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RESEARCH ARTICLE

ITOPRIDE: A PROKINETIC AGENT WITH DUAL MODE OF ACTION AND POSITIVE SAFETY PROFILE FOR THE MANAGEMENT OF UPPER GASTROINTESTINAL DYSMOTILITY DISORDERS

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ABSTRACT

Background: Patients with upper GI motility disorders encounter functional dyspepsia (FD) and gastroparesis as commonly occurring syndromes associated with gastric motor dysfunction. **Aim:** The aim of the present review is to provide a comprehensive view of the literature regarding the clinical efficacy and safety profile of itopride in the treatment of upper GI dysmotility disorders such as FD and gastroparesis. **Methods:** A literature search was performed using electronic databases like Pubmed/Medline to identify relevant articles from 1998 to 2014. The search yielded around 20 original studies and review articles from which relevant data was extracted. **Results:** Itopride improved postprandial fullness, bloating and global patient assessment scores compared to control groups (domperidone, mosapride or placebo) in patient with FD. Itopride at the dose of 50 mg, TDS when assessed by LDQ scores demonstrated significantly better symptomatic relief and improvement as compared to placebo. Furthermore, itopride reported moderate to complete relief of epigastric pain, nausea, heartburn and anorexia in about 73-85% of patients. Itopride has shown positive effect on gastric emptying and gastroduodenal motility by accelerating solid and liquid gastric emptying in gastroparesis patients. In the studies summarized for this secondary publication, no serious adverse events such as extrapyramidal symptoms or prolongation in QT interval have been observed with the use of itopride. **Conclusion:** Overall, based on the findings of studies, it can be concluded that itopride provides good therapeutic benefits in management of upper GI dysmotility disorders with a positive safety profile.

INTRODUCTION

Dysmotility is a condition where the intestinal tract loses its ability to coordinate the muscular contractions of the bowel giving rise to a number of clinical disorders such functional dyspepsia, gastroparesis, gastroesophageal reflux disease (GERD), irritable bowel syndrome, chronic intestinal pseudo-obstruction, diffuse esophageal spasm, and chronic idiopathic constipation.[1,2]Patients with upper GI motility disorders are commonly encountered in clinical practice. Of these, functional dyspepsia and gastroparesis are among the commonly occurring syndromes associated with gastric motor dysfunction.[3] Functional dyspepsia (FD) is a functional gastrointestinal disorder[3] which is a consequence of multiple pathophysiological mechanisms such as abnormal gastric motility, impaired fundic accommodation and gastric and duodenal hypersensitivity to acid [4]. As many as 60% of FD patients have gastric dysmotility.[5] Over the last years the definition of FD has undergone significant changes. On the basis of the most recent Rome IV definition, FD is defined as the presence of bothersome dyspeptic symptoms (early satiation, postprandial fullness, epigastric pain or burning) thought to originate from the gastroduodenal region, in the absence of any organic disease that is likely to explain the symptoms.[6] The Rome consensus has also proposed a distinction between meal-induced symptoms and meal-unrelated symptoms. Thus, FD now consists of two main diagnostic categories: i) meal-induced dyspeptic symptoms [postprandial distress syndrome (PDS)], characterized by postprandial fullness and early satiation, and ii) epigastric pain syndrome (EPS), characterized by epigastric pain and burning[6]

Globally the majority of the patients suffering from dyspepsia, accounting for approximately 5% of primary care patients, reside into the category of FD.[7] In a multi-center Asian study of 1,115 patients with uninvestigated dyspepsia from nine countries, 43% had FD after investigation.[8] Data on FD from India is sparse however, based on the limited data available, it may be concluded that about 7.6%-49% of the Indian population suffer from dyspeptic symptoms. This variation could largely be attributed to variation in criteria used to diagnose FD or due to geographic differences.[9]

Functional dyspepsia places a heavy burden on society[10] and has a significant impact on health related quality of life specifically in patients who experience significant levels of somatic symptoms such as abdominal pain and chronic fatigue that interrupt daily activities, as well as among those who experience considerable anxiety and demonstrate abnormal health-care-seeking behaviour.[11] Findings from a recent large observational study reported that FD negatively impacted domains describing physical, mental, and social aspects of health-related quality of life in the general population. [12] Additionally, findings of studies from Asian countries have also reported that FD is associated with substantial impairment of quality of life, work absenteeism, reduced productivity and use of health care resources, all of which can increase the economic burden of the condition.[13] Gastroparesis is a symptomatic chronic disorder of the stomach characterized by delayed gastric emptying in the absence of mechanical obstruction.[14] Gastroparesis typically affects patients of the female sex. It has significant impact on quality of life[15,16,17] increases direct health-care costs through hospitalizations, emergency room, or doctor visits, and is associated with morbidity and mortality.[18,19] Diabetes mellitus is the most common systemic disease associated with gastroparesis. Though diabetic gastroparesis is traditionally associated with type 1 diabetes with poor glycemic control, it is now being increasingly recognized in patients with type 2 diabetes.[20] In a population-based survey of 423 patients with diabetes (94.8% type 2 diabetes), a significantly higher incidence of upper gastrointestinal symptoms in patients with diabetes were reported.[21] The most frequently reported symptoms of gastroparesis include nausea, vomiting, early satiety and postprandial fullness.[15] Abdominal discomfort and pain also are noted by many, it affected patients and represent challenging symptoms to treat.[22] Weight loss, malnutrition and dehydration may be prominent in severe cases. In diabetics, gastroparesis may adversely affect glycemic control. The prevalence of gastroparesis is difficult to assess accurately as studies usually reflect single center experience, as well as there is some overlap between gastroparesis and functional dyspepsia as both symptoms and gastric emptying test results may meet definitions for both in a subset of patients.[14,23] However, by modeling the likelihood of gastroparesis based on the symptoms of general population, a recent study reported the prevalence of gastroparesis to be between 2%-4% in the general population which is consistent with the earlier study demonstrating a significant increase in the number of hospitalization for gastroparesis.[24,25,26]

In India, Itopride and Levosulpiride are approved for treatment of FD and gastroparesis.[87,88] Moreover, clinical use of prokinetic agents, such as domperidone, Metoclopramide and mosapride have also been noted. Furthermore, a recent meta-analysis by Hiyama T, *et al* showed a significant treatment benefit in favor of prokinetic agents in patients with FD.[27] Prokinetic agents represent a heterogeneous group of drugs that realize their effect through an effect on 5-HT receptors, dopamine D2 receptors (DD2Rs), or motilin and ghrelin receptors.[28] Following the withdrawal of cisapride due to its cardiacside effects, mosapride is widely used and believed to be devoid of pro-arrthythmic potential. However, one publication describes a case report where mosapride has been shown to give rise to torsades de pointes when used along with flecainide in presence of hypokalemia.[29] Cisapride and mosapride share the same metabolic pathway (cytochromeP450 enzyme system) and have been reported to have drug interaction potential with other commonly used drugs like macrolides, antifungals, etc.[30] Likewise, domperidone- a dopamine antagonist with antiemetic and gastroprokinetic properties - has also shown increased risk of QT prolongation and received safety alerts from Health Canada[31] and European Medical Agency (EMA).[32] EMA's Pharmacovigilance Risk Assessment Committee (PRAC) reviewed domperidone-containing medicines for symptoms of nausea, vomiting, fullness, abdominal discomfort and heartburn in 2014 and recommended its use to relieve symptoms of nausea and vomiting, restricting dose and length of the treatment. Further, PRAC recommended that domperidone should no longer be authorized to treat bloating or heartburn.[33] Moreover, D2 receptor antagonists crossing the blood brain barrier (BBB) viz. Metoclopramide, Levosulpiride etc. are known to cause CNS side effects like extrapyramidal symptoms such as dystonia, akathasia, tardive dyskinesia and parkinsonism which includes atypical involuntary muscle contraction affecting posture, movement and walking.[34,35,37,38,39] The blockade of dopamine transmission in nigrostriatal system is supposed to be likely cause for these side effects.[36] Thus, new agents that do not interfere with activity of central D_2 receptors and do not cross blood-brain barrier are desirable.[40] The prokinetic agent itopride works by both antagonizing dopamine D2 receptors and inhibiting the activity of acetylcholinesterase. It not only stimulates the release of acetylcholine, but also inhibits its degradation thereby promoting gastrointestinal motility. Thus itopride exhibits a dual effect on the motility of the GI tract and is not reported to cause extrapyramidal side effects - possibly because its high polarity largely prevents it from crossing the BBB.[28] The objective of present review article is to outline in detail the clinical efficacy and safety profile of itopride in the treatment of upper GI dysmotility disorders such as FD and diabetic gastroparesis.

METHODS

A literature review was performed using electronic databases such as Pubmed/Medline to identify relevant articles using relevant search terms for functional dyspepsia, gastroparesis, itopride, prokinetic agents. From this search, publications that met the following criteria:-original contributions of itoprider andomized control trials, observational studies, along with the review articles, systematic reviews and meta-analyses and reports limited to clinical human data that were published in the English language have been included in the review. Case reports and case series were not included in the review. All articles considered were published in the scientific literature. Full text articles of relevant abstracts were assessed and evaluated. The search yielded around 20 original studies (randomized controlled, open and observational), systematic reviews and meta-analysis evaluating clinical efficacy and/or safety of itopride in the management of gastric motility disorder.

Mechanism of Action of Itopride

Itopride is a novel orally active gastroprokinetic agent, whose main effect is influencing oesophageal peristalsis, stimulating gastric motility, and stimulating gastric emptying, with a positive influence on gastroduodenal coordination. Itopride has a dual effect on the motility of the GI tract. A stimulatory effect on the motility of the GI tract is mediated both by DD2R antagonist properties and by inhibiting the degradation of

acetylcholine.[38,39] Dopamine is a substance with an inhibitory effect on the motility of the GI tract.[40] D2 receptors are located predominantly in the upper digestive tract, particularly in the oesophagus and stomach, where the effect of itopride can be exhibited. The second mechanism of itopride activity is inhibition of acetylcholinesterase. Acetylcholinesterase inhibition increases the amount of acetylcholine at nerve synapses. The result is an increase in the motility of the oesophagus and stomach, including emptying.[41] Itopride dual action , i.e. influencing D2 receptors and inhibition of acetylcholinesterase, was demonstrable throughout the entire alimentary tract.[39] The effect of itopride is an increase in acetylcholine concentration, which increases the lower oesophageal sphincter (LOS) pressure, promotes gastric motility, accelerates gastric emptying, and improves gastroduodenal coordination.[42] Itopride has also shown its prokinetic effects on both the ileum and colon via inhibitory effects on acetylcholinesterase and antagonistic effects on dopamine receptor.[40]

Pharmacokinetic Characteristics of Itopride

Itopride is rapidly and almost completely absorbed from the gastrointestinal tract when administered orally. Relative bioavailability is calculated to be 60% due to liver first pass metabolism.[43] The peak plasma concentration is achieved within 35 minutes of oral administration.[28,42] Approximately 96% of Itopride hydrochloride is bound to plasma proteins. Albumin accounts for most of the binding.[44] Itopride has extensive tissue distribution, except in the tissues of CNS.[44] As itopride is highly polar molecule, it does not cross the blood-brain barrier readily.[45] Itopride undergoes extensive hepatic metabolism in humans.[43] It is metabolized in the liver by N-oxidation to inactive metabolites by a flavin-dependent mono-oxygenase (FMO3). Biotransformation of itopride does not involve the cytochrome P450 enzyme system unlike cisapride.[44] Thus, itopride is not associated with significant drug interaction with drugs that are also metabolized by cytochrome P450 like erythromycin, clarithromycin, antidepressants, antihypertensives, antidiabetics and ketoconazole.[44] Itopride hydrochloride and its metabolites are primarily excreted in the urine.[28,42].[42] The plasma half-life of itopride is about 6 hours.[44]

Clinical Efficacy of Itopride

Itopride in Functional Dyspepsia

Itopride is a commonly used prokinetic drug in the management of symptomatic FD patients. A recent meta-analysis evaluated the effect of itopride compared to domperidone, mosapride, and placebo in subjects with a diagnosis of FD. Data were analyzed from nine well designed randomized placebo controlled trials (RCT) involving a total of 2,620 individuals of which 1,372 were treated with itopride at the dose of 50mg TID each and 1,248 constituted the control group, who were treated with drugs such as domperidone, mosapride, or placebo. The effect of therapy in the group treated with itopride was significantly higher when compared with the control group. Individuals in the itopride group reported statistically significant improvement inpost-prandial fullness (RR: 1.21; 95% CI: 1.03-1.44; p=0.02), early satiation (RR: 1.24; 95% CI: 1.01-1.53; p=0.04), and global patient assessment scores (RR: 1.11; 95% CI: 1.03-1.19; p=0.006) compared to control group.[47] Further to support this data, study by Chojnacki C *et al* reported that, post-prandial distress syndrome and epigastric pain syndrome significantly improved in 70.3% and 56.0% patients after 4 weeks of itopride treatment.[35] From this study it can be concluded that itopride is an effective option for managing the symptoms of functional dyspepsia, especially the syndrome of early satiety and postprandial fullness.

In 2006, results of a prospective, randomized, multicenter study evaluating the results of itopride therapy in a representative sample of 523 persons, meeting the Rome II criteria, were published.[46] The studied subjects were randomized into three groups with a different dosing schedule. The first group received 50 mg of itopride TID, the second group 100 mg of itopride TID, and the third group was administered 200 mg of itopride TID. The study lasted for 8 weeks and factors evaluated were, the effect of therapy on changes in symptoms of dyspepsia determined using a standardized Leeds Dyspepsia Questionnaire (LDQ) and overall effect of therapy as reported by the patient himself/herself. All three doses of itopride demonstrated significantly better symptomatic relief and improvement when compared with placebo. Overall analysis revealed that itopride was significantly superior to placebo, with the greatest symptom-score improvement in the 100mg and 200 mg groups (-6.24 and -6.27, vs. -4.50 in the placebo group; p=0.05). Quality of life of patients in the itopride group was also better than those receiving placebo (mean score on the Nepean Dyspepsia Index: 18.0 $\pm$21.9 vs 13.2 $\pm$19.4; p=0.02). Similarly, results from two placebo-controlled, randomized controlled study involving 1170 FD patients reported a significant benefit of itopride over placebo for LDQ responders in International trial (62% vs. 52.7%; p=0.04) but not in North American trial (46.9% vs. 44.8%),[7] The most common adverse events reported were abdominal pain, diarrhea, constipation, and nausea.[46]

Similarly, findings from another randomized clinical trial reported that itopride use provided significantly more symptomatic relief to FD patients compared to those receiving domperidone (81% vs. 70%, p>0.05).[48] Itopride did not significantly improve epigastric discomfort compared to domperidone (RR: 1.00; 95% CI: 0.88-1.14; p=0.98)[47]but when a combined end point of epigastric pain and fullness was used in another randomized control trial, the itopride arm yielded a greater response rate than the placebo group (73% vs. 63%, p=0.04).[46] This could be a result of itopride's action of increasing postprandial gastric receptive relaxation[38]and gastrointestinal motility.[49] Further, findings from study by Otsubo T *et al*, reported that itopride demonstrated improved subjective symptoms by 72.7% while tachygastria (Increased electrical pacemaker activity of the stomach, 3.7 - 10 cycles per minute in this study, measured by Electrogastrography) showed significant decrease from pre to post administration of itopride(20.4% to 7.8%).[50] These findings are further supported by results from a prospective, multicenter, post-marketing observational study with 587 FD patients. Patients were prescribed itopride 50 mg TDS before meals for 4 weeks. Treatment response rate after 1 week of therapy in patients with ROME III criteria for functional dyspepsia were 35.50% and 75.15% after 4 weeks. No serious adverse reactions have been observed in this study.[51]

Furthermore, results from studies conducted among Indian patient population report itopride as an efficacious drug in the management of upper GI dysmotility disorders.[52-56] Findings

from a randomized and placebo-controlled study, in a group of 67 people with FD, who met the Rome II diagnostic criteria reported that the symptom score (assessed using Dyspepsia severity index of De Luca *et al*) of people of patients treated with itopride (50 mg, TID) was positively influenced (9.3 vs. 14.4, p=0.0004) in contrast to the placebo-treated group. The same study also reported subjective assessment of global relief which was significantly higher in the itopride group (11 of 33 patients) in comparison to placebo (1 of 34 patients).[52]Further to support this data, another randomized, comparative study reported moderate to complete relief of symptoms in 100% patients treated with itopride as compared to 53% patients treated with metoclopramide.[53] In two open-label, non-comparative study, itopride reported moderate to complete relief of symptoms such as epigastric distention or pain, nausea, heartburn, and anorexia assessed using a 5-point scalein about 73%-85% of patients.[54,55] Global efficacy rate as reported by a randomized study comparing itopride and mosapride reported excellent to good efficacy rate in significantly more number of patients in itopride group as compared to mosapride (93.3% vs. 63.33%, p<0.05).[56] Further to support this data, a post marketing surveillance study from India among 2,108 FD patients demonstrated that 49.64% patients reported global efficacy of itopride as excellent, 39.24% patients reported global efficacy as good, while 9.49% and 1.63% reported global efficacy of itopride as fair and poor respectively.[44] Thus, this post marketing study conducted in a larger population clearly indicates that itopride is efficacious in FD patients.

With respect to the impact of itopride treatment on quality of life, findings from a meta-analysis using two well designed placebo controlled RCTs reported that patients receiving itopride showed significant improvement on the dyspepsia severity score (mean score improvement:1.38; 95% CI:-1.75-1.01; p<0.01) measured using the LDQ compared to those receiving placebo.[47] This finding is further supported by data from a study that reported significant improvements (p<0.05)on the SF-36 mental health scale score, Gastrointestinal Symptom Rating Scale (GSRS) and indigestion syndrome score post administration of itopride compared to pre-administration.[57]

Itopride in diabetic gastroparesis

Prokinetic agents stimulate the contraction of the smooth muscle of the gastric wall, thereby affecting gastric emptying.[28]Itopride has been observed to have a positive effect on gastric emptying and gastroduodenal motility in humans. Two RCTs reported that itopride accelerates solid (p=0.09) and liquid (p=0.09) gastric emptying compared to placebo (p<0.03) and pantoprazole (p<0.001).[58,59] Furthermore, to support this data, a retrograde study in chronic gastritis Japanese patients wherein 50 mg itopride or placebo was administered 30 minutes prior to ingestion of drink containing 1.5g acetaminophen, reported that itopride accelerated gastric emptying.[60] Similarly, in two other Japanese study, 150 mg itopride administered for 2 weeks to diabetic gastroparesis patients reported that itopride significantly accelerated gastric emptying of a meal containing radiopaque capsules and acetaminophen compared to pre-treatment levels.[61,62] Conversely, in another study itopride reduced total gastric volume without accelerating gastric emptying or orocecal transit in healthy volunteers.[38]

In a recent study involving 34 type 1 diabetes mellitus patients (T1DM) when evaluated with ^{13}C-octanoic acid breath test reported, statistically significant decrease in the amount of time (T½) needed for gastric emptying (89.0 min to 53.0 min, p<0.001) after 6 weeks of itopride therapy indicating an accelerated gastric emptying in T1DM with delayed gastric emptying. Moreover, clinical symptoms such as heartburn (p=0.013) and diarrhea (p=0.005) significantly reduced after 6 weeks of itopride therapy.[63] Since the most convincing evidence for acceleration of transit by drugs has been detected in patients with delayed gastric emptying and not in healthy individuals with normal gastric emptying, the absence of an effect of itopride on gastric emptying in healthy volunteers needs further evaluation.[38] Furthermore, itopride showed a significant decrease in postprandial (222.40 mg/dl) blood sugar level in type 2 diabetes mellitus (T2DM) patients compared to placebo (222.40 mg/dl vs.331.8 mg/dl).This may be because delayed gastric emptying in T2DM patients decreases incretin release which in turn decreases early insulin response resulting in post prandial glucose surge and addition of itopride before meal facilitate food delivery to intestine, increasing incretin secretion and thus minimizing post prandial glycemic excursion.[64] However, another recent study in T1DM patients reported no change in the glycemic control parameters between itopride and control group.[63] Furthermore, a post marketing surveillance study in India among 573 delayed gastric emptying patients reported global efficacy of itopride as excellent (44.5%), good (40.14%), fair (13.61%) and poor (1.75%).[65] Table 1outlines the efficacy of itopride.

Safety and Tolerability Profile

Findings from several studies have reported itopride to be well tolerated by FD and diabetic gastroparesis patients. [47] The most commonly occurring adverse events as observed in patients with itopride group were abdominal pain, nausea, diarrhea, constipation with dizziness and drug eruption rarely being reported. No serious adverse events such as extrapyramidal symptoms, galactorrhoea or prolongation in QT interval were reported, however, though significant increase in prolactin levels was noticed, no association with any clinical symptoms was observed.[7,38,46,48,51,58,87] Further to support this data, findings from a randomized and placebo-controlled study, in a group of 67 people with FD, who met the Rome II diagnostic criteriareported that in the group with strictly set selection criteria, itopride proved to be an effective drug with positive safety profile. None of the treated individuals showed abnormal ECG changes in terms of prolongation of the QT segment, which is a known limitation of cisapride therapy in functional dyspepsia.[52] Findings from two randomized studies comparing itopride with controls (metoclopramide and mosapride) reported no change in QT interval and adverse events in itopride group as compared to control group which reported diarrhea, constipation, dizziness, fatigue, leg pain and headache as the adverse events.[53,56] Furthermore, two open-label non-comparative studies reported no prolongation of QT on ECG and no abnormalities in serum biochemistry.[54,55] In addition to this, findings from a study conducted on healthy volunteers, reported no statistically significant change in the QT interval when treated with itopride indicating it to be devoid of any abnormal effect on QT interval and unlikely to cause cardiac arrhythmias or ECG changes.[66] Similar results were observed in three other randomized clinical study which reported itopride to be well tolerated without causing any

Table 1 Clinical Efficacy of Itopride

Author	Study design	Sample size	Treatment arms	Result
Itopride in Functional Dyspepsia				
Chojnacki C *et al*.[35]	Open-label	52	Itopride	Itopride improved post-prandial distress syndrome and epigastric pain syndrome in 70.3% and 56.0% patients respectively.
Ganaton Post Marketing Surveillance study group [44]	Post marketing surveillance	2,108	Itopride	Global efficacy of itopride reported as excellent 49.64% patients, good in 39.24%, fair in 9.49% and poor in 1.63% patients
Holtmann G *et al*.[46]	RCT	554	Itopride vs. placebo	In patients with functional dyspepsia 50mg, 100mg, 200mg itopride and placebo yielded 57%, 59%, 64% and 41% patients' symptom free respectively. Itopride was reported to be significantly superior to placebo, with the greatest symptom-score improvement (p=0.05). Itopride yielded a greater response rate than placebo (73% vs. 63%, p=0.04)
Huang X *et al*.[47]	Meta analysis study	2,620	Itopride vs. domperidone	Itopride improved Postprandial fullness- RR:1.21 (95%CI:1.03-1.44, P=0.02) Early satiation- RR:1.24 (95%CI: 1.01-1.53, P=0.04) LDQ scores- WMD:-1.38 (95%CI: -1.75 to -1.01, P<0.01) Itopride had similar effect for epigastric discomfort-RR: 1.00 (95%CI: 0.88-1.14, P=0.98)
Sawant P *et al*.[48]	RCT	56	Itopride vs. domperidone	Complete symptomatic relief was observed in 81% patients in itopride group compared to 70% patients in domperidone group.
Otsubo T *et al*. [50]	-	11	Itopride	Itopride improved subjective symptoms by 72.7%.
Sun J *et al*.[51]	Prospective observational study	587	Itopride	75.15% treatment response rate was observed after 4 weeks with Itopride. Difference in the total symptom score before and after treatment was -5.62±3.27 corresponding to a 69.23±26.53% reduction from baseline (p<0.001).
Saji S *et al*.[52]	Randomized double-blind placebo-controlled study	67	Itopride vs. placebo	Symptom score significantly decreased in itopride group compared to placebo (9.3 vs. 14.4, P=0.0004) Itopride showed significant improvement in global assessment relief compared to placebo (11 patients vs. 1 patient)
Kamath S *et al*.[53]	Single-blind randomized comparative study	60	Itopride vs. Metoclopramide	Itopride showed moderate to complete relief of symptoms in 100% patients treated with itopride and 53% patients treated with metoclopramide
Shenoy KT *et al*.[54]	Open-label non comparative study	30	Itopride	Itopride showed moderate to complete symptom relief in 73% patients at the end of 2 weeks.
Kumar RA *et al*.[55]	Open-label non comparative study	36	Itopride	Itopride showed moderate to complete symptom relief in 85% patients at the end of 2 weeks.
Amrapurkar DN *et al*.[56]	Double-blind randomized comparative study	60	Itopride vs. Mosapride	Itopride reported global efficacy rate in significantly more number of patients than mosapride group (93.3% vs. 63.33%, P<0.05)
Chiba T etal. [57]	HRQoL	-	Itopride	Itopride significantly improved the SF-36 mental health scale, GSRS indigestion syndrome score and constipation syndrome score (p < 0.05).
Itopride in diabetic gastroparesis				
Stevens JE *et al*. [58]	Double-blind randomized	25	Itopride vs. placebo	Itopride accelerated both solid (p=0.09) and liquid (p=0.09) gastric emptying. Emptying with placebo was slower (solids: r=0.39, p=0.057; liquids: r=0.44, p<0.03).
Venkatesh V *et al*. [59]	Open label clinical trial	743	Itopride with pantoprazole	Itopride in combination with pantoprazole indicated a significant improvement in the severity and frequency of all the symptom parameters of the disease (p<0.001)
Budennaya I Yu *et al*. [63]	Randomized prospective open-label comparative study	34	Itopride vs. control	Significant decrease in the amount of time needed for delayed gastric emptying: 89.0 min to 53.0 min Decrease in the symptoms of intestinal dyspepsia (p=0.005)
Shah MA *et al*. [64]	Comparative study	100	Itopride vs. placebo	Itopride showed a significant decrease in post prandial glucose level compared to placebo (222.40 mg/dl vs. 331.8 mg/dl)
Ganaton Post Marketing surveillance study group. [65]	Post marketing surveillance study	573	Itopride	Global efficacy of itopride as excellent (44.5%), good (40.14%), fair (13.61%), and poor (1.75%)

serious side effects or discontinuation of the therapy in FD as well as gastroparesis patients.[30,38,58]A post marketing surveillance study conducted in India among FD patients reported itopride to be well tolerated in the management of FD with its global tolerability rated as excellent in 65.09% patients, good in 33.90% patients, and poor in 1.01% patients. The most common adverse events reported were diarrhea, dizziness, constipation and itching. The causality for these adverse events as judged by the investigators was not related to Itopride for 26 (16.3%) adverse events; possibly related to Itopride for95 (59.4%) adverse events; probably related to Itopride for 32 (20%) adverse events and definitely related to Itopride for 7 (4.3%) adverse events.[44] Similarly, another post marketing surveillance study in diabetic gastroparesis patients from India reported mild to moderate adverse events such as diarrhea, dizziness, abdominal pain, fatigue and insomnia and no severe adverse events with global tolerability of itopride rated as excellent in 62.65% patients, good in 36.65% patients and poor in 0.7% patients. The causality for these adverse events as judged by the investigators was not related to Itopride for 9 (27.27%) adverse events; possibly related to Itopride for 20 (60.61%) adverse events; probably related to Itopride for 4 (12.12%) adverse events and none of the adverse event were definitely related to Itopride.[65] As seen in several randomized clinical trials, itopride has shown more favorable efficacy and tolerability profile than the prokinetic agents such as metoclopramide or Levosulpiride, possibly because the

Table 2 Safety of Itopride

Author	Study design	Sample size	Treatment arms	Result
Adverse events reported under treatment with Itopride in functional dyspepsia				
Talley NJ *et al.*[7]	RCT	1170	Itopride vs. placebo	The safety and tolerability profile were comparable with placebo, with the exception of prolactin elevations, which occurred more frequently on itopride (18/579) than placebo (1/591).
Chojnacki C *et al*.[35]	Open-label	52	Itopride	Itopride showed few adverse events such as diarrhea, dizziness, increased salivation and facial flushing No changes in ECG were recorded
Holtmann G *et al*. [46]	RCT	554	Itopride vs. placebo	Abdominal pain, diarrhea, nausea, and constipation were the most frequently reported events Serious adverse events during the treatment period were seen in 2.8 percent of the patients in the placebo group and 1.2 percent of patients in the overall active-treatment group. Prolactin levels significantly increased during treatment with 100 mg and 200 mg of itopride given three times daily. Treatment with itopride was not associated with any electrocardiographic changes; in particular, there was no prolongation of the corrected QT interval.
Ganaton Post Marketing Surveillance study group [44]	Post marketing surveillance	2,108	Itopride	Global tolerability reported as excellent in 65.09% patients, good in 33.90% patients, and poor in 1.01% patients Adverse events reported were diarrhea, dizziness, constipation and itching.
Huang X *et al.*[47]	Meta analysis study	2,620	Itopride vs. domperidone, mosapride, placebo	Itopride treatment was well tolerated, few adverse events reported in patients in Itopride group were abdominal pain, diarrhea, nausea and constipation.
Sawant P *et al.*[48]	RCT	56	Itopride vs. domperidone	Itopride did not cause prolongation of QT interval nor any abnormality in any serum biochemistry values.
Sun J *et al.* [51]	Prospective observational study	587	Itopride	Nine patients (1.54%) had adverse events: four were probably related to the study drug (diarrhea [two cases], abdominal pain, drug eruption), three were possibly related (diarrhea [two cases], dizziness) and two were not related No adverse reactions were serious enough to warrant discontinuation of therapy.
Saji S *et al*.[52]	Randomized double-blind placebo-controlled study	67	Itopride vs. placebo	Itopride showed no prolongation of QT interval.
Kamath S *et al*.[53]	Single-blind randomized comparative study	60	Itopride vs. Metoclopramide	No adverse events reported in itopride treated group while one patient in metoclopramide reported moderate abdominal pain No abnormalities in serum chemistry or ECG observed
Shenoy KT *et al*.[54]	Open-label non comparative study	30	Itopride	Itopride exhibited excellent tolerability in 93% patients and good in 7% patients. No prolongation of QT on ECG observed No abnormality in haemogram or serum chemistry observed
Kumar RA *et al*.[55]	Open-label non comparative study	36	Itopride	Five patients reported adverse events such as headache, loose stool, giddiness, abdominal pain, and burning micturition. No prolongation of QT on ECG observed No abnormality in haemogram or serum chemistry observed
Amarapurkar DN *et al*.[56]	Double-blind randomized comparative study	60	Itopride vs. Mosapride	Tolerability of itopride versus mosapride reported as excellent 76.7% vs 26.7% ($P<0.05$) and poor in 0% vs. 20% None of the patients in itopride group reported any adverse events while five patients in mosapride group reported diarrhea, dry mouth fatigue, constipation, dizziness, and headache as adverse events.
Adverse events reported under Itopride treatment in diabetic gastroparesis				
Stevens JE *et al*.[58]	Double-blind randomized	25	Itopride vs. Placebo	No serious adverse events were reported.
Ganaton Post Marketing Surveillance study group [65]	Post marketing surveillance study	573	Itopride	Mild to moderate adverse events such as diarrhea, dizziness, abdominal pain, fatigue and insomnia and no severe adverse events reported. Global tolerability rated as excellent (62.65%), good (36.65%), and poor (0.7%).

polarity of itopride largely prevents it from entering the brain or the CNS. Further, when compared to prokinetic agents like cisapride, itopride does not have affinity for the 5-HT4 receptors in the heart that are implicated in the undesirable cardiac effects of cisapride. Clinically significant metabolic interactions are not to be expected since itopride is primarily metabolized by flavine monooxygenase and not by Cytochrome P450.[30] Table 2 lists safety profile of itopride in functional dyspepsia and diabetic gastroparesis.

Summary

Dysmotility is a term used to describe a variety of symptoms that occur when the gut does not function properly at moving its contents like food, tablets etc. Dysmotility occurs when the intestinal tract loses its ability to co-ordinate the muscular contraction of the bowel. Symptoms vary from one person to another in type and severity.[68]

Functional dyspepsia is a term used for a set of different symptoms, including epigastric discomfort, bloating, nausea, anorexia, postprandial fullness, belching, heartburn, and regurgitation. The fundamental requirement is to distinguish whether these symptoms are due to organic changes of the upper digestive tract, or whether it is functional dyspepsia, present in about 60% of patients with dyspeptic symptoms. In addition to this a wide range of dyspeptic symptoms reflect the high prevalence of functional disorders of the GI tract.[4,69] Gastroparesis also referred to as delayed gastric emptying is a disorder that slows or stops the movement of the food from stomach to small intestine. Gastroparesis occurs when the vagus nerve is damaged by illness or injury and the stomach muscles stop functioning normally causing food to move slowly from the stomach to the small intestine or stops moving altogether. Delayed gastric emptying is present in 20%-40% of patients with functional dyspepsia.[70]

One of the class of the drugs that are indicated and/or used for the treatment of functional dyspepsia symptoms and gastroparesis include prokinetic agents. Itopride is indicated in adult patients with functional dyspepsia, in patients with dyspeptic symptoms(i.e. early satiation, postprandial fullness, epigastric pain or burning),and in patients of diabetic gastroparesis with marked delay in gastric emptying, when these symptoms are present in the absence of structural or biochemical abnormalities and detected by routine diagnostic methods.[48] The therapeutic effect of itopride is connected with its dual effect, consisting in influencing the levels of the enzyme acetylcholinesterase, which consequently affects the level of acetylcholine. This results in increasing the contractility of the smooth muscle of the stomach wall through a D2 receptor which may facilitate gastric motility and gastric emptying. At the same time, itopride affects dopaminergic innervation of the smooth muscle of the upper GI tract by blocking DD2Rs; itopride is rapidly absorbed, and its peak serum concentration occurs 35 minutes after oral administration.[71]Itopride exhibits good tolerability in both young adult patients as well as elderly patients. A pre-registration trial undertaken in Japan and India reported approximately equivalent adverse events (2.45% and 6.14%) respectively. Post marketing surveillance study reported itopride to be well tolerated by a majority of patients with only 3.6% patients reporting adverse events which extends the safety findings of pre-registration trial and confirms that itopride is well tolerated when used in large population.[44] No clinical symptoms affecting the central nervous system and no change in ECG or in laboratory investigations were reported in the publications assessed for the purpose of this review.[35]

CONCLUSION

Overall, based on the findings of studies summarized in this paper, it can be concluded that itopride has good therapeutic benefits in management of upper GI dysmotility disorders with a positive CNS and cardiac safety profile. However, because of the existence of heterogeneity, large well-controlled studies with consistent indicators are probably warranted to further validate the safety and efficacy of itopride in real-world clinical settings.

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