

## Mosapride in the Treatment of Gastrointestinal Disorders

Bani Chander and Anish Sheth

Yale University School of Medicine, New Haven, CT 06510, USA. Email: anish.sheth@yale.edu

---

**Abstract:** Prokinetic drugs are being used with increasing frequency in the treatment of functional gastrointestinal disorders including functional dyspepsia (FD) and constipation-predominant Irritable Bowel Syndrome (IBS-C). Mosapride is a gastro-prokinetic agent that acts as a selective 5-HT<sub>4</sub> agonist thereby accelerating gastric emptying. It has been used for the treatment of irritable bowel syndrome (IBS), functional dyspepsia (FD), and gastroesophageal reflux (GERD). Mosapride shares physiologic effects with previous 5-HT<sub>4</sub> agonists, cisapride and tegaserod, but with a safer cardiac profile.

**Keywords:** irritable bowel syndrome, functional dyspepsia, mosapride, cardiovascular health

---

*Clinical Medicine Reviews in Therapeutics* 2010:2 53–58

This article is available from <http://www.la-press.com>.

© Libertas Academica Ltd.



## Introduction

Prokinetic drugs are being used with increasing frequency in the treatment of functional gastrointestinal disorders including functional dyspepsia (FD) and constipation-predominant Irritable Bowel Syndrome (IBS-C). In the United States and Europe, the prevalence of IBS approaches 10%–20% of the general population<sup>1</sup> and is the most common diagnosis encountered by gastroenterologists in clinical practice.<sup>2</sup>

Mosapride is a gastroprokinetic agent that acts as a selective 5-HT<sub>4</sub> agonist thereby accelerating gastric emptying. It has been used for the treatment of irritable bowel syndrome (IBS), functional dyspepsia (FD), and gastroesophageal reflux (GERD). In fact, prokinetic drugs along with fiber products have become the mainstay in the treatment of IBS-C. Although mosapride has not been well studied in the treatment of IBS, several studies have demonstrated the efficacy of tegaserod, another prokinetic 5-HT<sub>4</sub> receptor partial agonist, and cisapride (5HT-4 agonist/5HT<sub>3</sub> antagonist) in the treatment of IBS-C.<sup>3,4</sup> Unlike other medications for IBS that target specific symptoms, 5-HT<sub>4</sub> receptor agonists offer a novel mechanism of action in the treatment of IBS-C.

Cisapride was initially developed as a prokinetic agent which lacked the side effects of D<sub>2</sub> receptor antagonists. Cases of QTc prolongation leading to cardiac arrhythmias, including torsades de pointes, lead to its withdrawal from the market in 2000. In 2002, tegaserod was then introduced as a 5-HT<sub>4</sub> receptor agonist that lacked the 5-HT<sub>3</sub> receptor antagonist activity. In 2004, a Cochrane based review which also included the Cochrane Central Register of Controlled Trials and the Inflammatory Bowel Disease Review Group Specialized Trials Register, showed that tegaserod improved overall symptomatology in IBS-C and reduced frequency of bowel movements. Additionally, global relief in gastrointestinal symptoms was higher in the tegaserod group as compared to placebo. Tegaserod also improved abdominal pain in women with IBS-C.<sup>5</sup>

Although tegaserod appeared to be a promising medication in the treatment of IBS-C and chronic idiopathic constipation, problems with tegaserod also became apparent. In March 2007, Novartis Pharmaceuticals offered the FDA results of 29 clinical studies of 11,614 patients with Zelnorm<sup>®</sup> for the treatment of

a variety of gastrointestinal tract conditions. The data from all the studies were combined to assess the risk of side effects on cardiovascular health, including angina, myocardial infarction, and CVA.<sup>6</sup> Overall, patients treated with Zelnorm<sup>®</sup> had a higher risk of serious and life-threatening side effects as compared with placebo. Tegaserod is currently only available via the Treatment IND program administered by the manufacturer, Novartis. It is important to note, however, that the absolute number of patients with significant side effects was low. In fact, only thirteen patients treated with Zelnorm (0.1%) had serious cardiovascular side effect; among these, six had angina, four patients had a heart attack, and three had stroke.

## Mechanism of Action

While the precise pathophysiology of irritable bowel syndrome remains unclear, several different classes of medications have been used to manage IBS symptoms including fiber, antidiarrheal agents, antispasmodic agents, tricyclic antidepressants, SSRIs, and most recently, prokinetic agents. Aside from prokinetic agents, these treatments have been effective for isolated symptoms but have not been successful in the full range of symptoms in patients who suffer with IBS.

Studies in IBS have demonstrated abnormalities in the migrating motor complex (MMC) including short cycle length, stress induced irregular contractions, and even complete abolition of the MMC during periods of stress.<sup>7,8</sup> Serotonin (5-HT) is released from enterochromaffin cells in the gut and facilitates release of the neurotransmitter acetylcholine via 5-HT<sub>4</sub> receptors expressed on nerve terminals of gastrointestinal motor neurons and interneurons. The mechanism of prokinetic 5-HT<sub>4</sub> receptor agonism in IBS is thought to be in part due to their effect on acetylcholine concentrations, enhancing motility via the migrating motor complex.

5-HT<sub>4</sub> agonists' principal mode of action is via stimulation of 5-HT<sub>4</sub> receptors on intestinal enterocytes, leading to release of acetylcholine and subsequent enhanced propagation of contractions in the gastrointestinal tract. These medications also increase fluid secretion into the gut lumen, thus enhancing stool passage and transit.<sup>9</sup> In addition, 5-HT<sub>4</sub> receptors modulate visceral sensitivity, therefore, theoretically medications

**Table 1.** Human studies with mosapride.

Author, year	# of Subjects	Dose and duration	Results
<b>I. Functional dyspepsia</b>			
Chen et al (2004)	231	5 mg mosapride TID vs. 10 mg domperidone × 4 wk	Mosapride improved overall symptoms as compared to control
Otaka et al (2005)	81	Mosapride 15 mg/d vs. famotidine 20 mg/d × 4 wk	Both had similar efficacy in relieving FD symptoms
Kinoshita et al (2005)	79	mosapride vs. famotidine vs. tansospirone × 4 wk	Mosapride and famotidine improved symptoms significantly greater than tansospirone
Hallerback et al (2002)	140	Mosapride 5 mg, 7.5 mg, and 10 mg BID vs. placebo × 6 wk	Overall dyspeptic symptom score was similar between the 2 groups
Hiyama et al (2006)	797	Mosapride vs. cisapride vs. placebo (metanalysis 1951–2005)	Mosapride had a greater probability of producing a response compared to control; no effect observed with cisapride
Curran et al (2008)	1042	Mosapride vs. famotidine vs. itopride vs. teprenone × 2 wk	Mosapride more effective than tansospirone but similar efficacy to famotidine and itopride
Seno et al (2005)	64	Mosapride 15 mg/d vs. famotidine 40 mg/d vs. tansospirone 30 mg/d × 2 wk	Famotidine was significantly more effective than mosapride on a visual analogue scale
Amarapurkar et al (2004)	60	Mosapride 5 mg TID vs. itopride 50 mg TID × 2 wk	Global efficacy was rated excellent in significantly more patients in the itopride group vs. in the mosapride group
<b>II. GERD</b>			
Ruth et al (1998)	21	Mosapride 40 mg QD vs. placebo × 2 days	Mosapride significantly more effective than placebo in decreasing total number and time of reflux episodes
Ruth et al (2003)	23	Mosapride 60 mg BID vs. mosapride 30 mg TID vs. cisapride 20 mg QD wk	Mosapride had significant effects on peristaltic durations and amplitudes in 24 hr ambulatory motility recordings as compared to cisapride
Madan et al (2004)	61	Pantoprazole 40 mg BID vs. pantoprazole 40 mg BID + mosapride 5 mg TID × 8 wk	In non-erosive GERD, there was no significant difference in symptoms. In erosive esophagitis, symptomatic relief was more frequent in the combination of pantoprazole plus mosapride vs. pantoprazole alone
<b>III. Chronic Constipation</b>			
Liu et al (2005)	14	Mosapride 15 mg/day × 3 months	Mosapride improved bowel frequency and difficult defecation in Parkinson patients and shortened colonic transit time.



in this class should help alleviate abdominal pain associated with IBS-C.<sup>6</sup>

For several years, tegaserod was the single most used drug in this class and was widely used for treatment of FD, GERD and gastroparesis.<sup>10</sup> At present, other medications in this drug class are being utilized for the treatment of IBS-C, functional dyspepsia, and acid reflux. Renzapride (Alizyme) is another mixed 5-HT<sub>3</sub> receptor antagonist/5-HT<sub>4</sub> receptor agonist, which is presently in Phase III clinical trials for IBS-C. Prucalopride (Johnson & Johnson/Movetis) is a selective 5-HT<sub>4</sub> receptor agonist follow-up to cisapride, lacking hERG potassium channel liabilities. Positive data from Phase III studies in chronic constipation has been reported, however, Janssen has put its development on hold due to rat carcinogenicity findings. Mosapride is currently approved in Japan for gastritis and is now being studied for use in the United States in the management of FD, acid reflux, and IBS-C.

## Animal Studies

Several animal studies have demonstrated the efficacy of prokinetic 5-HT<sub>4</sub> agonists. Guinea pigs are known to have colonic 5-HT<sub>4</sub> receptors in a similar distribution to that in humans.

Inui et al, studied the effects of mosapride and cisapride on colonic motility in conscious guinea pigs implanted with force transducers. Mosapride and cisapride were administered intragastrically and were found to significantly enhance colonic motility. The enhancing effect of mosapride was antagonized by atropine or GR113808, a 5-HT<sub>4</sub>-receptor antagonist, but not by methylsergide, a 5-HT<sub>1</sub> and 5-HT<sub>2</sub> receptor antagonist. In vitro receptor autoradiography showed that mosapride and cisapride inhibit the specific binding of a selective radioligand of 5-HT<sub>4</sub> receptors in the colon of guinea pigs. Their findings show that 5-HT<sub>4</sub> agonists enhance colonic motility through the 5-HT<sub>4</sub>-receptor activation in guinea pigs and suggest that it may be useful for treating constipation in patients with colonic motility dysfunction.<sup>11</sup>

Mosapride has also been compared to erythromycin and cisapride in rats and has been shown to be superior to erythromycin and have an equal efficacy to cisapride in terms of gastric emptying. In addition, in conscious dogs with force transducers implanted chronically,

mosapride stimulated antral and duodenal motility with a potency equal to that of cisapride without demonstrating any of the adverse cardiovascular effects associated with cisapride.<sup>12</sup>

In addition, animal studies have also demonstrated both a neuroprotective and neurotrophic effect of 5-HT<sub>4</sub> agonists on enteric neurons. Gershon et al, studied the knockout of 5-HT<sub>4</sub> receptors in mice and demonstrated that it not only slowed gastrointestinal activity but additionally, after 1 month of age, there was also an increase in the age-related loss of enteric neurons and decreases in the size of neurons that survived. 5-HT<sub>4</sub> agonists, specifically tegaserod and RS67506, increased the number of enteric neurons developing from precursor cells and/or surviving in culture. These agonists were also found to increase neuronal outgrowth and decrease apoptosis. The 5-HT<sub>4</sub> receptor antagonist, GR113808, blocked all of these effects. The authors concluded that 5-HT<sub>4</sub> receptor agonists are neuroprotective and neurotrophic for enteric neurons in addition to their other known benefits.<sup>13</sup>

## Human Studies

While there have been several animal studies demonstrating the efficacy of 5-HT<sub>4</sub> agonists, fewer human studies have been performed with success. The majority of human studies with mosapride have studied its efficacy in patients with functional dyspepsia (FD).

## Functional dyspepsia

Chen et al, conducted a randomized control trial to study the effect of mosapride in a cohort of patients with functional dyspepsia (FD). In this cohort of 231 patients, mosapride was given three times daily for 4 weeks in the treatment group vs. a control of 10 mg of domperidone given three times daily for 4 weeks. Changes in symptom score and gastric emptying time were primary endpoints. Results showed that the total efficacy rates in early satiety and abdominal distension were 84.5% and 90.1% in mosapride after the 2 weeks of treatment. Mosapride also appeared to be more effective in improving symptoms of belching, heartburn, and abdominal distention as compared to the control group. Additionally, a decrease in the symptom score was more notable in the mosapride arm as compared to the control group. There was



no significant difference between the two groups in terms of side effects.<sup>14</sup>

One year later, Otaka et al, compared the efficacy of H<sub>2</sub> receptor antagonists (famotidine) as compared to 5-HT<sub>4</sub> receptor agonists (mosapride) in patients with FD. 81 patients were randomized to receive either famotidine or mosapride for 4 weeks and the efficacy was compared between the 2 groups using a 10 point visual analogue scale. As first line therapy, both famotidine and mosapride showed beneficial effects and similar efficacy (65% vs. 58.5%). Amitriptyline was given in patients who failed first step therapy.<sup>15</sup>

In 2006, Hiyama et al, performed a meta-analysis of randomized controlled trials comparing serotonin agonists with other types of prokinetics in patients with FD. They identified 5 studies by searching the Medline database (January 1951–January 2005) and Cochrane Library (Issue 4, 2004), and by manual searches. The studies included 5-HT<sub>4</sub> agonists (both cisapride and mosapride) and compared them to dopamine antagonists, including metoclopramide and domperidone, and an opiate agonist, trimebutine, in patients with FD. The difference in the probability of patients' responses between the serotonin agonists and control agents was used as a summary statistic for the treatment effect. Meta-regression analysis was used to detect sources of heterogeneity. A total of 467 subjects were assigned to a serotonin agonist arm and 322 subjects were assigned to a control arm. In the overall analysis, the summary statistic was 0.019 (95% confidence interval [CI]: -0.055 to 0.093;  $P = 0.612$ ), indicating that the patients' responses to serotonin agonists were similar to those to control agents. However, in the stratified meta-analysis of cisapride and mosapride, mosapride had a 6.7% greater probability of producing a response compared with control agents), whereas no significant effect was observed with cisapride. Their data suggest that mosapride may be more effective than cisapride for the treatment of FD.<sup>16</sup>

### GERD, functional dyspepsia, and chronic gastritis

Mosapride has also been shown to be effective in improving overall symptoms in patients with FD as well as other gastrointestinal disorders including gastroesophageal reflux disease (GERD), and chronic

gastritis. In a recent open-label trial of 1042 patients with GERD, FD, and chronic gastritis, mosapride was found to be more effective than tansospirone and as effective as both famotidine and itopride, in improving gastric stasis symptoms and gastric pain after only 2 weeks of therapy. Mosapride was also very well tolerated with minor side effects noted in less than 5% of patients.<sup>17</sup>

### Chronic constipation

Mosapride improves symptoms in patients with chronic constipation. Liu, et al conducted an open label trial of mosapride's effects on constipation in patients with Parkinson's disease. A total of 14 Parkinson patients (7 with Parkinson's disease, 7 with multiple system atrophy; 10 men, 4 women; mean age, 67 years) with constipation (10 with bowel movement <3 times/week; 14 with difficulty in defecation) were treated with 15 mg/day of mosapride for 3 months. Pre- and post-treatment objective parameters in colonic transit time (CTT) and rectoanal videomanometry were obtained. 13 patients reported subjective improvements in bowel frequency (>3 times/week) and difficult defecation. Mosapride shortened CTT of the left colon ( $P < 0.01$ ) and the total colon ( $P < 0.05$ ). During rectal filling, mosapride lessened the first sensation ( $P < 0.05$ ) and augmented the amplitude in phasic rectal contraction. During defecation, mosapride augmented the amplitude in rectal contraction ( $P < 0.05$ ) and lessened the volume of post-defecation residuals. This is the first study to show that mosapride augments lower gastrointestinal tract motility, as shown in CTT and videomanometry, and via this mechanism, relieved constipation in Parkinsonian patients.<sup>18</sup>

### Constipation predominant IBS

There is currently an ongoing study at the American University of Beirut Medical Center, which began in September 2008, looking at the effect of mosapride on the treatment of IBS-C. Men and women, aged 18–75, who fit Rome III criteria for IBS are being included in the study. Mosapride 5 mg TID  $\times$  8 weeks is being compared to placebo. Pre-determined outcomes include adequate relief of symptoms associated with constipation-predominant irritable bowel syndrome. Thus far, 130 patients have been enrolled and the estimated study completion date is September 2010.<sup>19</sup>



## Safety

Mosapride does not appear to share the significant cardiovascular risks of cisapride and tegaserod. This difference is likely due to mosapride's lack of effect on effect on cardiac K<sup>+</sup> channels. Encouragingly, studies thus far have not demonstrated QTc prolongation and cardiac arrhythmias.

## Conclusions/Future Studies

Better understanding of the role of serotonin and serotonin receptors in intestinal motility as well as in gut-brain signaling has led to use of prokinetic agents in patients with IBS-C, GERD, gastroparesis, FD and chronic constipation. These serotonergic agents have demonstrated modest clinical benefit but use of older generation medications has been limited by cardiac complications.

Mosapride, a selective 5-HT<sub>4</sub> agonist, shares physiologic effects with previous 5-HT<sub>4</sub> agonists, cisapride and tegaserod, but with a safer cardiac profile. In addition, research demonstrating age-related decline in numbers of enteric neurons may raises the possibility of utilizing mosapride for its neuroprotective properties.

No clinical studies have specifically examined the effects of mosapride in patients with IBS-C. Future long-term randomized control trials are needed to assess their efficacy in this subgroup of patients that could significantly benefit from 5-HT<sub>4</sub> serotonin receptor agonism without the harmful cardiovascular effects of its predecessors.

## Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors report no conflicts of interest.

## References

1. Videlock E, Chang L. Irritable Bowel Syndrome: Current Approach to Symptoms, Evaluation, and Treatment. *Gastroenterology Clin North Am.* 2007;36:666–85.
2. Sandler RS, Everhart JE, Donowitz M. The burden of selected digestive diseases in the United States. *Gastroenterology.* 2002;122:1500–11.
3. Beglinger C. Tegaserod: a novel, selective 5-HT<sub>4</sub> receptor partial agonist for irritable bowel syndrome. *Int J Clin Pract.* 2002 Jan–Feb;56(1):47–51.
4. Lacy BE, Yu S. Tegaserod: a new 5-HT<sub>4</sub> agonist. *J Clin Gastroenterol.* 2002 Jan;34(1):27–33.
5. Kale-Pradhan PB, Wilhelm SM. Tegaserod for Constipation-Predominant Irritable Bowel Syndrome. *Pharmacotherapy.* 2007 Feb;27(2):267–77.
6. FDA Public Health Advisory: Tegaserod maleate (marketed as Zelnorm). 2007 <http://www.fda.gov/cder/drug/advisory/tegaserod.html>.
7. Kellow JE, Gill RC, Wingate DL. Prolonged ambulant recordings of small bowel motility demonstrate abnormalities in the irritable bowel syndrome. *Gastroenterology.* 1990;98:1208–18.
8. Kumar D, Wingate DL. The irritable bowel syndrome: a paroxysmal motor disorder. *Lancet.* 1985;2:973–7.
9. Borman RA, Burleigh DE. Human colonic mucosa possesses a mixed population of 5-HT receptors. *Eur J Pharm.* 1996 Aug;309(3):271–4.
10. Giger R, Mattes H, Pfannkuche HJ. Case history on Tegaserod. *Ann Rep Med Chem.* 2007;42:195–209.
11. Inui A, Yoshikawa T, Nagai R, Yoshida N, Ito T. Effects of mosapride citrate, a 5-HT<sub>4</sub> receptor agonist, on colonic motility in conscious guinea pigs. *Jpn J Pharmacol.* 2002 Dec;90(4):313–20.
12. Yoshida N. Pharmacological effects of the gastroprokinetic agent mosapride citrate. *Nippon Yakurigaku Zasshi.* 1999 May;113(5):299–307.
13. Gershon MD, Liu MT. Serotonin and neuroprotection in functional bowel disorders. *Neurogastroenterol Motil.* 2007 Aug;19 Suppl 2:19–24.
14. Chen SY. A randomized controlled Multi-center clinical trial on mosapride in the treatment of functional dyspepsia. *Zhonghua Liu Xing Bing Xue Za Zhi.* 2004 Feb;25(2):165–8.
15. Otaka M. New Strategy of therapy for functional dyspepsia using famotidine, mosapride, and amitriptyline. *Alimen Pharmacol Ther.* 2005 Jun;21 Suppl 2:42–6.
16. Hiyama T. Treatment of functional dyspepsia with serotonin agonists: a meta-analysis of randomized controlled trials. *J Gastroenterol Hepatol.* 2007 Oct;22(10):1566–70.
17. Curran MP, Robinson DM. Mosapride in gastrointestinal disorders. *Drugs.* 2008;68(7):981–91.
18. Liu Z. Mosapride citrate, a novel 5-HT<sub>4</sub> agonist and partial 5-HT<sub>3</sub> antagonist, ameliorates constipation in parkinsonian patients. *Mov Disord.* 2005 Jun;20(6):680–6.
19. Sharara A. Randomized Trial of Mosapride Versus Placebo in the Treatment of Constipation-Predominant Irritable Bowel Syndrome. American University of Beirut Medical Center, NCT00742872.