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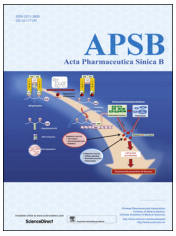

REVIEW

Current developments in pharmacological therapeutics for chronic constipation

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KEY WORDS

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Abstract Chronic constipation is a common gastrointestinal disease severely affecting the patient's quality of life. The traditional treatment of constipation is the use of laxatives. Recently, several new drugs including lubiprostone, linaclotide and prucalopride have been approved for treatment of chronic constipation. However, a significant unmet medical need still remains, particularly among those patients achieving poor results by current therapies. The 5-HT_4 receptor modulators velusetrag and naronapride, the guanylate cyclase C agonist plecanatide and the ileal bile acid transporter inhibitor elobixibat are recognized as the most promising drugs under investigation. Herein, we give a comprehensive review on the pharmacological therapeutics for the treatment of chronic constipation, with the purpose of reflecting the drug development trends in this field.

Abbreviations: 5-HT, serotonin; CaCC, calcium-activated chloride channel; CC, chronic constipation; CDCA, chenodeoxycholic acid; CFTR, cystic fibrosis transmembrane conductance regulator; CIC, chronic idiopathic constipation; ClC-2, chloride channel protein 2; ENaC, epithelial sodium channel; GC-C, guanylate cyclase C; GI, gastrointestinal; hERG, human ether-à-go-go–related gene; IBAT, the ileal bile acid transporter (also known as apical sodium-dependent bile acid transporter); IBS-C, irritable bowel syndrome with constipation; IPAN, intrinsic primary afferent neurons; LGP, lubricating gut pill; NHE3, sodium-hydrogen exchanger 3; OIC, opioid-induced constipation; PKGII, protein kinase II; SBMs, spontaneous bowel movements; TGR5, the G-protein-coupled bile acid receptor

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1. Introduction

Chronic constipation (CC) is a common gastrointestinal disorder in which patients have unsatisfying defecation associated with infrequent bowel movements (<3 bowel movements per week), hard stools and straining when passing stool, even compounded with abdominal discomfort and bloating[1]. It was estimated that constipation has a prevalence range from 8.75% in the Asian Pacific region to 27% in Western countries[2]. Constipation in women occurs twice as frequently as in men. Severe constipation (*e.g.*, only twice bowel movements a month) almost extensively occurs in women[3]. Constipation heavily impacts the patient's quality of life[4]. In addition to the direct economic burden caused by treatment, patients may face hardships such as missing school or work[5]. Inadequate intake of dietary fiber, lack of exercise, intestinal dysfunction, *etc*. can cause constipation. However, chronic primary or chronic idiopathic constipation (CIC), which is typically classified into three categories: outlet obstruction, normal-transit constipation and slow colonic transit[6], has no definitive cause. For the initial treatment of chronic constipation, increasing fiber intake or using lavatives is commonly recommended. Although clinical trials show that most lavatives achieve poor results, new pharmacological therapies with different mechanisms of action have been developed over the last decade for the treatment of chronic constipation.

2. Prokinetic agents

Main investigational prokinetic agents for the treatment of chronic constipation are listed in Table 1. Their mechanisms of action are illustrated in Fig. 1. 5-HT_4 agonists and motilin agonists, acting on 5-HT_4 receptors or motilin receptors located on epithelium, smooth muscle cells and intrinsic primary afferent neurons (IPAN), can directly or indirectly initiate the peristaltic or secretory reflex through the release of acetylcholine, resulting in decreased colonic transit time, improved bowel movement frequency and ameliorative bowel satisfaction[7].

2.1. 5-HT_4 agonists

Serotonin (5-HT) is involved in gastrointestinal secretion, sensation and motility. It was estimated that 95% of 5-HT is distributed in the enteroendocrine cells of gastrointestinal (GI) mucosa. Among the seven subtypes of 5-HT receptors[8], the gastrointestinal 5-HT_4 receptor is an extensively studied target for prokinetics.

Early 5-HT_4 receptor agonists (*e.g.*, tegaserod and cisapride) generally have low affinity and poor selectivity for the 5-HT_4 receptor, accounting for poor efficacy and relatively serious adverse effects. More recently, many highly selective 5-HT_4 receptor agonists (Fig. 2) have been investigated and may have a good profile of cardiovascular safety[9].

2.1.1. Prucalopride

Prucalopride (**1**, RO93877), initially developed by Janssen Pharmaceuticals, is presently licensed by Movetis to develop this agent as an orally administered, first-in-class drug for treatment of severe chronic constipation. As a very highly selective 5-HT_4 agonist, prucalopride has no measurable affinity for other receptors. In safety evaluation tests, prucalopride showed no hERG (human ether-à-go-go-related gene) channel inhibitory activity. At dosages of 2 mg and 4 mg per day, this drug produced a low incidence of QT interval prolongation. Even up to 20 mg per day (10-fold higher than the recommended dosage), prucalopride displayed no clinically relevant effects on cardiovascular parameters in healthy volunteers. Prucalopride improved stool frequency and consistency, and dose-dependently enhanced colonic transit in healthy controls or chronic constipation patients with no negative impact on gastric emptying or small bowel transit[10]. The patient′s quality of life was significantly improved by prucalopride treatment. Prucalopride was well absorbed from the gastrointestinal tract, with an absolute oral bioavailability of more than 90%. Its main elimination route was *via* the urine (60%–70% excreted unchanged in the urine). Because prucalopride has a low level of metabolism by liver, its pharmacokinetics is unlikely to be altered by hepatic impairment and no CYP3A4 drug interactions are anticipated. In Europe, 2 mg of prucalopride has been approved for the treatment of chronic constipation in women who have no adequate response to laxatives[11].

2.1.2. Velusetrag

Velusetrag (**2**, TD-5108) is an orally administrated available 5-HT_4 agonist developed by Theravance. Binding affinity of this drug for the 5-HT_4 receptor is over 500-fold that of other 5-HT receptor subtypes[12]. HRX-830449, the active metabolite of velusetrag, has a similar affinity and selectivity for 5-HT_4. Increased smooth muscle contractility of the antrum, fundus, duodenum and jejunum was observed in velusetrag-treated dogs[13]. The relief of constipation by velusetrag was also confirmed in chronic constipation patients[14]. The most common adverse

Table 1 Prokinetic agents for the treatment of chronic constipation.

Agent	Class	Company	Clinical consideration	Status
Tegaserod	5-HT_4 agonist	Novartis	Cardiovascular problem	Withdrawn in 2007
Prucalopride	5-HT_4 agonist	Movetis, Janssen	Accelerate colonic transit	Marketed in EU, Canada
Velusetrag	5-HT_4 agonist	Theravance, Alfa Wasserman	Accelerate colonic transit	Phase II
Naronapride	5-HT_4 agonist	Armetheon	Accelerate colonic transit	Phase II, but not active
YKP10811	5-HT_4 agonist	SK Biopharm	Improve gastric emptying, accelerate colonic transit and reduce visceral pain	Phase I
TD-8954	5-HT_4(c) agonist	Theravance	Increase bowel movement frequency, reduce time to first stool and cardiovascular risk	Phase II
Mitemcinal fumarate	Motilin agonists	Chugai Pharma	Strongly promote peristalsis	Preclinical