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## **ITOPRIDE: AN UPDATED REVIEW OF ITS PHARMACOLOGICAL PROPERTIES AND USE AS A PROKINETIC**

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### **ABSTRACT**

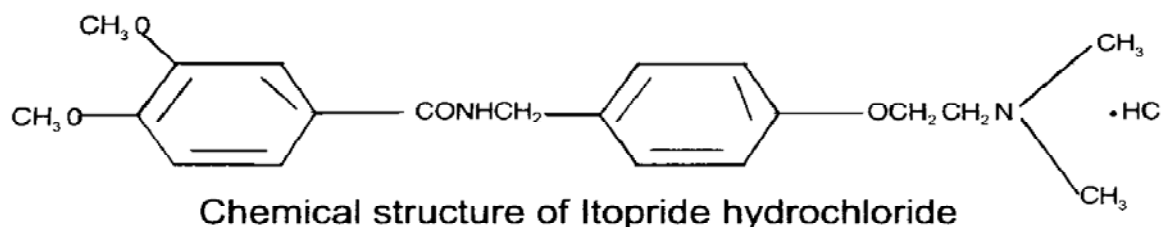
Itopride, a novel prokinetic agent is unique and different from the available prokinetics because of its dual mode of action and lack of significant drug interaction potential. Thus a prokinetic drug like Itopride, by virtue of its efficacy and tolerability could be considered as a drug of first choice and a welcome addition to the drug armamentarium for the symptomatic treatment of NUD and other gastric motility disorders including functional bowel disorders. This review article provides updated pharmacological as well as therapeutic properties of Itopride.

## INTRODUCTION

Itopride hydrochloride is an odourless, white to off white crystalline powder, Soluble in water, Methanol and sparingly soluble in Acetic Acid.

**Chemical name:** *N*-[[4-(2-Dimethylaminoethoxy)phenyl]methyl]-3,4-dimethoxybenzamide

**Structure:**



## PHARMACOLOGY

Itopride is used in the 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. Itopride has anticholinesterase (AChE) activity as well as dopamine D2 receptor antagonistic activity and is being used for the symptomatic treatment of various gastrointestinal motility disorders.

## PHARMACOKINETICS:

On oral administration, Itopride is rapidly and extensively absorbed and peak serum concentrations are achieved within 35 minutes after oral dosing.<sup>[1]</sup>

Thus it has a rapid onset of action, unlike cisapride and mosapride, which take around 60 minutes to reach peak plasma concentrations. Itopride is metabolized in the liver by N-oxidation to inactive metabolites by the enzyme flavin-containing monooxygenase(FMO).The half life of Itopride is about 6 hours.It is excreted mainly by the kidneys as metabolites and unchanged drug.<sup>[2, 3]</sup>

## PHARMACODYNAMIC:

Itopride has anticholinesterase (AChE) activity as well as dopamine D2 receptor antagonistic activity and is being used for the symptomatic treatment of various gastrointestinal motility disorders.<sup>[4, 5]</sup> It is well established that M3 receptors exist on the smooth muscle layer throughout the gut and acetylcholine (ACh) released from enteric nerve endings stimulates the contraction of smooth muscle through M3 receptors. The enzyme AChE hydrolyses the released

ACh, inactivates it and thus inhibits the gastric motility leading to various digestive disorders. Besides ACh, dopamine is present in significant amounts in the gastrointestinal tract and has several inhibitory effects on gastrointestinal motility, including reduction of lower esophageal sphincter and intragastric pressure. These effects appear to result from suppression of ACh release from the myenteric motor neurons and are mediated by the D2 subtype of dopamine receptors. Itopride, by virtue of its dopamine D2 receptor antagonism, removes the inhibitory effects on ACh release. It also inhibits the enzyme AchE which prevents the degradation of ACh. The net effect is an increase in ACh concentration, which in turn, promotes gastric motility, increases the lower esophageal sphincter pressure, accelerates gastric emptying and improves gastro-duodenal coordination (Figure). This dual mode of action of Itopride is unique and different from the actions of other prokinetic agents available in the market. [6- 11]

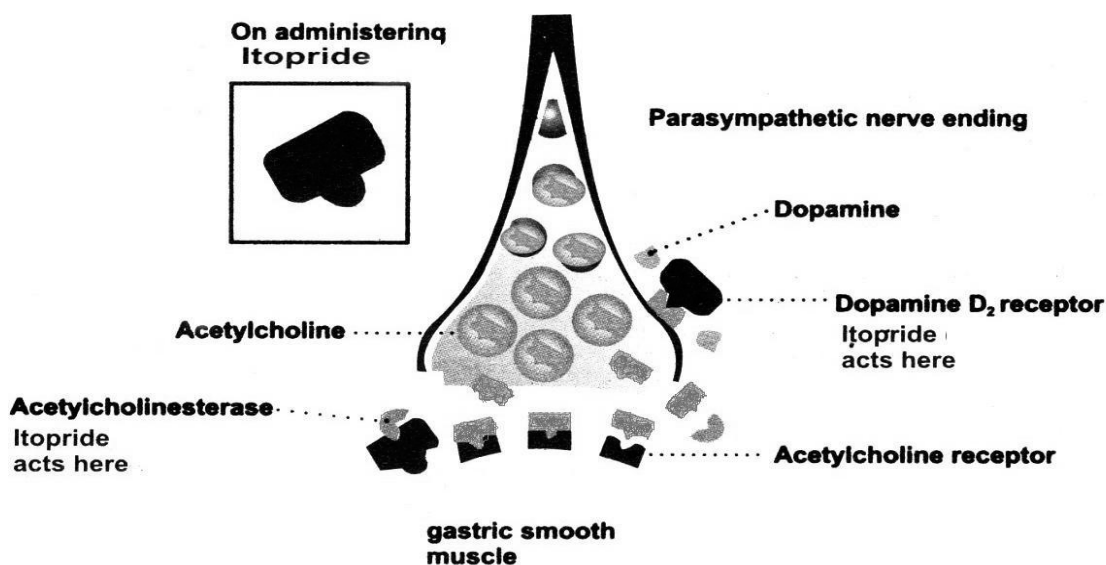


Figure: Mode of action of Itopride.

## THERAPEUTIC INDICATIONS

Various prokinetic studies were conducted in patients of NUD, reflux esophagitis and chronic gastritis, diabetic gastroparesis and functional dyspepsia. The results of these studies indicated that itopride is an effective prokinetic agent for the treatment of symptoms caused by altered gastrointestinal motility in all the above mentioned conditions. Few studies have shown that itopride is superior in efficacy to metoclopramide and cisapride in patients of NUD. Sawant *et al* in a comparative trial found itopride to be comparable in efficacy to Domperidone in the symptomatic management of NUD. [12- 17]

## **DRUG INTERACTIONS**

Unlike cisapride and mosapride citrate, itopride is metabolised by the enzyme flavin containing monooxygenase and not by the cytochrome P450 enzyme system. It is thus devoid of the risk of significant pharmacokinetic drug interaction with cytochrome P450 enzyme inhibitors such as macrolides and azole antifungal agents. <sup>[2]</sup>

## **TOLERABILITY**

Following the restriction imposed on cisapride usage and the subsequent report of the arrhythmic potential of mosapride, safety of a prokinetic drug has been a cause of concern. Itopride is well tolerated with few minor adverse drug reactions in the form of diarrhea, headache, abdominal pain etc. It has no significant effects on central nervous system and thus is devoid of extra pyramidal side effects and hyperprolactinaemia as is seen with other prokinetic drugs such as metoclopramide and domperidone. It also has no effect on the cardiovascular system. Preclinical and clinical studies till date indicate that this drug is not having the potential to cause prolongation of QT intervals unlike cisapride and mosapride. The affinity of cisapride for 5HT<sub>4</sub> receptors in the heart has been implicated in the undesirable cardiac effects of the drug but itopride has no affinity for 5HT<sub>4</sub> receptors which makes this drug a better and safer prokinetic agent. <sup>[18- 21]</sup> Safety of this drug has not been established in the pregnant females although no abnormalities in organogenesis and foetal developments were observed in animal studies. <sup>[22, 23]</sup>

## **CONTRAINDICATIONS**

Itopride should not be used in patients in whom an increase in gastrointestinal motility could be harmful, e.g. gastrointestinal hemorrhage, mechanical obstruction or perforation. Itopride should not be used in patients with known hypersensitivity to Itopride.

## **WARNINGS AND PRECAUTIONS**

### **Pregnancy**

The safety of this product in pregnant women has not been established. Therefore, this product should only be used in pregnant women or women suspected of being pregnant, provided that the expected therapeutic benefits are evaluated to outweigh the possible risk of treatment. No teratogenic effects have been detected in animals.

### **Lactation**

Itopride hydrochloride is excreted with the breast milk in lactating rats. Treatment with Itopride should be avoided during breast-feeding.

### **Pediatric use**

Safety of this product in children has not been established.

### **Geriatric use**

Since the elderly often have a physiological hypofunction, adverse reactions are likely to appear. The patients receiving this product, therefore, should be carefully observed and if any adverse reactions appear, appropriate measures such as reduction or interruption of the drug should be taken. In the clinical studies though, the rate of adverse drug reactions was not higher in the population with age of 65 and older than in younger patients.

### **Undesirable Effects**

The undesirable effects reported include:

**Allergic:** Rash, flare and itching sensation may occur rarely and should lead to discontinuation of therapy.

**Gastrointestinal:** Symptoms such as diarrhea, constipation, abdominal pain and increased saliva may occur infrequently.

**Psycho Neurologic:** Symptoms such as headache, irritated feeling, sleep disorder and dizziness may occur infrequently. Tremor has rarely been reported.

**Endocrine:** Increased prolactin may occur infrequently. Appropriate measures should be taken such as interruption or discontinuation of the treatment when any abnormality such as galactorrhea or gynecomastia is observed.

**Hematologic:** Leucocytopenia may occur infrequently. Careful observation should be made through hematological examination. The treatment should be discontinued when any abnormality is observed.

**Hepatic:** Increase in SGOT, SGPT, g-GTP and Alkaline phosphatase was rarely observed.

**Renal:** An increase in BUN and creatinine may occur infrequently.

**Others:** Chest or back pain and fatigue may occur infrequently.

### **OVERDOSAGE**

There have as yet been no reports of overdose in humans. The oral single dose LD 50 was > 2000 mg/kg in mice and rats and about 600 mg/kg in dogs. In case of excessive overdosage the usual measures of gastric lavage and symptomatic therapy should be applied. Itopride does not cause QT prolongation.

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