Inclusion criteria for pharmacodynamic and clinical trials in chronic idiopathic constipation: pitfalls in using Rome III for functional constipation

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Introduction

Selection of the appropriate patients to take part in any pharmacodynamic or clinical trial is essential for the context and relevance of the trial and to realistically assess the efficacy and safety of an experimental treatment for the condition of interest. There is continued interest in the development of medications for chronic idiopathic constipation or constipation resulting from use of opiates.

Rome criteria for functional constipation and functional defecation disorders

Rome III criteria for functional constipation [Longstreth *et al.* 2006], which are embedded in a document of functional bowel disorders, are often assumed to be appropriate as inclusion criteria for studies of chronic idiopathic constipation. The criteria pertaining to bowel function are as follows:

1. Must include two or more of the following:
    a. straining during at least 25% of defecations;
    b. lumpy or hard stools in at least 25% of defecations;
    c. sensation of incomplete evacuation for at least 25% of defecations;
    d. sensation of anorectal obstruction/blockage for at least 25% of defecations;
    e. manual maneuvers to facilitate at least 25% of defecations (e.g. digital evacuation, support of the pelvic floor);
    f. fewer than three defecations per week.
2. Loose stools are rarely present without the use of laxatives.
3. There are insufficient criteria for irritable bowel syndrome (IBS).

However, within the Rome III recommendations, the diagnostic criteria recommended for functional defecation disorders [Bharucha *et al.* 2006] are as follows:

1. The patient must satisfy diagnostic criteria for functional constipation.
2. During repeated attempts to defecate, the patient must have at least two of the following:
    a. evidence of impaired evacuation, based on balloon expulsion test or imaging;
    b. inappropriate contraction of the pelvic floor muscles (i.e. anal sphincter or puborectalis) or less than 20% relaxation of basal resting sphincter pressure by manometry, imaging, or EMG;
    c. inadequate propulsive forces assessed by manometry or imaging.

The combination of symptoms and objective physiological or anatomical testing to identify disturbances in the evacuation process has served clinicians and patients well because these criteria can be applied when caring for individual patients in the clinic.

What are the pitfalls when using these criteria?

Clinical trials may involve several hundred patients, and the application of these diagnostic tests is not generally feasible. In single-center, pharmacodynamic trials conducted in our laboratory, rectal evacuation disorders are routinely excluded when investigating the potential effects of secretagogues or prokinetics on colonic transit in patients with syndromes associated with

constipation [Manini *et al.* 2010; Andresen *et al.* 2007; Bharucha *et al.* 2006; Cremonini *et al.* 2005; Camilleri *et al.* 2004; Bouras *et al.* 2001]. We have always applied this approach because of concerns that in such small studies that typically involve 12 patients per treatment arm, it is necessary to include patients with constipation in whom the drug tested can be appropriately tested, without risking a negative result caused by failed evacuation. Such carefully controlled inclusion criteria have led to pharmacodynamic studies that have proven predictive of results in phase IIB and phase III clinical trials in which the sample size per treatment arm is around 200 [Camilleri, 2010]. The same consideration regarding abnormal defecation dynamics resulting in evacuation disorder is relevant in patients with nondiarrheal IBS [Prott *et al.* 2010]. In the last decade, medications developed for chronic idiopathic constipation have also been tested for efficacy in IBS with predominant constipation (e.g. tegaserod, lubiprostone); the same pitfall may negatively impact outcomes of these trials. Clinical experience and trials show that patients with evacuation disorders may not respond to laxatives [Chiarioni *et al.* 2006], and the same may apply to secretagogues or colonic prokinetics. Indeed, it is conceivable that the therapeutic benefit demonstrated in the reported large clinical trials that did not effectively screen out patients with chronic constipation with a component of evacuation disorder may have been diluted by the inclusion of patients who are less likely to respond to secretagogues and prokinetics. Thus, the estimated number needed to treat for prucalopride and linaclotide may be better than those reported for the endpoints of more than three spontaneous complete bowel movements (approximately seven) and more than three spontaneous bowel movements (approximately four) [Lembo *et al.* 2010; Quigley *et al.* 2009; Tack *et al.* 2009; Camilleri *et al.* 2008].

What proportion of patients with constipation have a component of evacuation disorder?

Defecatory disorders are assumed, from responses to questions associated with straining in epidemiological studies of adults [Talley *et al.* 1991] and older people [Talley *et al.* 1996], and in gastroenterological practices in adults [Surrenti *et al.* 1995] and adolescents [Chitkara *et al.* 2004]. In all of these studies, it is estimated that 25–40% of patients with symptoms of chronic constipation have a component of a defecatory disorder. Therefore, the potential for evacuation disorders impacting on the results of trials in patients with chronic constipation cannot be excluded, and this consideration clearly impacts important notions including the therapeutic benefit, the sample size of each treatment arm, the cost and time required for completion of the studies, and the ethical concern of patients who are not likely to benefit being included in a randomized controlled trial with an experimental medication whose side effects are unclear. In the latter situation, it could be argued that the risk to benefit ratio is close to infinite since the likelihood of benefit is close to zero.

It is relevant to note that the childhood and adolescent Rome III criteria for functional constipation do not include symptoms suggestive of disorders of evacuation [Rasquin *et al.* 2006].

Do clinical features help identification of disorders of evacuation?

Defecation-related symptoms

In a prospective study of 118 patients (27 men and 91 women) who fulfilled symptom and manometric criteria for dyssynergia (based on Rome II criteria), 84% reported excessive straining, 76% reported feeling of incomplete evacuation and 9.7% reported no urge to defecate [Rao *et al.* 2004]. More women reported infrequent bowel movements than men: 31% of women in this series reported having a bowel movement once a week. Moreover, 54% of women and 25% of men reported the use of digital maneuvers to evacuate; more than 50% of patients reported that stools were hard in consistency, 25% of women had a more frequent urge to defecate, and more women than men reported straining for 10 or more minutes in attempts to defecate.

Abdominal symptoms

In patients with evacuation disorders, there are also abdominal symptoms that are consistent with IBS such as abdominal bloating (in 74% of patients with dyssynergic defecation) [Rao *et al.* 2004]. Similarly, Chey's group showed that, compared with patients without dyssynergic defecation, those with the

evacuation disorder had higher scores for abdominal discomfort, abdominal pain, stomach cramps, bloating, having to be careful about what they ate, worrying about not being able to open their bowels when needed, and passing fewer bowel movements than they would like [Rangnekar *et al.* 2008].

Digital rectal examination

The sensitivity and specificity of digital rectal examination for identifying dyssynergia in patients with chronic constipation were 75% and 87% in the study by Rao's group of 209 patients with symptoms consistent with Rome III criteria of 'functional' chronic constipation [Rao *et al.* 2004]. In addition, there was 86% agreement for detecting normal resting anal sphincter tone between DRE and anorectal manometry and 43% agreement for increased resting sphincter tone [Tantiphlachiva *et al.* 2010].

Proposed inclusion criteria for chronic constipation trials

In planning inclusion criteria for multicenter clinical trials, it is important to note that four of the six criteria recommended by Rome III for inclusion in functional constipation are symptoms that are used to identify patients with functional defecatory disorders [Lembo and Camilleri, 2003]. These are:

1. straining during at least 25% of defecations;
2. sensation of incomplete evacuation for at least 25% of defecations;
3. sensation of anorectal obstruction/blockage for at least 25% of defecations;
4. manual maneuvers to facilitate at least 25% of defecations (e.g. digital evacuation, support of the pelvic floor).

Inclusion of patients with functional constipation with these symptoms may result in patients with defecatory disorders (anismus, pelvic floor dyssynergia, or descending perineum syndrome) entering the trials, potentially impacting response rates with secretagogues and prokinetics. In addition, it is conceivable that unbalanced, though randomized, assignment or distribution of such patients to the different treatment arms may also lead to erroneous conclusions from the study.

Since the childhood and adolescent Rome III criteria for functional constipation do not include symptoms suggestive of disorders of evacuation [Rasquin *et al.* 2006], there is actually inconsistency between the symptom criteria recommended for children and adolescents compared with those recommended for adults. The Rome III criteria for functional constipation in children (developmental age of at least 4 years) or adolescents must include two or more of the following with insufficient criteria for diagnosis of IBS:

1. two or fewer defecations in the toilet per week;
2. at least one episode of fecal incontinence per week;
3. history of retentive posturing or excessive volitional stool retention;
4. history of painful or hard bowel movements;
5. presence of a large fecal mass in the rectum;
6. history of large diameter stools that may obstruct the toilet.

Given the considerations discussed above, it is proposed that inclusion criteria for adults with chronic constipation be based on the following characteristics in order to avoid the pitfalls currently arising when the Rome III criteria for functional constipation are adopted as eligibility criteria for chronic idiopathic constipation:

1. Chronic constipation that includes the following:
    a. lumpy or hard stools in at least 25% of defecations;
    b. fewer than three defecations per week.
2. Loose stools are rarely present without the use of laxatives.
3. There are insufficient criteria for IBS or for functional defecation disorder.
4. There are insufficient criteria for defecatory disorders, that is, the following are absent:
    a. straining severity of 3 or 4 on a 5-point scale [0 (none) to 4 (most severe)];
    b. Manual maneuvers to facilitate at least 25% of defecations (e.g. digital evacuation, support of the pelvic floor).

Conclusions

There is a need to revise the inclusion criteria for patients participating in pharmacodynamic and clinical trials examining medications intended to

treat patients with chronic idiopathic constipation in the absence of evacuation or defecatory disorders. The same principles also apply for other forms of constipation that are associated with reduced colonic motility or secretion, as with opiate-induced constipation. Apart from refining these criteria, additional measures are needed to ensure appropriate selection of patients for clinical trials intended for those with functional or chronic constipation. These measures are to examine the patient's history for symptoms (such as a sense of incomplete rectal evacuation or digitation to facilitate evacuation), perform a digital rectal examination, and perform anorectal manometry or defecography if indicated by the clinical features.

Conflict of interest statement

No conflicts of interest exist.

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