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Research Article

Role of Levosulpiride in the Management of Functional Dyspepsia

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Abstract

Functional dyspepsia (FD) consist of variable combination of symptoms of gastrointestinal tract like abdominal pain, postprandial fullness, abdominal bloating, early satiety, nausea, vomiting, heartburn and acid regurgitation, without any definitive structural or biochemical cause for it. There are varieties of treatment options available for management of dyspeptic symptoms including, replacement of Non Steroidal Anti Inflammatory Drugs (NSAIDs) with COX-2 inhibitor, empirical treatment with Proton Pump Inhibitor and treatment of H.pylori infection. Refractory dyspeptic cases, who fail to respond conventional treatment of dyspepsia can be managed with antidepressant or pro kinetic drugs.

Levosulpiride is an atypical antipsychotic, acts by blocking the presynaptic D2 dopaminergic receptor in the dopaminergic pathway. It was found that levosulpiride have more efficacy in management of dyspeptic symptoms in comparison to antisecretary agents (cimetidine, ranitidine) and prokinetic agents (metaclopramide, domperidone). Levosulpiride is as effective as cisapride in management of dyspepsia, having better tolerability, and relatively milder adverse events. Levosulpiride improves the dyspeptic symptoms like pain, discomfort, fullness, bloating of abdomen, early satiety, nausea, vomiting, associated anxiety symptoms, and health related quality of life impaired by dyspeptic symptoms. Levosulpiride quicken gastric and gall bladder emptying. It also has gastro kinetic effect and improves glycemic control in diabetic gastroparesis. Galactorrhoea, somnolence, fatigue and headache are common adverse event seen with levosulpiride therapy. Majority of adverse events were occurred in first fifteen days of treatment with levosulpiride, and they improve gradually without discontinuation of treatment. Unlike cisapride, levosulpiride is devoid of serious cardiovascular adverse effect.

Keyword: Levosulpiride; Dyspepsia; Gastroparesis

Abbreviations

FD: Functional Dyspepsia; CNS-ENS: Central Nervous System-Enteral Nervous System; UD: Uninvestigated Dyspepsia; NSAIDs: Non Steroidal Anti-inflammatory Drugs; PPI: Proton Pump Inhibitor; GERD: Gastro Esophageal Reflux Disease; HRQoL: Health Related Quality of Life; IDDM: Insulin Dependent Diabetes Mellitus; HbA_{1c}: Glycosylated Hemoglobin.

Introduction

Dyspepsia is a group of symptoms referable to upper gastrointestinal tract rather than diagnosis itself [1,2]. It consists of variable combination of symptoms of upper gastrointestinal tract including abdominal discomfort or pain, postprandial fullness, abdominal bloating, early satiety, nausea, vomiting, heartburn and acid regurgitation [1,2]. There is a group of patients who do not have definite structural or biochemical cause for their symptoms, are considered for suffering from functional dyspepsia (FD) [1,2]. There are several pathophysiological correlates have been identified for functional dyspepsia, including gastro intestinal motor abnormalities, altered visceral sensation, central nervous system- enteral nervous system (CNS-ENS) integration dysfunctions and psychological factors [1,2]. It is a biopsychosocial disorder, having brain-gut axis dysregulation as centre for origin of the disease [1,2].

Aim of study

Dyspepsia is the most common gastrointestinal symptoms for health care consultation [3]. There is paucity of population based studies on true functional dyspepsia (FD), as there are logistic difficulties of excluding structural disease in large group of patients Prevalence of dyspepsia varied from 21% to 29% in various population based studies of Iran, US and UK [4,5,6,7]. The prevalence of uninvestigated dyspepsia (UD) varies from 7% to 45%. The difference of this large variation probably because of variation of difference in definition of dyspepsia and the different population studied [2,7]. Population based study from Iran found that females, NSAIDs users, water pipe smokers, persons having psychological distress, recurrent headache, anxiety, nightmares, past history of gastrointestinal disease, high caffine intake and persons from poor socio economical status are more likely to suffer from dyspepsia, while fruits, vegetables, dates, honey, walnut, yogurt, bread and caraway seeds are protective in dyspepsia [4,8]. There are 2-4% patients attending primary care clinic having presenting complaint of dyspepsia [3,9] and this percentage may go beyond 50% in specialist gastroenterology clinic [10].

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There is statistically significant impairment in health related quality of life in patients having dyspepsia in comparison to healthy control in two separate studies carried out in Malaysia [2,11,12]. There is significant impairment seen in all the domains of Euroqol quality of life instrument (EQ-5D) including mobility, self-care, usual activity, pain/ discomfort, anxiety / depression in patients with dyspepsia [2,11,12].

Methods

All published articles including clinical trials, case reports and review articles were searched in electronic database by using search engines like PubMed, Psych Info and Google Scholar. The keywords were "Levosulpiride", "Functional Dyspepsia", "Irritable bowel Syndrome", "Dyspepsia" and "Gastroparesis". The searches were carried out in April 2015. Two authors independently carried out search and the lists of relevant abstract were collected. Additionally we have identified relevant studies from cross references and reference list. We have not included unpublished material, non peer reviewed material and searches of libraries.

We have included studies published in peer reviewed journal of English language consisting research on dyspepsia, irritable bowel syndrome and levosulpiride were included. We have not included the article pertaining to ulcerative gastro intestinal illness.

Clinical evaluation and Management of dyspepsia

Evaluation of patient with dyspepsia should begin with thorough history taking and physical examination. Every patient presenting with dyspepsia should be inquired for alarm symptoms including unexplained weight loss, recurrent vomiting, progressive dysphagia, odynophagia, gastrointestinal blood loss and family history of carcinoma [13,14]. Endoscopic evaluation for the patients over age 50 or presence of alarm symptoms is recommended [13,14,15]. There are few studies contradicting the above studies, showing limited predictive value of presence of alarm symptoms for the diagnosis of malignancy or functional dyspepsia [16,17].

Direct questioning about use of Non Steroidal Anti-inflammatory Drugs (NSAIDs) is useful in eliciting the information about analgesic abuse for headache, backache, arthritis etc [14]. is important for identifying potential offending agents [14]. Special attention to stop offending agents and starting alternative medical treatment should be given [14]. If NSAIDs can't be stopped, then addition of Proton Pump Inhibitor (PPI) or changing NSAIDs to selective COX-2 inhibitor may be helpful to alleviate symptoms [14,18].

Rome III guideline acknowledges frequent overlapping of symptoms of Gastro Esophageal Reflux Disease (GERD) and dyspepsia [14,15]. Empirical treatment with PPI may help in reducing reflux symptoms of GERD [14]. Trial of empirical eradication therapy for H. pylori or 'test and treat' approach can be considered in younger patient without alarm features, once the symptoms of GERD or offending medications are excluded [14,19].

Patients who didn't responded empirical therapy with PPI, have normal endoscopy and have cleared the infection of H. pylori and having continue to have dyspepsia symptoms represent the challenging group termed as "refractory dyspepsia", and can be treated with antidepressant medications or prokinetic agents [14].

Antidopaminergic gastrointestinal prokinetic agents including bromopride, celebopride, domperidone, levosulpiride, and metoclopramide have been used clinically management for motor disorder of upper gastrointestinal tract [20,21]. These agents have properties to block enteric inhibitory D2; in this respect levosulpiride is selective D2 receptor antagonist with prokinetic activity [20,22]. It helps in controlling gastro intestinal motility by acting through dopaminergic pathway and its action on 5-HT4 receptor have role in management in functional dyspepsia [20,23]. High efficacy of levosulpiride in management of dyspeptic symptoms with limited side effect is reported in many studies [20,24,25,26,27].

Levosulpiride

Sulpiride is a substituted benzamide, having selective action on dopamine D2 receptors like family [28,29]. At low dosage (50-150 mg/day) it produce disinhibiting and antidepressant effect by facilitating dopaminergic neurotransmission, as it has action on presynaptic D2 auto receptor [28,29]. It is considered to be an atypical antipsychotic, considering its action on negative symptoms, partial activity against positive symptoms and low incidence of extra pyramidal adverse effects [28,29]. Having good safety margin at therapeutic dosage and toxic concentrations, it is advocated in elderly patients with schizophrenia [28,29].

Levosulpiride, a substituted benzamide is a levorotatory enantiomer of sulpiride [30]. It has antipsychotic, antidepressant, antiemetic and an antidyspeptic property as well as it is used in treatment of somatoform disorder [30]. The main mechanism of action consists of blocking the presynaptic D2 dopaminergic receptor in the dopaminergic pathway [30]. In comparison to dextro enantiomer or racemic mixture of drug, levosulpiride shows better pharmacological action and lower toxic effects [31]. Levosulpiride can be used in chemotherapy induced naused and emesis [32], accelerate gastric emptying and improves gastrointestinal symptoms in patients with functional dyspepsia [33,34], diabetic gastroparesis [35] and irritable bowel syndrome [36]. Recent study from Pakistan identified role of levosulpiride in enhancing sexual arousal and the ejaculatory threshold [37].

Result

Comparison of levosulpiride with other agents

A meta-analysis of 19 studies of prokinetics agents (cisapride, domperidone) and 10 studies of H2 receptor antagonist (cimetidine, ranitidine) suggested that both are superior to placebo in management of non ulcer dyspepsia, and prokinetic being superior in comparison to antisecretary agents like H2 antagonists [38]. Among prokinetic agents cisapride is considered to be more effective in comparison to domperidone and metaclopramide [39], and consistently showing its efficacy in various studies [40,41,42]. Suspension of cisapride from market in 2000 because of its cardiovascular adverse effect [43,44], aroused interest for the search of the alternatives treatment for the management of functional dyspepsia [45,46].

As levosulpiride showed to increase lower esophageal sphincter pressure [47], quicken gastric emptying [48], improves gallbladder emptying [33] and have gastrokineic effect and improves glycemic control in diabetic gastroparesis [35,49], and it shows improvement in day to activity and reducing symptoms of gastric distension by

Table 1: Studies evaluating efficacy of levosulpiride in comparison to placebo, anti secretary H2 receptor blocker and gastrointestinal prokinetic agents in patients with functional dyspepsia (FD).

Author	Methodology	Results
Lozano R et al [20]	A prospective, open-label, multicenter study of 342 patients with dysmotility-like functional dyspepsia (n=279) and nonerosive reflux disease (n=63), who received levosulpiride 25 mg 3 times daily orally for 4 weeks, were assessed for Individual symptoms (pain/discomfort, fullness, bloating, early satiety, pyrosis, regurgitation, and nausea/vomiting) and a global symptom score were assessed at 15, 30, and 60 days after starting treatment and adverse events.	At 15 day visit the global symptom score were reduced more than 50% with significant reduction in individual symptom intensity ($p<0.001$). At 30 day visit, all symptoms were almost disappeared, and that was maintained until last visit. Treatment with levosulpiride was well tolerated by majority of patients. There were only 40 adverse events and no patient had to abandon the study due to side effects.
Distrutti E et al [22]	Assessment of Gastro intestinal symptoms, perception score in eight healthy and 16 dyspeptic patients by isotonic distention by saline or levosulpiride.	Patients with FD showed marked gastric hypersensitivity compared to healthy subjects. Levosulpiride reduce perception of gastric distention in patients with FD, this action is unrelated to change of gastric tone. Chronic administration of levosulpiride significantly improves GI symptoms and discomfort.
Macarri G et al [24]	Double blinded study of 50 patients of FD have been treated with levosulpiride with metoclopramide for 30 days.	Both levosulpiride and metoclopramide reduces the symptoms of FD, levosulpiride was more effective on nausea, headache, epigastric pain and showed earlier effect in symptoms regression than metoclpramidie.
Corazza GR et al [26]	Double blinded multi centric study carried out to assess efficacy and safety of levosulpiride, domperidone, metoclopramide and placebo for 4 weeks in the treatment of dyspeptic symptoms.	Significant improvement was recorded for dyspeptic symptoms for all groups ($p<0.001$), but levosulpiride was found to superior to domperidone, metoclopramide and placebo. ($p<0.01$).
Corli O et al [32]	Thirty patients with advanced cancer studied for antiemetic efficacy of levosulpiride in comparison to metoclopramide in a randomized double blinded cross over study.	Both medicine reduces the nausea and vomitine. Levosulpiride being more effective than metoclopramide with p value of 0.0004 for nausea intensity and 0.041 for vomiting episode.
Arienti V et al [33]	Randomized double blinded placebo controlled study consisting 30 adult patients, treated with levosulpiride or placebo for 20 days. Gastric and gall bladder emptying were evaluated by gastric impedance (liquid meal) and real time ultrasonography (mixed meal).	Levosulpiride accelerate both gastric emptying ($p<0.001$ at 180 min, $p<0.05$ at 240 min) and gall bladder empting ($p<0.05$ at 60 and 120 min) in comparison to placebo. Levosulpiride improves dyspeptic symptoms in comparison to placebo ($p<0.025$).
Mansi C et al [34]	Thirty dyspeptic patients with functional gastroparesis were compared for efficacy and tolerability of levosulpiride and cisapride in a double blinded cross over comparison of four week administration of drugs.	Levosulpiride is as effective as cisapride in shortening gastric emptying time ($p<0.001$). Levosulpiride being more effective than cisapride in improving nausea, vomiting, early post prandial satiety and symptoms on the patient's day to day activity.
Mansi C et al [35]	Forty dyspeptic patients with long standing Insulin dependent diabetes mellitus were assessed for efficacy of levosulpiride on gastric emptying time, gastrointestinal symptoms score and glycemic control in a randomized double blinded plcebo controlled study.	Levosulpirie is more effective in gastric emptying time ($p<0.001$), gastro intestinal symptoms ($p<0.001$) in comparison to placebo. Reduction of mean plasma glycosylaed hemoglobin was not statistically significant.
Mearin F et al [46]	Randomized, double blinded, multicenter trial involving 69 patients on levosulpiride and 71 patients on cisapride to assess the improvement in individual in symptoms, global symptom score, Health related quality of life, anxiety status and adverse events.	Both levosulpiride and cisapride improves dyspeptic symptoms score, total symptom score (79.9% and 71.3% respectively) and health related quality of life. Patients on cisapride are more likely to experience adverse events and need to abandon the trial.
Melga P et al [49]	A randomized placebo controlled trial of forty patients of Insulin Dependent Diabetes Mellitus with clinical signs of autonomic neuropathy and delayed gastric emptying were assessed for effect of levosulpiride on gastric emptying time and glycemic parameters.	Levosulpiride improves glycemic control ($p<0.01$), gastric emptying ($p<0.001$) and dyspeptic symptoms.
Song CW et al [52]	Double blinded placebo controlled trial of 42 patients of functional dyspepsia accompanied by delayed gastric emptying were treated with levosulpiride and placebo for three weeks.	Patients receiving levosulpiride showed improvement of symptom score ($p<0.05$), reduction in gastric emptying time ($p<0.05$) in comparison to placebo. There was significant correlation between change in symptom score and gastric emptying time ($r=0.47$, $p=0.01$).

*Various double blinded randomised controlled studies among patients with functional dyspepsia (FD) reported that levosulpiride is significantly more effective in improvement in symptoms like nausea, vomiting, reduction in gastric and gall bladder emptying time in comparison to placebo, metaclopramide and domperidone.
*Efficacy of levosulpiride was found as good as that of cisapride. Patients on cisapride experienced more adverse events and need to abandon the trial.

reducing gastric sensation [34], the efficacy of levosulpiride 25 mg three times a day were compared with cisapride 10 mg three times a day in multicenter, randomized, double-masked trial [46]. They studied individual symptoms like pain, discomfort, fullness, bloating, early satiety, nausea, vomiting, their effect on health related quality of life (HRQoL), anxiety, patient and physician's perceptions of treatment efficacy and adverse events reported during the study period [46].

Another study consisting 140 patients randomly assigned for levosulpiride (69 patients) and cisapride (71 patients) administration for eight weeks [46], found both levosulpiride and cisapride to improve dyspeptic symptoms and total symptoms score (79.9% and 71.3% respectively) and improvement in health related quality of life. There were no effect on anxiety with either of the treatment and relatively more side effects were reported with levosulpiride (18.8%) in comparison to cisapride (11.3%) [46]. But majority of side

Table 2: Meta analysis evaluating efficacy of anti secretary H2 receptor blocker and gastrointestinal prokinetic agents in patients with functional dyspepsia (FD).

Author	Methodology	Results
Allescher HD et al [38]	Meta-analysis of 19 studies on gastrokinetic (cisapride, domperidone) and 10 studies of histamine H2 receptor antagonist (cimetidine, ranitidine) to provide valid treatment recommendations for patients with non-ulcer dyspepsia.	Both gastrokinetics and histamine H2 receptor antagonist are significantly more effective than placebo in the symptomatic treatment of non-ulcer dyspepsia, with gastroprokinetics (cisapride, domperidone) being more effective than histamine H2-receptor antagonists (cimetidine, ranitidine).
Finney JS et al [40]	Meta-analysis of 18 randomized controlled studies to assess the outcome of functional dyspepsia with treatment with antisecretary compounds (eg.cimetidien and ranitidine) and the gastrokinetic compounds (eg cisapride, domperidone) with placebo.	Gastrokinetic compounds shows greater success rate than anti-secretary compounds. Both are better than placebo.
Veldhuyzen van Zanten SJO et al [41]	Meta-analysis of seventeen studies of cisapride and four studies of domperidone to assess the global improvement by investigator or patients.	Both cisapride and domperidone seems to be efficacious in the treatment of functional dyspepsia.

*Gastrokinetic drugs like domperidone and cisapride seems to be efficacious in treatment of functional dyspepsia.
*Gastrokinetic drugs like domperidone and cisapride are significantly more effective than placebo, histamine H2 receptor antagonist like cimetidine and ranitidine.

effect noticed with levosulpiride were milder one, and significantly more (p=0.03) patients treated with cisapride had to give up the trial because of side effects [46] (Table 1).

Considering above mention findings levosulpiride can be considered at least as effective as cisaride [41], which is more effective than other antisecretary (cimetidine, ranitidine) [38] and other prokinetic drugs (metaclopramide, domperidone) [39]. As levosupiride had relatively milder side effect in comparison to cisapride and devoid of serious cardio vascular adverse effect [46], it can be considered as an attractive option for treatment of functional dyspepsia [46] (Table2).

Effect of levosulpiride in gastric emptying

Delayed gastric emptying, impaired gastric accommodation to meal, hypersensitivity to gastric distension, abnormal duodenojejunal motility were considered to be associated with functional dyspepsic symptoms [14,50]. There are several studies demonstrated cisapride and levosulpiride to be more effective in gastric emptying in comparison to placebo [33,34,51,52] and levosulpiride is effective in the gall bladder emptying as well [33,34]. Both cisapride and levosulpiride are helpful in reducing the symptoms related to gastric emptying pattern like epigastric discomfort, postprandial fullness and bloating, while nausea, vomiting and early satiety are more improved with levosulpiride treatment [34]. This behaviour could be related to inhibition of D2 receptor, not only in the enteric nervous system but also in the chemoreceptor trigger zone, by levosulpiride, while cisapride devoid of anti-dopaminergic activity [34]. Levosulpiride was found to have better antiemetic properties and less side effects in comparison to metoclopramide in both onchologic and nononchologic diseases [32,34,53].

Levosulpiride found to be superior to cisapride in improving dyspeptic symptoms, without improvement of gastric emptying [34], could be because of anti depressant property of levosulpiride exerted at low dose by selective inhibition of dopaminergic presynaptic receptors, with enhancement of functional dopamine transmission [34,54].

Levosulpiride for gastroparesis in patients with IDDM

Gastric motility disorder commonly occurs in about 50% of patients with diabetes mellitus [54], and delayed gastric emptying is more common in comparison to early emptying [55]. There are several mechanism involved for diabetic gastroparesis, including autonomic neuropathy [56] and hyperglycemia [57]. It was studied that rate of gastric emptying was a major factor in carbohydrate absorption and blood glucose homeostatic [58,59], making gastroparesis a contributing factor for poor glycamic control and continuation of the vicious cycle [57].

A randomized double blinded placebo control study of forty out patients having Insulin Dependent Diabetes Mellitus (IDDM) and dyspepsia, showed levosulpiride to improve gastric emptying and improving glycemic control, without any change in insulin dosage or increasing in of number of hypoglycemic episodes [49]. Value of glycosylated haemoglobin (HbA_{1c}) and mean daily glycemic value was improved significantly after three month treatment with levosulpiride in comparison to placebo [49]. This could be explained by a better synchronization between the onset of exogenous insulin and release of nutrients from the stomach into the intestine and their absorption in the general circulation [49]. The study finding supported the role of gastric emptying in maintaining glycemic control in IDDM patients [49]. Patients with unexplained poor glycemic control should be investigated for gastric emptying abnormalities, and levosulpiride constitute a safe therapeutic option for the chronic treatment of diabetic patients having dyspeptic symptoms [49].

Discussion

Benefits and limitations of levosulpiride

The incidence of adverse event with levosulpiride was 11% in 840 patients with dyspepsia in a review conducted to assess the clinical pharmacology, therapeutic efficacy and tolerability of levosulpiride [27]. Majority of adverse events were milder and only eight cases (0.9%) discontinued treatment because of adverse event [27]. Another prospective, multicentre, open label, observational study reported 40 adverse events in 342 patients having three follow up visits [20]. Galactorrhoea, somnolence, fatigue and headache were common adverse events [20]. And there were no patient to abandon the study because of adverse event [20]. More than two third side effects occurred in first fifteen days of treatment with levosulpiride and intensity of adverse events was higher at the first visit; few adverse events were persisted at follow up visit, and had milder intensity [20].

There is few case reports for adverse events by levosulpiride therapy have been reported including, levosulpiride induced rabbit syndrome [60], and levosulpiride induced resting orolingual tremors

[61] and tremors of neck and tongue [62]. There are cases reported for tardive dyskinesia with combination therapy of levosulpiride and lemotrigine [63], and extreme QT interval prolongation (650 milliseconds) with recurrent episodes of unsuspected polymorphic ventricular tachycardia on Electrocardiogram (ECG) with citalopram and levosulpiride therapy [64].

Conclusion

Dyspepsia is the most common symptom for the consultation to the medical professionals. About 2 to 4% patients attending primary care clinic and more than 50% patients attending gastroenterology clinic have dyspepsia as presenting complaint. Levosulpiride acts by blocking presynaptic D2 dopaminergic receptor in dopamidergic pathway can be useful in management of functional dyspepsia, diabetic gastroparesis and irritable bowel syndrome. Levosulpiride was found to be more effective than anti secretary drugs (cimetidine, ranitidine) and prokinetic agents (metaclopramide, domparidone). It is as efficacious as cisapride in management of dyspeptic symptoms and devoid of serious cardiovascular side effects. So in conclusion, levosulpiride found to be efficacious in management of dyspeptic symptoms with well tolerated adverse effect.

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