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Increased plasma donepezil concentration improves cognitive function in patients with dementia with Lewy bodies: An exploratory pharmacokinetic/pharmacodynamic analysis in a phase 3 randomized controlled trial

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ABSTRACT

Objective: To investigate whether increasing plasma donepezil concentration further improves cognitive function and neuropsychiatric symptoms without compromising safety in patients with dementia with Lewy bodies (DLB).

Methods: We analyzed data from a 12-week phase 3 trial of donepezil (5 and 10 mg/day) in patients with DLB. The contribution of factors affecting plasma donepezil concentration was evaluated using multivariate regression analysis. The relationships between plasma donepezil concentration and efficacy (cognitive function as measured by the Mini-Mental State Examination [MMSE], hallucinations and cognitive fluctuation), or safety (blood pressure, pulse rate, body weight, and parkinsonism as measured by the Unified Parkinson's Disease Rating Scale part III) were assessed by scatterplots and Pearson correlation.

Results: The data of 87 patients were used in the analyses. Plasma donepezil concentration increased proportionally with increasing dose from 5 to 10 mg/day. The dose (contribution rate: 0.39, $p < 0.0001$) and age (contribution rate: 0.12, $p = 0.0003$) were statistically significant contributing factors affecting plasma donepezil concentration. Plasma donepezil concentration correlated significantly with improvement of MMSE score ($p = 0.040$), but no significant correlations were found with the change in other tested parameters.

Conclusions: Plasma donepezil concentration correlated positively with change in cognitive function without affecting safety, and was affected mainly by dose and to a lesser extent by age. Therefore, for patients in whom safety concerns are not found at donepezil 5 mg/day, increasing the dose to 10 mg/day to increase plasma concentration is worthwhile to further improve cognitive function.

1. Introduction

Dementia with Lewy bodies (DLB) is the second most common type of dementia after Alzheimer's dementia (AD) [16]. Core features of DLB include parkinsonism and neuropsychiatric symptoms such as hallucinations and cognitive fluctuation, as well as cognitive impairment [14].

Cholinesterase inhibitors (ChEIs) are used to treat the symptoms of DLB based on its neurochemical features: loss of cholinergic neurons and choline acetyltransferase activity, but well-preserved postsynaptic cortical muscarinic receptors [13,24,25]. Galantamine, rivastigmine, and donepezil have been shown to be effective in treating DLB patients in several trials [5,7,11,12,15,19,20,22,27,29], and donepezil has been approved for treating DLB in Japan. A 12-week, phase 2, randomized controlled trial (RCT) of donepezil in DLB patients demonstrated improved cognitive function (evaluated by the Mini-Mental State Examination [MMSE]) and neuropsychiatric symptoms (evaluated by Neuropsychiatric Inventory [NPI]) at both 5 and 10 mg/day [19]. In the subsequent open-label extension (OLE) study, 5 mg/day donepezil was well tolerated and improved cognitive function and neuropsychiatric symptoms for up to 52 weeks [11]. In a phase 3 RCT of donepezil in DLB patients, cognitive function was significantly improved by 10 mg/day donepezil without serious safety concerns, although improvement of neuropsychiatric symptoms over placebo was not confirmed, owing to the unexpectedly high improvement in the placebo group [12]. The cognitive function improvement continued up to 52 weeks without an

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increased risk of clinically significant safety events in both 5 and 10 mg groups in the subsequent OLE study [20].

Improvement of cognitive function and neuropsychiatric symptoms by donepezil appeared to be dose-dependent in the above-mentioned RCTs. However, to the best of our knowledge, the pharmacokinetics (PK), the relationship between plasma concentration and efficacy, and the relationship between plasma concentration and safety of donepezil have not been assessed in DLB patients. Additionally, there are clinical concerns in increasing the ChEI dose in DLB patients, because in theory, ChEIs may cause bradyarrhythmia and worsening of parkinsonism [1,26,28,30]. These concerns and lack of data might deter physicians from increasing the ChEI dose in patients whose cognitive function and/or neuropsychiatric symptoms need further improvement.

To investigate whether higher plasma donepezil concentrations further improve cognitive function and neuropsychiatric symptoms without compromising the safety of DLB patients, we assessed the relationship between plasma donepezil concentration and efficacy or safety parameters, using data derived from the phase 3 RCT of donepezil [12].

2. Methods

2.1. Data source

We analyzed data from the 12-week RCT phase of the phase 3 study of donepezil in DLB patients [12]. The original study was a 52-week study, which integrated a placebo-controlled, 16-week RCT phase (consisting of a 12-week confirmatory phase followed by a 4-week transition period) and a 36-week OLE phase [12,20]. Patients were randomly allocated to the placebo, 5 mg/day donepezil, or 10 mg/day donepezil groups. In both donepezil groups, 3 mg/day was administered for the first 2 weeks. For the 10 mg group, the dose was titrated to 5 mg/day for another 4 weeks prior to administering 10 mg/day. Eligibility criteria were as follows: (1) outpatients aged ≥50 years, (2) diagnosis of probable DLB according to the consensus diagnostic criteria [14], (3) mild to moderate-severe dementia (10–26 on the MMSE and a Clinical Dementia Rating of ≥0.5), and (4) presence of neuropsychiatric symptoms (NPI-plus [12 items with original NPI-10 items, an item of sleep [3,4], and an item of cognitive fluctuation reported as Cognitive Fluctuation Inventory (CFI) [9,22]] ≥ 8 and NPI-2 [composite score of NPI hallucinations and CFI] [19] ≥ 1). Exclusion criteria were: (1) Parkinson's disease that was diagnosed at least 1 year prior to the onset of dementia, (2) focal vascular lesions visible on MRI or CT scans that might cause cognitive impairment, (3) other neurological or psychiatric diseases, (4) systolic hypotension (<90 mm Hg), (5) bradycardia (<50 bpm), (6) sick sinus syndrome, (7) atrial or atrioventricular conduction block, (8) QT interval prolongation (≥450 ms), (9) hypersensitivity to donepezil or piperidine derivatives, (10) severe parkinsonism (Hoehn and Yahr stage ≥ IV) [10], and (11) treatment with ChEIs or any investigational drug within 3 months prior to screening. ChEIs, antipsychotics, and anti-Parkinson drugs other than levodopa or dopamine agonists were prohibited during the study. The following subjects were excluded from the present PK/pharmacodynamic analysis; those who did not take the study drug the day before plasma collection, those who took study drug just before plasma collection, and those whose drug compliance rate of <75%. The trial was conducted in 72 sites throughout Japan from 2011 to 2013 in accordance with the principles of the Declaration of Helsinki. The protocol was approved by the institutional review board at each participating center. Written informed consent was obtained from the patients (if at all possible) and from the primary caregiver.

2.2. Plasma concentration measurement

Plasma concentration was measured in patients who had at least one plasma sample collected at a steady state. Plasma was collected after 4, 8, and 12 weeks of treatment before taking donepezil, or at the time of discontinuation. Plasma donepezil concentrations were analyzed using a validated liquid chromatography–tandem mass spectrometry (LC–MS/MS) method. Plasma donepezil concentrations of the placebo group were excluded from the analysis.

2.3. Factors affecting plasma donepezil concentration

The contributing factors affecting plasma donepezil concentration were explored using a multivariate regression analysis after selecting the factors to be included in the model. These factors were: dose (5 and 10 mg/day), patient demographics (sex, age, weight, CYP2D6 phenotype), and baseline characteristics (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin, albumin, alkaline phosphatase [ALP], creatinine clearance, concomitant CYP2D6 inhibitor, concomitant CYP3A4 inhibitor/inducer). The clinical laboratory data were categorized as normal or abnormal. One of the correlated variables was selected for multicollinearity analysis.

2.4. Exposure–response analysis

To investigate the relationship between plasma donepezil concentration and efficacy/safety, we analyzed patients who received donepezil for at least 4 weeks (3 mg/day for 2 weeks followed by 5 mg/day for 2 weeks), and who had one or more data of efficacy/safety parameters assessed at the same time point as plasma donepezil collection.

MMSE and NPI-2 scores, co-primary endpoints of the phase 3 RCT, were selected as efficacy parameters in this analysis. These were measured at Weeks 0, 4, 8, and 12, or at the time of discontinuation. The MMSE score was used to evaluate cognitive impairment. Scores ranged from 0 to 30, with higher scores indicating better cognitive function. The NPI-2 score was calculated as the sum of the hallucinations and cognitive fluctuation scores. Scores ranged from 0 to 24, with lower scores indicating improved neuropsychiatric symptoms.

Blood pressure (systolic or diastolic), pulse rate, body weight, and the Unified Parkinson's Disease Rating Scale (UPDRS) part III [6] were selected as safety parameters. These were measured at Weeks 0, 4, 8, and 12, or at the time of discontinuation, except UPDRS part III, which was measured at Weeks 0 and 12, or at the time of discontinuation, and evaluated the severity of parkinsonian symptoms. Scores ranged from 0 to 108, denoting “no” to “severe” symptoms, respectively.

Exposure–response analysis was performed using plasma donepezil concentration and changes from baseline of efficacy/safety parameters at Week 12, the last observation carried forward (LOCF), as responses. A scatter plot was used to illustrate the relationship between donepezil plasma concentrations and changes in efficacy/safety values at Week 12 (LOCF). After this, relationships between plasma concentrations and parameters were assessed by Pearson correlation. Statistical tests were two-tailed, and conducted with a significance level of 0.05.

3. Results

3.1. Patients

Overall, 87 patients (5 mg/day, 39; 10 mg/day, 48) were included in the exploratory analyses. Patient baseline demographic characteristics are shown in Table 1. The mean (standard deviation, SD) age was 78.3 (6.2) years, the mean body weight was 51.6 (9.7) kg and 56.3% of participants were female. The baseline MMSE scores were 20.3 (4.5); NPI-2, 7.3 (4.7); and UPDRS part III, 19.7 (12.1).