Original Article

A Prospective Multicentric Postmarketing Observational Study to Characterize the Patient Population with Reduced Gastrointestinal Motility among Indian Diabetic Patients Receiving Itopride: The Progress Study

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Abstract

Aims: This study was intended to assess the clinical profile of Indian diabetic patients with reduced gastrointestinal (GI) motility and to understand the role of itopride in addressing reduced GI motility (gastroparesis) symptoms and maintaining glycemic control. **Material and Methods:** Patients with established reduced GI motility (scintigraphy), with varying degree of GI symptoms, receiving itopride 150 mg as per physicians' discretion were enrolled. Clinical profile, changes in symptom severity, glycemic indices, tolerability, and quality of life (QoL) after 8-week therapy (Patient assessment of upper GI disorders-QoL [PAGI-QoL]) were assessed. **Results:** Mean ± standard deviation age of enrolled population (n = 41) was 51.8 ± 12.39 years. Average duration of gastroparesis since underlying etiology was 67.7 ± 59.76 months. Common symptoms reported at baseline were bloating (68.3%), postprandial fullness (61.0%), nausea (51.2%), early satiety (41.5%), heartburn (39.0%), and vomiting (9.8%). Itopride therapy resulted in significant improvement in all symptoms ($P < 0.001$), which correlated with improved QoL (PAGI-QoL score reduction: 13.8 ± 11.48; $P < 0.0001$). Moreover, significant improvement in glycemic indicators was also evident (mean change from baseline hemoglobinA1c –0.5 ± 1.18; fasting plasma glucose –15.3 ± 43.61; postprandial plasma glucose –24.6 ± 57.20). **Conclusions:** Itopride showed effectiveness in addressing symptoms of reduced GI motility in diabetics, with improved QoL. Significant improvement in glycemic indices was also evident posttreatment with itopride. This study sheds light on the role of prokinetics, not only for symptom relief but also for improving glycemic control in diabetic patients with reduced GI motility, thus providing a holistic approach for the management of these patients.

Keywords: *Diabetes mellitus, gastroparesis, glycemic indices, hemoglobin A1c, itopride*

Introduction

India is recognized as the "Diabetes Capital of the World" with about 72.9 million diabetic patients, which is projected to reach 134.3 million by 2045.[1] Reduced gastrointestinal (GI) motility or (diabetic) gastroparesis is one of the common secondary complications associated with long-standing diabetes mellitus, largely because of autonomic neuropathy, which may result in postprandial glycemic surge.[2] It affects nearly 20%–50% of patients with type-1 and type-2 diabetes.[3]

Gastric emptying plays an important role in blood glucose homeostasis. The rate of gastric emptying is a predeterminant of the initial postprandial glycemic response, and delayed gastric emptying can cause postprandial hypoglycemia in insulin-treated individuals. Diminished incretin response due to delayed gastric emptying may contribute to impaired insulin secretion in patient with diabetes, resulting in poor glycemic control. Moreover, the absorption kinetics of drugs could also be influenced by changes in gastric emptying. Poor glycemic control in turn can exacerbate neuropathy, thereby reducing GI motility.[2,4-6] The American College of Gastroenterology and American Gastroenterological Association guidelines recommend the use of prokinetics for their ability to intervene or arrest this vicious cycle thereby improving glycemic control.[4-6] The prokinetic agent – itopride works by both, antagonizing dopamine D_2 receptors and inhibiting the activity of acetylcholinesterase. It not only stimulates the release of acetylcholine but also inhibits

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its degradation thereby promoting GI motility. Thus, itopride exhibits a dual effect on the motility of the GI tract and is not reported to cause extrapyramidal side effects,[7-9] possibly because of its high polarity which may largely prevent it from crossing the blood–brain barrier.[7]

Clinical studies have shown the safety and efficacy of itopride for conditions associated with reduced GI motility in diabetes.[8,9] A double-blind randomized study reported acceleration of solid and liquid gastric emptying in itopride group compared to the placebo group in patients with diabetic gastroparesis.[10] Similarly, few other studies exhibited significant decrease in the time of gastric emptying[7] and postprandial glucose level after itopride therapy.[2] Moreover, in combination with pantoprazole, a significant improvement in the severity and frequency of all symptoms was reported in diabetic gastroparesis patients.[11]

Nevertheless, there is a paucity of data on the use of itopride in Indian diabetic patients characterized with reduced GI motility. Hence, this study was intended to assess the clinical profile of Indian diabetic patients with reduced GI motility and to understand the role of itopride in addressing GI symptoms and maintaining glycemic control. The quality of life (QoL) of these patients and tolerability profile of itopride was also assessed.

Subjects and Methods

Study design and patient population

This multicentric, prospective study was conducted between September 2017 and April 2018 across six centers in India (Jaipur, Bhopal [2 centers], Guwahati, Hyderabad, and Ahmedabad). Diabetic patients (males and females) between 18 and 65 years of age, diagnosed with reduced GI motility through gastric scintigraphy conducted within 6 months of enrolment, who presented with varying degrees of symptoms of reduced GI motility for at least 12 weeks (not necessarily continuous) and prescribed itopride 150 mg (Ganaton® OD, Abbott India Ltd.) were enrolled in the study. Patients with obstructed gastric outlet, small bowel, or colon, GI hemorrhage or perforation; severe cardiac, hepatic, neurological, or renal diseases; or any other condition, which in the opinion of the clinician/investigator could interfere significantly with the treatment and assessment process were excluded from the study. Pregnant or lactating women and patients already undergoing treatment with itopride or any other prokinetic agents were also excluded. Contraindications to itopride treatment as per the local approved label (including known hypersensitivity); participation in any other interventional trial within the last 30 days of enrollment; and unwillingness to adhere to the protocol, or comply with 8-week follow-up visits and provide written authorization were other exclusion criteria.

The study protocol was approved by Institutional Ethics Committees and conducted in accordance with the principles of Declaration of Helsinki, International Council on Harmonization Good Clinical Practice (GCP) guidelines, and Indian regulatory guidelines (Indian Council of Medical Research and Indian GCP guidelines). All patients provided written consent in the patient authorization form to participate in the study.

Study endpoints

The primary study endpoints were to evaluate the demographic characteristics of Indian diabetic patients with reduced GI motility and to assess the proportion of physicians prescribing itopride due to various reasons. The secondary endpoints included change in severity and frequency of clinical signs and symptoms and change in total Patient assessment of upper GI disorders-QoL (PAGI-QoL) score from baseline to week 8. In addition, change in glycemic indicators (hemoglobin [Hb] A1c, fasting plasma glucose [FPG], postprandial plasma glucose [PPG]), and safety/tolerability from baseline to week 8 after itopride therapy were also assessed.

Study assessment tool – patient assessment of upper gastrointestinal disorders-quality of life and symptoms severity score

Disease (reduced GI motility)-specific QoL was assessed by the PAGI-QoL survey with scoring on a 6-point Likert scale. The questionnaire was administered by a physician or designee. It was used to assess the patients' health-related QoL within the last 2 weeks.[12] It consisted of 30 items assessing five domains: daily activities, clothing, diet and food habits, relationship, and psychological well-being and distress.[13,14] The PAGI-QoL provides numerical values for QoL in patients with disordered gut motility.[15] Each symptom was scored based on its severity; mild = 1, moderate = 2, severe = 3, and extremely severe = 4, and the mean scores at each visit were compared to understand the effect of itopride therapy from baseline to week 8.

Statistical methods

No formal sample size calculation was done for this study. Continuous variables were summarized using descriptive statistics n (number of patients), mean and standard deviation (SD). Summary of categorical data was evaluated through numbers and percentages. PAGI-QoL questionnaire was assessed by 2 sample *t*-test. The statistical analysis was done using Statistical Analysis System® version 9.4 software.

Results

Demographic and baseline characteristics

Forty-one patients met the inclusion criteria of this study, which included 19 males (46.3%) and 22 (53.7%) females [Table 1]. The mean ± SD (Min: Max) age, weight, height, and body mass index (BMI) of all study

patients was 51.8 ± 12.39 years (24.0:65.0), 69.9 ± 8.62 kg (48.0:87.4), 162.7 ± 8.10 cm (143.2:176.0), and 26.5 ± 3.77 kg/m^2 (19.2:42.6), respectively. Based on the Kuppuswamy socioeconomic classification, over 60% (25/41) patients were from upper middle class, while approximately 30% (12/41) were from lower middle class.

The mean ± SD (minimum:maximum) duration of diabetes mellitus of all enrolled patients was 81.4 ± 65.38 months (4.0:262.0). Average duration of gastroparesis development was 67.7 ± 59.76 months (3.0:244.0). All patients were diagnosed with confirmed gastroparesis.

Change in symptoms severity and different rationale of prescribing itopride

All enrolled patients presented one or more of the classical symptoms of reduced GI motility at baseline visit [Table 2]. Most patients (28 [68.3%]) reported bloating at baseline of either moderate or severe nature. After 4 weeks (visit 2) and 8 weeks (visit 3) of itopride treatment, the number of patients presenting with symptoms was reduced, with none having severe symptoms. Twenty-five (61.0%) patients presented with postprandial fullness of moderate (13 [52.0%]) and severe (11 [44.0%]) nature at baseline. Notably at visit 2, patients presenting with severe symptoms were only 3 (17.6%), which reduced to none by visit 3. Fourteen (66.7%) of 21 (51.2%) patients who presented with nausea at baseline had severe symptoms. Remarkably, 50% patients completely recovered after 4 weeks of itopride treatment, while after 8 weeks of treatment, none presented with severe nausea any more.

Similar observations were noted in patients presenting other symptoms such as early satiety, heartburn, and vomiting at baseline with a significant reduction in the number of patients and symptom severity after 4 and 8 weeks of itopride treatment. As a result, significant ($P < 0.001$) improvement in severity or complete recovery of the symptom(s) was recorded [Table 3].

Different rationale for prescribing itopride by the physicians was studied. Most physicians prescribed itopride for its efficacy (19 [46.4%]) while others prescribed it for its rapid symptomatic relief (12 [29.2%]) or as a standard of care (10 [24.4%]).

Patient assessment of upper gastrointestinal disorders-quality of life score

The mean total score reduction at visit 8 from baseline was – 13.8 ± 11.48, suggesting a significant ($P < 0.0001$) improvement in patient's QoL [Figure 1].

Glycemic indicators

We observed a significant improvement in each of the glycemic indicators (mean change from baseline HbA1c – 0.5 ± 1.18 ($P < 0.001$); fasting glucose – 15.3 ± 43.61; and postprandial glucose – 24.6 ± 57.20; $P < 0.001$) after 8 weeks of itopride treatment [Table 4 and Figure 2a, b].

Safety

No adverse drug reactions were reported during the study.

Discussion

This study enrolled 41 patients from 6 centres across India based on the study inclusion criteria. Mean ± SD age of the enrolled population was 51.8 ± 12.39 years which was in accordance with a study conducted in Pakistan that

Table 1: Summary of patient demographics and baseline characteristics

Parameters	Overall (*n*=41)
Gender, *n* (%)	
Male	19 (46.3)
Female	22 (53.7)
Age (years), mean±SD (minimum:maximum)	51.8±12.39 (24.0:65.0)
Weight (kg), mean±SD (minimum:maximum)	69.9±8.62 (48.0:87.4)
Height (cm), mean±SD (minimum:maximum)	162.7±8.10 (143.2:176.0)
BMI (kg/m^2), mean±SD (minimum:maximum)	26.5±3.77 (19.2:42.6)
Socioeconomic status*	
Lower class, *n* (%)	0
Upper lower class, *n* (%)	3 (7.3)
Lower middle class, *n* (%)	12 (29.3)
Upper middle class, *n* (%)	25 (61.0)
Upper class, *n* (%)	1 (2.4)
Total score, mean±SD	18.0±4.57
Age at diagnosis of reduced GI motility (years), mean±SD (minimum:maximum)	51.1±12.34 (23.0:65.0)
Duration of DM (months) (T2DM), mean±SD (minimum:maximum)	81.4±65.38 (4.0:262.0)
Duration for development of reduced GI motility (months) since the underlying etiology, mean±SD (minimum:maximum)	67.7±59.76 (3.0:244.0)

*Kuppuswamy classification. SD: Standard deviation; DM: Diabetes mellitus; T2DM: Type 2 DM; GI: Gastrointestinal; BMI: Body mass index

Table 2: Summary of signs and symptoms of patients with reduced gastrointestinal motility

Sign and symptoms of reduced GI motility	Baselin (*n*=41), *n* (%)	Week 4 (*n*=41), *n* (%)	Week 8 (*n*=41), *n* (%)
Nausea	21 (51.2)	15 (36.6)	13 (31.7)
Mild	1 (4.8)	2 (13.3)	6 (46.2)
Moderate	5 (23.8)	6 (40.0)	7 (53.8)
Severe	14 (66.7)	7 (46.7)	0
Extremely severe	1 (4.8)	0	0
Vomiting	4 (9.8)	3 (7.3)	1 (2.4)
Absent	37 (90.2)	38 (92.7)	40 (97.6)
Rare (once/week)	0	2 (66.7)	0
Occasional (2-3 times/week)	4 (100.0)	1 (33.3)	1 (100.0)
Postprandial fullness	25 (61.0)	17 (41.5)	21 (51.2)
Mild	0	5 (29.4)	18 (85.7)
Moderate	13 (52.0)	9 (52.9)	3 (14.3)
Severe	11 (44.0)	3 (17.6)	0
Extremely severe	1 (4.0)	0	0
Early satiety	17 (41.5)	16 (39.0)	13 (31.7)
Mild	0	4 (25.0)	12 (92.3)
Moderate	5 (29.4)	10 (62.5)	1 (7.7)
Severe	10 (58.8)	2 (12.5)	0
Extremely severe	2 (11.8)	0	0
Bloating	28 (68.3)	18 (43.9)	18 (43.9)
Mild	0	6 (33.3)	13 (72.2)
Moderate	14 (50.0)	11 (61.1)	5 (27.8)
Severe	14 (50.0)	1 (5.6)	0
Anorexia	3 (7.3)	3 (7.3)	3 (7.3)
Mild	0	0	3 (100.0)
Moderate	0	3 (100.0)	0
Severe	3 (100.0)	0	0
Heartburn	16 (39.0)	16 (39.0)	13 (31.7)
Mild	0	4 (25.0)	12 (92.3)
Moderate	5 (31.3)	10 (62.5)	1 (7.7)
Severe	10 (62.5)	2 (12.5)	0
Extremely severe	1 (6.3)	0	0

GI: Gastrointestinal

Table 3: Summary of symptoms by severity based on score (*n*=41)

Symptoms	Baseline	Week 4	Week 8	*P*
Nausea	2.714±0.64	2.333±0.72	1.538±0.52	<0.001
Postprandial fullness	2.520±0.59	1.882±0.70	1.143±0.36	<0.001
Early satiety	2.824±0.64	1.875±0.62	1.077±0.28	<0.001
Bloating	2.500±0.51	1.722±0.57	1.278±0.46	<0.001
Anorexia	3.000±0.00	2.000±0.00	1.000±0.00	0.0183
Heartburn	2.750±0.58	1.875±0.62	1.077±0.28	<0.001
Vomiting	1.600±0.89	1.333±0.58	1.000±1.41	0.632

Symptom severity was scored as; Mild: 1; Moderate: 2; Severe: 3; Extremely severe: 4

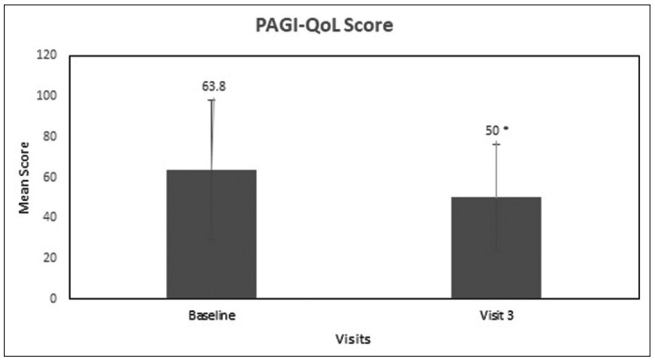

Figure 1: Patient assessment of upper gastrointestinal disorders-quality of life score (*n* = 41), patient assessment of upper gastrointestinal disorders-quality of life instrument consisted of 30 items, each with response options based on a 6-point Likert scale, **P* < 0.0001 compared to baseline

reported the mean age of patients with reduced GI motility as 50 years, while another study of US reported the mean age as 42.4 years.[2,16]

Reduced GI motility (gastroparesis) in diabetics is reported to be common in females,[17] which was observed in our study as well. The mean ± SD weight, height, and BMI of overall patients were 69.9 ± 8.62 kg, 162.7 ± 8.10 cm, and 26.5 ± 3.77 kg/m^2, respectively. Our findings are in line with other studies which have reported that most diabetic patients with reduced GI motility were obese with higher BMI.[17-19]

Table 4: Summary of glycemic indicators (*n*=41)

Glycemic indicators	Baseline	Week 4	Change from baseline to week 4	Week 8	Change from baseline to week 8
HbAlc					
Mean±SD	7.8±1.12	7.5±0.91	−0.3±1.12	7.3±0.87	−0.5±1.18
P			0.010		<0.001
Fasting plasma glucose (mg/dl)					
Mean±SD	143.4±60.89	134.8±38.23	−8.6±43.84	128.1±27.34	−15.3±43.61
P			0.074		0.004
Postprandial plasma glucose (mg/dl)					
Mean±SD	211.4±62.48	193.0±44.91	−18.4±52.87	186.8±40.54	−24.6±57.20
P			0.006		0.004

SD: Standard deviation; HbAlc: Hemoglobin A1c

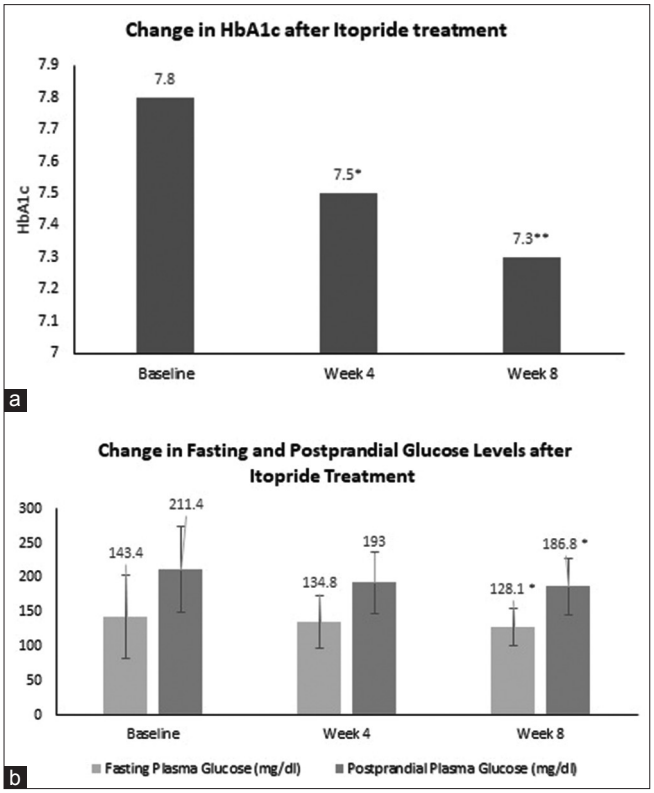

Figure 2: (a) Change in hemoglobin A1c after itopride treatment, *P < 0.05, **P < 0.001 compared to baseline. (b) Change in fasting and postprandial glucose levels after itopride treatment, *P = 0.004 compared to baseline

In our study, average duration of gastroparesis development since the underlying etiology was found to be 67.7 ± 59.76 months. Kashyap and Farrugia reported disease duration of diabetes as a risk factor for developing gastroparesis.[6] Some patients may develop gastroparesis within few years of onset of diabetes, while others may take longer time depending on their glycemic control.[4]

The classical symptoms of reduced GI motility in diabetics observed at baseline were bloating, postprandial fullness, nausea, early satiety, heartburn, vomiting, and anorexia, which is in agreement with the published literature.[3] Moreover, our study demonstrated a significant improvement in symptoms of reduced GI motility after 4 and 8 weeks of itopride treatment, reiterating the findings from earlier studies.[7,11]

In addition, this is the first study to assess different rationales for prescribing itopride by Indian clinicians. Efficacy of itopride was the key reason for using the same which is well established by studies performed by Venkatesh and Kulkarni[11] and Budennaya *et al*.[7] These observations revalidate the efficacy of itopride as a prokinetic agent.

Reduced GI motility in diabetes is known to affect patients' QoL significantly due to the primary disease and associated symptoms and complications. The PAGI-QoL questionnaire was used to assess the effect of itopride treatment on patients' QoL.[12] Our study demonstrated that there was a significant (P < 0.0001) improvement in patients' QoL after 8 weeks itopride therapy, primarily due to its ability to induce rapid symptomatic relief.[20]

Our study demonstrated a positive role of itopride in improving glycemic indices (HbA1c, fasting, and postprandial glucose level), thus offering profound benefits in diabetes management. A study by Abid Shah *et al*.[2] demonstrated that addition of itopride before meals facilitates food delivery to the intestine, increases incretin secretion, and thus improves the glycemic parameters. Thus, our findings further confirm the role of itopride in improving glycemic control in diabetic patients, besides offering symptom relief.

Itopride was found to be well tolerated, with no adverse drug reactions reported during the study. This observation support the positive benefit-risk profile of itopride as also highlighted in published literature.[20]

Our study has several strengths. First, this was a first of its kind Pan-India study that demonstrated itopride mediated symptomatic relief in diabetic patients with reduced GI motility. Second, patients of varying age and socioeconomic status were evaluated. This study has used standard and validated methods for diagnosis of delayed gastric emptying, giving credibility to results obtained.

Further, all the questionnaires used in the study were administered to the patients by a physician or a designee, which enabled to capture information with greater accuracy and confidentiality. However, this study also has some limitations. First, the study was conducted for 8 weeks, and hence, long-term outcome data are lacking. Second, this was an observational study; hence, no control group was present for comparative analysis.

Conclusions

Itopride showed effectiveness in addressing symptoms of reduced GI motility in diabetics, with improved QoL. Significant improvement in the glycemic indices such as HbA1c, FPG, and PPG was also evident posttreatment, which could be attributed to the positive effects of itopride in facilitating gastric emptying, thus restoring altered kinetics of food and drug absorption. This study sheds light on the role of prokinetics, not only for symptomatic relief but also for improving glycemic control in diabetic patients with reduced GI motility, thus providing a holistic approach for the management of these patients.

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This study was funded by Abbott India Ltd.

Conflicts of interest

Dr Rooprai, Dr Choubal, Dr Agarwal, Dr Khaliq, Dr Farishta, Dr Harwani, and Dr Kumar received research funding from Abbott India Ltd.

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