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Original Article

Pharmacology Section

Efficacy and Tolerability of Levosulpiride, Domperidone and Metoclopramide in Patients with Non-Ulcer Functional Dyspepsia: A Comparative Analysis

HARMINDER SINGH[1], RITU BALA[2], KAMALPREET KAUR[3]

ABSTRACT

Objective: This is a prospective, randomized study designed to demonstrate the efficacy of three study drugs (Levosulpiride, Domperidone and Metoclopramide) in Functional Dyspepsia. Subject recruitment was done from medicine outpatient department of the teaching hospital from June 2013 to November 2013.

Materials and Methods: The data collection was performed by the Short-Form Leeds Dyspepsia Questionnaire (SF-LDQ), a question instrument for assessing the dyspeptic symptoms of functional dyspepsia in patients enrolled for the study. The symptoms were assessed at base line (Prior to initiation of therapy) and at 4 weeks, on a 5-point scale.

Result: Among 120 patients 113 patients completed this study in three groups (G-1 Levosulpiride 40 patients, G-2 Domperidone 35 patients and G-3 Metoclopramide 38 patients) were followed up. Female gender dominated (75), occupation wise most of patients belonged to labour class (49). Highly significant improvement in symptoms scale was noticed in G-1 Levosulpiride 40 patients' group.

Conclusion: Functional Gastrointestinal disorders are not serious ailments but have a key impact on quality of life. Overall dyspeptic symptom relief rates were significantly high in the Levosulpiride group ($p<0.004$) as compared to Domperidone and Metoclopramide groups. A proper understanding of disease process by health care personnel and by sufferer is obligatory to enhance the quality of life and daunt the self/over the counter medication in this condition.

Keywords: Gastrointestinal disorders, Prokinetic, Quality of life

INTRODUCTION

Functional Gastrointestinal disorders are not serious ailments, but they are worth in conflict, because the patients with them have a compromised quality of life. Symptoms and anxiety associated with these disorders, frequent inconvenience and put off the individuals affected from leading full and industrious lives [1].

The Rome III accord defined functional dyspepsia (FD) as the presence of epigastric pain or burning, postprandial fullness, or early satiation in the absence of either underlying organic disease detected by oesophago-gastro-duodenoscopy (OGD) or metabolic disease [2,3]. In general clinical practice FD (non-ulcer) is defined as continuous or frequently recurring epigastric pain or discomfort for which no organic cause can be determined. Epigastric pain or discomfort may be associated with other symptoms, such as upper abdominal bloating, excessive burping or belching, early satiety and nausea [2]. The pathophysiological mechanisms in FD are varied and comprise altered gastrointestinal motility, visceral hypersensitivity, *Helicobacter pylori* infection, psychosocial factors, and other undefined causes [4,5].

Studies have shown that, 10-30% prevalence of FD worldwide, highlighting the importance of FD as a healthcare issue and most of the patients go for over the counter or homemade medication /therapy [6]. Prokinetic drugs have been extensively experienced in the treatment of FD. This is because gastrointestinal motor abnormalities i.e. delayed gastric emptying has been frequently accounted in patients suffering from this frequent syndrome [7]. Gastrointestinal prokinetics encourage or increase the harmonization of the gut wall contractions leading to augmentation of propulsive motility. They are considered drugs of option for the handling of upper gastrointestinal tract functional motor disorders such as those associated with gastro esophageal reflux, chronic dyspepsia and gastroparesis. Currently available drug classes with prokinetic properties include anti-dopaminergic agents (eg. Domperidone, Levosulpiride and Metoclopramide) and serotonergic agents (e.g. cisapride, mosapride).

The most frequently used Prokinetic drugs like Metoclopramide, Levosulpiride and Domperidone augment gastric emptying, avert retention and reflux of acid or food and relieve symptoms of dyspepsia. However, Metoclopramide causes dystonic reactions and drowsiness, while Domperidone has been reported to cause galactorrhoea and gynaecomastia [8].

Among prokinetic drugs, numerous clinical studies have offered facts on the efficacy of dopamine receptor antagonists such as Metoclopramide, Domperidone and Levosulpiride in the treatment of functional dyspepsia [9]. Metoclopramide, Domperidone and Levosulpiride have both antiemetic and prokinetic properties since they antagonize dopamine receptors in the central nervous system as well as in the gastrointestinal tract where dopamine apply compelling inhibitory effects on motility [10].

Levosulpiride is the levorotatory enantiomer of sulpiride, a substituted benzamide. Levosulpiride is a prokinetic agent which amplifies the lower esophageal sphincter pressure more speedily and efficiently than other therapeutic agents [11]. The prokinetic effect of Levosulpiride is mediated through the blockade of enteric (neuronal and muscular) inhibitory dopamine D2 receptors. Consequences also show that Levosulpiride also acts as a reasonable agonist at the 5-HT4 receptor [12]. On the other hand Domperidone has a dual anti-emetic effect. First, it acts on dopamine receptors in the chemoreceptor trigger zone in the area postrema (does not normally cross the blood-brain barrier) and Second, it acts on D2-receptors at the gastro-esophageal and gastroduodenal junctions apart from these effects it may also inhibit cholinesterase activity [13,14].

In view of above background this study compared the efficacy of Levosulpiride, Domperidone and Metoclopramide in FD. The Primary

objective of our study was to evaluate pre and post functional dyspeptic symptoms improvement in each patient including: Epigastric pain, Epigastric postprandial fullness and discomfort, nausea, vomiting, early satiety, etc. The presence and intensity of above symptoms of functional dyspepsia in patients enrolled in the study were assessed at base line (Prior to initiation of therapy) and at 4 weeks, on a 5-point scale. Secondary objective: tolerability of all the three study drugs during the study period was also taken into account.

MATERIALS AND METHODS

This is a prospective, randomized study designed to demonstrate the efficacy of three study drugs (Levosulpiride, Domperidone and Metoclopramide) in FD. Subject recruitment was done from medicine outpatient department of the teaching hospital from June 2013 to November 2013. All study linked credentials were approved by the Institutional Ethics Committee and the study was conducted in accordance with the Indian Council of Medical Research guidelines for Biomedical Research on Human subjects and the Declaration of Helsinki. An informed consent was obtained from the study participants.

The inclusion criteria for the patient to be enrolled in the study are as follows: Adult patients of either sex, who had symptomatic presentation (pain and discomfort), and who agreed to give written informed consent.

The patients with chief complain of gastroesophageal reflux disease (GERD), identified history of peptic ulcer, any cancerous growth, pregnancy, hepato-biliary disease, and lactating mothers were excluded from the present study. Gastrointestinal prokinetics and anti-kinetics Drugs (eg: 5-HT4 agonists, D2 antagonists, cholinergic, macrolide antibiotics, calcium antagonists, beta-blockers, anti-cholinergic drugs, anti-convulsants, opiates, etc.), proton pump inhibitors, antacids were discontinued two weeks earlier to the beginning of the study. All study medication was purchased by patients as per the given prescriptions.

All clinical evaluation and laboratory investigations were done at the initial enrollment and at the end of four week of management. A 12-lead ECG was done on each patient at the screening visit to exclude QT prolongation, and at the end of four weeks to detect any effect of drugs on the QT interval. Biochemical investigation like complete hemogram, serum creatinine, blood glucose and liver function tests etc. were done at the screening visit and at the end of treatment. Adverse events were monitored throughout the study and suspected drugs and associate Adverse Drug Reactions were noted by treating clinician.

The sample size was calculated using standard formula for sample size calculation for clinical study and patients were randomly (randomized block design with 40 cases in each block) allocated to receive either one tablet of Levosulpiride 15 mg, three times daily or one tablet of Domperidone 10 mg, three times a day or Metoclopramide 10 mg three times a day 15-30 minutes before food for four weeks. Patients were advised to avoid alcohol and smoking during the study period.

Patients' symptoms were graded according to the Short-Form Leeds Dyspepsia Questionnaire (SF-LDQ); it is a five question instrument for assessing the dyspeptic symptoms. Five symptoms including epigastric pain, postprandial distention, indigestion, heartburn and nausea were graded for severity on a five-point Likert scale from very mild to very severe: no symptoms (0 point), mild symptoms without influence on regular work (1 point), mild symptoms with influence on regular work (2 points), moderate symptoms (3 points), severe symptoms (4 points) and extremely severe symptoms (5 points). SF-LDQ is a validated and reliable tool to assess the dyspeptic symptoms of patients with FD with higher scores indicating worse dyspeptic outcomes [15,16].

STATISTICAL ANALYSIS

Data were presented as Mean ± SD. Pre and post symptom summary Scores presented as mean (range) and 95% confidence intervals (CI). Comparative Statistical analysis was done using two-tailed paired t-test and statistical significance was defined as $p<0.05$.

RESULT

One hundred twenty patients were enrolled in the study, 7 patients were lost to follow up, so finally 113 patients completed this study in three groups (G-1 Levosulpiride 40 patients, G-2 Domperidone 35 patients and G-3 Metoclopramide 38 patients) were followed up. Among 113 patients female gender dominated (75), by occupation most of patients belonged to labour class (49). Illiterate patients (68) dominated the entire study group, with regard to drug history, tea intake was predominant (110) followed by alchohol (22) [Table/Fig-1]. Over all common ADRs are cited in [Table/Fig-1], the highest number of ADR were reported from Metoclopramide treatment group. The baseline and final mean (SD) serum biochemistry parameters of all the patients in respective groups defined in [Table/Fig-2].

Variables	G-1 Levosulpiride n=40	G-2 Domperidone n=35	G-3 Metoclopramide n=38
Gender			
Male (38)	16	08	14
Female (75)	24	27	24
Age mean in years			
Male (38)	46.63	35.80	47.07
Female (75)	43.70	45.46	42.88
Occupations			
Farmer (11)	04	03	04
laborer (49)	17	16	16
Business man (10)	04	03	03
Retired (5)	03	01	01
Housewife (33)	11	10	12
Student (3)	01	01	01
Teacher (2)	00	01	01
Education			
Illiterate (68)	23	18	27
Primary (9)	04	01	04
Metric (25)	09	11	05
Post metric (11)	04	05	02
Drug history			
NSAIDs (14)	04	04	06
Oral Contraceptive (6)	01	02	03
Alcohol (22)	05	06	10
Tea (110)	38	35	37
Common ADR			
Fatigue (6)	03	01	02
Headache (7)	01	02	04
Diarrhea (5)	00	02	03
Dizziness (4)	02	01	01
Xerostomia (5)	01	00	04
QT prolongation (2)	01	00	01
Elevated Serum - creatinine (1)	00	00	01

[Table/Fig-1]: Demographic data of study population

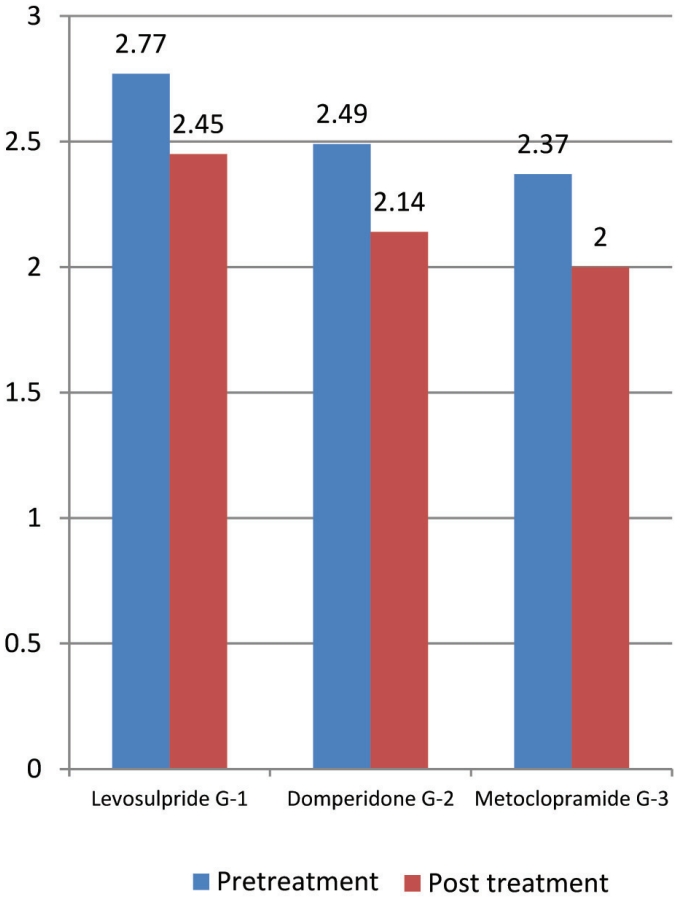
	Pre-treatment mean symptom score (SD)	Post-treatment mean symptom score (SD)	significance (two-tailed paired t-test)
G-1			
Mean	2.77(1.11)	2.45(0.98)	<0.004
95 % CI	2.93	2.61	
G-2			
Mean	2.49(1.23)	2.14(1.0)	<0.01
95% CI	2.67	2.34	
G-3			
Mean	2.37(0.95)	2.00(0.89)	<0.02
95% CI	2.55	2.23	

[Table/Fig-2]: The statistical comparison of three treatment group

The efficacy comparison of three treatment group i.e. G-1 Levosulpiride 40 patients, G-2 Domperidone 35 patients and

	G-1 Levosulpiride n = 40		G-2 Domperidone n = 35		G-3 Metoclopramide n = 38	
	Pretreatment	Posttreatment	Posttreatment	Posttreatment	Posttreatment	Posttreatment
Hb (gm/dL)	11.2 ± 1.76	11.0 ± 2.05	10.55 ± 2.05	11.49±1.87	10.18 ± 2.1	10.21 ± 2.5
WBC-TC (/cumm)	6925 ± 2412	6600 ±2148	6494 ± 2827	6500 ± 2479	6084 ± 2527	6284 ± 2227
Creat (mg/ml)	0.80 ± 0.1	0.82± 0.13	0.78 ± 0.11	0.79 ± 0.11	0.75 ± 0.10	0.88 ± 0.11
AST (Units/L)	26.62±9.17	26.25 ± 9.16	27.85±8.09	25.74±6.87	25.85±9.09	26.85±8.09
ALT (Units/L)	28.11±9.02	28.92 ± 10.16	31.67±8.19	30.11±6.98	31.01±9.0	33.67±8.19
Alk. Phos. (Units/L)	132 ± 23.5	141 ± 24.5	133.8±23.3	128.11± 33.8	132.8±25.0	133.8±27.3
Bilirubin (mg/dl)	0.98±0.3	0.97 ± 0.2	0.95±0.3	0.89±0.2	0.91±0.5	0.95±0.1
FBS (mg/dl)	82.8 ± 17.1	84.96 ± 8.5	82.1±9.4	81.8±8.2	84.1±9.1	83.1±8.4
QT interval (millisec)	0.35 ± 0.044	0.33 ± 0.042	0.32 ±0.5	0.31 ± 0.046	0.39 ±0.6	0.38 ±0.5

[Table/Fig-3]: Serum Biochemistry & QT interval changes with 4 weeks treatment in three groups



[Table/Fig-4]: SF-LDQ scores in 3 groups

G-3 Metoclopramide 38 patients were analyzed (pre and post treatment symptom improvement) a highly significant improvement in symptoms scale were noticed in G-1 and significant improvement were noticed in G-2, G-3 [Table/Fig-3,4].

DISCUSSION

There are several approaches for the management of FD, according to likely pathogenesis; prokinetic agents are used to correct disordered gastrointestinal motility, and antisecretory drugs are used to decrease gastric acid secretion. Agents with property of opioid agonists or serotonin type-3 receptor antagonists are considered to diminish visceral hypersensitivity, and *Helicobacter pylori* infection eradication therapy has also been considered, although the usefulness of these therapies has not been confirmed and mostly a combination of above is required to tackle the condition [17,18].

At present, prokinetic and antisecretory agents are recommended as first-line treatment for FD. Prokinetics are reported to be considerably superior to placebo (relative risk reduction, 40%). The reported studies in favor of prokinetic have shown statistically significant cure rates [19,20]. In a previous double-blind crossover comparison performed by Mansi et al., Levosulpiride was effective in reducing gastric emptying time and improving symptoms in patients with functional dyspepsia [20].

The present study was an open labeled, randomized, three parallel group's comparative study on the efficacy of Levosulpiride 15 mg, Domperidone 10 mg and Metoclopramide 10 mg three times a day for the treatment of Rome III-based FD. All three therapeutic intervention i.e. Levosulpiride, Domperidone and Metoclopramide were visibly effective in improving dyspeptic symptoms. However, the overall dyspeptic symptom relief rates were significantly higher in the Levosulpiride group ($p<0.004$) as compared to Domperidone and Metoclopramide group at week 4 [Table/Fig-3]. These results are consistent with the finding of other studies in which Levosulpiride demonstrated significant clinical improvement when compared to placebo [21].

The superior beneficial effects of Levosulpiride, compared to other two groups on symptoms of patients' every-day activities, possibly will be related to the affirmative effects exerted by Levosulpiride on the patients' comfort, which might be credited to the induced facilitation of dopaminergic neurotransmission [22]. Apart from above mechanism it has been demonstrated that, in the gastrointestinal tract, Levosulpiride also interacts with 5-HT4 receptors and, to a lesser extent, with 5-HT3 receptors, without exerting any anticholinesterase activity [23]. This effect on serotonin receptors may explain in part the prokinetic action of Levosulpiride on the gastric and small bowel motility. There is evidence that 5-HT3 and 5-HT4 receptors modulate visceral sensation and it has been suggested that specific 5-HT3 and 5-HT4 agonists or antagonists may be beneficial in treating gastrointestinal functional disorders [24,25].

Few studies including Corazza et al., has shown that Levosulpiride, when compared with Metoclopramide or Domperidone, proved to be appreciably more useful in controlling chemotherapy- induced nausea and vomiting and dyspeptic symptoms in FD [26-28]. The antidepressive properties of Levosulpiride might bring about a favorable effect; i.e., antidepressive agents and prokinetic agents may act synergistically [20,29].

Adverse Reaction Profile

The rate of adverse events was very low as shown in [Table/Fig-1]. The incidence and nature of the adverse events observed are in concurrence with what has been reported in other studies and are considered an extension of the pharmacological profile of the drugs, and these were mild in nature [30,31]. During the 4 weeks study period, adverse drug reactions like headache, lethargy ,giddiness, diarrhea, xerostomia and QT prolongation were found in Metoclopramide and Levosulpiride groups while headache, lethargy, giddiness, diarrhea were found in Domperidone group and

were managed with symptomatic treatment and did not necessitate stoppage of study medication or study exclusion.

CONCLUSION

Functional dyspepsia is a very common disorder seen in general practice and by physician/ gastroenterologists. FD seems to be a vague aliment with variable pathophysiologic disturbances and associated with different symptom profiles. The existing choice for the treatment of functional dyspepsia is of partial worth, which most likely imitates the shortened understanding of the nature of this disorder. Current knowledge is in hold of empirical treatment with prokinetics and acid-suppressive agents or combination. Refractory patients may benefit from some kind of psychological interventions. A proper understanding of disease process by health care personnel and by sufferer is obligatory to enhance the quality of life and daunt the self/over the counter medication in this condition.

REFERENCES

[1] Beattie DT, Smith JA. Serotonin pharmacology in the gastrointestinal tract: a review. *Naunyn Schmiedebergs Arch Pharmacol.* 2008;377(3):181-203.
[2] Talley NJ, Stanghellii V, Heading RC, et al. Functional gastroduodenal disorders. *Gut.* 1999;45(suppl 2):1137-42.
[3] Tack J, Talley NJ, Camilleri M, et al. Functional gastroduodenal disorders. *Gastroenterology*. 2006;130:1466–79.
[4] Suzuki H, Nishizawa T, Hibi T. Therapeutic strategies for functional dyspepsia and the introduction of the Rome III classification. *J Gastroenterol.* 2006;41(6): 513-23.
[5] Suzuki H, Moayyedi P. *Helicobacter pylori* infection in functional dyspepsia. *Nat Rev Gastroenterol Hepatol*. 2013;10:168-74.
[6] Mahadeva S, Goh KL. Epidemiology of Functional Dyspepsia: a Global Perspective. *World.* 2006;12(17):2661-62.
[7] Malagelada JR. Gastrointestinal motor disturbances in functional dyspepsia. *Scand J Gastroenterol.* 1991;26(182):29-32.
[8] Keith A. Sharkey, John L. Wallace. Treatment of disorder of Bowel motility and water flux; antiemetic; Agents used in billiary & pancreatic diseases. In: Laurence L. Brunton. (Editor). Goodman and Gilman's The Pharmacological Basis of Therapeutics, 12th edition, New York, McGraw Hill, 2011;1323-28.
[9] Song CW, Chun HJ, Kim CD, Ryu HS, Choe JG, Hyun JH. Effects of Levosulpiride in patients with functional dyspepsia accompanied by delayed gastric emptying. *Korean J Intern Med.* 1998;13:15-21.
[10] Nagahata Y, Azumi Y, Kawakita N, Wada T, Saitoh Y. Inhibitory effect of dopamine on gastric motility in rats. *Scand J Gastroenterol.* 1995;30:880-85.
[11] M Guslandi. The clinical use of Levosulpiride. *Current Therapeutic Research*. 1993;53(5):484-501.
[12] Tonini M, Cipollina L, Poluzzi E, Crema F, Corazza GR, De Ponti F. Review article: clinical implications of enteric and central D2 receptor blockade by antidopaminergic gastrointestinal prokinetics. *Aliment Pharmacol Ther*. 2004;19(4):379-90.
[13] Barone JA. Domperidone: a peripherally acting dopamine2-receptor antagonist. *Ann Pharmacother.* 1999;33:429-40.
[14] Prakash A, Wagstaff AJ. Domperidone. A review of its use in diabetic gastropathy. *Drugs.* 1998;56:429-45.
[15] Fraser A, Delaney BC, Ford AC, Qume M, Moayyedi P. The Short-Form Leeds Dyspepsia Questionnaire validation study. *Aliment Pharmacol Ther.* 2007;25:477-86.
[16] Moayyedi P, Duffett S, Braunholtz D, Mason S, Richards ID, Dowell AC, et al. The Leeds Dyspepsia Questionnaire: a valid tool for measuring the presence and severity of dyspepsia. *Aliment Pharmacol Ther.* 1998;12:1257-62.
[17] Talley NJ. Review article: functional dyspepsia-should treatment be targeted on disturbed physiology? *Aliment Pharmacol Ther.* 1995;9:107-15.
[18] Miwa H, Hirai S, Nagahara A, Murai T, Nishira T, Kikuchi S, et al. Cure of Helicobacter pylori infection does not improve symptoms in non-ulcer dyspepsia patients-a double-blind placebo-controlled study. *Aliment Pharmacol Ther.* 2000;14:317-24.
[19] Moayyedi P, Soo S, Deeks J, Forman D, Harris A, Innes M, et al. Systematic review: antacids, H2-receptor antagonists, prokinetics, bismuth and sucralfate therapy for non-ulcer dyspepsia. *Aliment Pharmacol Ther.* 2003;17:1215-27.
[20] Mansi C, Borro P, Giacomini M, Biagini R, Mele MR, Pandolfo N. gastric emptying and symptoms in patients with functional dyspepsia and gastroparesis. *Aliment Pharmacol Ther.* 2000;14:561-69.
[21] Arienti V, Corazza GR, Sorge M. The effects of Levosulpiride on gastric and gall-bladder emptying in functional dyspepsia. *Aliment Pharmacol Ther.* 1994;8:631-38.
[22] Bocchetta A, Bernardi F, Burrai C, Pedditzi M, Del Zompo M. A double-blind study of L-sulpiride versus amitriptyline in lithium-maintained bipolar depressives. *Acta Psychiatr Scand.* 1993;88:434-39.
[23] Tonini M, Spelta V, De Giorgio R. A re-assessment of the pharmacodynamics of Levosulpiride in the guinea pig gastrointestinal tract. *Gastroenterology.* 1999;116:1035-42.
[24] Talley NJ. 5-hydroxytryptamine agonists and antagonists in the modulation of gastrointestinal motility and sensation: clinical implication. *Aliment Pharmacol Ther.* 1992 6:273-89.
[25] Camilleri M, Von der Ohe MR. Drugs affecting serotonin receptors. *Bailliere's Clin Gastroenterol.* 1994;8:301-19.
[26] De Rossi S, Cosmacini G, Cosmacini P. sulpiride in the radiologic examination of the gastrointestinal tract. *Curr Ther Res.* 1990;47:707-16.
[27] Masci E, Sorghi M, Tosi T, Testoni PA, Tottobello A. Levosulpiride and domperidone in the treatment of reflux esophagitis: results of a double-blind study versus placebo. *Curr Ther Res Clin Exp.* 1992;51(6):814-8.
[28] Corazza GR, Biagi F, Albano O, Porro GB, Cheli R, Mazzacca G, et al. Levosulpiride in functional dyspepsia: a multicentric, double-blind, controlled trial. *Ital J Gastroenterol.* 1996;28:317-23.
[29] Distrutti E, Fiorucci S, Hauer SK, Pensi MO, Vanasia M, Morelli A. Effect of acute and chronic Levosulpiride administration on gastric tone and perception in functional dyspepsia. *Aliment Pharmacol Ther.* 2002;16:613-22.
[30] Mansi C, Savarino V, Vigneri S, Perilli D, Melga P, Sciabà L,et al. Gastrokinetic effects of Levosulpiride in dyspeptic patients with diabetic gastroparesis. *Am J Gastroenterol.* 1995; 90: 1989-93.
[31] Rossi F, Forgione A. Pharmacotoxicological aspects of Levosulpiride. *Pharmacol Res.* 1995;31:81-94.

PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Pharmacology, G.G.S. Medical College, Faridkot, Punjab, India.
2. 3nd year Post-graduate Resident, Department of Pharmacology, G.G.S. Medical College, Faridkot, Punjab, India.
3. Assistant Professor, Department of Pharmacology, G.G.S. Medical College, Faridkot, Punjab, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Harminder Singh,
Associate Professor, Department of Pharmacology, G.G.S. Medical College, Faridkot -151203,
(Baba Farid University of Health Sciences), Punjab, India.
E-mail: dr_harminderchahal@rediffmail.com

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