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Pharmacokinetics and safety/efficacy of levodopa pro-drug ONO-2160/ carbidopa for Parkinson's disease

Masahiro Nomoto[a,*], Masahiro Nagai[a], Noriko Nishikawa[a], Rina Ando[a], Yoshifumi Kagamiishi[b], Koji Yano[b], Shigeto Saito[b], Atsushi Takeda[c]

[a] Department of Neurology and Clinical Pharmacology, Clinical Research Trial Center, Phase-I Unit, Ehime University Graduate School of Medicine, Tohon, Ehime, Japan
[b] Translational Medicine Center, Ono Pharmaceutical Co., Ltd, Osaka, Japan
[c] National Hospital Organization, Sendai-Nishitaga Hospital, Sendai, Japan

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ABSTRACT

We conducted a phase I study investigating the efficacy, safety, and tolerability of ONO-2160, a newly developed levodopa pro-drug, and carbidopa compared with levodopa and carbidopa to stabilize levodopa plasma concentration fluctuations in Japanese patients with Parkinson's disease. In an open-label two-period design, patients (n = 12) with Parkinson's disease received levodopa and carbidopa for 3 days before 7 days of treatment with ONO-2160 and carbidopa. Patients were primarily evaluated using the Unified Parkinson's Disease Rating Scale Part III, a Parkinson's disease symptom diary, and analysis of adverse events. Pharmacokinetic analysis of plasma levodopa concentration was also performed.

ONO-2160 and carbidopa therapy stabilized effective plasma levodopa concentration. No adverse events with safety concerns were observed. The combination of ONO-2160 and carbidopa produced a prolonged and stable plasma levodopa concentration with a reduction in Unified Parkinson's Disease Rating Scale Part III total scores. The combination was well tolerated, with no safety concerns, when administered to Japanese patients with Parkinson's disease.

1. Introduction

Parkinson's disease (PD) is the most common form of parkinsonism and is characterized by tremors, muscle rigidity, postural instability, and bradykinesia. These motor deficits are a result of progressive neurodegeneration of dopaminergic neurons in the substantia nigra. Although there is no cure for PD, there are treatments that can effectively manage the symptoms. Levodopa is a dopamine precursor and is a first-line treatment that can restore motor function in PD patients [1]. The combination with levodopa and a dopa-decarboxylase inhibitor (DDCI), such as carbidopa or benserazide, reduces the peripheral DDC breakdown of levodopa and improves the proportion of peripheral levodopa crossing the blood–brain barrier. Appropriate treatment strategies can offer effective symptomatic relief for a few years; however, after several years of therapy, motor fluctuations emerge.

There are some levodopa modification strategies available to patients who begin to show symptoms of wearing-off [2–4]. Some of these strategies include using lower and more frequent doses of levodopa, changing to a treatment formulation that provides a more controlled release of levodopa, or adding in a dopamine agonist [5–7]. Alternatively, the addition of a catechol-*O*-methyltransferase (COMT) inhibitor, such as entacapone or tolcapone, can also be used. This combination also prevents the degradation of levodopa in the periphery. In some patients, the administration of carbidopa and entacapone with levodopa results in a significant increase in the duration of levodopa's therapeutic activity [8,9].

However, these strategies have limitations. Patients with moderate-to-severe motor fluctuations have a poor predictability of response with inconsistent reductions in symptom OFF-time [10–12]. The extended release formulation delays the onset of effects and increases dyskinesias at peak dose [13,14]. Therefore, there is a need for better formulations that provide a more consistent delivery of levodopa that improves symptomatic relief and prevents motor complications.

ONO-2160 is a newly developed pro-drug of levodopa that has been designed to minimize fluctuations of plasma levodopa concentrations and to prolong its efficacy. In vivo rat data suggest that ONO-2160 is

Abbreviations: AE, adverse event; ADR, adverse drug reactions; CD, carbidopa; COMT, catechol-*O*-methyltransferase; DDCI, dopa-decarboxylase inhibitor; MMSE, Mini-Mental State Examination; PD, Parkinson's disease; SD, standard deviation; SE, standard error; UPDRS, Unified Parkinson's Disease Rating Scale

* Corresponding author at: Department of Neurology and Clinical Pharmacology, Ehime University Graduate School of Medicine, Tohon, Ehime 791-0295, Japan.
E-mail address: nomoto@m.ehime-u.ac.jp (M. Nomoto).

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passively and slowly absorbed throughout the gastrointestinal tract into the blood, where it is efficiently hydrolyzed by esterase enzymes into levodopa before crossing the blood–brain barrier and conversion to dopamine in the brain (data not shown), increasing dopamine stores. This non-randomized, open-label phase I study aimed to evaluate the safety, pharmacokinetic profile, and efficacy of ONO-2160 and carbidopa (ONO-2160/CD) combination therapy, and to compare it against an active comparator, the immediate-release formulation of levodopa and carbidopa (levodopa/CD) combination therapy, in Japanese patients with PD.

2. Methods

2.1. Ethics

This study complied with the ethical principles based on the Declaration of Helsinki, the standards stipulated in Article 14 - Paragraph 3 and Article 80-2 of the Pharmaceutical Affairs Law (or the "Law on Securing Quality, Efficacy and Safety of Pharmaceuticals and Medical devices" since November 25, 2014), and the "Ministerial Ordinance on Good Clinical Practice (GCP)" (MHW Ordinance No. 28).

The study protocol was approved by the institutional review board of the Graduate School of Medicine at Ehime University. Trial registration number: JapicCTI-142,702.

2.2. Study design and interventions

This open-label, phase I study was carried out in Japanese patients with Parkinson's disease who exhibited motor fluctuations and who were currently on levodopa therapy. The study started with a 3-day observation period (days 1–3) with patients remaining on their established levodopa/CD dose followed by an equivalent ONO-2160/CD dosage (ONO-2160/CD 300/25 mg is approximately equal to levodopa/CD at 100/10 mg; Fig. 1). The dose was then steadily increased to a maximum dose of either ONO-2160/CD 600/50 mg (group 1) or ONO-2160/CD 900/75 mg (group 2). The patients received the doses three times daily at 5-h intervals over 5 days (days 4–8). This was done by increments of 150/12.5 mg until efficacy and pharmacokinetic analysis on day 9 and day 10, respectively.

2.3. Patients

This open-label study involved 12 Japanese patients based on the following key inclusion criteria: male or female patient aged ≥20 to < 80 years and was given a diagnosis of PD on the basis of the Clinical Diagnostic Criteria of the UK PD Society Brain Bank; a Modified Hoehn and Yahr Scale stage 1 to 3; and ≥24 points in Mini-Mental State Examination (MMSE) at screening [15–17].

Patients also had to have ≥2 h of OFF-time per day on average in the previous 7 consecutive days; be receiving levodopa products (levodopa/CD) at a consistent dose and dosage frequency for the previous 7 days before the start of the study; and be judged capable of accurately recording symptom variations in a PD symptom diary.

The key exclusion criteria included the presence of any of the following: parkinsonism other than PD; received or due to receive surgical treatment for PD; psychiatric symptoms related to PD; concurrent angle closure glaucoma; stomach or duodenum ulcers; diabetes mellitus; heart or lung disease; underwent ≥400-ml blood collection within 90 days or ≥200-ml blood collection within 30 days; history of serious drug or food allergies; alcohol or drug abuse; or judged ineligible to be a study subject by the investigators as a result of clinical observation, laboratory test, physical examination, ECG, and ophthalmological examination.

2.4. Pharmacokinetic analysis

Pharmacokinetic analysis involved venous blood sampling throughout the study for evaluating plasma concentrations of levodopa as measured by the LC/MS/MS facility at Sumika Chemical Analysis Service, Ltd., Osaka, Japan.

2.5. Motor function evaluation

The Unified Parkinson's Disease Rating Scale (UPDRS) Part III (motor evaluation) was carried out on PD patients given a diagnosis of motor fluctuations, before each dose and every hour for 10 h after each dose.

2.6. Safety and tolerability

For adverse events (AEs) and adverse drug reactions (ADRs), incidences and number of events were calculated. A physical examination (blood pressure, pulse rate, respiratory rate, body temperature, and body weight) was carried out at baseline and at regular time points throughout the study, and the changes over time were recorded. Quantitative analysis of common laboratory tests, including blood biochemistry, hematology, coagulation, and urinalysis, was carried out at baseline and at regular time points throughout the study; the changes over time were also recorded.

2.7. Statistical analysis

The analysis set for safety and pharmacodynamics included patients who had received the study drug at least once. The motor function and pharmacokinetic analysis sets included patients who met the inclusion criteria and none of the exclusion criteria, who had received the study drug at least once and also had their data recorded at least once after administration of the study drug in the ONO-2160/CD period. For drug

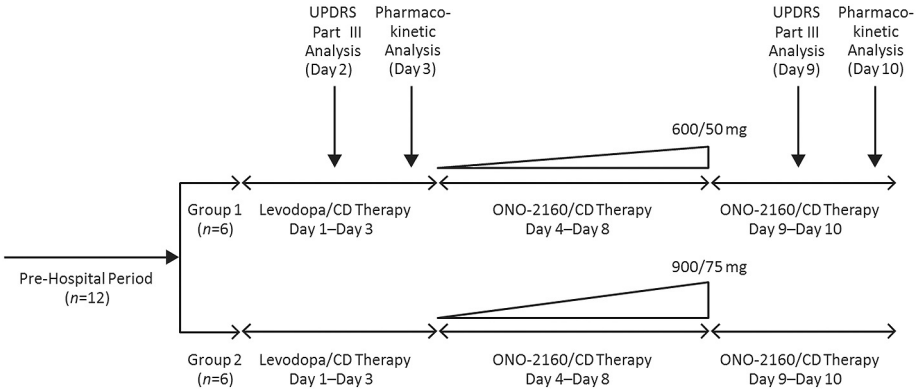

Fig. 1. Study design.