Itopride in the Treatment of Dysmotility-like Functional Dyspepsia: A Randomized, Placebo-Controlled Trial

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ABSTRACT

Background and Objectives: The treatment of patients with functional dyspepsia remains unsatisfactory, though prokinetic drugs are widely used for treatment of functional dyspepsia. We designed a randomized, placebo-controlled trial to assess the efficacy and safety of a new prokinetic drug itopride hydrochloride, a dopamine D2 antagonist with anti-acetylcholinesterase effects, in patients with dysmotility-like functional dyspepsia.

Methods: Sixty-seven eligible patients were enrolled and were randomly assigned to receive either itopride 10 mg three times a day or placebo for a period of 4 weeks. Patients were re-assessed at 2 and 4 weeks for improvement in dyspepsia-specific symptom score (pain/discomfort, fullness, bloating, early satiety, and nausea/vomiting), global symptom score and the effect on subjective global assessment of relief. Adverse events also were recorded.

Results: The symptom scores prior to treatment were comparable in the both groups. After completion of 2-week and 4-week treatment, the symptom scores were significantly lower in the itopride group compared to the placebo group (11.2 ± 4.0 vs 15.03±4.2; \( p = 0.0003 \)) and (9.3±4.1 vs 14.4±5.8; \( p = 0.0004 \)), respectively. The subjective assessment of global relief was significantly higher in the itopride group (11 of 33 patients) compared to 1 of 34 patients in the placebo group.

Conclusions: Itopride is superior to placebo in the treatment of functional dyspepsia having bloating and fullness as their predominant symptoms. It can be used safely in this subset of patients where proton pump inhibitors may not be very effective. (J Dig Endos 2010;1(4):171-75)

Keywords: Itopride - Functional dyspepsia - Placebo

Introduction

Chronic or relapsing dyspeptic symptoms that occur in absence of clinically identifiable structural lesions are called functional dyspepsia. Dyspepsia is a common problem encountered in clinical practice. Dyspepsia by definition is not one symptom but a constellation of symptoms which include bloating, early satiety, post prandial fullness, nausea, anorexia, heartburn, regurgitation and burping. Treatment approaches that have been tested include use of anti secretory agents, prokinetic agents and H.pylori eradication. But the benefits of such approaches have been modest. About 40% of patients with functional dyspepsia suffer from delayed gastric emptying or disturbed gastrointestinal function which is believed to play a role in development of symptoms. Meta-analysis by Moayyedi et al demonstrated that patients with dysmotility symptoms (bloating, early satiety, post prandial fullness) do not respond to anti secretory treatment. In this sub group of patients prokinetic agents like cisapride has demonstrated superiority over placebo. But safety profile of these agents are major concern which restricts their use. So there is a strong need for identifying an effective
and safe prokinetic agent.

Itopride is one such drug with gastroprokinetic action due to its dual mode of action viz. dopamine D2 receptor antagonist and acetylcholine esterase inhibition.\(^{11}\) This will lead to increased levels of acetylcholine in upper gastrointestinal tract leading to stimulation of gastric motility.\(^ {12}\) As itopride has no affinity for 5HT4 receptors it has no undesirable cardiac effects.\(^ {13}\) Since it is not metabolized by cytochrome p450 enzyme it does not have any significant drug interactions.\(^ {14}\)

Little is known about the dose response of itopride in these functional dyspepsia patients with dysmotility symptoms as their predominant complaint. Efficacy of itopride in various populations also has to be determined.\(^ {15}\)

Hence we aimed to study the efficacy and safety of itopride in patients with functional dyspepsia having bloating and post prandial fullness as their predominant symptom.

**Materials and Methods**

**Study design**

The present study was a randomized double blind placebo-controlled trial conducted in the Department of Gastroenterology between January 2006 to December 2006. The study was approved by institutional ethics committee. All patients enrolled for the study gave written informed consent for the study.

**Patient populations**

Patients who satisfied Rome II criteria\(^ {16,17}\) in the age group of 18 to 60 yrs with predominant bloating and post prandial fullness were eligible for the study. Functional dyspepsia was diagnosed if persistent upper abdominal discomfort was present. Discomfort was characterized by presence of early satiety, post prandial fullness and bloating present for at least 12 weeks in a period of 12 months, without an identifiable structural or biochemical abnormality to which it can be attributed.

Exclusion criteria were: organic gastrointestinal or systemic diseases; diabetes mellitus; pregnancy or lactation; previous abdominal surgery (except appendectomy); mental disorders; and the use of drugs interfering with gastrointestinal motility, cardiac disease, hypersensitivity reactions, predominant reflux symptoms, unwilling for follow up and those on medication altering gut function (macrolides). Consecutive patients who satisfied the strict inclusion criteria were only included.

**Dyspeptic symptom scoring**

Before the patients could be included in the trial, demographic data and baseline symptoms were recorded in a proforma. Individual symptoms were assessed using modified mean global severity index (Dyspepsia severity index of De Luca et al)\(^ {18}\) a validated scoring system. A total of five following symptoms were evaluated prior to enrolment and 2-week and 4-week after treatment: (1) upper abdominal pain or discomfort (2) post prandial fullness, (3) bloating, (4) early satiety and (5) nausea/vomiting. Each symptom was graded according to the intensity and frequency on a 4-point score from zero to three. Adding together we get the total score of each symptom and adding all the scores we get the global dyspepsia symptom score. By dividing the global dyspepsia symptom score by 5 we get the mean global dyspepsia score. The intensity of discomfort was scored as: 0, no discomfort; 1, mild discomfort; 2, moderate discomfort; and 3, severe discomfort. The frequency was scored as: 0, never; 1, 1-2 days a week; 2, 3–4 times per week; 3, 5 or more times per week.

A complete physical examination and routine blood investigations (hemogram, blood glucose, urea and creatinine, liver function tests, serum electrolytes) were done to rule out organic diseases. All the patients underwent upper gastrointestinal endoscopy and ultrasonography to rule out a structural cause for the symptoms. Electrocardiogram was performed before the drug was administered and corrected QT interval calculated.

**Randomization and blinding**

Randomization was done using random table allocation. Group A received Itopride 50mg thrice daily half an hour before major meals (itopride group) and Group B received identical looking placebo tablets three times daily before major meals in a double blind fashion for 4 weeks (placebo group). The drugs were dispensed only for 2 weeks at a time so as to check the dyspepsia symptom score, side-effects and compliance by means of pill count at review visit.

**Outcome measures**

Patients were reviewed every 2 weeks. At each visit symptom scores were calculated and subjective global assessments of relief of symptoms were also calculated. Any adverse events occurring were also recorded. At the end of 4 weeks an ECG was taken. If at review patient had intractable symptoms only antacids were allowed to take.

Subjective global assessment (SGA) of relief\(^ {19}\) was assessed by answering following questions. Please consider how you felt in the past 2 weeks with regard to your functional dyspepsia symptoms in particular overall well being and symptoms of abdominal discomfort, bloating, post prandial fullness, early satiety and nausea. Compared to the way you usually felt before entering the study, how would you rate your relief of symptoms during past 2 weeks? Possible answers were: completely relieved; considerably relieved; some what relieved; unchanged; or worse.

Bloating and fullness are considered as two most important symptoms of functional dyspepsia evaluated in our study. We evaluated the severity of bloating and fullness after food intake as important end points. Only those who became completely symptom free and markedly improved were
Outcome variables – change in symptom score and SGA of relief at 2 and 4 weeks of treatment were the outcome variables assessed in our study.

**Statistical analysis**

It was done using SPSS version 10. Data were expressed as mean ± SD. Comparison between itopride and placebo was done using paired ‘t’ test and Wilcoxon signed rank test. *p* value of less than 0.05 was accepted as statistically significant.

**Results**

Ninety-two patients were screened for the study; of them 67 patients with predominant bloating and post prandial fullness were included in the study. Thirty-three patients were randomly assigned to receive itopride and 34 were assigned to receive placebo. There were seven drop outs, three in the itopride and four in the placebo groups. Six of them (3 each in itopride and placebo groups) did not return for follow up. One patient had met with an accident. The data reported are only for the intent-to-treat population. An overview of the trial is illustrated in Figure 1. The baseline demographics of the patients were comparable in both treatment groups (Table 1).

**Response to treatment**

The symptom scores prior to the initiation of treatment was comparable in both groups (16.9±3.7 in the itopride group and 16.7±4.3 in the placebo group). After 2 weeks of treatment the symptom score was significantly lower (11.2±4.0) in itopride group compared to the placebo group (15.03±4.2; *p* = 0.0003). After completion of treatment the decrease in symptom score was significant (*p*=0.0004) with 9.3±4.1 in the itopride group and 14.4±5.8 in the placebo group. (Figure 2)

**Subjective global assessment of relief**

After 2 weeks of treatment 5 patients in itopride group and one patient in placebo group had grade 1 or 2 SGA of relief. After completion of treatment 11 patients in itopride group and one patient in placebo group had significant improvement in symptoms assessed by SGA of relief.

**Adverse events**

No major adverse effects were noted during the study. Two patients in the itopride group developed adverse effects consisting of aphthous ulceration and abdominal discomfort in one patient each. Constipation occurred in five patients in the placebo group. ECG taken prior to treatment and after treatment did not show any prolongation of corrected QT interval.

**Discussion**

Disturbance in gastrointestinal motility and sensory function are believed to play a key role in development of symptoms in patients with functional dyspepsia.

Itopride is known to exert prokinetic effect by way of...
antidopaminergic and anti acetylcholine esterase action and so have effects on gastric accommodation and gastric hypersensitivity. The symptoms of bloating and post prandial fullness are linked to gastric accommodation and hypersensitivity. Hence itopride giving significant relief of bloating and fullness in patients with functional dyspepsia is tenable.

There are only very few randomized double blind placebo controlled trials of itopride available in the literature. Most of the studies are on patients with functional dyspepsia. None of the studies have compared the efficacy of itopride in subgroup of patients with predominant bloating and fullness. That too in one of the large studies, itopride had shown significant improvements in symptoms of functional dyspepsia.23

But some studies did not report significant difference in relief of symptom when compared to placebo.2 This may be due to inclusion of all patients with functional dyspepsia instead of those with predominant motility. There are no studies available in the literature in which itopride has been tried in the subgroup of patients with dysmotility symptoms. Itopride has also been compared with domperidone25 as well as with mosapride26 and was found to have better efficacy and tolerability.

This trial had strict entry criteria (only those with predominant bloating and fullness) and application of valid outcome measures. Those with predominant reflux symptoms were excluded from the study, as they may have response to prokinetics.

The data shows that itopride is effective in this subgroup of functional dyspepsia patients when compared to placebo. We observed a statistically significant difference in symptom score of patients with functional dyspepsia (predominant bloating and distention) in the itopride group when compared to the placebo group as early as 2 weeks after initiation of treatment. This statistically significant difference in the symptom score persisted at completion of treatment. Our results showed an advantage for itopride in patient’s overall satisfactory relief from functional dyspepsia symptoms measured by SGA of relief, a validated efficacy measure that assess the impact of treatment on functional dyspepsia related symptoms.

**Conclusion**

In summary results of our study shows that itopride is superior to placebo in the treatment of functional dyspepsia having bloating and fullness as their predominant symptoms. It can be used safely in this subset of patients where proton pump inhibitors may not be very effective.

**References**


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