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Research article

Comparison of subjective and objective measures of constipation – Employing a new method for categorizing gastrointestinal symptoms

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ABSTRACT

Introduction: Correlations between subjective and objective measures of constipation have seldom been demonstrated. This could be due to multiple confounding factors in clinical studies and the broad span of symptoms represented in questionnaires used to assess constipation. We developed a new method for categorizing gastrointestinal (GI) symptoms into relevant symptom groups, and used this in a controlled experimental study aimed to investigate whether GI transit times and colonic volumes were correlated to self-reported GI symptoms.
Methods: Twenty-five healthy male participants were enrolled in a randomized, double-blinded, placebo-controlled, five-day crossover study with the treatments oxycodone and placebo. Objective measures of GI transit times and colonic volumes were obtained by the means of the 3D-Transit System and magnetic resonance colonography, whereas subjective GI symptoms were measures via three validated questionnaires. The symptoms were then categorized into five groups; "abdominal symptoms", "defecation difficulties", "incomplete bowel evacuation", "reduced bowel movement frequency", and "stool symptoms". Spearman's rank order correlation was used to determine correlations between the five groups of symptoms and the objective measures.
Results: No correlations between the GI symptoms and transit times or colonic volumes were found (all $P > 0.05$).
Discussion: GI transit times and colonic volumes were not correlated to self-reported GI symptoms even in a controlled experimental study and when symptoms were categorized into relevant symptom groups. Thus, both subjective and objective measures must be considered relevant when assessing constipation in clinical and research settings, ensuring that both physiological aspects as well as the severity and impact of symptoms experienced by patients can be assessed.

1. Introduction

Constipation is a common condition that affects people of all ages, with a prevalence estimation of up to 27% in the population of Western countries (Pare, Ferrazzi, Thompson, Irvine, & Rance, 2001; Peppas, Alexiou, Mourtzoukou, & Falagas, 2008). The causes of constipation are multiple, ranging from physical inactivity, pharmacological-induced motility dysfunction (e.g. induced by opioids and anticholinergics), to advanced cancer illness (Hayat, Dugum, & Garg, 2017). To handle constipation in the clinic, and to investigate physiological mechanisms of constipation in research studies, valid subjective and objective methods are of great importance. Subjective questionnaires such as the Bowel Function Index (BFI) and Cleveland Clinical Constipation scores are commonly used to evaluate the severity and impact of gastrointestinal (GI) symptoms experienced by patients with constipation, and to guide clinicians in diagnostics and choice of treatment (Argoff et al., 2015). The purpose of objective measures is to gain insights into underlying physiological aspects of GI function, and to assess the efficacy of pharmacological treatment options (Nilsson et al., 2016; Olesen & Drewes, 2011). Usually, a combination of measures are applied. However, if subjective and objective measures of constipation are directly correlated, it may be beneficial utilizing merely the subjective measures as this would reduce clinical trial costs, ease participant discomforts, and increase compliance (Grønlund et al., 2018; Stotzer, Fjälling,

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Grétarsdóttir, & Abrahamsson, 1999). Nevertheless, previous clinical studies regarding GI function in patients with constipation have not found any correlations between subjective and objective measures (Chaussade et al., 1989; Cowlam et al., 2008; Knudsen, Krogh, Østergaard, & Borghammer, 2017). An explanation for this may lie within the design of clinical studies in which confounding factors, e.g. multiple GI diseases, psychological factors, and concomitant drug use to a great extent can influence the results. A better alternative may be to investigate such correlations in a more controlled setting, e.g. in opioid-induced constipation in healthy participants. Opioids cause GI dysmotility through multiple mechanism; decreased neuronal excitability of the enteric nervous system, decreased gut secretion and gut sphincter dysfunction (Brock et al., 2012). Thus, Nilsson et al., and Poulsen et al., recently conducted a crossover study employing a model of oxycodone-induced constipation to investigate whether self-reported GI symptoms (measured with three questionnaires) were correlated to GI transit times (measured with the 3D-Transit system), and colonic volumes (measured using magnetic resonance imaging (MRI)) (Nilsson et al., 2016; Poulsen et al., 2016).

However, no correlations between the subjective and objective measures were found here either. This could be due to the very broad span of symptoms appearing in the applied questionnaires.

Thus, it may be beneficial to stratify the GI symptoms assessed in the questionnaires and categorize these into relevant symptoms groups, to simplify the correlations and decrease the risk of type 1 errors. The aim of the current study was to investigate correlations between GI symptoms and GI transit time/colonic volume using a new method categorizing symptoms into symptom-and GI regions-specific groups approach. We hypothesized that using this approach, significant correlations between the subjective and objective measures would be found.

2. Methods

2.1. Data source

The study from which these data origin was designed as a randomized, double-blinded, placebo-controlled, crossover trial to assess how opioids affect the GI tract. The North Denmark Region Committee on Health Research Ethics (N-20130030) and the Danish Medicines Agency (2013070299) approved the study, and it was conducted in accordance with the principles of ICH-GCP of the European Union. The full trial protocol is registered at www.clinicaltrialsregister.eu (EudraCT no. 2013–001540-60). Twenty-five healthy male participants with no current symptoms or history of GI disease were recruited. All underwent a screening session in which a physician obtained their medical history and performed a physical examination, and the participants gave written informed consent. The study consisted of two separate five-day periods, in which the participants were randomized using computer generated block-randomization to receive either oral prolonged-release oxycodone (OxyContin®, 5 mg twice on day 1, 10 mg twice on day 2–4, and 10 mg once on day 5) or placebo. Medication was provided by Mundipharma Research Ltd. (Cambridge, UK). In short, oxycodone treatment induced constipation by the means of significantly increased GI symptoms, increased total GI transit time and colonic transit time, and increased volume in the cecum/ascending- and transverse colon. Further details on in- and exclusion criteria, study design, experimental procedures, and results are found in the previous publications from the study (Nilsson et al., 2016; Poulsen et al., 2016). For the current sub-study, merely data from the oxycodone treatment period was used in the correlation analyses.

2.2. Subjective measures

To assess GI symptoms, participants filled in the Danish versions of three well-validated questionnaires; The BFI (Table 1), the Gastrointestinal Symptom Rating Scale (GSRS) (Table 2), and the Patient Assessment of Constipation Symptoms (PAC-SYM) (Table 3). The BFI and GSRS were filled in at day 1 and 5, whilst PAC-SYM was filled in once daily throughout the study period. For the present study, data from day 5 of all three questionnaires were used in the correlation analyses.

Table 1
The Bowel Function Index (BFI) items.

Item
1. Ease of defecation during the last 7 days according to patient assessment
2. Feeling of incomplete bowel evacuation during the last 7 days according to patient assessment
3. Personal judgement of patient regarding constipation during the last 7 days

Table 2
The Gastrointestinal Symptom Rating Scale (GSRS) syndromes and items.

Syndrome	Item	
Gastroesophageal reflux	2	Heartburn
	3	Acid regurgitation
Abdominal pain	1	Abdominal pains
	4	Sucking sensation in the epigastrium
	5	Nausea and vomiting
Indigestion	6	Borborygmus
	7	Abdominal distension
	8	Eructation
	9	Increased flatus
Diarrhea	11	Increased passage og stools
	12	Loose stools
	14	Urgent need for defecation
Constipation	10	Decreased passage of stools
	13	Hard stools
	15	Feeling of incomplete evacuation

Table 3
Patient Assessment of Constipation Symptoms (PAC-SYM) domains and items.

Domain	Item
Abdominal	1. Discomfort in your stomach
	2. Pain in your stomach
	3. Bloating in your stomach
	4. Stomach cramps
Rectal	5. Painful bowel movements
	6. Rectal burning during or after bowel movement
	7. Rectal bleeding or tearing during or after bowel movement
Stool	8. Incomplete bowel movements, like you did not finish
	9. Bowel movements that were to hard
	10. Bowel movements that were to small
	11. Straining or squeezing to try to pass a bowel movement
	12. Feeling like you had to pass a bowel movement but could not ("false alarm")

The BFI is a 3-item questionnaire to measure constipation. All three items are evaluated by the patient on a numeric analogue scale from 0 to 100 where 0 = no problems and 100 = most severe problems. The BFI has been validated against bowel movements and laxative use, and assesses the severities of three GI symptoms; defecation difficulties, feeling of incomplete evacuation, and personal judgement of constipation (Ducrotté & Caussé, 2012; Rentz, Yu, Müller-Lissner, & Leyendecker, 2009). The symptoms are rated on a numerical rating scale from 0 to 10, 0 signifying 'not at all' and 10 signifying 'very strong'. It is the only scale specially designed for opioid-induced constipation (Olesen & Drewes, 2011).

The GSRS is a well-validated questionnaire composing of 15 items assigned to five syndromes: gastroesophageal reflux, abdominal pain, indigestion, diarrhea, and constipation. Each question is rated on a 7-point Likert scale, where 1 represents absence of symptoms and 7 represents very bothersome symptoms (Kulich et al., 2008; Revicki,