A PROKINETIC AGENT WITH A DUAL EFFECT – ITOPRIDE – IN THE TREATMENT OF DYSMOTILITY

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Disclosure: Authors declare that they have nothing to disclose.
Received: 12.09.14 **Accepted:** 17.10.14
Citation: EMJ Gastroenterol. 2014;3:42-47.

ABSTRACT

A wide range of dyspeptic symptoms in clinical practice reflect the high prevalence of functional disorders of the gastrointestinal (GI) tract. Prokinetic agents are the current mainstay in the therapy of functional dyspepsia. One of these drugs is itopride. We evaluated therapeutic efficacy of itopride according to the literature review. The therapeutic potential of itopride is connected with a dual effect: influencing of enzyme acetylcholinesterase activity and blocking dopamine D2 receptors. After the itopride administration, the contractility of smooth muscle in the upper GI tract increases. Itopride is a drug with rapid absorption from the small bowel; its peak serum concentration occurs 35 minutes after oral administration. Itopride does not pass the blood-brain barrier and does not affect the heart rate by influencing the QT segment. Itopride is a safe prokinetic agent with positive influence on the symptoms of functional dyspepsia such as postprandial fullness, bloating, and gastric emptying. Itopride could also be used for the therapy of the mild form of gastro-oesophageal reflux.

Keywords: Gastro-oesophageal reflux, gastric motility, gastroduodenal coordination, functional dyspepsia, prokinetic agents, itopride, dopamine D2 receptor, acetylcholinesterase.

INTRODUCTION

Patients with impaired gastric motility rank among the most examined groups of patients. The physiological gastric motor function includes the ability of the stomach to act as a reservoir of food during food intake, gastric emptying, and coordination of interdigestive motility.[1] Functional dyspepsia and gastroparesis are the main syndromes associated with gastric motor dysfunction. Failure of gastric emptying was demonstrated in 30% of patients with functional dyspepsia.[2] The concept of functional dyspepsia is the relationship between psychosocial and physiological factors, functional gastrointestinal (GI) symptoms, and clinical outcome. Early in life, genetic as well as environmental factors may affect psychosocial development and the development of gut dysfunction. A crucial role is played by the brain-gut axis. Persons with high life-stress, coexisting psychosocial comorbidities, or maladaptive coping could develop a syndrome, e.g. postinfectious dyspepsia. There is no doubt that genetics, environmental factors, and psychosocial factors significantly influence physiological functions of the GI tract (motility, sensation, inflammation, and bacterial flora).

Therapy aimed at correction of the symptoms of functional dyspepsia and gastroparesis is medically based on the effect of drugs referred to as prokinetic agents. GI prokinetic agents stimulate the contraction of the smooth muscle of the gastric wall, thereby affecting gastric emptying. Prokinetic agents represent a heterogeneous group of drugs that realise their effect through an agonistic effect on 5-HT receptors, dopamine D2 receptors (DD2Rs), or motilin and ghrelin receptors. This group also includes a prokinetic agent of a new generation, having the dual effect on motility - itopride.

CHARACTERISTICS OF ITOPRIDE

Itopride is a prokinetic agent with a slight antiemetic effect, 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.[3] Dopamine is a substance with an inhibitory effect on the motility of the GI tract.[4] D2 receptors are located only 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.[5] Dependence on the administered dose of the substance has been proven; this observation is important, when in the experiment the overall effect of itopride, i.e. influencing D2 receptors and inhibition of acetylcholinesterase, was demonstrable throughout the entire alimentary tract.[3]

The effect of itopride is an increase in acetylcholine concentration, which promotes gastric motility, increases the lower oesophageal sphincter (LOS) pressure, accelerates gastric emptying, and improves gastroduodenal coordination. The significant itopride pharmacokinetic properties include its very rapid absorption when administered orally; the maximum plasma has been shown as early as 35 minutes after administration.[6] Itopride is metabolised in the liver by the enzyme Flavin, containing monooxygenase, and its excretion from the body occurs primarily through the kidneys, where part of itopride is eliminated, unchanged, in the urine, mainly in the form of its metabolite.[6]

Itopride does not cross the blood-brain barrier; it has no relevant drug-drug interactions, probably because it is not metabolised in the liver by the cytochrome P450 activity. Itopride is considered a safe drug; in the Holtmann et al.[7] study, the most frequent adverse symptoms were dull abdominal pain, diarrhoea, or vice versa constipation, and nausea. Their frequency, however, did not differ from the group treated with a placebo.[7] Prolactinaemia, galactorrhoea, or leukopaenia are rarely present. Because itopride is excreted in breast milk, the drug is not recommended for pregnant women and children.

Indications

Generally, itopride is indicated in patients with symptoms of impaired oesophageal motility, impaired gastric emptying, including disorders of gastric emptying in diabetic patients, and those with functional dyspepsia and gastro-oesophageal reflux (GOR).

CLINICAL RESULTS

Itopride was developed in Japan; the first clinical studies in international journals were published in India. The first Indian studies evaluated the changes of initial subjective symptoms in people with dyspepsia in whom endoscopic examination did not lead to conclusive diagnosis of gastritis or peptic ulcer disease. In >70% of subjects, a significantly positive effect on symptoms was described after 14-day itopride medication at a dose of 50 mg, thrice a day (TID).[8] The second Indian study compared the influence of therapy with itopride or domperidone on subjective symptoms in patients with functional dyspepsia. The effect of therapy was higher in the group treated with itopride.[9] A similar conclusion was reached by the third study, comparing itopride with mosapride, which demonstrated better effect in the itopride group. In all studies, itopride was a safe drug.[10]

Itopride in the Treatment of Functional Dyspepsia

In 2006, results of a prospective, randomised, and multicentric study evaluating the results of itopride therapy in a representative sample of 523 persons, meeting the Rome II criteria,[7] were published. The studied subjects were randomised 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 the evaluated factors were the effect of the therapy, changes in symptoms of dyspepsia according to a standardised questionnaire and a five-point scale (some changes were evaluated, such as abdominal pain, the presence of nausea, or early satiety feeling), and the overall effect of the therapy by the patient himself/herself was also assessed.

All three doses of itopride demonstrated significantly better symptomatic relief and improvement when compared with the placebo. Overall analysis revealed that itopride was significantly superior to placebo, with the greatest symptom-score improvement in the 100 and 200 mg groups, when the statistical significance of difference between the placebo and dosage of 200 mg TID was at p<0.001. The quality of life (QoL) of the treated individuals, evaluated at the end of the study, was also better than in the placebo group. The Nepean Dyspepsia Index QoL score improved by a mean of 13.2±19.4 with placebo, and by 18.0± 21.9 with itopride. The dosage used within the study with two groups exceeded the recommended dosage for clinical practice (50 mg TID). It is therefore interesting that the percentage of side-effects in all three treated groups did not differ significantly, and it was not even different compared to the placebo. The most common side-effects were abdominal pain, diarrhoea, constipation, and nausea. Prolactin levels were higher, mainly in groups with higher drug dosage; however, no relevant clinical symptoms of prolactinaemia have been recorded.

Soji[11] investigated the effect and safety of itopride in a randomised and placebo-controlled study, in a group of 67 persons with functional dyspepsia. Participants met the Rome II diagnostic criteria; the subject age ranged from 18-60 years and a predominance of symptoms of early satiety, post-prandial fullness, and bloating were selected. The subjects were randomised; one group was treated with itopride at a dose of 50 mg TID, the other with a placebo. After 4 weeks of therapy, the symptom score of people treated with itopride was positively influenced in contrast to the placebo-treated group, statistically significant at p=0.0004 (before the start of itopride or placebo therapy, the symptom score in both groups was identical). In this study, in the group with strictly set selection criteria, itopride proved to be an extremely effective medicine with minimal side-effects (abdominal discomfort in two persons). None of the treated individuals showed abnormal ECG changes in terms of prolongation of the QT segment, which is a known limitation of functional dyspepsia cisapride therapy.

In 2011 Sun et al.[12] published the data from a prospective, multicentre, post-marketing observational study. 576 patients with functional dyspepsia were enrolled. Patients were prescribed itopride 50 mg TID before meals for 4 weeks. The treatment response rates after 1 week of therapy in patients with ROMA I, ROMA II, and ROMA III criteria for functional dyspepsia were 33.68%, 34.71%, and 35.50% respectively, and 72.82%, 73.54%, and 75.15% after 4 weeks. Itopride was well tolerated; there were no serious adverse reactions.

In 2012, Huang et al.[13] published a meta-analytic study evaluating the effect of itopride in the treatment of functional dyspepsia. It evaluated the effect of itopride, domperidone, mosapride, and placebo in subjects with a diagnosis of functional dyspepsia. The results of 9 randomised, placebo-controlled trials involving a total of 2,620 treated individuals were evaluated. 1,372 patients were treated with itopride at a dose of 50 mg TID each, and 1,248 persons constituting the control group were taking other drugs, i.e. domperidone, mosapride, or a placebo. The effect of therapy in the group treated with itopride was significantly higher when compared with the control group (p=0.006 placebo, p=0.02 persons treated with domperidone, and p=0.04 in subjects treated with mosapride) for global patient assessment, postprandial fullness, and early satiety. The earliness of therapy side-effects was similar for all administered drugs; statistically, it did not significantly differ. From this study it can be clearly concluded that itopride is an effective and safe remedy for the symptoms of functional dyspepsia, especially the syndrome of early satiety and postprandial fullness.

Itopride and Gastric Emptying

In experimental animal studies, itopride stimulates the motility of the stomach, duodenum, small intestine, and colon.[14,15] Choung et al.[16] in a double-blind, randomised, placebo-controlled trial of itopride on gastric motor activity and sensory function in healthy volunteers, monitored 16 people with itopride medication at a dose of 100 mg TID, 16 people with medication at a dose of 200 mg TID of itopride, and 15 persons with a placebo.[16] In healthy volunteers, the authors - contrary to others[17] - did not show the effect of itopride on gastric emptying, but they believe that itopride may have the effect due to increasing muscle contractility of the proximal and distal stomach after eating. An interesting finding is the significant acceleration of small bowel transit time after administration of 200 mg of itopride when compared with the placebo. The authors did not demonstrate that itopride in large doses significantly affects the stomach and gastric sensory function in healthy people. It can, however, be considered that the

effect in healthy persons may be different from that in patients with functional dyspepsia.

An interesting observation is published by Lim et al.,[18] who evaluated the effect of prokinetics, including itopride, on electrogastrography parameters, according to symptomatic changes in patients with functional dyspepsia. He concluded that prokinetic drugs could improve the symptoms of functional dyspepsia by regulating gastric myoelectrical activity. This finding is important only because gastric dysrhythmias are described in 31-69% of patients with functional dyspepsia.[19] Simanenkov et al.[20] demonstrated that itopride therapy at a dose of 50 mg TID led, by affecting gastric function, to significant suppression of the initial symptom, which was epigastric pain syndrome.

In individuals with concurrent diabetes mellitus Type 1 or 2, 30-50% of patients have delayed gastric emptying. It has been shown[21] that, compared to a placebo, itopride effect in those persons leads to a significant acceleration of discharging both liquid and solid food from the stomach. The effect of itopride does not contribute to changes in glucose levels during medication. However, it is beyond any doubt that failure of gastric emptying is closely associated with glycaemic control, which in itself significantly affects gastric evacuation.[22,23]

GOR

Scarpellini et al.[24] examined itopride effect on the function of the LOS during fasting and after eating in a group of 12 volunteers. After 3-day itopride premedication at a dose of 50 mg (BID), 100 mg (BID), or administering a placebo, oesophageal manometry was carried out. The drugs were administered 30 minutes before the application of a standardised diet. Resting pressure of LOS, swallow-induced relaxations, or duration of peristaltic contractions were not altered by both doses of itopride. Itopride pre-treatment inhibited the meal-induced rise of transient LOS relaxations. Itopride inhibited the transient LOS relaxation without a significant influence on oesophageal peristaltic function or LOS pressure. Kim et al.[25] studied the effect of itopride in patients with GOR. Patients with GOR disease were treated with 150 mg and 300 mg of itopride, thrice a day. Prior to the study, which lasted for 8 weeks, and after it finished, a 24-hour pH monitoring was carried out. The total symptom score was significantly improved after treatment with both doses of itopride used, while a greater effect was observed in the group receiving 300 mg itopride daily, using the DeMeester score, and the total pH time of 4.0. The Korean study[26] investigated whether the addition of itopride to proton pump inhibitors affects the healing effect in patients with a laryngeal form of reflux. The authors have not demonstrated that dual therapy yields better results than therapy with proton pump inhibitors only.

Itoprid and Colonic Function

In an experimental study, when the effect of itopride was evaluated in the excised distal ileum from a guinea pig, acceleration of peristaltic velocity was at higher dosage, whereas neostigmine accelerated it only with a lower dosage. Dopamine-decelerated velocity was recovered by itopride infusion. Itopride has prokinetic effects on both the ileum and colon via inhibitory effects on acetylcholinesterase and antagonistic effects on dopamine receptor.[4]

SUMMARY

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 a functional dyspepsia, present in about 60% of patients with dyspeptic symptoms. A wide range of dyspeptic symptoms reflect the high prevalence of functional disorders of the GI tract.[27,28] The drugs that are indicated in the treatment of functional dyspepsia symptoms include prokinetic agents. Itopride ranks among the prominent prokinetic agents.

Itopride is indicated in all patients with functional dyspepsia, in patients with dyspeptic symptoms, when these symptoms are present in the absence of structural or biochemical abnormalities and detected by routine diagnostic methods. Functional dyspepsia is defined as the presence of symptoms thought to originate in the GI region in the absence of organic, systemic, and metabolic disease that is likely to explain the symptoms.[28] 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 intestinal wall through a D3 receptor. At the same time, itopride affects dopaminergic innervation of the smooth muscle of the upper GI tract by blocking

DD2Rs; itopride is extremely rapidly absorbed, and its peak serum concentration occurs 35 minutes after oral administration.[29]

In a meta-analytic study evaluating the effect of itopride in functional dyspepsia, published by Huang et al.[13] authors collected 328 articles, 319 of them were excluded, and 9 randomised controlled trial articles were included. Included studies contained a total of 2,620 patients; 1,327 were treated with itopride and 1,248 received placebo. Efficacy of itopride with respect to postprandial fullness in patients with functional dyspepsia was significantly demonstrated (p=0.02). This effect was more significant than the effect of domperidone. Itopride also significantly improved symptoms of early satiation in patients with functional dyspepsia (p=0.04). In placebo-controlled studies evaluating LDQ-scores (Leeds Dyspepsia Questionnaire) in patients with functional dyspepsia, itopride improved the LDQ scores more significantly than placebo (p<0.001). Itopride and domperidone had similar efficacy on epigastric discomfort of functional dyspepsia (p=0.98).

Itopride is a safe drug and, unlike (for example) metoclopramide, it does not pass the blood-brain barrier; additionally, unlike cisapride, it does not affect the heart rate by prolonging QT segment.[30] According to these results there is no doubt that itopride therapy positively influences the symptoms of functional dyspepsia, especially postprandial fullness, bloating, and LDQ. Itopride in clinical studies positively affected conditions with prolonged gastric emptying, including disorders of gastric emptying in diabetic patients. In the mildform of GOR, itopride was proven as a potential part of the treatment armentaria, where a fundamental role is played by the blockades of the proton pump.

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