DRUG REVIEW

Itopride : A Novel Prokinetic Agent

Seema Gupta, V. Kapoor, B. Kapoor

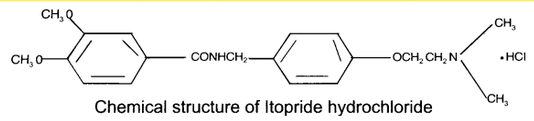
Non-ulcer dyspepsia (NUD), gastro-esophageal reflux disease (GERD), gastritis, diabetic gastroparesis and functional dyspepsia are commonly encountered disorders of gastric motility in clinical practice. Prokinetic drugs such as metoclopramide, domperidone, cisapride, mosapride etc. are the mainstay 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]ethoxyl]benzyl] veratramide hydrochloride. Its molecular formula is $C_{20}H_{26}O_4$. HCl (6).The chemical structure of Itopride hydrochloride is depicted below:



Chemical structure of Itopride hydrochloride

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 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 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).

From the Post-Graduate Department of Pharmacology & Therapeutics, Govt. Medical College, Jammu (J&K).
Correspondence to : Dr. Seema Gupta, Demonstrator, PG Deptarement of Pharmacology & Therapeutics, Govt. Medical College, Jammu.

Itopride, by virtue of its dopamine D_2 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.

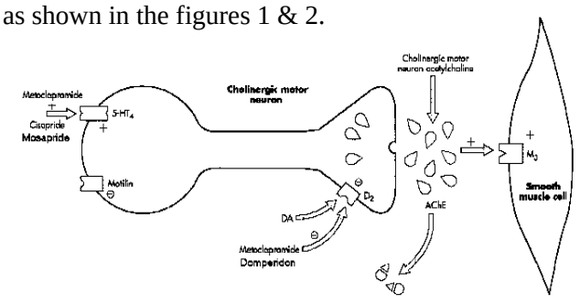


Fig. 1. Mechanism of action of prokinetic agents.

Fig. 2. Mode of action of Itropide.

Pharmocokinetics

On oral administration, Itopride is rapidly and extensively absorbed and peak serum concentrations are achieved within 35 minutes after oral dosing1 (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).

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 metabilised by the enzyme flaving 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 $5HT_4$ receptors in the heart has been implicated in the undesirable cardiac effects of the drug but itopride has no affinity for $5HT_4$ receptors which makes this drug a better and safer prokinetic agent (2). Safety of this drug

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 symptomtomatic treatment of NUD and other gastric motility disorders including functional bowel disorders.

References

1. Mcquaid KR.Dyspepsia. In: Mark Feldman *et al* (eds.), Sleisenger & Fordtran's Gastrointestinal and Liver Disease Pathophysiology/Diagnosis/Management.7th edition 2002; 1pp 102-18.
2. Pasricha PJ. Prokinetic agents, antiemetics agents used in irritable bowel syndrome. In: Hardman JG *et al* (eds.), Goodman and Gilman'ss The Pharmacological Basis of Therapeutics, 10th edition, New York, McGraw Hill Book Inc. 2001; pp 1021.
3. Wysowski DK, Corken A, Gallo TH *et al*. Post-marketing reports of QT prolongation & ventricular arrhythmias in association with cisapride and food and Drug administration regulatory actions. *Am J Gastroenterol* 2001; 96: 1698-1703.
4. Mushiroda T, Douya R, Takahara E, Nagata O. The involvement of flavin containing monooxygenase but not CYP3A4 in metabolism of itopride hydrochloride, a gastrokinetic agent: comparison with cisapride and mosapride citrate. *Drug Metab Dispos* 2000; 28: 1231-37.
5. Banka NH. Role of prokinetics in dyspepsia. *Gastroenterol Today* 2003; 7: 1-4.
6. Hokuriko Seiyaku Co. Ltd. Data on file. Revised: April 2001 (2nd version of new form).
7. Iwanga Y, Kemura T, Miyashita N *et al*. Characterisation of acetylcholinesterase inhibition by itopride. *Jpn J Pharmacol* 1994; 66: 317-22.
8. Iwanga Y, Miyashita N, Morikawa K, Mizumoto A, Kondo Y, Itoh Z. A novel water soluble dopamine-2 antagonist with anticholinesterase activity in gastrointestinal motor activity. *Gastroenterol* 1990; 99: 57-64.
9. Tadashi Tsubouchi, Takaharu Saito, Fujie Mizutani, Toshie Yamauchi,Yuji Iwanga. Stimulatory action of Itopride hydrochloride on colonic motor activity in vitro and in vivo. *J Pharmacol Exp Therapeut* 2003; 306: 787-93.
10. Iwanga Y, Suzuki N, Kato KI, Morikawa K, Kato H, Ito Y, Gomi Y. Stimulatory effects of HSR-803 on ileal motor activity. *Jpn J Pharmacol* 1993; 62: 395-401.
11. Iwanga Y, Miyashita N, Mizutani F,et al. stimulatory effect of N-[-4[2-(dimethyl-amino)ethoxy]benzyl]-3-4-dimethoxy-benzamide hydrochloride (HSR-803) on normal and delayed gastrointestinal propulsion. *Jpn J Pharmacol* 1991; 56: 261-69.
12. Nakajima M, Uematsu T, Nakajima S, Nagata O, Yamaguchi T. Phase 1 study of HSR-803. *Jpn Pharmacol Ther* 1993; 21(11): 4157-73.
13. Noda T. Effects of meal on Pharmacokinetics of HSR-803 in Humans. Hokuriku Seiyaku Co Ltd. Data on file. Revised: April 2001.
14. Otsuba T, Mizokami Y, Shiraishi T, Narasaka T. Nakamura H, Takeyama H *et al*. Effect of Itopride hydrochloride on non-ulcer dyspepsia. *Clin Med* 1998;14: 94-97.
15. Inoue K, Sanada Y, Fujimura J, Mihara O. Effect of Itopride hydrochloride on the digestive symptoms of chronic gastritis with reflux esophagitis.*Clin Med* 1999; 15: 1803-09.
16. Noritake M, Kikuchy Y, Otsubo T *et al*. Effect of itopride hydrochloride on diabetic gastroparesis. *Kiso To Rinsho* 1997; 31(8): 2785-91.
17. Kamath, Vinod K, Verghese J, Bhatia S. Comparative evaluation of the efficacy and tolerability of Itopride and Metoclopramide in patients with NUD. *JAMA* 2003; 2(8): 95-98.
18 Miyoshi A, Masamime O, Sekiguchi T *et al*. Clinical evaluation of itopride hydrochloride for gastrointestinal symptoms associated with chronic gastritis: a multicentre double blind clinical trial using cisapride as control drug. *Clin Pharmacol & Therap* 1994; 4 (2): 261-79.
19. Sawant P, Kalokhe S, Patil S. Comparative evaluation of itopride hydrochloride and domperidone in patients with dyspepsia and chronic gastritis. *Gastroenterol Today* 2002; 2: 1-4.
20. Kakuichi M, Saito T, Ohara N *et al*. Pharmacological evaluation of itopride hydrochloride with regard to drug induced arrhythmia. *Jpn Pharmacol Ther* 1997; 25: 822-27.
21. Takuma K, Ohtani K, Kotaki H, Iga T. Comparative studies of drug induced arrhythmia in guinea pigs by cisapride and itopride hydrochloride: prolongation of QT interval and search for alternative drugs to avoid side effect. The Annual meeting of Hospital and Pharmaceutical society of Japan, Nagoya. Sep 13-14, 1997.
22. Ohki R, Takahashi M, Mizuno O, Fujikawa H *et al*. Torsades de pointes ventricular tachycardia induced by mosapride and flecainide in the presence of hypokalemia. *Pacing Clin Electophysiol* 2001; 24: 119-21.
23. Kawakami Y, Nomura G, Hatakeyama Y *et al*. A reproductive and developmental study by oral administration of HSR -803 before and during the early stages of gestation period in rats. *Preclin Rep Cent Inst Exp Anim* 1992; 18 (2): 87-102.
24. Shimomura K *et al.* A dose finding experiment for a study by oral administration of HSR-803 during the period of fetal organogenesis in rabbits. *CLEA Preclin Res Rep* 1992; 18 (2):145.