most of the cases having Los Angeles Grade A or B.

In the present study, alcohol consumption was recorded in 28% and smoking in 24.5% cases. Heavy smoking, alcohol and excessive food are independently associated with GERD and significant relationship between GERD symptoms and smoking has been reported.¹² There is also a positive association between GERD and alcohol consumption.¹³

No association with consumption of excess fat, chocolate, mint, coffee, onions, citrus fruits and tomato, size of meals or time of the last meal of the day has been confirmed.¹⁴ Improvement in symptoms was observed during the treatment in 53% of levosulpiride group and 41% of itopride group. More than 50% of patients showed a significantly positive effect on symptoms after 15 days. The symptom recovery during treatment was good with both the drugs, but was more pronounced with levosulpiride. In a study by Choi et al, itopride decreased the total symptoms after treatment and they found 300 mg of itopride to be more effective than 150 mg. No adverse effects were reported in their study.

Rahul Kumar et al¹⁵ observed combination of itopride and rabeprazole had significantly better results, both symptomatically and endoscopically in comparison to the combination of domperidone and rabeprazole. In a study by Corazza et al,¹⁶ (n=1298) on levosulpiride in functional dyspepsia, levosulpiride was found significantly ($p < 0.01$) superior to domperidone, metoclopramide and placebo as it gave better improvement clinically and improved the symptoms of postprandial bloating, epigastric pain, heartburn also. Active treatments and placebo were comparable regarding side-effects (12-20%) including galactorrhea, breast tenderness and menstrual changes. Mansi et al¹⁷ compared levosulpiride and cisapride in dyspeptic patients (n=30) and found levosulpiride to be significantly more effective ($P < 0.01$) than cisapride in improving the patient's everyday activities and dyspeptic symptoms.

Karamanolis¹⁸ observed levosulpiride to be at least as effective as cisapride in the treatment of dysmotility-like functional dyspepsia. Chronic administration of levosulpiride may reduce gastric sensitivity and decrease dyspeptic symptoms, but it does not modify gastric fundus compliance. It may have extrapyramidal reactions and hyperprolactinaemia as side effects. Lozano et al¹⁹ studied (n=342), levosulpiride in dysmotility-like functional dyspepsia and in nonerosive reflux disease and found it to be an effective and safe drug. During the treatment, adverse effects were observed in both the groups. The common adverse effects were abdominal pain, nausea, diarrhoea and constipation. Adverse effects reverted to normal after stopping specific treatment.

Nausea was observed more in itopride group during and after treatment than levosulpiride group. Nausea was seen in 50.70% cases before treatment and in 18.14% cases after

treatment with levosulpiride and with itopride it was 35% before and 71.40% after treatment. Hence, the percentage of nausea was high with itopride than levosulpiride. Hence, levosulpiride is a better drug in this aspect. Improvement in oesophagitis grades from baseline to end line was observed in 83.6% of patients in levosulpiride in comparison to 54.5% in itopride patients. Hence, at the end of the therapy, decrease in the number of symptoms was significantly higher in group of patients receiving levosulpiride with lesser adverse effects.

Gupta et al²⁰ have reported various side effects of levosulpiride such as abnormal limb and facial movements, hyperprolactinaemia, neuroleptic malignant syndrome, tardive dyskinesia and others. Cezary et al²¹ observed that itopride is effective in the treatment of functional dyspepsia as it was well tolerated and had only few adverse drug reactions in the form of diarrhoea, dizziness, increased salivation and facial flushing. Thus, individual drug dose selection is advisable.

After 15 days of therapy, the symptom score of patients treated with levosulpiride was positively influenced with better symptomatic relief and improvement in contrast to the itopride group. Overall analysis revealed that levosulpiride was superior to itopride with the greatest symptom score improvement. Itopride offered no additional healing benefit over that afforded by levosulpiride, but it resulted in slightly better scores in some assessment of symptoms.

In present study, the efficacy of levosulpiride was compared to itopride in relieving symptoms. It was comparable in efficacy to itopride in relieving symptoms was well tolerated and devoid of much adverse effects. The rate of treatment success was better with levosulpiride than itopride.

CONCLUSION

Gastroesophageal reflux disease is a very common problem frequently seen in both genders and especially in the younger age group. It has a varied clinical presentation. Treatment with prokinetics especially levosulpiride and itopride give relief.

The extent of relief is early and more prominent with levosulpiride than itopride. Adverse effects are seen with both drugs, but more so with itopride than levosulpiride. Both the drugs did not show any neurological, psychiatric or hyperprolactinaemic effects in our study. Endoscopic recovery was seen early with patients on levosulpiride.

Levosulpiride gives better quality of life earlier in the treatment than itopride and has lesser side effects and better healing outcome.

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