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DA-9701 on gastric motility in patients with Parkinson's disease: A randomized controlled trial

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ABSTRACT

Introduction: To evaluate the effect of DA-9701, a novel prokinetic drug, on gastric motility evaluated by magnetic resonance imaging in patients with Parkinson's disease (PD).

Methods: Forty PD patients were randomly allocated to receive either domperidone or DA-9701. Their gastric functions were evaluated using magnetic resonance imaging before and after 4-week treatment period. Information on levodopa daily dose, disease duration, and Unified PD Rating Scale scores was collected. In 18 patients (domperidone: 9, DA-9701: 9), plasma levodopa concentrations were determined. Primary outcome was assessed by a one-sided 95% confidence interval to show non-inferiority of DA-9701 *vs.* domperidone with a predetermined non-inferiority margin of -10%.

Results: Thirty-eight participants (19 men and 19 women; mean age, 67.1 years) completed the study protocol (domperidone: DA-9701 = 19:19). Gastric emptying rate at 120 min (2-hr GER) was comparable between the 2 groups; it was not correlated with levodopa daily dose or disease duration or Unified PD Rating Scale scores (all $p > 0.05$). DA-9701 was not inferior to domperidone in changes of 2-hr GERs before and after the treatment (absolute difference, 4.0 %; one-sided 95% confidence interval, – 3.7 to infinity). However, a significant increase in 2-hr GER was observed only in DA-9701 group (54.5% and 61.8%, before and after treatment, respectively, $p < 0.05$). Plasma levodopa concentration showed an insignificant but increasing trend in DA-9701 group. There were neither adverse reactions nor deteriorations of parkinsonian symptoms observed in the study participants.

Conclusion: DA-9701 can be used for the patients with PD to enhance gastric motility without aggravating PD symptoms (ClinicalTrials.gov number: NCT03022201).

1. Introduction

Patients with Parkinson's disease (PD) have impaired gastric function which can cause unpredictable absorption profiles of oral dopaminergic drugs and predispose suboptimal responses among these patients [1]. Prokinetic drugs are commonly prescribed to PD patients to prevent nausea and vomiting induced by anti-parkinsonian drugs and to reduce response fluctuations.

Among prokinetic drugs, metoclopramide, a dopaminergic 2 (D_2)-receptor antagonist, is known to increase gastrointestinal (GI) motility and accelerate gastric emptying [2]. Metoclopramide accelerates GI absorption, shortens time to onset of action, and increases blood concentrations of concomitantly administered medications [3]. However, metoclopramide can pass through the blood brain barrier (BBB) and induce extrapyramidal symptoms. Domperidone also increases gastric emptying. Since it rarely passes through BBB, it is regarded as a safe drug in drug-induced Parkinsonism [3]. However, previous studies on domperidone in patients with PD have reported inconsistent results [1,4,5]. Mosapride, a 5-hydroxytryptamine type 4 (5-HT_4) agonist, has been reported to increase gastric motility and reduce response fluctuations among PD patients [6].

DA-9701 is a novel drug for functional dyspepsia that has been

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marketed in South Korea since 2011 [7]. DA-9701 is formulated as 50% ethanol extract from *Corydalis Tuber* and *Pharbitidis Semen,* used in oriental traditional medicine for treatment of GI disorders. In a recent phase III trial, DA-9701 has shown non-inferior efficacy to itopride in patients with FD [8]. DA-9701 has prokinetic effects and improves gastric accommodation and visceral hypersensitivity. A recent study using magnetic resonance imaging (MRI) has shown that DA-9701 can enhance both gastric accommodation and gastric emptying among healthy volunteers [9]. As oral administration of DA-9701 at effective dose in humans did not lead to sufficient brain concentrations to exert central D_2 receptor antagonism, this drug has potential to be used for PD patients safely [10].

From this background, we evaluated the effect of DA-9701 on gastric motility based on MRI and parkinsonian symptoms among PD patients.

2. Materials and methods

2.1. Study subjects

PD patients between 20 and 80 years old were eligible for this study. They were recruited from Seoul National University Bungdang Hospital between May 2013 and May 2016. Inclusion criteria were (1) subjects who were diagnosed with parkinsonism using the United Kingdom Parkinson's Disease Society Brain Bank criteria; (2) subjects who could explain symptoms they experienced and complete relevant assessment and examinations including questionnaires; (3) subjects who could understand the purpose and protocols of this study and agreed to participate in the study. Although some patients reported a predictable, minimal, or mild fluctuation, significant motor fluctuation was not present.

Exclusion criteria were (1) subjects who experienced psychiatric disorders or cognitive impairment; (2) subjects who were on prokinetics which they could not cease; (3) subjects who had neurological or gastrointestinal disorders which could affect gastrointestinal motility; (4) subjects with a history of gastrectomy or colectomy; (5) subjects diagnosed with Parkinson plus syndrome; (6) subjects who were unable to receive or complete the course of medication due to other comorbidities; (7) subjects who were unable to undergo MRI scan for safety reasons due to claustrophobia or certain devices such as cardiac pacemakers or aneurysm clips. A recent Korean study have reported that standard deviation of gastric emptying rate at 120 min (2-hr GER) in healthy individuals were 10% [9], so non-inferiority limit was pre-determined to be - 10%. *A priori* power analysis determined that, if there is no difference between domperidone and DA-9701 treatment, 36 patients (18 per each group) are required to be 90% sure that the lower limit of a one-sided 95% confidence interval (CI) (or equivalently a 90% two-sided CI) will be above the non-inferiority limit of - 10% [11]. This study protocol was conducted in accordance with the Declaration of Helsinki. It was approved by the Institutional Review Board at Seoul National University Bundang Hospital (IRB No. B-1210/173-006). All subjects provided written informed consent before inclusion. The study was registered at ClinicalTrials.gov (NCT03022201).

2.2. Study protocol

This study was a randomized, double-blind, and non-inferiority clinical trial. The study flow chart is summarized in Fig. 1. Eligible subjects were randomly allocated 1:1 using a blocked randomization method (block size = 4) to receive either DA-9701 (experimental drug) or domperidone (active comparator drug). A third party generated permuted-block allocation table. Allocation number and medicine containing both active drugs and placebo were provided to research nurses and pharmacist, respectively. Participants in DA-9701 group received DA-9701 30 mg plus placebo domperidone 10 mg three times per day 30 min before meal for 4 weeks while participants in domperidone group received domperidone plus placebo DA-9701 tablet three times per day 30 min before meal for 4 weeks.

Following a 2-week screening period, study participants in each group were given study drugs for 4 weeks. All patients (n = 38) underwent MRI examinations before the treatment, but one patient in DA-9701 group refused to undergo follow-up MRI. All study paticipants filled gastrointestinal symptom diary before and during the treatment period. Additionally, they submitted Patient's Global Assessment (PGA) for dyspeptic symptoms at the end of the treatment period. To evaluate any deterioration in PD, Unified Parkinson's Disease Rating Scale (UPDRS) parts III and IV score was assessed before and after the treatment. Blood levodopa concentrations 30 min after L-dopa dose administration were also measured in 18 patients before and after treatment. Concomitant *anti*-PD medications were allowed without any modification during the trial.

2.3. MRI protocol

We modified MRI technique reported previously [9,12]. Gastric MRI was performed in supine position. Study participants underwent overnight fasting (6–8 h). After ingestion of 400 cc fluid meal (Nucare®, carbohydrate: protein: fat = 57:15:27; Daesang, Seoul, Korea), post-meal MRI was performed at 5, 10, 15, 30, 60, 90, and 120 min after completing test meal which was defined as time 0 min. Gastric volume was measured with axial 3D T1 mDixon, covering stomach, slice thickness of 4 mm, slice interval of 2 mm, and acquisition time of 16 s (one breath hold).

2.4. Laboratory tests

For all study participants, blood was drawn by venipuncture at baseline and at the 4-week follow-up to determine serum levels of liver enzymes [alanine transaminase (ALT)/aspartate transaminase (AST)], blood urea nitrogen (BUN), creatinine, and fasting glucose. In addition, 12-lead electrocardiogram was obtained for each patient before and after the treatment period.

2.5. Outcomes

Primary outcome was changes in 2-hr GER evaluated by MRI from baseline to 4 weeks after the treatment period in the 2 groups. GER was calculated as follows: (gastric contents volume [GCV] at 5 min after the test meal – GCV at 10, 15, 30, 60, 90, 120 min after the test meal)/(GCV at 5 min after the test meal) × 100 (%). Percentage of gastric retention is calculated as 100 – GER (%). Secondary outcomes were changes of patient's symptoms of dyspepsia and constipation assessed by patient's diary. In addition, PGA for dyspeptic symptoms at the end of the treatment period was compared between the 2 groups. Other outcomes included changes in plasma levodopa concentration 30 min after L-dopa administration and changes in UPDRS part III score before and after treatment in the 2 groups.

2.6. Safety assessments

Safety was evaluated based on full clinical and laboratory assessment at every visit. Adverse events were checked during the treatment period, Dates of onset and resolution, severity, relationship with the study drug, and outcomes were recorded.

2.7. Statistical analyses

Data are expressed as means ± SD or numbers and percentages. Characteristics of the study population were compared using Student's t-test or χ^2 test. This study was designed to test DA-9701 in terms of 2-hr GER with a non-inferiority margin of -10%. DA-9701 was determined to be non-inferior to domperidone when the lower limit of