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Reduction of gastrointestinal symptoms in Parkinson's disease after a switch from oral therapy to rotigotine transdermal patch: A non-interventional prospective multicenter trial

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ABSTRACT

Introduction: Gastrointestinal (GI) symptoms are common among patients with Parkinson's disease (PD), due to both the disease itself and anti-PD drugs. We hypothesized that transdermal drug administration may result in fewer GI problems. This prospective observational study (ClinicalTrials.gov: NCT01159691) investigated effect of switching to rotigotine transdermal patch from oral anti-PD medications in patients with PD and existing GI symptoms.

Methods: Patients were enrolled if their physician was planning to switch them to rotigotine because of GI symptoms experienced while receiving oral anti-PD medications. Effectiveness assessments included a visual analog scale (VAS) measuring intensity of GI symptoms from 0 (no disorder) to 100 mm (extremely severe disorder), a questionnaire on the frequency and intensity of six individual GI complaints (heartburn, bloating, nausea, vomiting, abdominal pain, diarrhea), each rated 0–12 for a sum score of 0–72, and patient satisfaction regarding GI symptoms over approximately 6 weeks after switching.

Results: Of 75 patients who received rotigotine, 58 had follow-up data available for final analysis. Intensity of GI complaints improved numerically on both the VAS (47.5 ± 24.4 mm [$n = 65$] at baseline, 19.7 ± 23.3 mm [$n = 58$] after around 6 weeks) and the sum score of GI complaints (11.2 ± 9.0 at baseline, 2.1 ± 4.4 [$n = 58$] after around 6 weeks). Fifty of 58 patients were “satisfied” or “very satisfied” regarding GI symptoms over around 6 weeks following switch to the patch.

Conclusion: This study suggests that a switch from oral anti-PD medications to rotigotine transdermal patch may improve existing GI symptoms among patients with PD. Additional controlled studies are needed to confirm this finding.

1. Introduction

Gastrointestinal (GI) symptoms are common non-motor symptoms of Parkinson's disease (PD) [1–3] that present a significant burden on patients' quality of life [4]. GI dysfunction, which includes but is not limited to GI symptoms, is one of the most frequently observed non-motor features of PD and can involve the entire GI tract and occur at any stage of the disease [1]. GI symptoms can include salivary excess, dysphagia (difficulty swallowing), nausea, ‘gastroparesis’ (delayed gastric emptying), decreased motility of the colon leading to decreased frequency of bowel movements, and defecatory dysfunction [1]. Dysphagia and gastroparesis can serve to decrease ingestion and absorption of levodopa and other oral anti-PD medications, further challenging effective patient care.

The pathophysiological mechanisms that underlie GI symptoms in PD are likely to be multifaceted; they may be directly related to the underlying pathology of PD itself, as well as GI side effects of

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anti-PD medications. Control of GI function involves the central, autonomic, and enteric nervous systems. In PD there is evidence of Lewy pathology and loss of dopaminergic neurons in the autonomic innervation of the gut (parasympathetic dorsal motor nucleus of the vagus, sacral parasympathetic nucleus, and sympathetic ganglia), and also at multiple levels of the enteric nervous system itself [5–8]. GI symptoms can be evident very early in the course of PD; gastroparesis has been identified in individuals with early, untreated PD [1,9,10], and constipation may precede the development of motor dysfunction in individuals with PD by many years [1,11,12].

A known GI side effect of anti-PD dopaminergic drugs is their central nausea-inducing effect via stimulation of receptors in the area postrema. Dopaminergic agents may also cause GI-related symptoms via inhibition of intestinal motility as a result of D_2 receptor-related stimulation of intestinal dopaminergic neurons [13,14]. These symptoms can lead to disturbed ingestion and drug absorption, and also decreased drug compliance. Delayed drug absorption may possibly constitute one of the mechanisms for the development of wearing-off motor fluctuations in PD [15]. In addition, heartburn in patients with PD may arise from increased occurrence of gastric acid resulting from the stimulating effect of dopamine-substituting compounds on pancreatic release [16,17]; this is often treated with antacids or proton pump inhibitors to reduce pyrosis (or gastric reflux) in clinical practice.

Rotigotine is a dopamine receptor agonist with activity across D_1 through D_5 receptors as well as noradrenergic and serotonergic sites [18]. Continuous transdermal delivery of rotigotine maintains stable plasma levels over 24 h with a single daily application [19], independent of GI absorption. In randomized controlled trials in PD patients rotigotine has demonstrated clinical benefit, including improvements in motor function and reduction in daily off time [20–24]. Given its route of administration via a once-daily transdermally applied patch, rotigotine may have potential for treatment of patients with PD who have GI symptoms. We conducted this pilot study to assess changes in GI symptoms in patients with PD after switching to rotigotine transdermal patch from oral anti-PD medications.

2. Methods

2.1. Patients

Key eligibility criteria for this study included diagnosis of idiopathic PD, GI complaints of any reason at any time during the 6 weeks before baseline, and treatment with an oral PD medication during the 6 weeks before baseline.

2.2. Design

This non-interventional, prospective, single-arm, observational study was conducted in routine daily practice settings in Germany between June 2010 and January 2012 (ClinicalTrials.gov: NCT01159691). The observational plan, amendment, and patient data consent form were reviewed by the Ethics Committee of the Ruhr University Bochum, and the study was conducted in compliance with local legal requirements for non-interventional studies.

The study included patients with PD who were experiencing GI symptoms while being treated with oral anti-PD medications, and who could therefore be switched to rotigotine transdermal patch based on the decision of their treating physician, independent of his/her decision to include the patient in the study. Patients provided consent regarding data transfer and use, and were free to discontinue from further data collection at any time during the study. Physicians were also free to stop rotigotine treatment at any time.

Rotigotine was applied as a once-daily transdermal patch. Physicians were advised to follow the European Summary of Product Characteristics (SmPC) for guidance on rotigotine drug titration and treatment [25]. Following the initial visit, rotigotine treatment was initiated by an overnight switch for patients already receiving a dopamine receptor agonist (per the recommended dose equivalent). If the patient was not being treated with a dopamine receptor agonist, titration to optimal dose rotigotine was recommended (initiated at 2 mg/24 h and titrated in weekly increments of 2 mg/24 h to a maximal dose of 8 mg/24 h). Study duration was approximately 6 weeks (observation period) and included three time points for data collection: before switch from oral therapy to rotigotine (baseline visit), at 2–4 weeks (interim visit), and after around 6 weeks (final visit). Study-specific data were collected via patient files according to routine clinical practice, and for structured documentation, an electronic case report form was used.

2.3. Primary effectiveness variables

The primary variables for evaluating the effectiveness of switching to rotigotine transdermal patch included: change in intensity of GI complaints from baseline to approximately 6 weeks following switch, as measured by a visual analog scale (VAS); change in sum score of several GI complaints using questions derived from the Rome III Diagnostic Criteria (Table 1) [26]; and patient satisfaction regarding improvement in GI symptoms. Secondary variables included change in single-item scores for each of the GI complaints measured in the sum score.

Patients were asked to classify the intensity of all their GI complaints by marking one 100 mm VAS with a straight line at each visit. The exact position of this line was recorded; where 0 mm reflected no disorder and 100 mm indicated extremely severe disorder.

The sum score of GI complaints was reported for patients with valid scores for each of 6 symptoms (heartburn, bloating, nausea, vomiting, abdominal pain, and diarrhea) recorded using a GI complaints questionnaire. For each symptom, intensity of burden was rated 0–3 (for none, mild, moderate and severe) and frequency of symptoms was rated 0–4 (Table 1). Ratings for intensity and frequency were multiplied, resulting in a score for each symptom of 0–12, and a possible sum score for the 6 symptoms of 0–72. A seventh question on swallowing difficulties was recorded at baseline only.

Patient satisfaction regarding improvement in GI symptoms at the interim visit (2–4 weeks after switching) and over approximately 6 weeks after switching was rated as “very satisfied”, “satisfied”, “moderately satisfied”, or “not satisfied” in response to the question: “How satisfied are you with switching to the patch; in particular, when it comes to gastrointestinal complaints?”.

Table 1
Questionnaire assessing frequency of gastrointestinal complaints.

Question	Frequency responses	Score
Oesophageal symptoms		
1. In the last week, how often did you have heartburn (a burning discomfort or burning pain in your chest)?	- Never.	0
	- One day during the week.	1
2. In the last week, how often did you feel uncomfortably full after a regular-sized meal?	- Two days during the week.	2
	- Three or more days during the week, but not every day.	3
	- Every day.	4
Gastric and intestinal symptoms		
3. In the last week, how often did you have bothersome nausea?	- Never.	0
4. In the last week, how often did you vomit?	- One day during the week.	1
5. In the last week, how often did you have discomfort or pain anywhere in your abdomen?	- Two days during the week.	2
	- Three or more days during the week, but not every day.	3
	- Every day.	4
6. In the last week, how often did you have 4 or more bowel movements a day?	- Never or rarely.	0
	- Sometimes.	1
	- Often.	2
	- Most of the time.	3
	- Always.	4

One additional question was assessed at baseline only: “How often did you have swallowing disorders last week?”

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