Prucalopride: safety, efficacy and potential applications

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***Abstract*:** Chronic constipation is a very common functional gastrointestinal disorder which can be associated with significant impairments in quality of life for some people with the condition. Its management has, traditionally, been based on dietary and lifestyle changes and the use of a variety of laxative agents. The evidence base for the efficacy of the latter is, in many cases, slim. Not surprisingly, many patients remain dissatisfied with laxatives thus leading to the development of more pharmacological approaches. Among these approaches is the use of prokinetic agents; while prior molecules have been troubled by lack of selectivity and cardiac side effects, the new agent, prucalopride, appears to be highly selective for the serotonin 5-HT4 receptor and is, therefore, a potent stimulator of gut motility. In three large pivotal randomized controlled trials, prucalopride has been effective in relieving the cardinal symptoms of chronic constipation; these effects have been sustained in open-label follow up for as long as 18 months. The safety profile has been encouraging and, especially so, the absence of arrhythmogenic potential. Studies in men, in constipation-predominant irritable bowel syndrome and in other motor disorders are eagerly awaited.

***Keywords*:** constipation, irritable bowel syndrome, prucalopride, prokinetic, colonic motilty

The clinical context

Chronic constipation

Chronic constipation (CC) is certainly common, with prevalence rates of up to 28% being reported in the USA [Sonnenberg and Koch, 1989]. Constipation is at least twice as common in women as in men and its occurrence increases with advancing age, particularly after age 65 [Drossman *et al*. 1993; Talley *et al*. 1992; Sonnenberg and Koch, 1989]. While constipation may be associated with, or caused by, many underlying disease entities and a long list of pharmacological agents, we will confine our discussion to those in whom there is no obvious or detectable primary cause for their constipation: functional constipation. This entity is also known as chronic idiopathic constipation and is often referred to in the literature as simply CC. Nowadays, the selection process for the inclusion or exclusion of people for entry into a clinical trial involving CC is usually dictated by the Rome criteria, the most recent iteration of which, Rome III, defined functional constipation as a symptom complex which must include at least two of the following: straining*, lumpy or hard stools*, sensation of incomplete evacuation*, sensation of anorectal obstruction/blockage*, manual maneuvers to facilitate defecation (e.g. digital evacuation, support of the pelvic floor)*, less than three defecations/week. Furthermore, each of the symptoms denoted by an asterisk must occur in relation to at least 25% of defecations. In addition, loose stool should rarely be present without the use of laxatives and there must be insufficient criteria for the diagnosis of constipation-predominant irritable bowel syndrome (IBS-C) [Longstreth *et al*. 2006].

Chronic idiopathic constipation is traditionally divided into two broad categories, slow-transit constipation (colonic inertia) and 'outlet-type' constipation, also referred to as defecatory dysfunction or anismus [Brandt *et al.* 2005]. In terms of symptom associations, the former would, in theory, manifest as infrequent stools, the latter as some difficulty associated with the act of defecation (straining, sense of incomplete evacuation, rectal fullness). While this distinction is attractive from the pathophysiological point of view, such a clear separation is often difficult, if not impossible, in clinical practice. Indeed, it is

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commonplace to find patients complain of symptomatology suggestive of both disorders, that is, infrequent stool frequency combined with straining and/or a sensation of incomplete evacuation, for example. These distinctions have important therapeutic implications given that prokinetic agents, such as the compound that is the focus of this review, would be expected to have their greatest impact among those with delayed transit and that colectomy, the most drastic intervention that one may contemplate in the management of constipation, should be considered only among those with severe refractory colonic inertia. As a corollary, colectomy should not be contemplated in any patient where symptoms and/or evaluation suggest the presence of pelvic floor or other 'outlet' problems. Because of the limitations of symptoms in predicting underlying pathology, and the aforementioned overlap, in a given patient, between the two broad categories of constipation, the clinical reality is that many patients, including those entered into clinical trials, will exhibit features of both delayed colon transit and defecatory dysfunction; a factor that must be borne in mind in interpreting the results of any therapeutic intervention. It should come as no surprise, therefore, that constipation represents a significant therapeutic challenge!

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is one of the most common disorders encountered in modern medicine; community surveys in Western Europe and North America suggesting a prevalence of around 10% in the adult population [Brandt *et al*. 2009; Quigley *et al*. 2007]. It should be stressed, in addition, that IBS appears to be common worldwide regardless of geography or socioeconomic status. There is no single specific diagnostic test for IBS; its definition relies, therefore, either on the exclusion of diseases that may share its symptomatology in whole or in part, or on the application of symptom-based criteria the integrity of which has been validated in cross-sectional and longitudinal studies. The cardinal symptoms of IBS are abdominal pain/discomfort and bowel dysfunction; typically, these are interrelated such that, for example, an affected patient may report that his or, more likely, her symptoms worsen when constipated, only to be relieved once a bowel movement has been achieved. In clinical research, most studies apply the definitions enshrined in the Rome criteria, whose third iteration (Rome III) was released in early 2006 and defined IBS as:

> Recurrent abdominal pain or discomfort (an uncomfortable sensation not described as pain) at least 3 days per month in the last 3 months associated with 2 or more of the following:
>
> 1. improvement with defecation,
> 2. onset associated with a change in frequency of stool,
> 3. onset associated with a change in form (appearance) of stool.

These criteria should have been fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis [Longstreth *et al*. 2006].

IBS is further subtyped based on predominant bowel habit at the time of presentation as:

> IBS-D, where diarrhea is the predominant bowel habit,
>
> IBS-C, where constipation predominates; hard or lumpy stools (scored as 1 or 2 on the Bristol Stool Form Scale) $\geq$25% of defecations and, in conjunction, loose or watery stools (scored as 6 or 7 on the Bristol Stool Form Scale $<$25% of defecations,
>
> IBS-M (mixed), where both diarrhea and constipation occur, and,
>
> IBS-U (unclassified), where the subject does not fit into one of the above categories.

Where does chronic constipation end and irritable bowel syndrome begin?

Currently, IBS lacks an objective test or biomarker to confirm or refute the diagnosis, monitor progress or evaluate response to treatment; this remains a major obstacle to progress. As individual IBS symptoms are very nonspecific and may occur in a host of other clinical conditions, the potential for diagnostic confusion is considerable. Even when taken collectively, as in the Rome criteria, the potential for diagnostic overlap persists unless the criteria become overly restrictive and this is of special relevance to the potential for overlap between IBS-C and CC. Where, indeed, does IBS-C end and CC begin? Right now this is a value judgment and is based on how much pain and discomfort one is prepared to accept in a patient with constipation. It will be the experience of every clinician that many

patients with constipation complain of bloating, distension and abdominal discomfort; cardinal symptoms of IBS. It is the opinion of this author that it is only the degree or prominence of these symptoms that differentiates IBS-C from CC, a differentiation that often seems arbitrary, if not impossible, in clinical practice. It should come as no surprise that many of the therapeutic classes that demonstrate efficacy in CC are then evaluated in IBS-C. However, given the primacy of pain in IBS and slow colonic transit in CC, it stands to reason that results with a new therapeutic agent or class in one may not translate into similar efficacy in the other.

Motility in constipation and irritable bowel syndrome

While defecatory dysfunction is thought to be due to difficulties at the level of the pelvic floor and, thus, is not a colonic motor disorder *per se*, slow-transit constipation is presumed to reflect a primary disorder of colonic motility. In support of this presumption, these patients who, by definition, have slow colonic transit, have been shown to demonstrate a variety of motor abnormalities on manometric studies of the colon. Foremost among these and the colonic function that has been most widely adopted for use in clinical trials, is slow transit through the entire colon or segments of the colon.

In clinical practice, colon transit is most usually measured using the radio-opaque marker technique [Lin *et al.* 2005]. This approach has been shown to provide an accurate and reproducible assessment of overall colonic transit and by examining the distribution of retained markers may give some hints as to whether the underlying problem is colonic inertia or defaecatory dysfunction. To plan appropriate treatment strategies, however, further testing may be required.

More accurate and dynamic assessments of colon transit, including the determination of transit within various segments of the colon can be obtained from radio-isotopic approaches. Though these methodologies have been largely confined to a few centers, they have been widely used in the initial assessment of potentially colo-kinetic drugs in clinical research protocols [Odunsi and Camilleri, 2009; von der Ohe and Camilleri, 1992].

More direct assessments of colonic motor function can be obtained by manometry. However, colonic manometry presents formidable challenges, foremost among these being that of positioning the catheter assembly in the first place and ensuring that it retains its position throughout the period of study. Furthermore, patterns of colonic motility are poorly defined and subject to tremendous variation between normal people, not to mention disease states. While the absence of the most recognizable pressure wave pattern, the high amplitude power contraction (HAPC), during a recording period of adequate duration, or following exposure to adequate stimulation, has been proposed as being of diagnostic value among children and both a reduced frequency and amplitude of HAPCs and an impaired colonic motor response to food and exercise have been reported among adults with CC, there is at present no consensus with regard to the utility of colonic manometry in clinical practice in the adult patient [Camilleri *et al* 2008a, 1998] and the role of this modality in drug development has been limited.

Conditions such as CC and IBS, whose definitions rest exclusively on the interpretation of symptoms, are likely to encompass a heterogeneous population whose constituents may ultimately be found to have different causes. Not surprisingly, the search for a unifying hypothesis to explain all CC or IBS has proven unfruitful. Several phenomena undoubtedly contribute to symptom genesis, including disordered bowel motility ('spasm'), increased bowel sensitivity (visceral hypersensitivity or hyperalgesia in IBS, hyposensitivity in some with CC), altered cerebral processing of gut events, environmental stressors and intrinsic psychopathology [Quigley, 2003].

While a variety of abnormal electromyographic and motor patterns have been described in the various parts of the gastrointestinal tract in IBS, the specificity of any of these for IBS remains unclear [McKee and Quigley, 1993] and interest has shifted to the role of colorectal sensation as well as dysfunction along the brain–gut axis in the pathogenesis of symptoms in IBS [Bouin *et al.* 2002].

Prucalopride for constipation

Prucalopride is a highly selective serotonin 5-HT_4 receptor agonist which has been shown to stimulate gut motility *in vitro* and in *vivo*

[Sanger and Quigley, 2010]. In healthy volunteers, scintigraphic studies demonstrated that prucalopride accelerated whole gut and colonic transit but not gastric emptying or small bowel transit [Bouras *et al*. 1999]. Among patients with constipation, however, the very same authors using the exact same scintigraphic technique found that prucalopride in doses of 2 or 4 mg daily accelerated whole gut, gastric, small bowel and colonic transit in constipated patients [Bouras *et al*. 2001]. Importantly, prucalopride did not appear to adversely affect a number of parameters of anorectal motor function or impair rectal sensation in either healthy volunteers or patients with constipation [Sloots *et al*. 2002; Bouras *et al*. 2001; Poen *et al*. 1999; Emmanuel *et al*. 1998]. In studies of colonic motility, prucalopride has been shown to be stimulatory [De Schryer *et al*. 2002; Emmanule *et al*. 2002].

Given the profile of pharmacological effects described for prucalopride *in vivo*, it should come as no surprise that the major clinical focus of prucalopride has been in constipation [Emmanuel *et al*. 2002; Camilleri *et al*. 2008b; Quigley *et al*. 2009; Tack *et al*. 2009]. Indeed, each of the three major studies of prucalopride in humans has been in CC [Tack *et al*. 2009; Quigley *et al*. 2009; Camilleri *et al*. 2008b] (Table 1). For reasons related to the transfer of the drug from one company to another, these trials have only been published recently, even though they were actually designed and completed some time ago. These three trials, which became pivotal in terms of regulatory submission, featured a randomized, placebo-controlled, parallel group design. The major inclusion criterion was the presence of CC, defined as two or fewer spontaneous complete bowel movements (SCBMs) per week for at least 6 months prior to screening plus any one of the following: hard/very hard stools, a sensation of incomplete evacuation, or straining, during defecation in relation to at least 25% of bowel movements. After a 2-week baseline period, eligible patients were randomized to either a placebo, or 2 mg or 4 mg of prucalopride for 12 weeks. The primary endpoint, in each study, was the proportion of patients passing at least three SCBMs per week during the 12 weeks of the trial, based on an intention-to-treat analysis. All three trials (which assessed 620, 641, and 713 patients, respectively) demonstrated a significant increase in the proportion of patients achieving at least three SCBMs per week compared with placebo. Response rates ranged from 19.5% to 31% with 2 mg prucalopride, 24% to 28% with 4 mg prucalopride, and 9.6% to 12% with placebo. Clinically relevant and statistically significant improvements were also demonstrated in a number of secondary endpoints, including satisfaction with bowel function, perception of constipation severity, and patient-assessed symptom scores. A validated, disease-specific quality of life instrument (Patient Assessment of Constipation-Quality of Life – PAC-QOL) [Dubois *et al*. 2010], but not a generic quality of life instrument (Short Form 36 – SF-36), showed significant improvements with prucalopride [Tack *et al*. 2009; Quigley *et al*. 2009; Camilleri *et al*. 2008b]. Even though men and women were enrolled in these studies, over 85% of evaluated patients were female. While this led

Table 1. Main results of the three pivotal trials of prucalopride in gastrointestinal chronic constipation.

Reference	Study design (No. of patients)	Outcomes (2 mg and 4 mg prucalopride *versus* placebo)
[Camilleri *et al*. 2008b]	12 weeks (620) Prucalopride 2 mg or 4 mg daily *versus* placebo	No. of patients achieving 1. ≥3 SCBMs/week: 30.9% and 28.4% *versus* 12% 2. An increase of ≥1 SCBM/week: 47.3% and 46.6% *versus* 25.8%
[Quigley *et al*. 2009]	12 weeks (641) Prucalopride 2 mg or 4 mg daily *versus* placebo	No. of patients achieving: 1. ≥3 SCBMs/week: 23.9% and 23.5% *versus* 12.1% 2. An increase of ≥1 SCBM/week: 42.6% and 46.6% *versus* 27.5%
[Tack *et al*. 2009]	12 weeks (713) Prucalopride 2 mg or 4 mg daily *versus* placebo	No. of patients achieving: 1. ≥3 SCBMs/week: 19.5% and 23.6% *versus* 9.6% 2. An increase of ≥1 SCBM/week: 38.1% and 44.1% *versus* 20.9%

SCBM, spontaneous complete bowel movement.

to the approval of the drug being restricted to women, it needs to be stressed that this should not be taken to imply prucalopride is not effective in men but, rather, that it has not been adequately tested in this gender. Though two doses, 2 mg once daily and 4 mg once daily, were tested in these studies, a dose–response effect was not obvious, thus the recommended dose is 2 mg.

CC is not a short-term problem; long-term results are critically important for such a chronic problem. Experience over a longer term is based on open-label follow up, for up to 24 months, of 86% of those patients who had completed the three randomized, double-blind pivotal studies described above [Camilleri *et al.* 2010]. Improvement in the PAC-QOL observed in the double-blind phase was maintained during open-label treatment for up to 18 months.

These benefits were supported in smaller studies of CC [Emmanuel *et al.* 2002; Sloots *et al.* 2002] as well as in studies of special populations: elderly people [Müller-Lissner *et al.* 2010], those with severe, refractory constipation [Coremans *et al.* 2003], opioid-induced constipation [Sloots *et al.* 2010], and constipation related to spinal cord injury [Krogh *et al.* 2002].

Prucalopride in other motility disorders

To date, there are very limited data on the impact of prucalopride on motility disorders affecting other parts of the gastrointestinal tract [Boecxstaens *et al.* 2002] and it is certainly too early to assess its potential usefulness in disorders such as gastroparesis, intestinal pseudo-obstruction, functional dyspepsia and, most importantly, IBS-C.

Safety

Given the cardiac adverse event history that led to the withdrawal of the less selective serotonergic agonists, cisapride [Quigley, 2011] and tegaserod [Chan *et al.* 2009], considerable attention has been paid to the safety profile of prucalopride and to its cardiac toxicity, in particular. In the pivotal studies, which collectively represent the largest experience with the drug, the most common treatment-associated adverse events were headache (25–30% prucalopride; 12–17% placebo), nausea (12–24%; 8–14%), abdominal pain or cramps (16–23%; 11–19%) and diarrhea (12–19%; 3–5%) [Tack *et al.* 2009; Quigley *et al.* 2009; Camilleri *et al.* 2008b]. A majority of these adverse events occurred within the first 24 h of treatment and were short lived [Quigley *et al.* 2009]. Where reported, the prevalence of serious adverse events was similar for placebo and prucalopride [Tack *et al.* 2009; Quigley *et al.* 2009; Camilleri *et al.* 2008b].

Of critical importance, given the experience with cisapride, is that prucalopride has not been found to interact with either the hERG potassium channel (relevant to cisapride-induced arrhythmias) or $5HT_{1B}$ receptors (where tegaserod may have affinity) [Potet *et al.* 2001] – both postulated to be responsible for the development of adverse cardiovascular effects with other $5HT_4$ agonists. Furthermore, no significant hemodynamic or clinically relevant electrocardiographic changes were detected in healthy control studies [Boyce *et al.* 2009], nor were they detected in any of the major clinical trials [Tack *et al* 2009, 2008; Quigley *et al.* 2009; Camilleri *et al.* 2008b]. In a smaller study conducted in a relatively high-risk population, 89 elderly nursing home residents of whom 80% had a prior history of cardiovascular disease, no significant hemodynamic or electrocardiographic changes were detected. Specifically, there was no evidence of an increase in the incidence of prolongation of the QTc interval [Camilleri *et al.* 2009].

What is the place of prucalopride in the management of constipation and other gastrointestinal disorders?

To date, high-quality evidence for prucalopride exists only in the area of CC and, then, only for women. Given the aforementioned clinical overlap between CC and IBS, studies in IBS-C are eagerly awaited, as are studies in motor disorders of the foregut and midgut. Efficacy in these latter areas would be of relevance to patients with CC given the frequency with which symptoms such as heartburn, dyspepsia and postprandial fullness occur in these patients.

Currently, prucalopride is approved in a number of countries in Western Europe for use in the management of constipation in women with CC in whom laxatives fail to provide adequate relief; approval is, no doubt, being sought throughout the world. Given the limited number of men included in the pivotal studies, the restriction of approval to women makes sense pending positive data for men. The restriction to laxative failures is also very much in keeping with a number of

authoritative guidelines which suggest a step-up approach to the treatment of constipation: beginning with dietary and lifestyle changes, progressing through osmotic laxatives (such as polyethylene glycol derivatives) and reserving pharmacological therapies for people whose condition fails to respond to these steps [Lindberg *et al*. 2011; Tack *et al*. 2011; Emmanuel *et al*. 2009; Brandt *et al*. 2005]. It must be stressed that there are very few studies comparing the efficacy of a new pharmacological agent with a traditional laxative; for this reason, the real therapeutic gain attributable to prucalopride over and above a laxative remains somewhat conjectural. The one study that compared a new agent, tegaserod, with a laxative, polyethylene glycol, found the latter to be more effective; a salutary lesson [Di Palma *et al*. 2007].

As a prescription drug for the management of constipation and given the virtual demise of other prokinetic agents for this indication, prucalopride competes primarily with another class of agents: those that stimulate secretion. Two drugs in this class have been extensively studied: the type-2 chloride channel stimulant, lubiprostone and the guanylate cyclase C agonist, linaclotide. Both have demonstrated efficacy in CC and C-IBS [Johnston *et al*. 2010; Lembo *et al*. 2010; Drossman *et al*. 2009; Johanson *et al*. 2008a, 2008b]. Interestingly, linaclotide has shown an effect against abdominal pain in IBS-C, an effect that seems independent of laxation and is postulated to represent inhibitory activity on sensory afferent nerves [Johnston *et al*. 2010]. Both drugs are well tolerated, though nausea has been somewhat common with lubiprostone [Drossman *et al*. 2009; Johanson *et al*. 2008a, 2008b]. There have been no comparisons with prucalopride.

Conclusions

Prucalopride is a highly selective serotonin 5-HT_4 receptor agonist which acts as a prokinetic in the gut. Data from large randomized, controlled clinical trials indicate that it is effective in CC and offers a new therapeutic alternative for those whose condition fails to respond to conventional laxatives. To date, cardiac toxicity, which bedeviled other drugs in this class, has not been a major issue. Long-term studies and postmarketing data will be critical in assessing the real benefits and risks of this promising compound.

Conflict of Interest

Eamonn Quigley has served on the advisory board of Shire and Movetis.

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