Product Monograph

Volapride-25

Levosulpiride 25mg Tab.

In

GERD

Dyspepsia

Constipation &

Diabetic Gastroparesis

CONTENTS PAGE

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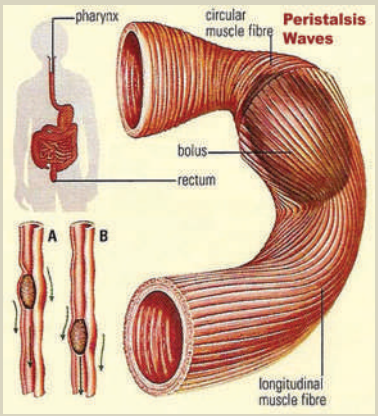
GASTROINTESTINAL MOTILITY

Peristaltic motor activity of the gut is an essential activity for digestion and absorption of nutrients to sustain life. Several factors and mechanisms are in place that have the ability to coordinate the contractile activity of the gut under all circumstances and in response to a variety of stimuli. The advantage of this multiple control is that gut motility control can withstand injury to one or more of its components without much negative effect on the overall health of the individual. All systems together reliably perform the task of moving and mixing gut content ensuring better absorption leading to enhanced digestion and overall wellbeing.

As the ball of food (bolus) formed in the mouth enters the pharynx, a reflex action is initiated.
This produces slow, wave-like contractions in the walls of the esophagus and later along the whole length of the tract.
These peristaltic waves involve the contraction of the circular muscle fibres behind the bolus (A) and the relaxation in front of the bolus. Longitudinal muscles provide the wave-like action. The two functions together push the ball down the tract (B).



Gut is made up of smooth muscles and smooth muscle contraction depends upon acetylcholine. Dopamine decreases the acetylcholine level while serotonin increases acetylcholine level, therefore dopaminergic and serotonergic activity balances the gut motility.

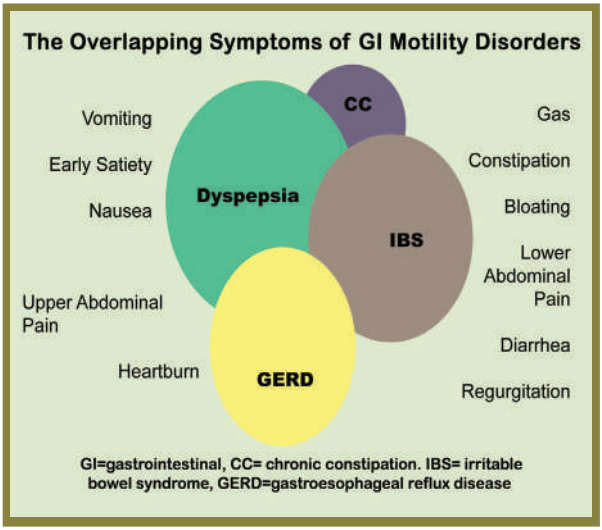
Dopamine is a biogenic amine synthesized in various areas of the central and peripheral nervous system.[1] Dopamine, while acting through specific dopaminergic receptors, inhibits lower esophageal sphincter (LES) pressure and gastroduodenal motility observed from the esophagus to the colon.

In the gut, serotonin (5-hydroxytryptamine: 5-HT) also exerts a variety of effects on intrinsic enteric neurons, extrinsic afferents, enterocytes and smooth muscle cells, which are related to the expression of multiple 5-HT receptor types and subtypes regulating motility, vascular tone and secretion.[2] Serotonin dysfunction is involved in the pathophysiology of a number of functional GI disorders, such as chronic constipation, irritable bowel syndrome, diabetic gastroparesis, functional dyspepsia and GERD.[3]

Functional GI disorders are not life-threatening diseases, but they are important because the patients with them have a poor quality of life. Symptoms associated with these disorders often are bothersome and prevent those affected from leading full and productive lives.

Symptoms of GI motility disorders often overlap with one another, and comorbidity among these disorders is high. **For instance, 22% to 50% of patients with functional dyspepsia also have GERD, and 29% of patients with GERD have chronic constipation. Results of a systematic review of published data (1996-2002) demonstrate that 23% to 87% of patients with IBS also have dyspepsia, 13% to 87% of patients with dyspepsia also have**

IBS, 46.5% of patients with IBS also have GERD, and 47% of patients with GERD also have IBS. In a recently published population based study (n = 643), overall prevalence rates were as follows: IBS, 12%; dyspepsia, 14%; GERD, 20%; diarrhea, 21%; and constipation, 17%.



OTHER FACTORS THAT AFFECT GI MOTILITY

Food intake**:** Clear fluids empty rapidly ($t_{1/2} \pm 30$ min). Solids stay in stomach longer ($t_{1/2} >$ 1-2 hours). Protein empties fastest, followed by carbohydrates. Fats take longest to empty. Fat and protein breakdown products in the small intestine inhibits gastric emptying. Oily foods and coffee cause relaxation of gut muscles.

pH of the stomach: **Hyperacidity slows down GI motility**. pH of chyme in the small intestine of < 3.5-4 will activate reflexes to inhibit stomach emptying.

Patient factors**:** Pregnancy, anxiety, pain and elderly.

Disease states: e.g. diabetes mellitus (autonomic neuropathy), post-operative bowel surgery with resultant ileus, high intra-abdominal pressure.

Drugs: e.g. opioids, codeine, dicyclomine.

TREATMENT OPTIONS

Gastrointestinal prokinetics promote or increase the coordination of the gut wall contractions leading to enhancement of propulsive motility.

They are considered drugs of choice for the treatment of upper gastrointestinal tract functional motor disorders such as those associated with gastrooesophageal reflux disease, chronic dyspepsia and gastroparesis (idiopathic or secondary to other diseases).

THERAPEUTIC INDICATIONS

- Functional dyspepsia
- Gastro-esophageal reflux disease
- Irritable bowel syndrome with constipation
- Diabetic gastroparesis
- Post-operative nausea and vomiting
- Nausea and vomiting induced by chemotherapy

Currently available drug classes with prokinetic properties include antidopaminergic agents (e.g. domperidone, levosulpiride and metoclopramide) and serotonergic agents (e.g. cisapride, mosapride). **The antiemetic and prokinetic effects of levosulpiride are unique, and permit the treatment of a larger number of gastrointestinal disorders than other drugs in its class**.

LEVOSULPIRIDE

Levosulpiride is the levorotatory enantiomer of sulpiride, a substituted benzamide. **Levosulpiride is a prokinetic agent which increases the lower esophageal sphincter pressure more rapidly and effectively than other therapeutic agents**.[4]

Mechanism of action

As a prokinetic**:** The prokinetic effect of Levosulpiride is mediated

through the blockade of enteric (neuronal and muscular) inhibitory dopamine D_2 receptors.[5] Results also show that levosulpiride also acts as a moderate agonist at the 5-HT_4 receptor. **The serotonergic (5-HT_4) component of levosulpiride may enhance its therapeutic efficacy in gastrointestinal disorders. This property, together with antagonism at D_2 receptors, may contribute to its gastrointestinal prokinetic effect**.[6]

As an antiemetic**:** The antiemetic effect of levosulpiride is due to inhibition of dopamine transmission and antagonism with D_2 receptors of the neurons in the area postrema of the vomiting center (IV ventricle) or chemoreceptor trigger zone in the CNS, blocking the inhibitory effect of dopamine on cholinergic neurons and therefore permitting a sustained cholinergic induced contraction of smooth muscle cell in the myenteric plexus of the esophagus, stomach and intestine.

CLINICAL EFFICACY AND SAFETY STUDIES

GASTROESOPHAGEAL REFLUX DISEASE

Gastroesophageal reflux disease (GERD) describes the retrograde movement of gastric contents through the lower esophageal sphincter (LES) to the esophagus. Symptoms include heartburn, acid regurgitation, noncardiac chest pain and dysphagia. The various agents currently used for treatment of GERD include mucoprotective substances, antacids, H_2 blockers, prokinetics and PPIs.[7]

In a number of patients the therapeutic effects of drugs inhibiting gastric acid secretion are not satisfactory enough. For that reason other medicines are added as concomitant therapy, e.g. prokinetics. **New prokinetics and inhibitors of transient lower esophageal**

sphincter relaxations (TLESRs) can potentially reduce both acid and non-acid reflux.[8]

Effect of Levosulpiride on reflux oesophagitis

The effects of Levosulpiride were examined when used to treat reflux oesophagitis in patients. **It was found that the symptoms of patients with reflux oesophagitis were alleviated and the endoscopic and ultrastructural lesions of patients with minor oesophagitis were also decreased**.[9]

FUNCTIONAL DYSPEPSIA

Dyspepsia refers to group of upper gastrointestinal symptoms such as pain, indigestion, nausea, early satiety and bloating that occur commonly in adults. Dyspepsia is known to result from organic causes, but the majority of patients suffer from non-ulcer or functional dyspepsia.

Globally, the prevalence of uninvestigated dyspepsia varies between 7% - 45%, depending on definition used and geographical location, whilst the prevalence of functional dyspepsia has been noted to vary between 11% - 29.2%.

It is clear that dyspepsia and functional dyspepsia in particular are common conditions globally, affecting most populations, regardless of location.[10] Risk factors for functional dyspepsia have been shown to include females and underlying psychological disturbances, whilst environmental/ lifestyle habits such as poor socio-economic status, smoking, increased caffeine intake and ingestion of non-steroidal anti-inflammatory drugs appear to be more relevant to uninvestigated dyspepsia.

In an Indian urban city study, dyspepsia was reported by almost one-third of the population; and significant symptoms

occurred in 12%.[11] **Prokinetics are an important class of medicinal products for the treatment of all clinical forms of dyspepsia.**[12]

Levosulpiride proves to be significantly superior to domperidone, metoclopramide and placebo both in the overall clinical improvement scale as well as in a subgroup of symptoms

Levosulpiride in functional dyspepsia

A total of 1298 patients were enrolled in a double-blind multicentric study carried out in forty-five Gastroenterology Departments. Patients were randomly assigned to either **levosulpiride (25 mg tid)**, domperidone (10 mg tid), metoclopramide (10 mg tid) or placebo (1 tablet tid) **for 4 weeks**.

Significant improvement was recorded for all symptoms at days 10 and 28 in all groups ($p < 0.001$), but levosulpiride was significantly ($p<0.01$) superior to domperidone, metoclopramide and placebo both in the overall clinical improvement scale as well as in a subgroup of symptoms (postprandial bloating, epigastric pain, heartburn).[13]

Levosulpiride in dysmotility-like FD and non-erosive reflux esophagitis

Levosulpiride in patients with dysmotility-like functional dyspepsia including non-erosive reflux esophagitis was assessed.

It was found that at the 15-day visit, a decrease greater than 50% in the global symptom score was observed. The frequency and intensity of individual symptoms showed a statistically significant decrease ($p<0.001$) at all visits compared with baseline.

At the 30-day visit, all symptoms had almost disappeared, a trend

that was maintained until the last visit. **Levosulpiride is an effective and safe drug in the treatment of dysmotility-like functional dyspepsia and non-erosive reflux disease**.[14]

Levosulpiride on gastric and gall-bladder emptying in functional dyspepsia

Levosulpiride, with respect to placebo, accelerated the mean gastric half-emptying time of liquids ($P < 0.05$), gastric emptying ($P < 0.001$ at 180 min; $P < 0.05$ at 240 min), and gall-bladder emptying ($P < 0.05$ at 60 and 120 min) emptying after a solid-liquid mixed meal. **Both the mean cumulative index ($P < 0.05$) and the overall intensity ($P < 0.025$) of dyspeptic symptoms were reduced significantly by levosulpiride**.[15]

DIABETIC GASTROPARESIS

Gastroparesis is a chronic disorder of gastric motility that is characterized by delayed emptying of either solids or liquids from the stomach in the absence of any mechanical obstruction. Diabetic gastroparesis is a disorder that occurs in both type 1 and type 2 diabetes.

Among the agents developed for diabetic gastroparesis, 5-HT_4 serotonin receptor agonists and dopamine D_2 receptor antagonists are the most promising

Upper gastrointestinal symptoms, particularly postprandial fullness, nausea, vomiting and abdominal bloating, occur in 30-50% of patients with diabetes. **It is important to identify and diagnose gastroparesis to prevent morbidity by controlling gastrointestinal symptoms, and to enhance glucoregulation**.[16]

Levosulpiride in dyspeptic patients with diabetic gastroparesis

This study was performed on long-standing diabetics with clinical signs of autonomic neuropathy and delayed gastric emptying (Table 1).

Table 1. The effect of chronic administration of levosulpiride (L) versus placebo on the glycemic control of IDDM subjects after 6 months

	Glycemic control (Hb_{A1c} %, $P < 0.01$)	Mean daily glycemia (mmol/l, $P < 0.05$)	Gastric emptying time (min, $P < 0.001$)
Placebo	6.7 ± 0.4	10.9 ± 0.8	321 ± 14
L	5.7 ± 0.3	8.8 ± 0.4	261 ± 9

Results showed the importance of gastric emptying in the maintenance of glycemic control and the usefulness of chronic administration of levosulpiride in diabetic subjects with gastroparesis.[17]

IBS WITH CONSTIPATION

Irritable bowel syndrome (IBS) affects 3-20% of the population and it is characterized by a symptom complex of abdominal pain and abnormal bowel habits that present as diarrhea or constipation, and general physical weakness.

Traditional laxatives are often ineffective, especially in more severe constipation over the long term. The mainstay of intervention is treatment with prokinetics and high-fiber diets for constipation.[18] **A partial 5-HT_4 receptor agonist has been approved by the FDA and other regulatory agencies for the treatment of women with constipation-predominant IBS**

(C-IBS) or functional constipation.[19,20]

LEVOSULPIRIDE VS DOMPERIDONE

Levosulpiride was compared with domperidone for treatment of functional dyspepsia. **Both drugs had a positive influence on dyspeptic symptoms and on gastric and gallbladder emptying, but the latter parameters were improved significantly more effectively by levosulpiride.**[21]

Domperidone possesses cardiac electro-physiological effects similar to those of cisapride and class III antiarrhythmic drugs. Therefore, domperidone should not be considered a no-risk alternative to cisapride, a drug withdrawn from the US market.[22]

LEVOSULPIRIDE VS CISAPRIDE

The effects of levosulpiride and cisapride on the gastric emptying rate and on symptoms were evaluated in dyspeptic patients with functional gastroparesis. The efficacy of levosulpiride was similar to that of cisapride in significantly shortening ($P < 0.001$) the $t_{1/2}$ of gastric emptying. **The impact of symptoms on patients' everyday activities and the improvement of some symptoms such as nausea, vomiting and early satiety was more evident with levosulpiride than cisapride.**[23]

LEVOSULPIRIDE AS AN ANTI-EMETIC

Levosulpiride has an antiemetic activity which is 3-8 times more potent than the racemic form and the d-isomer. Its mode of action is partially central (inhibition of dopaminergic receptors at the trigger zone for vomiting) and partially peripheral (normalization of motor

activity of stomach and gall-bladder).[24]

The antiemetic efficacy of levosulpiride was compared to metoclopramide in a double-blind, randomized, crossover study (Table 2).

There was a carry-over effect in favor of levosulpiride. Data indicates that both levosulpiride and metoclopramide reduce nausea and vomiting, but levosulpiride is more effective.[25]

Levosulpiride is found to be effective in the prevention of chemotherapy-induced and post-operative vomiting as well as in the treatment of nausea and vomiting during hepatic, biliary and gastroduodenal disorders, organic and functional dyspepsia, motion sickness and vertigo

Another study was done to test two different antiemetic regimens for preventing nausea and vomiting in patients undergoing systemic chemotherapy (Fig.1). This study showed that both the levosulpiride based and metoclopramide based combinations resulted in a high percentage of complete protection from emesis.

Both regimens were well tolerated; however, when both antiemetic regimens were administered at a higher dose, the levosulpiride-based

Table 2. The antiemetic efficacy of levosulpiride (L) vs metoclopramide (M)

	L	M
	(mean value/day/patient)	
Hours with nausea (P = 0.002)	1.08	2.01
Nausea intensity (P = 0.0004)	0.76	1.42
Vomiting episodes (P = 0.002)	0.38	0.70
	(%)	
Complete control of nausea (P = 0.0034)	84.6	42.3
Vomiting disappeared (P = 0.041)	81.5	51.8

combination showed significantly lower toxicity (p = 0.035).

The higher incidence of side effects observed with metoclopramide makes the levosulpiride based regimen preferable for patients receiving chemotherapy.[26]

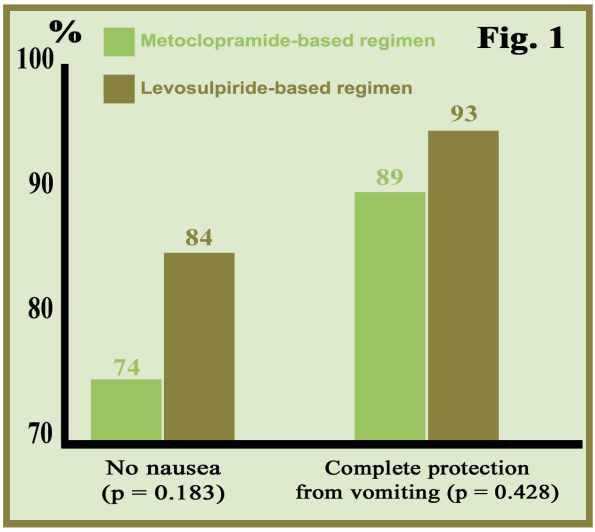


Fig. 1

CONTRAINDICATIONS

- Levosulpiride is contraindicated in patients with known hypersensitivity or intolerance to the drug.
- Because of the possible correlation between the hyperprolactinemia effect of the dopaminergic antagonists and the apparition of mammary dysplasia, it should not be used in patients with malignant mastopathy.
- Do not use during presumed or confirmed pregnancy, nor lactation period, since adequate and controlled studies have not been made on pregnant and lactating women.

GENERAL PRECAUTIONS

- Levosulpiride must not be used when stimulation of GI motility can be hazardous, for example, in presence of GI hemorrhages, mechanical obstructions or perforations.
- It is recommended to be cautious when administering Levosulpiride

altogether with alcohol intake, since it can produce an increase in the sedative effects of alcohol.

- Levosulpiride can cause somnolence or sedation and dyskinesia in some patients; if some of these symptoms appear, avoid driving a vehicle or machinery.
- Special caution is recommended in case of administering Levosulpiride together with psychopharmaceutical drugs, since an increase of undesired effects may occur.

SECONDARY AND ADVERSE REACTIONS

- Treatment with levosulpiride is well tolerated and adverse events may include galactorrhea, somnolence, fatigue, hyperprolactinaemia, extrapyramidal dystonic reactions and headache.[27]

INTERACTIONS

- The effects of Levosulpiride on gastric motility can be antagonized by anticholinergic drugs, narcotics and opioid analgesics, that is, if administered together, Levosulpiride's gastroprokinetic efficacy can be decreased.
- Association with psychopharmaceutical drugs require special precautions and monitoring to avoid undesired and unexpected effects because of interactions. High doses can produce hyperprolactinemia, therefore special control during treatment is advised.

CARCINOGENESIS, MUTAGENESIS, TERATOGENESIS AND FERTILITY EFFECTS

Both the acute, subacute, chronic and local toxicity trials, and the studies on reproduction toxicity, mutagenic potential and oncogenic/

carcinogenic potential, demonstrate that levosulpiride is well tolerated at doses higher than those effective in human therapy. Moreover, the findings from the experimental studies on levosulpiride lead to exclude the toxicity from accumulation, tolerance, dependence or withdrawal syndrome. [28]

LEVOSULPIRIDE PHARMACOLOGY SUMMARY

Indications:	Gastro-oesophageal reflux disease, Irritable bowel syndrome, Dyspepsia, Diabetic Gastroparesis.
Dosage:	Adult: 25 mg tid with meals.
Elderly:	**Dose reductions may be necessary.**
Contraindications:	Phaeochromocytoma, epilepsy, manic states, hyperprolactinaemia, mammary dysplasia, malignant mastopathies, cardiac impairment. GI bleeding, mechanical obstruction or perforation.
Special Precautions:	May impair ability to drive or operate machinery. Pregnancy and lactation.
Adverse Drug Reactions:	Amenorrhoea, gynaecomastia, galactorrhoea, changes in libido. **Potentially Fatal:** Neuroleptic malignant syndrome.
Drug Interactions:	Reduced bioavailability with sucralfate, aluminium- and magnesium- containing antacids. **Effect on GI motility may be antagonised by anticholinergic agents, narcotics and analgesics.** Avoid alcohol.
Plasma half-life:	6 to 8 hours (oral)

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Volapride-25

Levosulpiride 25 mg Tab.

Superior To Itopride

Parameters	VOLAPRIDE-25 (Levosulpiride)	ITOPRIDE
Prokinetic efficacy	**Increases motility of both solids & liquids**	Increases motility of liquids only
Anti-emetic action	✓	✗
Per day therapy cost	**Less**	More

Superior To Domperidone And Metoclopramide

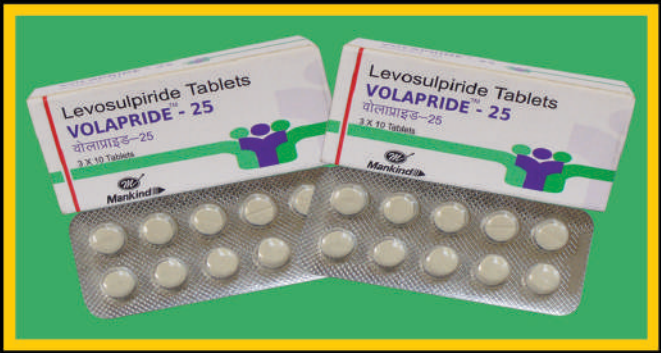
Parameters	VOLAPRIDE-25	Domperidone	Metoclopramide
Anti-emetic & Prokinetic efficacy	**More**	Less	Less
Site of Prokinetic action	**Entire gut**	Upper gut	Upper gut
Role in IBS - constipation	**Yes**	No	No

Volapride-25

Levosulpiride 25mg Tab.

₹3.50/ Tab.

- Unique antiemetic and prokinetic effects
- Faster relief of postprandial bloating, epigastric pain and heartburn
- High percentage of complete protection from emesis
- Valuable addition as adjunct therapy when others fail



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