

## Itopride : A Novel Prokinetic Agent

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Non-ulcer dyspepsia (NUD), gastro-esophageal reflux disease (GERD), gastritis, diabetic gastroparesis and functional dyspepsia are commonly encountered disorders of gastric motility in clinical practice. Prokinetic drugs such as metoclopramide, domperidone, cisapride, mosapride etc. are the mainstay of therapy in these disorders. These drugs are used to relieve symptoms such as nausea, vomiting, bloating, belching, heartburn, epigastric discomfort etc.

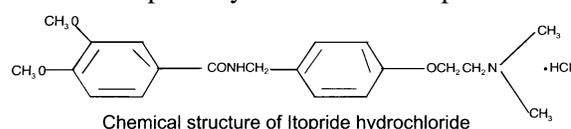
Prokinetic drugs act by promoting gastric motility, increase gastric emptying, prevent the retention and reflux of gastric contents and thus provide symptomatic relief (1). All the drugs in this group are efficacious with modest prokinetic activity but the matter of major concern is their side effect profile. The main side effects of metoclopramide are extra pyramidal such as dystonic reactions and domperidone, though is devoid of extra-pyramidal effects but is associated with galactorrhoea or gynaecomastia (2). Cisapride has the potential to cause QT prolongation on ECG, thus predisposing to cardiac arrhythmias and its use has been restricted by the US FDA (3). Mosapride too belongs to the same group and although its side effects are not well documented, it has drug interaction potential similar to that observed with cisapride(4). In this context a prokinetic agent with good efficacy and at the same time favourable tolerability profile is the need of the hour in the treatment of dyspepsia.

Itopride hydrochloride, a novel prokinetic agent has been introduced in the Indian market a few months

back(5). This drug was first developed by Hokuriku Seiyaker Co. Ltd. and has been marketed in Japan since Sept. 1995 (6).

### Chemistry

Chemically it is N-[P-[2-[dimethyl amino]ethoxy]benzyl] veratramide hydrochloride. Its molecular formula is  $C_{20}H_{26}O_4 \cdot HCl$  (6). The chemical structure of Itopride hydrochloride is depicted below:



### Mechanism of action

Itopride has anticholinesterase (AChE) activity as well as dopamine  $D_2$  receptor antagonistic activity and is being used for the symptomatic treatment of various gastrointestinal motility disorders (7, 8).

It is well established that  $M_3$  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  $M_3$  receptors (9). 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  $D_2$  subtype of dopamine receptors (2).

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Itopride, by virtue of its dopamine D<sub>2</sub> receptor antagonism, removes the inhibitory effects on Ach release. It also inhibits the enzyme AchE which prevents the degradation of ACh (8,10) 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. This dual mode of action (7,8,11) of Itopride is unique and different from the actions of other prokinetic agents available in the market as shown in the figures 1 & 2.

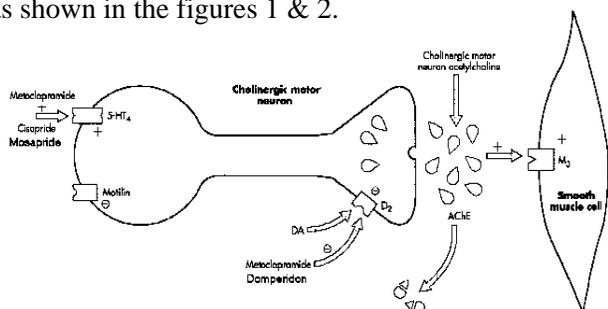


Fig. 1. Mechanism of action of prokinetic agents.

### 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 (9,14,15,16). Few studies have shown that itopride is superior in efficacy to metoclopramide (17) and cisapride (18) 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 (19).

### Dosage and Administration

The usual daily dosage for adults is 50mg of itopride hydrochloride orally in 3 divided doses before each meal (5).

### 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 (4).

### 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 (6). 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 (5). 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 (20, 20-22). 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 (2). Safety of this drug

Fig. 2. Mode of action of Itopride.

### Pharmacokinetics

On oral administration, Itopride is rapidly and extensively absorbed and peak serum concentrations are achieved within 35 minutes after oral dosing (12). Thus it has a rapid onset of action, unlike cisapride and mosapride, which take around 60 minutes to reach peak plasma concentrations (5). Food does not affect its absorption (13).

Itopride is metabolized in the liver by N-oxidation to inactive metabolites by the enzyme flavin-containing monooxygenase (FMO) (4). The half life of Itopride is about 6 hours (5). It is excreted mainly by the kidneys as metabolites and unchanged drug (4,5).

has not been established in the pregnant females (6) although no abnormalities in the organogenesis and foetal developments were observed in animal studies (23, 24).

### Conclusion

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.

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