Gastroesophageal reflux disease (GERD) is a common condition characterized by heartburn and acid regurgitation. These symptoms are among the most common complaints encountered by the general physician. The classic definition of GERD consists of chronic symptoms of mucosal damage produced by the abnormal reflux of gastric contents into the esophagus. The main impact of GERD is from symptoms (heartburn and acid regurgitation) that ultimately affect patients’ quality of life. Patients with GERD score lower in quality-of-life assessment than patients with congestive heart failure or angina. The burden of illness of GERD is an important consideration for management care and other decision makings. While the diagnosis may be confirmed with pH metry, fibroscopy may be needed to evaluate the anatomical situation and the effect of the esophagitis on the upper digestive tract. The efficacy of antireflux medications in symptom relief and healing of mucosal injury can now be judged from well-designed clinical trials with clinically meaningful endpoints. Prokinetics have been found to be very effective in the treatment of gastroesophageal symptoms and hold an important place in the drug armamentarium of gastroenterologists. Itopride is one such novel prokinetic which has proved itself effectively in many gastric conditions such as GERD, non ulcer dyspepsia, chronic gastritis etc.

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**GERD**

**Introduction**

Gastroesophageal reflux disease (GERD) is one of the most prevalent upper gastrointestinal disorders in clinical practice. GERD is a chronic disease with relapsing symptoms, and lifelong treatment is required in 25% to 50% of patients. For decades, gastroesophageal reflux disease has been approached as a spectrum of disease. On one end of the spectrum are the patients with classic symptoms of GERD and normal esophageal mucosa. The other end of the spectrum is occupied by patients with GERD complications such as stricture, Barrett’s esophagus, and adenocarcinoma of the esophagus. Removing the spectrum concept and approaching the GERD population as three unique groups of patients (nonerosive reflux disease, erosive esophageal, and Barrett’s esophagus) will dramatically shift our focus from esophageal mucosal injury to mechanisms leading to symptom generation in each group and foster specific therapeutic modalities that benefit each individual group of patients.

**Pathophysiology**

The cause of GERD is unknown. The pathophysiology involves contact of the esophagus with noxious substances in refluxed gastric juice. Everyone experiences episodes of GER, however, and a cornerstone for the development of GERD is that the contact time between noxious substances in gastric juice with the esophagus must be of sufficient duration to result in damage to the epithelium. Sufficient duration to cause GERD can occur in one of two general ways: (1) when contact time between epithelium and gastric contents is so prolonged that the noxious agents in gastric juice overwhelm an otherwise healthy esophageal epithelium and (2) when contact time between epithelium and gastric contents is essentially normal, yet still adequate to produce damage because of the greater potency to the refluxate or presence of defects thins the epithelium.

**Symptoms**

Depending on the patient’s age during the first symptoms, GER may have several meanings and clinical courses. There are two forms of presentation: in children and in adults. In the first case, the symptoms appear during the first months of life and improve up to 12-24 months in 80% of the cases. The second type may be a continuation of the first one, or appear later; it has persistent symptoms and usually requires treatment.

The main symptoms are persistent heartburn and acid regurgitation. Some people have GERD without heartburn. Instead, they experience pain in the chest, hoarseness in the morning, or trouble swallowing. GERD can also cause a dry cough and bad breath.

The clinical manifestations may be: specific, such as rumination, vomits, regurgitations, eructation; related to esophagitis, such as pain, anemia, and bleeding; respiratory, such as bronchospasm and repeated pneumonia; otorhinolaryngological, such as laryngitis, sinusitis, otitis, and others.

**Treatment options**

Since the 1980s, there have been major advancements in the medical management of gastroesophageal reflux disease (GERD). The most successful therapies have decreased acid secretion and volume with H2-receptor antagonists...
and especially proton-pump inhibitors. Sucralfate, a mucosal protector, had minimal effect on the treatment of GERD except in the rare patient with severe ulcerative esophagitis. Despite GERD being considered motility disorder, such promotility drugs as bethanechol, metoclopramide, and cisapride have had marginal efficacy in treating GERD patients except in patients with nonerosive disease or dyspepsia with associated delayed gastric emptying. Through various mechanisms, these drugs were reported to increase lower esophageal sphincter (LES) pressure and improve acid clearance, but in reality they did little in patients with more severe disease other than improving gastric emptying. None of these promotility agents had an apparent effect on the major motor mechanism underlying reflux episodes, transient LES relaxations (TLESRs).^4

**Other indications for usage of prokinetics**

The prokinetics are important therapeutic tools in the treatment of GERD. They determine an increase in the LES pressure, and stimulate esophageal peristalsis and gastric emptying.

**Diabetic gastroparesis**

Diabetic gastroparesis is a common and debilitating condition affecting millions of patients with diabetes mellitus worldwide. Although gastroparesis in diabetes has been known clinically for more than 50 years, treatment options remain very limited. Until recently, the scientific literature has offered few clues regarding the precise aetiology of gastric dysfunction in diabetes. Up to 50% of patients with diabetes may experience postprandial abdominal pain, nausea, vomiting and bloating secondary to gastric dysfunction. There is no clear association between length of disease and the onset of delayed gastric emptying. Gastroparesis affects both type 1 (insulin dependent) and type 2 (non-insulin dependent) forms of diabetes. Diagnosis requires identifying the proper symptom complex, while excluding other entities (peptic ulcer disease, rheumatological diseases, medication effects). The diagnosis of gastroparesis may be confirmed by demonstrating gastric emptying delay during a 4-hour scintigraphic study.\(^5\)

Prokinetics are effective in improvement of delayed gastric emptying, which leads to better glycemic control in diabetic patients. Through the mechanism of how prokinetics act on gastric electrical events, improvement of delayed gastric emptying in patients with autonomic neuropathy should be achieved not only for the relief of GI symptoms but also for stable glycemic control.\(^5\)

**Non-ulcer dyspepsia**

Dyspepsia, defined as pain or discomfort centered in the upper abdomen, accounts for up to 5% of all visits to primary care physicians. In the majority of patients evaluated, no clear cause of symptoms can be identified, and the condition is termed functional or nonulcer dyspepsia (NUD). The pathophysiology of NUD remains unclear, but
disturbances in gastrointestinal motility or sensation are often found. Clinically, NUD can be subdivided into dysmotility-like (in which discomfort, fullness, bloating, early satiety, or nausea [but not pain] predominate) or ulcer-like (in which epigastric pain is predominant).  

Optimal therapy for patients with non-ulcer dyspepsia still remains elusive. Increasing consensus on the definition of non-ulcer dyspepsia may improve the design of clinical trials and result in more effective therapies for this common condition. Prokinetics and, to a lesser extent, H2-receptor antagonists are the main medications of choice.  

Chronic gastritis  
Chronic gastritis may be caused by prolonged irritation from the use of nonsteroidal anti-inflammatory drugs (NSAIDs), infection with the bacteria Helicobacter pylori, pernicious anemia, an autoimmune disorder, degeneration of the lining of the stomach with age, or chronic bile reflux. Many people with chronic gastritis have no symptoms of the condition. Risk factors include a history of pernicious anemia, blood or lymph system disorders, age over 60 years and use of NSAIDs. The incidence is 2 out of 10,000 people. Symptoms of Chronic gastritis are upper abdominal pain, abdominal indigestion, loss of appetite, nausea, vomiting, vomiting blood or coffee-ground like material and dark stools.

Introduction  
Prokinetic drugs such as domperidone, metoclopramide, mosapride and cisapride are used in the treatment of upper gastrointestinal disorders such as non-ulcer dyspepsia (NUD). By promoting emptying of the stomach, these drugs prevent the retention and the reflux of acid and food. These agents thereby relieve symptoms of NUD such as bloating, belching and epigastric pain. Cisapride and metoclopramide have been reported to have a modest prokinetic effect. Moreover, metoclopramide on account of its potential to cause extra-pyramidal side-effects (EPS) and domperidone, by virtue of its potential to cause gynecomastia and galactorrhea, are riddled with problems of tolerability. Recently cisapride has been reported to have a potential to prolong the QT interval in the ECG, and thus predispose to serious cardiac arrhythmias on rare occasions. Itopride hydrochloride improves gastro-intestinal motility by a dual mode of action. First, it enhances the release of acetylcholine in the myenteric plexus by antagonising the action of dopamine on the D2-receptors on the postsynaptic cholinergic nerves; secondly, it prevents hydrolysis of the released acetylcholine by the enzyme acetylcholinesterase in the smooth muscle of the upper gastro-intestinal tract. This dual mode of action differentiates itopride from the available prokinetics such as metoclopramide and domperidone. Moreover, itopride has no affinity for the 5-HT4 receptors, unlike cisapride and mosapride, which are 5-HT4 agonists. The affinity of cisapride for 5-HT4 receptors in the heart has been implicated in the undesirable cardiac effects of the drug.

Itopride  
Itopride hydrochloride, N-[p-[2-(dimethylamino)ethoxy]benzyl]veratramide hydrochloride, is a synthesized gastroprokinetic agent with a benzamide structure. A novel gastroprokinetic agent, itopride hydrochloride (itopride), simulates gastrointestinal motor activity through synergistic effects of dopamine D2-receptor blockade and acetylcholine esterase inhibitors. Itopride undergoes extensive hepatic metabolism in humans. The primary metabolite in humans in the N-oxide, generated by oxidation of the tertiary amine N-dimethyl group (Nakashima et al, 1993). The urinary excretions of itopride and its N-oxide were 3.7% and 75.4%, respectively, in healthy subjects after a single oral administration at a therapeutic dose (Nakashima et al, 1993). However, the enzymes involved in the metabolic pathway have not been fully characterized.
Mechanism of action

Itopride hydrochloride’s mechanism of action has been shown to involve an amplification of the prokinetic action of acetylcholine in the gastrointestinal tract by increasing the release of acetylcholine through the inhibition of the D2 receptors, as well as decreasing the metabolism of this transmitter by inhibiting the acetylcholinesterase enzyme. Itopride stimulates postprandial gastric motility therefore enhances gastric contraction evoked by ACh infusion. Itopride inhibits electric eel AChE (IC50 = 2.9 mM) and enhances ileum contraction evoked by ACh in vitro. These results suggest that AChE inhibition is involved in the mechanism of the itopride-induced stimulation of gastric motility. Itopride exerts a selective and reversible AChE inhibition and enhances AChE-induced contraction. Itopride thus effectively controls the gastric symptoms because of its dual mechanism of action.

Indications for usage

Itopride is indicated in various digestive conditions giving rise to symptoms such as heartburn, regurgitation, epigastric pain, esophagitis etc. These conditions include GERD, non ulcer dyspepsia, chronic gastritis and a very important complication seen in diabetics wherein the gastric emptying is markedly reduced i.e. diabetic gastroparesis.

Dosage

Recommended dose of itopride is 150 mg in three divided doses orally before meals.

Advantage over other prokinetics

Recently, potentially life-threatening ventricular arrhythmias have been associated with concurrent administration of cisapride, a widely used drug in the same therapeutic class as itopride and imidazole nonfungals or macrolide antibiotics (Ahmad and Wolfe, 1995; Wysowski nd Baesanyi, 1996). Cisapride is mainly metabolized to the N-dealkylated form (norcisapride) in humans (Meuldermans et al, 1988), principally by cytochrome P450 (CYP3A4) (Bedford and Rowbotham, 1996). The imidazole antifungals, such as ketoconazole, and macrolides are potent and relatively specific inhibitors of CYP3A4 activity (Newton et al, 1995).

Co-administration of cisapride with such CYP3A4 inhibitors impairs CYP3A4-dependent presystemic extraction, causing greatly elevated plasma concentrations of unchanged cisapride compared with those after administration of cisapride alone (Before and Rowbotham, 1996; Haarst et al, 1998). The resultant high levels of cisapride produce adverse effects, such as QT interval prolongation, leading to the risk of ventricular arrhythmias (Bedford and Rowbotham, 1996). This study, therefore, aimed to identify the enzyme responsible for metabolism of itopride and to investigate...
the likelihood of drug interaction involving itopride in vitro and in vivo compared with other gastroprokinetic agents, cisapride and mosapride citrate.

Itopride N-oxide formation was inhibited in the presence of methimazole and thiourea, alternative substrate-competitive inhibitors of FMO (Fig. 1). In addition, the decrease in itopride N-oxide formation to 0% of the control caused by treatment at 45°C for 5 min suggests a heat-mediated inactivation of FMO that was delayed when NADPH was included (Fig. 2).

Pre-retreatment with ketoconazole did not alter the metabolism of itopride in rats, whereas it caused accumulation of unmetabolized cisapride and mosapride. In addition, itopride showed no inhibitory effect on five specific CYP-mediated reactions in human liver microsomes. It is concluded that itopride is unlikely to cause clinically significant pharmacokinetic drug interactions.

Conclusion

Itopride hydrochloride is a novel prokinetic drug for the treatment of disorders characterized by reduced gastric motility. Gastric motility disorders like non-ulcer dyspepsia, gastro-esophageal reflux disease and diabetic gastroparesis are frequently encountered conditions in clinical practice. Thus a prokinetic drug, which restores gastric natural tone, has a unique dual mechanism of action and negligible potential for drug interactions would be welcome in controlling symptoms in these conditions.

References


Current Abstracts

Gastroprokinetic effect of a new benzamide derivative itopride

The novel benzamide derivative itopride was assayed for its effect on gastrointestinal motility in conscious dogs when it was administered intraduodenally (i.d.). Gastrointestinal motility was measured by means of chronically implanted force transducers, and itopride at a dose of 10 mg/kg, i.d. or more increased the gastric contractile force during the digestive state. Intraduodenal cisapride, domperidone and metoclopramide also stimulated gastric motility, and their threshold doses were 1, 3 and 1 mg/kg, respectively. Dopamine infusion (1 mg/kg/hr, i.v.) caused the postprandial gastric motility to disappear, but it was immediately restored by itopride at a dose of 3 mg/kg, i.d. With itopride at 1 and 3 mg/kg, i.d., acetylcholine (0.05 mg/kg/min)-induced contractions were greatly enhanced. In addition to its gastric stimulation, itopride at doses of 10-100 mg/kg, p.o. inhibited apomorphine (0.1 mg/kg, s.c.)-induced vomiting in dogs. In conclusion, intraduodenal itopride stimulates gastric motility through both anti-dopaminergic and anti-acetylcholinesterase actions. Its gastroprokinetic threshold dose was as large as 3-10 times those of cisapride, domperidone and metoclopramide. These findings suggest that itopride is an orally active gastroprokinetic with a moderate anti-emetic action.

Stimulatory action of itopride hydrochloride on colonic motor activity in vitro and in vivo

The authors investigated the effects of itopride hydrochloride, a gastroprokinetic agent, on the colonic motor activity in vitro and in vivo, in comparison with benzamides, cisapride hydrate (cisapride), and mosapride citrate (mosapride). Itopride stimulated both peristaltic and segmental motility induced by applying intraluminal pressure to the isolated guinea pig colon. Although cisapride and mosapride enhanced the segmental motility, they markedly reduced the peristaltic motility. In conscious dogs with implanted strain gauge force transducers, itopride stimulated contractile activity in the gastrointestinal tract from the stomach to the colon. Cisapride stimulated contractile activity in the gastric antrum, ileum, and ascending colon. Mosapride stimulated contractile activity only in the gastric antrum and ileum. In guinea pigs and rats, itopride accelerated colonic luminal transit. On the other hand, cisapride and mosapride failed to enhance colonic transit. These results demonstrate that itopride has a stimulatory action on colonic peristalsis, propelling colonic luminal contents, different from that of cisapride and mosapride. Therefore, itopride may be a useful drug for the treatment of functional bowel disorders such as functional constipation.


Efficacy and tolerability of itopride hydrochloride in patients with non-ulcer dyspepsia

To document the clinical efficacy and tolerability of itopride hydrochloride in patients with non-ulcer dyspepsia an open-label, non-comparative study, was undertaken at the Medical College, Thiruvananthapuram, among patients with endoscopically confirmed diagnosis of non-ulcer dyspepsia or chronic gastritis. Itopride hydrochloride 50 mg (1 tablet) thrice a day for 2 weeks was administered among them. Relief of symptoms at the end of two weeks treatment, assessed as marked/complete, moderate, slight, none or worse; QT interval on ECG; adverse events; hemogram; serum chemistry for hepatic and renal functions. None had QT prolongation on ECG. At the end of 2 weeks’ treatment, moderate to complete relief of symptoms was reported by 22 patients (73%), whereas 5 (17%) reported slight improvement, and 3 (10%) reported no improvement. Clinical tolerability was excellent in 28 patients (93%) and good in 2 (7%). None of the patients had any prolongation of QT on ECG, nor did any patient show any abnormality in hemogram or serum chemistry during the treatment. Itopride is thus an effective drug with a very good safety profile.

For the use only of a Registered Medical Practitioner or a Laboratory or a Hospital

ABRIDGED PRESCRIBING INFORMATION

ITOZ

Composition: Each film coated tablet contains: Itopride hydrochloride ...50 mg. Indications: Treatment of gastrointestinal symptoms caused by reduced gastrointestinal motility, like feeling of gastric fullness, upper abdominal pain, anorexia, heartburn, nausea and vomiting, non-ulcer dyspepsia or chronic gastritis. Contraindications: GI hemorrhage, mechanical obstruction or perforation, hypersensitivity. Warnings: To be used with caution as it enhances the action of acetylcholine. Safety in children less than 12 years, pregnancy and lactation has not been established. Hence, treatment should be avoided in these conditions. Drug Interactions: Anticholinergic drugs may reduce the action of itopride. No interactions detected with warfarin, diazepam, diclofenac, nifedipine and nicardipine. Metabolic interactions are not to be expected because itopride is mainly metabolized by flavin monoxygenase. Adverse Effects: Hypersensitivity, diarrhea, constipation, abdominal pain, increased salivation. Neurologic, endocrinologic and hematologic adverse effects have been reported infrequently, therapy should be discontinued if hypersensitivity is seen. Dosage: The usual daily dosage is 150 mg of itopride hydrochloride orally in three divided doses before meals. The dose may be reduced, if required, depending on the patient’s age and symptoms at discretion of physician. This drug should be discontinued if no improvement of gastrointestinal symptoms is observed. Presentation: Blister pack of 10 tablets.