5-HT₄ Receptor Agonists in the Treatment of Gastrointestinal Motility Disorders: Current Status and Perspective

Min Jung Lee ¹,²*, Sunghak Choi¹ and Weonbin Im¹

¹Dong-A St Research Institute, 21 Geunhwa-ro, 105beon-gil, Giheung-gu, Yongin-si, Gyeonggi-do, 446-905, Korea
²Department of Anatomy and Cell Biology, School of Medicine, Sungkyunkwan University, Suwon-si, Gyeonggi-do, 440-746, Korea

Abstract

Background: 5-HT₄ receptor plays important roles regulating gastrointestinal motility, enteric neuronal signaling and visceral pain in the gastrointestinal tract. Over the past decade, the 5-HT₄ receptor has been highlighted as an attractive drug target for the treatment of gastrointestinal motility disorders such as irritable bowel syndrome, chronic constipation, functional dyspepsia, gastroparesis and so on.

Objectives: This article aims to provide an overview of serotonin receptors related to the gastrointestinal motility disorders, and to address the characteristics of past, current and future 5-HT₄ receptor agonists for treatment of functional gastrointestinal disorders, focusing on the pharmacology, efficacy and safety profile.

Methods: A literature search was performed using databases including MEDLINE (1974-July 2014), SCOPUS, Google Scholar, abstracts presented at the gastroenterology meetings and unpublished data from pharmaceutical companies. Specific search terms used were "5-HT₄, receptor agonist", "gastrointestinal motility disorder", "irritable bowel syndrome" and "chronic constipation".

Conclusion: In contrast to nonselective 5-HT₄ receptor agonists such as tegaserod and cisapride, which were withdrawn due to cardiovascular adverse effects, several potent and selective 5-HT₄ receptor agonists have been found to display the improved safety profile and the therapeutic potential in clinical trials and preclinical studies. These include agents such as prucalopride, velusetrag, naronapride, YKP10811 and DA-6886. These compounds differ in chemistry, efficacy, adverse effects and pharmacokinetics. The various properties of 5-HT₄ receptor agonists will help us not only to enable adequate treatment to be tailored to the needs of each patient but also to stimulate further efforts to develop promising innovative drugs for gastrointestinal motility disorders.

Introduction

Gastrointestinal (GI) motility disorder including irritable bowel syndrome, chronic constipation, functional dyspepsia and gastroparesis is a common and debilitating disease that has a profound effect on patient's quality of life and imposes a substantial economic burden. Irritable bowel syndrome (IBS) is characterized by abnormalities in motility and visceral hypersensitivity [1]. The underlying cause is thought to involve dysfunction in GI motility, psychological factors, hypersensitivity and inflammation of the bowel, and aberrant autonomic function. In meta-analysis, the overall IBS prevalence was 11.2% with variation by geographic region; the lowest occurring in South Asia (7.0%) and the highest in South America (21.0%) [2]. Several Asian studies showed that the prevalence of IBS in Singapore, Tokyo and South Korea was 8.6%, 9.8% and 6.6%, respectively [3,4]. According to predominant bowel habit disturbance (described in the Rome III criteria), IBS patients were classified as IBS with constipation (IBS-C), IBS with diarrhea (IBS-D) and mixed form (IBS-M). The relative proportion of IBS-C is reported to range from 5.2% to 66%[5]. Patients with IBS reported considerable impairments in health status having not only poor health-related quality of life (HRQOL) with dietary restrictions, mood disturbance and interference with daily activity but also severe symptoms as pain, bowel difficulties, bloating and eating/dietary restrictions [6,7].

In terms of GI motility, chronic constipation (CC) and IBS-C overlap symptoms. CC patients exhibit little or no abdominal pain, whereas IBS-C patients experience it. Chronic constipation is a highly common bowel disorder that affects up to approximately 27% of the North American population [8,9]. Constipation affects older age groups disproportionately, with a prevalences of 50% in community-dwelling elderly and 74% in nursing-home residents [10]. In addition, secondary constipation is caused by medication as well as pathophysiological conditions including malignancy, endocrine disorders, neurologic disorders, metabolic diseases and pregnancy. The medications causing constipation as a side effect include antacids, calcium and iron supplements, antidiarrheal agents, nonsteroidal anti-inflammatory agents, opioids, tricyclic antidepressants, diuretics, anticholinergic agents, antihistamines and so on [11,12].

Functional dyspepsia (FD) and gastroparesis (GP) are the two most common motility disorders of the upper gastrointestinal tract. The prevalence of FD was between 11.5% and 14.7%, and that of GP was approximately 1.5–3% [13,14]. Functional dyspepsia is characterized by the presence of chronic or recurrent symptoms of upper abdominal pain or discomfort in the absence of any known specific structural cause [15]. Gastroparesis is a disorder characterized by delayed gastric emptying [14,16]. It is believed to be caused by not only diseases such as diabetes mellitus, peptic ulcer and gastroesophageal reflux but also surgery with partial gastric resection.

Keywords:
5-HT₄ receptor agonist, Irritable bowel syndrome, Constipation, Tegaserod, Cisapride, Prucalopride, Velusetrag, Naronapride, YKP10811, DA-6886

Acknowledgments:
This work was supported by the project 20140158 awarded by the Ministry of Science, ICT and Future Planning, South Korea.

References:

Copyright: © 2014 Lee MJ et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Currently, a variety of medication to treat these GI motility disorders are available. Traditional laxatives including bulk ing agents, stool softeners, osmotic laxatives and stimulant are effective in defecation, but the laxatives demonstrate a limited level of efficacy in long-term use, abdominal discomfort or bloating. A number of new medications include the prokinetic selective 5-HT₄ receptor agonist (prucalopride), the intestinal chloride channel activator (lubiprostone) and the guanylate cyclase-C agonist (linaccotide). 5-HT₄ receptor has been highlighted as an attractive drug target for the treatment of GI motility disorders. 5-HT₁₇ receptor agonists such as tegaserod, cisapride, prucalopride and mosapride have been demonstrated to be efficacious in patients with gastrointestinal disorders [17,18,19,20]. Despite of the proven efficacy, some of these agents were not 5-HT₄ receptor-selective, and the lack of selectivity continued to make severe adverse effects. Cisapride was withdrawn due to cardiovascular adverse effects associated with QT prolongation because it is a potent blocker of the hERG (human ether-a-go-go related gene) channel [21]. Tegaserod, the first drug approved by the FDA for the treatment of chronic idiopathic constipation and IBS-C has also been withdrawn from the market due to a higher chance of ischemic adverse events. Therefore, a real need exists for more effective, well-tolerated and safe pharmacological agents to manage the common and troublesome symptoms of these GI motility disorders.

The aims of this review are to discuss how advance in our understanding of 5-HT receptors, and to overview the previous and ongoing research and development of 5-HT₁₇ receptor agonists in treatment for gastrointestinal motility disorders. The review focuses on seven 5-HT₁₇ receptor agonists that are currently of interest: Tegaserod, Cisapride, Prucalopride, Naronapride, Velusetrag, YKP10811 and DA-6886.

Serotonin Receptors in Gastrointestinal Tract

Serotonin (5-hydroxytryptamine, 5-HT) is the main enteric neurotransmitter regulating gastrointestinal motility, smooth muscle tone, mucosal secretion and neuronal signaling [22-5], and 95% of serotonin is found in the gastrointestinal tract, and released from enterochromaffin cells distributed throughout the gut mucosa [26].

The physiological role of enteric serotonin is determined by which serotonin receptors are activated. It means specific serotonin receptors provide the site of action for therapeutic agents for gastrointestinal motility disorders. Seven molecularly distinct subtypes (5-HT₁₇, 5-HT₂B, 5-HT₅, 5-HT₆, 5-HT₇ and 5-HT₁₇) receptors are distributed in the enteric nervous system or smooth muscle in the rat esophagus [27,28]. 5-HT₁₇ receptor inhibit neurotransmitter release while 5-HT₆, 5-HT₇, 5-HT₁₇ and 5-HT₁₇ receptors are distributed in the enteric nervous system or smooth muscle in the gut. 5-HT₁₇ receptor inhibits the release of acetylcholine and the contraction of smooth muscle [29]. Buspirone, 5-HT₁₇ receptor agonist, enhanced gastric accommodation in patients with functional dyspepsia in clinical studies [30]. Also, buspirone increases lower oesophageal sphincter tone and slows gastric emptying in human [31]. Sumatriptan, a selective 5-HT₁₇ receptor agonist, induces a lag phase for gastric emptying of liquids [32], and increases the amplitude and duration of esophageal contractions in humans [33].

In smooth muscle, 5-HT₁₇ mediates contraction, while 5-HT₄ and 5-HT₁₇ receptor mediates relaxation [34]. 5-HT₁₇ receptors are widely distributed in peripheral tissues including heart, skeletal, intestine, CNS. In gastrointestinal tract, 5-HT₂B receptors contribute to 5-HT-induced colonic smooth muscle hypersensitivity [35]. It has been reported that 5-HT transport and 5-HT transporter-mediated antidepressant recognition are controlled by 5-HT₁₇ receptor in serotonergic neuronal cells [36]. In cardiovascular system, activation of 5-HT₁₇ receptors is believed to be necessary to produce 5-HT-induced valvulopathy [37,38]. The withdrawal of fenfluramine from the market in 1997 was due to valvular heart disease [39]. There have been many cases of serotonergic medications increasing the risk of developing the valvular heart disease via the activation of 5-HT₁₇ receptors [40].

5-HT₁₇ receptor is a ligand-gated cationic ion channel located on post-synaptic and sensory neurons in enteric nervous system, vagus and brain. This receptor exerts rapid depolarization response in myenteric neurons, leading to increased release of acetylcholine from cholinergic neurons [41]. 5-HT₁₇ receptor antagonists have been reported to reduce visceral pain reflex induced by duodenal distension in rats [42]. It was reported that ondansetron, a 5-HT₁₇ antagonist reduces the postprandial colonic hypertonic response in patients with carcinoid diarrhea [43].

5-HT₁₇ receptors consisting at least nine splice variants are positively linked to Gq proteins, resulting in stimulation of adenyl cyclase and increase in cellular cyclic AMP, and located in the nerve terminals on both cholinergic interneurones and motor neurones. Activation of 5-HT₁₇ receptors on effenter myenteric cholinergic excitatory neurons induces neuronal release of acetylcholine, substance P and calcitonin gene-related peptide producing coordinated contraction and relaxation of gastrointestinal smooth muscle [29,44], accelerating upper gastrointestinal transit as well as increasing in colonic motor activity. Thus, it affects all components of the peristaltic reflex [45]. 5-HT₁₇ receptor agonists have been shown to produce tonal relaxation of smooth muscle in the rat esophagus [46] and the canine rectum and human colon [47]. There are growing evidences that the 5-HT₄ receptor may be involved in the pathophysiology of visceral pain which is a main symptom of IBS. Mosapride diminished visceral pain in a rat model [48], and tegaserod produced analgesia via activation of supraspinal 5-HT₁₇ receptors [49]. The mucosal administration of 5-HT₁₇ receptor agonists alleviated visceral pain [50]. The 5-HT₁₇ receptor is also expressed in brain, and functions in long-term potentiation and synaptic plasticity. It has a tonic positive influence on serotonin neurons in the dorsal root ganglia and modulates 5-HT content in the raphe nuclei, showing behavior which enhance learning and memory in animal models [51,52]. Indeed, the 5-HT₁₇ receptor could be a successful pharmaceutical target in functional gastrointestinal motility disorders. Some 5-HT₁₇ receptor agonists such as tegaserod, cisapride have been withdrawn for non 5-HT₁₇ receptor-associated side effects. To date, selective 5-HT₁₇ receptor agonists are available or in different phases of clinical studies (Table 1). In the next chapter, we will discuss in more details about the characteristics of 5-HT₁₇ receptor agonists in regard of chemistry, pharmacology, efficacy and safety.

5-HT₁₇ Receptor Agonists in the Treatment of Gastrointestinal Motility Disorders

Chemical property and pharmacology

Most of benzamides (metoclopramide, clebopride, cisapride, mosapride, renzapride; figure 1) are not highly selective 5-HT₁₇ receptor agonists.

### Table 1: 5-HT₄ receptor agonists in development for the treatment of GI motility disorders

<table>
<thead>
<tr>
<th>Compound</th>
<th>Stage of Development</th>
<th>Mechanism of action</th>
<th>Company</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoclopramide</td>
<td>Launched</td>
<td>D₂ antagonist, 5-HT₃ antagonist, 5-HT₄ agonist</td>
<td>Sanofi-Aventis</td>
<td>Nausea-vomiting, GERD, diabetic gastroparesis</td>
</tr>
<tr>
<td>Clebopride (Cleboril™)</td>
<td>Launched</td>
<td>5-HT₄ agonist, 5-HT₃ antagonist, D₂ antagonist</td>
<td>Almirall</td>
<td>Nausea-vomiting</td>
</tr>
<tr>
<td>Cisapride (Prepulsid™)</td>
<td>Restricted use</td>
<td>5-HT₄ agonist, 5-HT₃ antagonist, 5-HT₂ antagonist</td>
<td>Johnson &amp; Johnson</td>
<td>GERD, gastroparesis</td>
</tr>
<tr>
<td>Mosapride (Gasmotin™)</td>
<td>Launched</td>
<td>5-HT₄ agonist, 5-HT₃ antagonist</td>
<td>Dainippon-Sumitomo</td>
<td>Gastritis, GERD</td>
</tr>
<tr>
<td>Tegaserod (Zelnorm™)</td>
<td>Restricted use</td>
<td>5-HT₄ agonist, 5-HT₃ antagonist, 5-HT₂ antagonist</td>
<td>Novartis</td>
<td>IBS, Chronic idiopathic constipation</td>
</tr>
<tr>
<td>Prucalopride (Resolor™)</td>
<td>Launched</td>
<td>5-HT₄ agonist</td>
<td>Movetis</td>
<td>Chronic constipation</td>
</tr>
<tr>
<td>M0003, M0004</td>
<td>Phase II, discontinued</td>
<td>5-HT₄ agonist</td>
<td>Movetis</td>
<td>GERD, gastroparesis</td>
</tr>
<tr>
<td>Renzapride</td>
<td>Phase III, discontinued</td>
<td>5-HT₄ agonist, 5-HT₃ antagonist, 5-HT₂ antagonist</td>
<td>Alizyme</td>
<td>IBS-C, IBS-M</td>
</tr>
<tr>
<td>E-3620</td>
<td>Phase II, discontinued</td>
<td>5-HT₄ agonist, 5-HT₃ antagonist</td>
<td>Eisai</td>
<td>GI motility disorders</td>
</tr>
<tr>
<td>Naronapride</td>
<td>Phase II</td>
<td>5-HT₄ agonist</td>
<td>ARYx Therapeutics</td>
<td>Chronic idiopathic constipation, GERD, gastroparesis</td>
</tr>
<tr>
<td>Velusetrag</td>
<td>Phase II</td>
<td>5-HT₄ agonist</td>
<td>Theravance</td>
<td>Chronic constipation, gastroparesis</td>
</tr>
<tr>
<td>TD-8954</td>
<td>Phase I/II</td>
<td>5-HT₄ agonist</td>
<td>Theravance</td>
<td>Eating disorder</td>
</tr>
<tr>
<td>YKP10811</td>
<td>Phase II</td>
<td>5-HT₄ agonist</td>
<td>SK biopharm</td>
<td>Chronic constipation, IBS-C</td>
</tr>
<tr>
<td>TD-2749</td>
<td>Phase I</td>
<td>5-HT₄ agonist</td>
<td>Theravance</td>
<td>GI motility disorders</td>
</tr>
<tr>
<td>AU-228</td>
<td>Phase I</td>
<td>5-HT₂ agonist</td>
<td>Abbott</td>
<td>GI motility disorders</td>
</tr>
<tr>
<td>DA-6886</td>
<td>Phase I</td>
<td>5-HT₁ agonist</td>
<td>Dong-A ST</td>
<td>IBS-C</td>
</tr>
<tr>
<td>RQ-10</td>
<td>Phase I</td>
<td>5-HT₄ agonist</td>
<td>RaQualia</td>
<td>GI motility disorders</td>
</tr>
<tr>
<td>YH-12852</td>
<td>Phase I</td>
<td>5-HT₄ agonist</td>
<td>Yuhan</td>
<td>IBS-C</td>
</tr>
</tbody>
</table>

Table 1: 5-HT₄ receptor agonists in development for the treatment of GI motility disorders

Figure 1: Chemical structures of some 5-HT₄ receptor agonists mentioned in the text. The figure shows compounds acting as prokinetic agents.
agonists. Metoclopramide (4-amino-5-chloro-N-(2-(diethylamino)ethyl)-2-methoxybenzamide), the prokinetic benzamide was originally identified in 1960s as a potential treatment for nausea and vomiting, and now it is also useful in diabetic gastroparesis and esophageal reflux, but not lower GI diseases. This compound was characterized to have dopamine (D₂) receptor antagonism, 5-HT₄ receptor antagonism and 5-HT₂ receptor agonism. Since the discovery of metoclopramide, many progenitors and congeners of the benzamide class have been synthesized by introducing other substitutions. Clebopride (4-amino-N-(1-benzylpiperidin-4-yl)-5-chloro-2-methoxybenzamide) was designed to increase the antidopaminergic activity compared to metoclopramide, and it also acts on upper GI. Unlike metoclopramide and clebopride, cisapride (4-amino-5-chloro-N-[3-[4-(fluorophenoxy)propyl]-3-methoxy-piperidin-4-yl]-2-methoxybenzamide) showed a lack of D₂ receptor antagonism, resulting that it could be devoid of hyperprolactinemic side effects, but inefficient in emesis. It was efficacious on gastric emptying and LES tone through 5-HT₄ agonism and 5-HT₃ antagonism. However, cisapride was a potent blocker of the hERG causing a delay in ventricular repolarization and QT prolongation [53, 54]. Like cisapride, mosapride (4-amino-5-chloro-2-ethoxy-N-((4-(4-fluorobenzoyl)-2-morpholinyl)methyl)benzamide) is a gastrokinetic having 5-HT₄ receptor agonism, 5-HT₃ receptor antagonism but not D₂ receptor antagonism. While cisapride was suspended from market, mosapride has not been limited due to the risk of arrhythmias, but it might not be safe because the metabolisms of both cisapride and mosapride are inhibited by CYP3A4 inhibitors. Renzapride (4-amino-N-[4S,5S]-1-azacycloc[3.3.1]nonan-4-yl)-5-chloro-2-methoxybenzamide) is a racemate of two enantiomers with the combined activities of 5-HT₄ receptor antagonist and 5-HT₂ receptor agonist. The compound is absorbed rapidly with a T½ of 1.4 h [55], and it is unlikely to inhibit the major drug-metabolizing enzymes in the liver [56]. Naronapride (6-((3R,4R)-4-(4-amino-5-chloro-2-methoxy-benzoylamo)-3-methoxy-piperidin-1-yl)-hexanoic acid 1-aza-bicyclo[2,2,2]oct-(R)-3-yl ester dihydrochloride; ATI-7505) is one of the latest benzamide derivatives. Prucalopride is a highly selective 5-HT₄ receptor agonist having negligible binding affinity for hERG channel and 5-HT₃ receptor. The bioavailability of prucalopride is very high (>90%), and plasma protein binding is about 30%. Prucalopride has a plasma half-life of 21 hr, minor amounts of metabolites in human and a very low interaction potential for CYP450 inhibitors. Approximately 60% of the active prucalopride administered is excreted in urine, and 6% in feces [63].

**Efficacy**

Tegaserod was primarily indicated for the treatment of women with IBS-C, and the indication was extended to chronic idiopathic constipation. Many preclinical studies has demonstrated that tegaserod stimulates motility of both the upper and lower GI tract [61,66]. In rats, intraperitoneal administration of tegaserod attenuates both acute colorectal hypersensitivity induced by acetic acid and chronic hypersensitivity in TNBS-induced colitis model [67]. The therapeutic efficacy of tegaserod in the treatment of patients with IBS-C was shown in various clinical trials [18,68-70]. The results of these large, randomized, double-blind, placebo-controlled trials suggested tegaserod (2 and 6 mg twice daily for 12 weeks) showed that it is effective and well tolerated in the treatment of IBS-C in women. Global relief response rates, which were assessed using 5-point scale with descriptors of well-being, abdominal discomfort/pain and bowel habit, were 38.8% (p<0.05) with tegaserod 2 mg twice daily, 38.4%-46.8% (p<0.05-0.0001) with tegaserod 6 mg twice daily, superior compared to placebo (28.3-38.8%). Tegaserod was also active against chronic idiopathic constipation. In the two large randomized, double-blind, controlled trials [71,72], patients with chronic constipation treated with tegaserod (2 and 6 mg twice daily for 12 weeks) demonstrated statistically significant improvements in both complete spontaneous bowel movement (CSBM) per week and secondary endpoints (number of bowel movements, stool form, abdominal bloating, straining, and abdominal discomfort) compared to placebo. Upper gastrointestinal motility disorders could be treated with

---

They demonstrated that these highly selective 5-HT4 receptor agonists (prucalopride 2 mg versus placebo (37.9% vs. 17.7% for ≥3 spontaneous bowel movements) in men with chronic constipation [88], showing the effectiveness of prucalopride in improving bowel movements.

In a phase III clinical trial for 12 weeks in patients with chronic idiopathic constipation (>1977 patients) [85-87], the patients treated with prucalopride reported a statistically significant (p<0.001) increase in the number of bowel movements compared with the placebo (prucalopride 2 and 4 mg, 23.6% and 24.7%, respectively vs. placebo 11.3%). Prucalopride once-daily at 2 mg dose improved the frequency of bowel movements (prucalopride 2 and 4 mg, 23.6% and 24.7%, respectively vs. placebo 23.4%). A recent study found that prucalopride is effective in men with chronic constipation [88], showing the effectiveness of prucalopride 2 mg versus placebo (37.9% vs. 17.7% for ≥3 spontaneous complete bowel movements (SCBM)/week).

YKP-1081, a new highly selective 5-HT4 receptor agonist, has reached the Phase II clinical trial phase. It is a selective 5-HT4 receptor agonist with hERG blockade activity, was withdrawn due to a high risk of QT prolongation causing cardiac arrhythmias [53].

Compared to these nonselective 5-HT4 receptor agonists, selective 5-HT4 receptor agonists exert improved safety profile for the treatment of gastrointestinal disorders without cardiovascular adverse effects [58]. Highly selective 5-HT4 receptor agonists (prucalopride, velusetrag, naronapride) have not been found to interact with the hERG channel, therefore are unlikely to prolong cardiac action potentials [106,107]. In the Phase III clinical trials, there were no differences in ECG parameters between patients randomized to placebo or prucalopride (2, 4 mg) [85-87].

A recent meta-analysis revealed that the frequent adverse event of highly selective 5-HT4 receptor agonist including prucalopride, velusetrag, naronapride was headache (5-HT4 receptor agonists 21.1% vs. control 13.0%) [82]. The highest relative risk (RR) was observed for diarrhea (RR=3.08, 95% CI, 2.31-4.09). The other adverse events were often disappointing partly due to off-target activities associated with cardiovascular, neurological side effects. Metoclopramide was found to note extrapyramidal side effects due to its dopaminergic antagonism in the central nervous system. Adverse reactions (mainly stress, somnolence, fatigue, increased mammary glands, galactorrhea and menstrual disorders) were noted in 20% of metoclopramide-treated patients. Approximately 1-2% of patients treated with metoclopramide had extrapyramidal symptoms. The U.S. FDA required boxed warning against high doses or chronic use of metoclopramide linked to tardive dyskinesia in 2009 [99]. In addition, metoclopramide caused cardiovascular adverse effects such as cardiac arrhythmias, specifically multifocal ventricular contractions [100]. The cardiovascular side effect has been a major concern since cisapride, a nonselective 5-HT4 receptor agonist with hERG blockade activity, was withdrawn due to a high risk of QT prolongation causing cardiac arrhythmias [53].

Several 5-HT4 receptor agonists have been tried in the treatment of gastrointestinal motility disorders for decades, but the results are often disappointing partly due to off-target activities associated with cardiovascular, neurological side effects. Metoclopramide was found to note extrapyramidal side effects due to its dopaminergic antagonism in the central nervous system. Adverse reactions (mainly stress, somnolence, fatigue, increased mammary glands, galactorrhea and menstrual disorders) were noted in 20% of metoclopramide-treated patients. Approximately 1-2% of patients treated with metoclopramide had extrapyramidal symptoms. The U.S. FDA required boxed warning against high doses or chronic use of metoclopramide linked to tardive dyskinesia in 2009 [99]. In addition, metoclopramide caused cardiovascular adverse effects such as cardiac arrhythmias, specifically multifocal ventricular contractions [100]. The cardiovascular side effect has been a major concern since cisapride, a nonselective 5-HT4 receptor agonist with hERG blockade activity, was withdrawn due to a high risk of QT prolongation causing cardiac arrhythmias [53].

In 2007, Tegaserod was withdrawn after an analysis found that 13 of 11,614 patients (0.11%) treated with tegaserod had ischemic cardiovascular events, compared with 1 of 7,031 placebo-treated patients (0.01%) [101]. Although the exact mechanism of ischemic cardiovascular adverse effect has not yet been elucidated, 5-HT4 receptor has been proposed to mediate contraction of human coronary arteries in patients with coronary artery disease [102]. It was reported that the most common AEs of tegaserod were diarrhea, headache and abdominal pain [103-105].

A recent meta-analysis revealed that the frequent adverse event of highly selective 5-HT4 receptor agonist including prucalopride, velusetrag, naronapride was headache (5-HT4 receptor agonists 21.1% vs. control 13.0%) [82]. The highest relative risk (RR) was observed for diarrhea (RR=3.08, 95% CI, 2.31-4.09). The other adverse events were often disappointing partly due to off-target activities associated with cardiovascular, neurological side effects. Metoclopramide was found to note extrapyramidal side effects due to its dopaminergic antagonism in the central nervous system. Adverse reactions (mainly stress, somnolence, fatigue, increased mammary glands, galactorrhea and menstrual disorders) were noted in 20% of metoclopramide-treated patients. Approximately 1-2% of patients treated with metoclopramide had extrapyramidal symptoms. The U.S. FDA required boxed warning against high doses or chronic use of metoclopramide linked to tardive dyskinesia in 2009 [99]. In addition, metoclopramide caused cardiovascular adverse effects such as cardiac arrhythmias, specifically multifocal ventricular contractions [100]. The cardiovascular side effect has been a major concern since cisapride, a nonselective 5-HT4 receptor agonist with hERG blockade activity, was withdrawn due to a high risk of QT prolongation causing cardiac arrhythmias [53].

Several 5-HT4 receptor agonists have been tried in the treatment of gastrointestinal motility disorders for decades, but the results are often disappointing partly due to off-target activities associated with cardiovascular, neurological side effects. Metoclopramide was found to note extrapyramidal side effects due to its dopaminergic antagonism in the central nervous system. Adverse reactions (mainly stress, somnolence, fatigue, increased mammary glands, galactorrhea and menstrual disorders) were noted in 20% of metoclopramide-treated patients. Approximately 1-2% of patients treated with metoclopramide had extrapyramidal symptoms. The U.S. FDA required boxed warning against high doses or chronic use of metoclopramide linked to tardive dyskinesia in 2009 [99]. In addition, metoclopramide caused cardiovascular adverse effects such as cardiac arrhythmias, specifically multifocal ventricular contractions [100]. The cardiovascular side effect has been a major concern since cisapride, a nonselective 5-HT4 receptor agonist with hERG blockade activity, was withdrawn due to a high risk of QT prolongation causing cardiac arrhythmias [53].
nausea and abdominal pain. The majority of AEs was generally minor and transient. The pivotal Phase III trials found that common adverse events of 2 or 4 mg of prucalopride were headache (prucalopride 25-30% vs. placebo 12-17%), nausea (12-24% vs. 8-14%), abdominal pain (16-23% vs. 11-19%) and diarrhea (12-19% vs. 3-5%) [85,86,87]. Common adverse events associated with velusetrag in dose of 50 mg were reported to be diarrhea, headache, nausea and vomiting, occurring on day 1 or 2 of treatment [90]. In the 4-week Phase II trial, naronapride (20, 40, 80, 120 mg) was well tolerated, and its frequent adverse events at maximum dose were headache and abdominal pain [91].

Conclusion

There is little doubt that 5-HT₄ receptor agonists are effective in the treatment of gastrointestinal motility disorders. However, previously available agents, such as cisapride and tegaserod, were withdrawn by cardiovascular adverse effects associated with off-target activities. More selective and potent 5-HT₄ receptor agonists has shown the improved safety profile and the therapeutic potential in clinical trials and preclinical studies. Prucalopride, which is currently available for clinical trials, velusetrag and naronapride, which has passed phase II clinical trials, provide robust GI prokinetic activity, acceptable safety and tolerability profile. The newly introduced agents such as YKP10811 and DA-6886 are progressed to anticipate advanced-phase clinical trials.

Competing Interests

The authors declare that they have no competing interests.

Author's contribution

All authors contributed substantially to conception and design, acquisition and analysis of data and interpretation of results.

Funding

This study was supported in part by a grant of the Health & Medical Technology R&D program, Ministry of Health, Welfare and Family Affairs, Republic of Korea (Grant: A100022).

References


98. Theravance, Inc. (2012) A Phase 1, Multiple Intravenous Dose Study to Examine the Safety, Tolerability, and Pharmacokinetics of Intravenous TD-8954, a 5-HT4 Receptor Agonist, in Healthy Subjects.


