Original paper

The efficacy and safety of itopride as an add-on therapy to a proton pump inhibitor in the treatment of gastroesophageal reflux disease

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Abstract

Introduction: The primary objective was to demonstrate the efficacy and safety of itopride as an add-on therapy to a proton pump inhibitor (PPI) in the treatment of gastroesophageal reflux disease.

Aim: Reflux disease affects the largest percentage of the population worldwide, symptoms overlap with many other conditions which hamper diagnostic and therapy presenting challenges in treating patients and prompting an intensive search for new, more effective therapeutic regimens.

Material and methods: A retrospective study was undertaken with 140 enrolled patients with reflux disease, confirmed by 24-hour pH impedance previously treated with PPIs without any significant improvement. Itopride was added to the PPI therapy in a dose of 150 mg/day, after which the severity of reflux disease symptoms was reassessed.

Results: The greatest improvement after the combined treatment ($p < 0.001$) was experienced in the context of heartburn, nausea and laryngopharyngeal symptoms. There was also a high percentage of statistically significant ($p < 0.01$) improvement in burning in the oesophagus and stomach and regarding postprandial fullness, gastric retention and swallowing disorders. No adverse effects were noted.

Conclusions: The presented study clearly demonstrates that in patients ineffectively treated with PPIs, the addition of itopride to the therapy for 8 weeks without changing the PPI dose, significantly improves the efficacy of treatment of reflux disease and thus shortens the need for medication usage and reduces the costs of therapy, potential side effects of PPI, improves the patient's quality of life and decreases the frequency of medical appointments.

Introduction

Gastroesophageal reflux disease (GERD), as defined by the World Gastroenterology Organisation, is a range of unpleasant symptoms that significantly reduce the quality of life, resulting from an abnormal backflow of gastric contents into the oesophagus, pharynx, mouth and respiratory tracts [1]. This may result in oesophageal and extra-oesophageal complications, demanding complex diagnostics and treatment. The incidence rate of GERD is estimated to be between 10% and 30% in Western populations; in Poland, it is estimated to be above 30%, which is one of the most common reasons to visit general practitioners (GPs) [2, 3]. Although reflux disease is considered a condition mild in character, it may lead to significant oesophageal complications, such as erosive oesophagitis, Barrett's oesophagus with the risk of oesophageal adenocarcinoma or ulceration and stenosis in the part of the oesophageal body.

The following two groups of factors, favouring the disease may be distinguished in the pathogenesis of GERD: primary and secondary oesophageal motility disorders, such as reduced lower oesophageal sphincter (LES) pressure, impaired oesophageal clearance, impaired oesophageal body motility, delayed gastric emptying, pyloric dysfunction and, relatively rarely, excessive gastric acid secretion (the Zollinger-Ellison syndrome – ZES) [1, 4]. The symptoms, such as heartburn and regurgitation, are considered to be typical of GERD [1]; however, they may co-occur relatively often with other

symptoms, indicative of upper gastrointestinal motor dysfunction which would sometimes require a modification of therapeutic management. Such symptoms include a feeling of postprandial fullness, retention of gastric contents, swallowing disorders, belching and many others [1, 4, 5].

According to the American Gastroenterology Association (AGA), the primary goal in the treatment of GERD is the resolution of symptoms, healing of inflammatory lesions in the oesophagus and prevention of disease recurrence and complications [6]. The first-line drugs are PPIs which show high efficacy in healing erosive and inflammatory lesions of the oesophagus and reduce the typical symptoms of GERD [7], though without any therapeutic effects on oesophageal and gastric motility disorders. It seems that adding a prokinetic drug to a PPI would result in an effective causal treatment of GERD [8]. Itopride is a new-generation prokinetic drug with a high safety profile [9, 10], which by promoting the motor activity through a dual mechanism of action – as a dopamine D2 receptor antagonist and a cholinesterase inhibitor [11] – improves the components of oesophageal clearance, known as the 'swallowing rate', reduces transient LES relaxations (TLERs) [12], as well as accelerates gastric emptying and modulates gastric motor functions [13, 14]. The combination of two drug groups, i.e. PPIs and the prokinetic in GERD therapy acts, therefore, synergistically by reducing acid production, as well as improving oesophageal motility, thus providing a better therapeutic response.

Despite the numerous reports, confirming the efficacy of itopride in dyspepsia in terms of improving the upper gastrointestinal motor disorders, there are still only few studies in the current literature evaluating the use of itopride in GERD, even though the same motor disorders are present in both disease entities.

Aim

The goal of the study was to demonstrate the efficacy and safety of itopride, administered as an add-on therapy to a PPI in the treatment of GERD.

Material and methods

The retrospective study presented here involved 140 patients, who had reported symptoms typical of GERD, persisting despite an earlier treatment with PPIs lasting for no less than 8 weeks twice daily. Before functional tests, esophagogastroduodenoscopy (EGD) was performed to exclude other causes of symptoms. Each patient was submitted to a high-resolution manometry test to determine the position of the impedance catheter and to assess oesophageal motor function. Twenty-four-hour measurements of intra-oesophageal pH impedance confirmed the diagnosis of GERD. Patients presented to the Gastrointestinal Motility Laboratory at the Department of Gastroenterology and Hepatology of the Medical University and to the outpatient laboratory. All tests were performed using the same systems (ManoScan™ ESO Sierra Instruments and Digitrapper pHz), which enabled us to standardise the collected data. Each patient, after examinations, test and the confirmation of GERD, had been added itopride to the PPI treatment (with no change in the dose or drug type) at a daily dose of 150 mg, administered in three divided subdoses of 50 mg, 30 min before meals, for 8 weeks. The disease symptoms were also assessed at follow-up visits, including burning in the oesophagus, heartburn, regurgitation, postprandial fullness and the retention of gastric contents, bloating, belching, posseting, nausea, swallowing problems, epigastric pains and laryngopharyngeal symptoms. Regarding the two visits – initial and follow-up – 94, out of 140 patients, attended each visit, the median age for women was 42.5 (21–72 years) and for men – 39.0 (17–80 years). The patients gave written informed consent before each examination. The patients who did not attend a follow-up were excluded from the project.

The data on the GERD symptoms, collected before and after the treatment, were qualitative and the McNemar test was used in their analysis. A three-degree scale was considered as the level of significance: $p < 0.05$; $p < 0.01$ and $p < 0.001$.

Results

The characteristic features of the patients are presented in Table I. A total of 140 patients were enrolled into the study but only 94 patients attended the 2nd follow-up visit after the 2-month therapy period. The population was well selected and represented a broad age range of 17–80 years old. At the same time, the mean age of the patients before (median of 46 years) and after (median of 42 years) the treatment was comparable. Based on the information obtained via interviews with the patients, there was observed a statistically significant reduction in the symptoms including heartburn, burning in the oesophagus and stomach, postprandial fullness and gastric retention, nausea, laryngopharyngeal symptoms and swallowing disorders. The greatest improvement after the combined therapy ($p < 0.001$) was observed in the context of heartburn, nausea and laryngopharyngeal-symptoms. There was also a high percentage of statistically significant ($p < 0.01$) improvement in burning in the oesophagus and stomach and regarding postprandial fullness, gastric retention and swallowing disorders. Noteworthy the subjectively identified improvement in wellbeing was observed regardless of either the age or the gender.

Table I. Patients' characteristics

Parameter	Before treatment	After treatment	*P*-value
Patients [*n*]	94	94	–
Heartburn [*n*]	75	9	< 0.001
Regurgitations (content reflux, return) [*n*]	47	3	0.002
Burning in esophagus and (or) stomach [*n*]	29	4	< 0.001
Postprandial fullness and (or) gastric retention [*n*]	16	7	< 0.001
Bloating	29	26	NS
Belching [*n*]	38	37	NS
Abnormal return of stomach content [*n*]	6	1	< 0.001
Nausea [*n*]	35	12	0.042
Swallowing disorders [*n*]	15	2	< 0.001
Epigastric pain [*n*]	31	10	NS

The presented data come from an observational study, therefore it is a limitation: lack of randomization and the control group, lack of standardized questionnaires for symptom assessment, the possible positive effect of placebo (especially considering the functional background), lack of objective reflux-symptom analysis.

Discussion

Despite the undeniable advances in the diagnostics and treatment of GERD, it still remains a kind of challenge, while some patients do not fully benefit from the proposed therapeutic management. It would seem that the introduction of PPIs would solve this problem, however, a significant proportion of patients still suffer from the typical symptoms of the disease and, recently, we are increasingly talking about the reflux disease refractory to PPI treatment [15].

Taking into account the epidemiological data, GERD continues to represent a huge and still growing therapeutic challenge. Based on population-based studies, the incidence of typical symptoms of GERD has been estimated a minimum of once a week to be around 13% of subjects, with clear geographical differences [16]. The incidence rate of GERD is estimated to be between 10% and 30% in Western populations; in Poland, it is estimated to be above 30%, which is one of the most common reasons to visit GP offices [2, 3]. The discomforts associated with the disease impact on many spheres of patients' lives, impairing their quality of life in relation to all possible aspects, including deterioration of physical, mental, emotional wellbeing, vitality, increased pain and withdrawal from many social functions [17–19]. A recent systematic review and a meta-analysis confirm the strong association and interaction between psychosocial disorders and GERD [20].

The other problems, broadly associated with GERD, include the absence from work and low productivity of the patients due to experienced discomforts. The European RANGE (Retrospective Analysis of Gastroesophageal reflux disease (GERD)) study aimed at identifying and assessing differences among the patients who visited a GP for GERD-related reasons in terms of symptoms, diagnosis and management, the response to treatment and the impact on their productivity, costs and the health-based quality of life, which made it possible to determine the impact of GERD on the productivity, both at work and in daily life. The average costs of GERD-related absenteeism at work were significant in all the countries (ranging from €55/week per employed patient in the UK to €273/week/patient in Sweden). Declines in daily life productivity of up to 26% were observed in European countries. Thus, GERD is relevantly a burden on primary care patients in terms of absenteeism from work and daily life. The resulting costs to the local economy may be really significant. A more effective treatment of GERD may then be expected to help diminish the impact of the disease on productivity and reduce the overall costs [21].

Similar conclusions are presented by the authors of US reports on the same issues. The increasing severity and frequency of GERD symptoms are associated with more comorbidities (overlap syndromes), a lower quality of life, work productivity and increased healthcare use/abuse, what suggests that the patients with moderate to severe GERD should receive targeted treatment, based on the most effective pharmacological strategies [22]. Therefore, all the efforts undertaken to increase the efficiency and shorten the treatment time of GERD seem to be fairly logical measures, enabling to reduce the overall costs, diminish absenteeism at work and improve the quality of life of affected patients.

A milestone in the treatment of GERD was the introduction of PPIs, which now occupy a fundamental place in the treatment of acid-dependent diseases, including GERD. Nevertheless, the potential side effects of PPIs have recently been more widely discussed than the undoubted benefits of their therapeutic efficacy [23, 24]. PPIs are the most effective drugs to suppress gastric secretion, which is of great importance in reducing the acidity and volume of gastric contents and potentially reducing the volume of refluxate, but the pathophysiological basis of reflux disease is also underpinned by functional disorders of the oesophagus and stomach, not just by the overproduction of gastric acid. Therefore, it seems reasonable to introduce prokinetics into the therapy, in addition to gastric secretion suppressants [8].

The prokinetic drugs, available in Poland for oesophageal motility disorders, include itopride (a dopamine D2 receptor antagonist and acetylcholinesterase inhibitor), cisapride (a serotonin 5-HT4 receptor agonist) and metoclopramide (a D2 receptor antagonist and a 5-HT4 receptor agonist). The prokinetic agents of the older generation (metoclopramide, cisapride) caused numerous side effects, so the use of cisapride requires precautions in patients with cardiovascular burden, while metoclopramide has been withdrawn from chronic use because of adverse neurological effects (extrapyramidal symptoms, late dyskinesias) and endocrine effects (hyperprolactinaemia, gynaecomastia, menstrual disorders in women), and therefore those molecules have been reserved exclusively for short-term episodic treatment in specific clinical situations [25, 26].

Itopride is a new-generation prokinetic agent with a very high safety profile, devoid of the side-effects, found in the previous drug group, and well tolerated by patients [9, 27]. It exhibits a dual mechanism of action as it blocks the dopamine D2 receptor and stimulates the release of acetylcholine, causing the increase of its levels in smooth muscle tissues, thereby improving the strength of contraction and motility of the gastrointestinal tract [11]. As a result, it improves oesophageal clearance by reducing TLERs and the so-called 'swallowing rate' [12], accelerates gastric emptying, modulates gastric sensorimotor function [14, 15, 28] and contributes to stimulating colonic motility [29], which is important for the treatment of overlap syndromes. Itopride is a drug broadly used in Poland both by GPs and gastroenterology specialists, due to its efficacy and high safety profile.

There are only few studies available in the literature, supporting the efficacy and indication for the use of itopride as an add-on therapy to PPIs in GERD, which, with reference to the cited data, was the main point of interest in the presented study.

Oesophageal motility disorders, present both in dyspepsia and in reflux disease, are not different in high-resolution manometry, the gold standard for their diagnosis, and are based on the Chicago Classification. Hence, itopride, a drug that regulates the upper gastrointestinal motility with a recognised indication for a treatment of functional dyspepsia, should have the same efficacy and safety profile in the treatment of GERD.

In the results presented in the study, the patients experienced a significant improvement after 8 weeks of treatment, when itopride was added to the PPIs, in terms of the resolution of discomforts, such as heartburn, burning in the oesophagus and stomach, postprandial fullness and gastric retention, nausea, swallowing disorders and laryngopharyngeal symptoms. All the study patients continued their treatment with a PPI at the fixed dose, recommended before the addition of itopride. Based on the results of our study, one may conclude that adding itopride to PPI in GERD (irrespective of the type of the PPI) there was achieved improvement with regard to most of symptoms, both those related to acid overproduction (heartburn, burning in the oesophagus and stomach) and those associated with motility disorders (dysphagia, postprandial fullness, retention of contents, nausea), but also with regard to laryngopharyngeal complications. The results obtained are also confirmed by literature data.

A randomised, prospective, double-blind study of 100 persons, diagnosed with GERD and divided into 2 groups (pantoprazole 40 mg + placebo and pantoprazole 40 mg + itopride 3 × 50 mg), continued for 16 weeks, with a follow-up visit every 4 weeks, proved that the addition of itopride to PPIs in the treatment of GERD increased the efficacy of the therapy, reduced the symptoms faster and diminished the recurrence rate [30]. Similar results were obtained in a prospective randomised trial of itopride, 150 mg/day, with lansoprazole, 30 mg, achieving a complete resolution of symptoms after 12 weeks of treatment [31] or with rabeprazole, 20 mg, noting an improvement after 6 weeks [32]. Reports from comparative efficacy studies of itopride and domperidone with PPIs (20 mg rabeprazole for 8 weeks and esomeprazole 40 mg for 4 weeks) are also available in the literature, not only highlighting the superiority of itopride over domperidone, but also confirming the high safety and efficacy of itopride in combination therapies [33, 34].

Another multicentre study evaluated the efficacy of itopride in the monotherapy of GERD at a short 2-week follow-up, with regard to the severity of heartburn symptoms and their incidence rate and to the incidence of regurgitation and cardiovascular side effects, using a dose of 150 mg/day. The authors of the

report described an effective and statistically significant reduction in the incidence of heartburn and regurgitation, with some patients already showing a reduction in heartburn after day 3 of the therapy. No cardiovascular complications were reported (a continuous monitoring of the patients was carried out) [35]. The efficacy and safety of itopride in GERD monotherapy are also confirmed by a randomised trial in which itopride was used for 4 weeks at a dose of either 150 mg or 300 mg/day and then assessed in the context of heartburn and all the other GERD symptoms. As a result, the total symptoms and heartburn were significantly reduced after the treatment, both with 150 mg and 300 mg/day, although better results were achieved with the 300 mg dose, with no side effects in either group, further confirming the safety profile of the drug [36].

One of the forms of GERD is the occurrence of extraoesophageal complications, which, being very difficult and persistent, are usually resistant to a PPI treatment. In our results, the patients already experienced a statistically significant reduction in the severity of laryngopharyngeal symptoms after 8 weeks of the applied therapy. These results are supported by data from other authors, who suggest that itopride may be considered as the secondary agent in the PPI treatment of LPR patients [37, 38]. The relatively short duration of therapy versus the 6 months of intensive PPI therapy, as suggested in the literature, sometimes at a double dose, demonstrates the very good synergistic effect of the two drug groups in this particular respect. The efficacy of PPIs in the treatment of GERD, including its extra-oesophageal complications, is confirmed by randomised trials and meta-analyses [39]. These studies indicate that a better symptom control is achieved when PPIs are combined with other management strategies, such as lifestyle modification, but that even greater efficacy may be achieved by combining a PPI with a prokinetic agent [40]. Randomised trials confirm the efficacy of itopride polytherapy in reducing oesophageal and extra-oesophageal symptoms and in preventing GERD recurrence episodes. The addition of itopride to PPIs in randomised trials, regardless of the PPI type improved the treatment efficacy, enabling the use of proven PPIs for the entire treatment period and without any need to modify the established therapy [30, 31]. Itopride, administered three times a day in combination with PPIs, may be an alternative to PPI treatment in monotherapy as it accelerates the relief of reflux symptoms in patients with laryngopharyngeal reflux (LPR) [30, 31], reduces the severity of symptoms such as heartburn, regurgitation, coughing, grunting, pharyngeal obstruction (RSI – Reflux Symptom Index), and improves some morphological changes in the larynx, such as swelling, erythema, granulomas (Belafsky's RFS). A reduction in the recurrence rate of LPR symptoms was also shown when itopride had been added to a PPI therapy [30].

The lack of improvement, noted in the results with regard to bloating, belching or regurgitation, may have been due to the frequent overlap of reflux disease with other functional disorder syndromes such as irritable bowel syndrome (IBS) or various forms of dyspepsia. Clinical manifestations are very non-specific for all disease entities, while a broad range of symptoms does not narrow the list of potential diagnoses. Thus, the lack of improvement could suggest concomitance of overlap syndromes in that group of patients and, therefore, no full efficacy of the applied therapy could be observed in this particular regard.

The fact, which is worth highlighting, is that there was observed improvement, independent of the gender and age of the patients because it further strengthens the indications and confirms the safety profile of the drug in any patient group, including seniors, who usually demonstrate concomitant conditions and require a dedicated therapy. Summing up, itopride did not show any interactions which could have posed any risk of complications or significant side effects.

The presented study suggests that, in patients ineffectively treated with a PPI in monotherapy, the addition of itopride, a prokinetic drug, to the PPI for 8 weeks only and in a dose of 150 mg/day, taken in three divided subdoses of 50 mg each, without changing the PPI dose, significantly improves the efficacy of treatment of GERD in terms of symptoms improvement. The future studies should assess if addition of itopride to PPIs may improve the quality of life, reduce the frequency of medical appointments and reduce the dose of PPI and therefore possible side effects of PPI and treatment costs.

Our results confirm that the treatment efficacy was the same regardless of the type of the PPI applied.

Equally important is the fact that the observed improvement was irrespective of the age as well as of the gender of the patients, thus proving that the PPI/itopride combination therapy ensured an effective and causal synergistic effect in GERD in all the patients.

Conflict of interest

The authors declare no conflict of interest.

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