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REVIEW

Prucalopride: For functional constipation only?

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Abstract Prucalopride is a new prokinetic agent, recently available in Europe for the treatment of functional constipation in adults in whom treatment with laxatives failed to provide adequate relief. However, due to its intrinsic properties (highly selective agonist activity and high affinity for 5-HT4 receptors, neuroprotection), this drug has shown the potential to be used in other pathologic conditions, in and outside of the gastrointestinal tract. We performed a systematic review of the evidence supporting these possible alternative uses of prucalopride. Further studies in this area are, however, mandatory.

Keywords Alternative uses · Constipation · Prucalopride · Treatment

Introduction

Prucalopride is a dihydro-benzofurancarboxamide derivative with highly selective agonist activity and high affinity for 5-HT4 receptors promoting cholinergic, nonadrenergic and noncholinergic neurotransmission by enteric neurons [1], approved by the European Medicine Agency for the treatment of functional constipation in adults in whom treatment with laxatives failed to provide adequate relief [2].

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Although prucalopride has been developed for and extensively studied in functional constipation (and this will surely be the main indication in the near future also) [3], there is some evidence mainly originating from pilot studies or exploratory trials, generally carried out in small groups of patients, suggesting the potential use of this 5-HT4 agonist also in different clinical scenarios. These possible alternative uses of prucalopride will be reviewed and discussed here.

Prucalopride use in different clinical gastrointestinal conditions

After showing the importance of 5-HT4 receptors in modulating upper gut motility in experimental animal models [4, 5], in vitro studies on human tissues have shown that prucalopride is able to exert prokinetic effects not only in the colon but also in the esophagus and the stomach [6, 7]. This suggests that the drug, in addition to being used for the large bowel, could be used to treat upper gut dysfunctions characterized by abnormal motility. Indeed, prucalopride increases not only colonic transit but also gastroesophageal motility, as shown by a placebo-controlled, randomized study conducted in 21 healthy volunteers in which the drug was able to accelerate gastric emptying and to decrease esophageal acid exposure time [8].

Gastroesophageal reflux disease

Concerning the use in pathological conditions, a case series study conducted in 4 constipated female patients with gastroesophageal reflux symptoms demonstrated by pH/multichannel impedance monitoring, and refractory to

treatment with ranitidine and proton pump inhibitors, showed that treatment with prucalopride (2 mg/daily) decreased the number of acid and nonacid reflux episodes and gave objective symptomatic relief [9].

Systemic sclerosis

Prucalopride was tested in 2 female patients with scleroderma complaining of dysphagia, early satiety, abdominal distension and constipation, and featuring delayed esophageal transit, gastric emptying and gut transit, in whom other treatments, including prokinetic drugs and octreotide, had no effect. In these patients, prucalopride improved symptoms and accelerated gastrointestinal motility [10].

Opioid-induced constipation

An interesting and possible likely application, due to the main topic affinity, might be that related to the treatment of secondary forms of constipation. In a study conducted on 196 patients with opioid-induced constipation, these patients were given prucalopride (2 or 4 mg) or placebo for 4 weeks [11]. The primary endpoint, defined as an increase of $\geq$1 spontaneous complete bowel movements/ week, was reached by 23 (34.8 %) patients with 2 mg, and 25 (39.1 %) patients with 4 mg, compared to 15 (22.7 %) patients receiving placebo. However, the differences between prucalopride and placebo were significant only in the first week of treatment, probably due to the small sample size, even though a consistent trend was observed concerning the effects of prucalopride on bowel movements, symptoms and quality of life.

Constipation due to spinal cord injury

Prucalopride (1 or 2 mg) was also tested in 23 patients with constipation due to spinal cord injury, with a significant improvement of constipation severity (measured by a visual analog scale) compared to placebo [12]. A further report in a 55-year-old woman with spinal cord injury and opioid-induced constipation, scarcely responsive to conventional medical treatment, showed marked improvement of bowel habits and of abdominal pain after adding prucalopide (2 mg/day) to macrogol treatment [13].

Multiple sclerosis

A double-blind, randomized, placebo-controlled phase II investigation, carried out in 11 constipated patients with multiple sclerosis, showed that 4-week treatment with prucalopride (1–2 mg) increased the number of bowel movements and decreased the time to first bowel movement and the need for laxatives (prucalopride 57 % vs. placebo 25 %), in a dose-dependent manner [14].

Postoperative ileus

Following the report of a consistent prokinetic effect of prucalopride in rats with postsurgical ileus [15], a preliminary study in humans was carried out by means of *s*ubcutaneous administration of prucalopride (0.5, 2 or 4 mg) for 3 days after surgery in 317 patients undergoing elective colectomy [16]; a significantly shorter median time to the first flatus or stool and a shorter (although not significant) hospital stay compared to placebo were reported in this study, suggesting that the drug could be used in the treatment of postoperative ileus. A subsequent phase II randomized clinical trial conducted on 110 patients demonstrated that oral prucalopride (2 mg/daily) was a safe and effective treatment to reduce postoperative ileus in patients undergoing elective gastrointestinal surgery [17].

Chronic intestinal pseudo-obstruction

The drug was tried in a 37-year-old woman with myotonic dystrophy and chronic constipation with episodes of intestinal pseudo-obstruction refractory to other laxatives [18]: Prucalopride 2 mg/once a day restored normal defecation with daily stool frequency, a couple of weeks after starting the treatment. At 6-month follow-up, normal bowel frequency was maintained and no more episodes of intestinal pseudo-obstruction were reported.

In a randomized controlled trial conducted for 48 weeks in 7 patients with chronic intestinal pseudo-obstruction, prucalopride significantly improved pain in 3 of 4 patients, nausea in 2, vomiting in 1, and bloating in 4, although bowel function was not significantly modified. Three patients abandoned the trial [19]. Of interest, stool consistency and frequency and laxative use were not affected by the drug, suggesting that the mechanisms of action of prucalopride in these patients might be due to the effects of the drug in the proximal gut [20, 21].

Colonic pseudo-obstruction

Prucalopride, 2 mg/day per os, was also successful in relieving acute refractory colonic pseudo-obstruction in a 55-year-old man with previous spinal injury, in whom colonoscopic decompression and intravenous neostigmine were ineffective [22].

It has been suggested, on the basis of the results obtained in in vitro studies from human colonic tissues [23], that prucalopride could be used together with low-dose cholinesterase inhibitors to treat severe intestinal dysmotilities. This is further supported by the recent

demonstration of a significant neuroprotective effect of prucalopride in human enteric neurons exposed to oxidative stress challenge [24].

Prucalopride use outside the gastrointestinal tract

Since 5-HT4 agonists have demonstrated neuroprotective and neurotrophic effects [25], prucalopride could be also used in other different fields. For instance, a failure of tight control of MHC class II expression on astrocytes may play a role in the development of autoimmune responses in multiple sclerosis. Prucalopride and cisapride reduced by approximately 50–60 % interferon-γ-induced MHC class II immunostaining in cultured rat astrocytes. The effect was comparable to that of interferon-β and suggested some possible therapeutic role in multiple sclerosis through inhibition of up-regulation of immune responsiveness of astrocytes in the central nervous system [26]. Again, due to evidence on the beneficial effects of 5-HT4 receptor agonists in memory and learning, a possible strategy to treat Alzheimer's disease might consist in increasing the soluble form of amyloid precursor protein, a promnesic protein. On these grounds, some authors investigated the effects of subcutaneous injection of prucalopride in mice, reporting a significant increase in amyloid precursor protein levels in the hippocampus and cortex [27]. Moreover, a combined treatment of prucalopride with donepezil (an acetylcholinesterase inhibitor) yielded positive effects on memory in mice [28], suggesting that 5-HT4 receptors play a key role in the nonamyloidogenic pathway of amyloid precursor protein metabolism in vivo and supporting a possible use of 5-HT4 agonists for this condition.

Finally, a recent observation suggests that activation of 5-HT4 receptors could enhance the ability of L-DOPA of stimulating depolarization-dependent outflow of dopamine from 5-HT neurons and that prucalopride stimulates L-DOPA-induced dopamine release in restricted brain regions of the hemiparkinsonian rat; this observation might thus represent an interesting starting point for further research on new treatments of Parkinson's disease [29].

Conclusions

In addition to its proven efficacy for the treatment of functional constipation, there is now some indirect evidence, even though specific studies are lacking, of a possible future use of prucalopride in other pathologic conditions of the gastrointestinal tract, due to its intrinsic prokinetic properties and neuroprotective effects. Moreover, having a highly favorable safety profile [3], the drug might be usefully employed in combination with other drugs to improve the therapeutic gain.

Finally, the intriguing neuroprotective and neurotrophic effects of 5-HT4 agonists might eventually lead to the use of this drug for the treatment of some neurodegenerative diseases. Further studies in this area are, however, mandatory to confirm these observations.

Compliance with ethical standards

Conflict of interest Gabrio Bassotti and Massimo Bellini have received lecture fees from Shire Pharmaceutical for educational symposia; Dario Gambaccini declares no conflict of interest.

Ethical approval For this type of study ethical approval is not necessary.

Informed consent For this type of article, informed consent is not required.

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