Effects of Body Weight on the Safety of High-Dose Donepezil in Alzheimer’s Disease: Post hoc Analysis of a Multicenter, Randomized, Open-Label, Parallel Design, Three-Arm Clinical Trial

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Keywords
Alzheimer’s disease · Donepezil · Safety · Body weight · Adverse events · Dose-titration

Abstract

**Background:** Donepezil 23 mg is considered for Alzheimer’s disease (AD) to optimize cognitive benefits; however, increased adverse events (AEs) can negatively influence drug adherence. We investigated whether body weight (BW) differs based on the presence of AEs, and which baseline factors were relevant to the safety of high-dose donepezil. **Methods:** This study was a post hoc analysis of a multicenter randomized trial between 2014 and 2016. We included patients with moderate to severe AD treated with 10 mg/day of donepezil, and the daily dose was escalated to 23 mg with/without dose titration. Dose titration indicates 15 mg/day of donepezil before escalation or 10 mg and 23 mg/day on alternate days before escalation during the first 4 weeks. The patients were divided into 2 groups based on occurrence of AEs of special interest (AESIs) to compare baseline characteristics. We also assessed relationships between BW and AESIs. **Results:** Among the 160 participants in the safety population, the baseline BWs differed between the AESI (+) (n = 67) and AESI (−) (n = 93) groups. Baseline BW was inversely correlated with the occurrence of AESIs (p = 0.020), and this relationship was prominent in the no-dose titration group (p = 0.009) but absent in the dose-titration groups (p > 0.05). **Conclusions:** BW is the most important factor that correlated with cholinergic AEs. Hence, stepwise dose titration should be considered, particularly in patients with low BW, to minimize the inverse relationship between BW and the occurrence of AEs (“Clinicaltrials.gov” No. NCT02550665 registered on September 15, 2015).
**Introduction**

In moderate to severe Alzheimer’s disease (AD), higher doses of acetylcholinesterase inhibitors (AChEIs) are used to optimize cognitive benefits, as cholinergic neuronal loss is aggravated by disease progression and AChEIs have dose-related cognitive benefits in AD [1–3]. Donepezil 23 mg has been approved for the symptomatic pharmacological treatment of moderate to severe AD after a large phase 3 clinical trials showed the efficacy of 23 mg/day of donepezil compared with 10 mg/day [4]. This approach can be considered in patients with insufficient or waning responses to standard doses; however, the number of reported adverse events (AEs) also increased, which can negatively affect drug compliance and limit the usefulness of donepezil 23 mg [5–9]. In our previous study, we reported that high-dose donepezil (23 mg/day) was intolerable; this result might have been attributable to a slow-release formulation of donepezil 23 mg, and that dose titration during the first 4 weeks reduced AEs, particularly nausea, dizziness, and headache [10]. However, donepezil 23 mg was associated with more frequent cholinergic AEs than was standard-dose donepezil regardless of dose-escalation method, and the incidence of cholinergic AEs in high-dose donepezil was higher than for those reported in previous Western studies, which might be explained by the relatively lower body weights (BWs) in Asian populations [11–15]. Hence, we hypothesized that a lower baseline BW would increase the risk of AEs irrespective of dose-escalation strategy and studied the relationships between BW and AEs in patients treated with high-dose donepezil. The objective of this post hoc analysis was to investigate whether baseline characteristics including BW differ based on reported AEs and which factors might be relevant to the safety of high-dose donepezil.

**Materials and Methods**

**Study Design and Patient Population**

This study was a post hoc analysis that used data from a randomized, multicenter, open-label, parallel group, prospective clinical trial named Optimal Dose-Escalation Strategy to Successful Achievement of High-Dose Donepezil 23 mg (ODESA). Detailed study design and methods are described in a previous report. In brief, this study was conducted at 6 centers in South Korea between December 2014 and August 2016 to investigate the safety and tolerability of high-dose donepezil based on dose-escalation methods during the first 12 weeks. The study included consecutive patients with moderate to severe AD dementia. Inclusion criteria were as follows: (1) age between 45 and 90 years; (2) clinical diagnosis of probable AD dementia [16]; (3) use of donepezil 10 mg daily for at least 3 months prior to screening; (4) a score of 0–20 on the Korean version of the Mini-Mental State Examination [17]; and (5) a clinical dementia rating [18] score ≥2 or a global deterioration scale (GDS) [19] score ≥4. Patients with any neurological/psychiatric disorders that might cause dementia not related to AD, severe medical conditions, or previous history of intolerance or hypersensitivity to AChEIs were excluded. Participants were randomized into 3 groups in a 1:1:1 ratio using web-based randomization: groups 1 and 2 received dose titrations during the first 4 weeks using 2 different titration methods (group 1: 15 mg of donepezil before escalation; group 2: 10 and 23 mg on alternate days before escalation), and group 3 did not receive a dose titration and was directly escalated to 23 mg donepezil. In the current study, the participants were divided into 2 groups based on presence of AEs and baseline BW, regardless of the dose-escalation method.

The study protocol and informed consent form were reviewed and approved by the institutional review board of each center. The study was conducted in accordance with the Declaration of Helsinki and principles of Good Clinical Practice. The reporting of the trial followed the CONSORT guideline (www.consort-statement.org).

**Safety Outcome Variables**

Safety and tolerability were assessed at each visit during the study period (baseline and at weeks 4, 8, and 12). The primary safety outcome variable was the incidence of treatment-emergent AEs of special interest (AESIs). We defined the 8 most common cholinergic symptoms as AESIs: nausea, vomiting, diarrhea, anorexia, abdominal pain, headache, bradycardia, and weight loss. We assessed physical and neurologic examinations, weight, vital signs, and AE at every study visit. Nausea, vomiting, diarrhea, anorexia, abdominal pain, and headache were assessed by patient and caregiver self-reports. Bradycardia was indicated by a pulse below 50 at any study visit, and weight loss was indicated by a ≥7% decrease compared with baseline BW at any time during the study. Other safety outcome variables included drop-out rates, drug compliance (ratio of drug taken to drug prescribed), AE gastrointestinal symptoms (including anorexia, nausea, vomiting, and diarrhea), and any AE occurrence. In this post hoc study, we primarily used AESI incidence because it was the primary outcome and mainly is composed of cholinergic symptoms. Subjects who discontinued the study before 12 weeks were asked to complete all end-point assessments at the time of early termination.

**Group Comparisons**

Clinical characteristics were compared according to occurrence of AESIs, which was the primary safety outcome variable. Second, we divided all participants into 2 groups according to baseline BW: the low BW group (baseline BW <55 kg) and the high BW group (baseline BW ≥55 kg). The cutoff value of 55 kg was based on the previous studies that reported a higher incidence of AEs in a lower BW <55 kg group than those in higher BW groups [4, 7]. However, because high and low BW groups showed different gender distributions, male and female participants were separately analyzed to assess whether incidences of AESIs are different according to quartile (in male) and tertile (in female) BW groups.

**Statistical Analyses**

Baseline demographic and clinical characteristics were compared using an independent t test or the Mann Whitney U test for
continuous variables and χ² tests or Fisher’s exact tests for categorical variables. Group comparisons for incidence of AEs were performed using χ² tests or Fisher’s exact tests. Relationships between the occurrence of AESIs and baseline characteristics were assessed using binary logistic regression analysis. Univariable analysis was used to assess each baseline factor separately to measure the relationships. Using multivariable analysis, the 5 most relevant baseline factors were analyzed together to compare the relationships between baseline characteristics and the occurrence of AESIs. Significance for all tests was set at a two-tailed α = 0.05. All statistical analyses were performed using SPSS 19.0 (SPSS, Chicago, IL, USA).

**Results**

**Patient Enrollment**

Patient enrollment and study design are as described previously [10]. In brief, among 175 patients who were eligible and randomized, we included 160 participants who underwent randomization, took at least one study drug, and underwent at least one follow-up evaluation in the safety set population. Fifty participants who discontinued the study due to AEs also were included in the study analyses. We show the analyses using the entire safety population (n = 160) to focus on the safety and tolerability of the study drug based on baseline characteristics.

**Clinical Characteristics Based on the Occurrence of AESI**

The results indicated no significant differences between participants who experienced AESIs (n = 67) and those who did not (n = 93) with regard to baseline characteristics, except for BW and body mass index (BMI) (Table 1). Baseline BW (55.90 ± 8.56 kg in the AESI [+] group vs. 59.84 ± 10.81 kg in the AESI [-] group, p = 0.011) and BMI (23.27 ± 3.07 kg in the AESI [+] group vs. 24.30 ± 3.20 kg in the AESI [-] group, p = 0.042) were lower in the participants with AESIs (Table 1).

Second, we divided participants in the no-titration group (n = 54, no-dose titration during the first 4 weeks of escalation to donepezil 23 mg) into 2 groups based on the occurrence of AESIs. Participants who experienced AESIs (n = 25) and those who did not (n = 29) showed similar baseline characteristics except for BW and BMI (p < 0.05, Table 1). The BW difference was more prominent in the no-titration group (p = 0.011) compared to that in all groups (p = 0.011). While, baseline BW did not differ significantly between participants with and without AESIs in the dose-titration groups (n = 106, dose-titration groups during the first 4 weeks of escalation to donepezil 23 mg, data not shown).

**Relationship between AE and BW**

We measured the risks of AESIs based on baseline clinical factors including age, gender, group allocation, base-
line cognitive status, educational levels, donepezil medication duration, and BW (Table 2). Baseline BMI was not included in the multivariable analyses because baseline BW was more relevant to AESI occurrence, and the 2 factors are closely related. Multivariable analyses were performed using the most relevant factors from the univariate analyses to identify the most relevant factors for the occurrence of AESIs. In both, all safety population (n = 160) and the no-titration group (n = 54), BW stood out as the only significant factor related to the occurrence of AESIs (odds ratio 0.953, p = 0.020 in all groups; odds ratio 0.890, p = 0.009 in the no-titration group, Table 2); patients with higher BW had a lower risk of AESIs at 12 weeks from initiation of high-dose donepezil. However, no significant baseline factors related to AESIs were identified in the dose-titration groups (Table 2).

**Safety and Tolerability according to Body Weight: All Groups**

The participants were divided into low BW (n = 63) and high BW groups (n = 97). Baseline demographics and clinical characteristics were similar between the 2 groups except for age and gender distribution (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000518470). Participants with low baseline BW were older (mean age: 77.1 ± 8.0) and tended to be female (81%) compared with those in the high BW group (mean age: 74.1 ± 8.9 and female 48.5%) (online suppl. Table 1). Therefore, male and female participants were separately analyzed to compare occurrences of AESIs based on baseline BW groups (Table 3). As results, female participants with lower BW (≤57 kg, lower 66.6% of BW among tertile groups) showed higher incidences of AESIs than that in the female participants with higher BW (Table 3). Male participants with BW below 58 kg (the lowest 25% of BW among quartile groups) revealed higher incidences of AESIs than those in the male participants with higher BW (Table 3).

**Safety and Tolerability according to Body Weight in the No-Titration Group**

Participants in the no-titration group (n = 54) were divided into a low BW group (baseline BW <55 kg; n = 22) and a high BW group (baseline BW ≥55 kg, n = 32) to assess AESIs based on baseline BW. Baseline clinical characteristics are listed in online supplementary Table 1; participants with low BW tended to be female (81.8%, p = 0.017). Hence, male and female participants were separately analyzed to compare AESIs in the no-titration group. Female participants with lower BW (≤57 kg) showed higher incidences of AESIs than that in the higher BW (online suppl. Table 2). Male participants with lower BW (≤58 kg) also showed more AESIs than those with higher BW in the no-titration group; however, it did not reach statistical significance (online suppl. Table 2).

**Discussion**

We conducted a post hoc analyses of a 12 week, multicenter, randomized, three-arm prospective clinical trial that investigated the safety and tolerability of high-dose...
donepezil (23 mg). In this study, we assessed whether participants who experienced AESIs differed from those without AESIs with regard to baseline clinical characteristics; we also investigated baseline factors that correlated with the occurrence of AESIs.

Our study showed 2 main findings. First, baseline BW was lower in participants who experienced AESIs compared to those that did not. Patients with higher BW might have a lower risk of AEs during the first 12 weeks after dose escalation to 23 mg/day. Consistently, BW was the most relevant factor related to the occurrence of AEs. Second, dose titration during the first 4 weeks might weaken the relationship between BW and the incidence of AESIs, while direct escalation to donepezil 23 mg might strengthen the negative association between BW and AESI. This relationship between BW and AEs is consistent with the previous studies that reported that patients with low BW or BMI reported a higher number of AEs and poorer tolerability after dose escalation to donepezil 23 mg [8, 11, 20]. Our study differs from previous reports in some important ways. In our data, we adopted different BW cutoff values according to the gender distribution and binary classification using cutoff values of BW (≤57 kg in female; ≤58 kg in male) showed different incidences of AESIs between lower and higher BW groups. The BW cutoff values were not same with the cutoff value of 55 kg in previous reports that had shown higher AEs in patients with low BW (<55 kg) regardless of gender distributions [4, 7]. We focused on AESIs that consisted of the 8 most common cholinergic AEs related to the use of AChEi; we also measured the relationships between baseline factors and the occurrence of AESIs according to dose-escalation method. As a result, dose-titration is assumed to weaken the inverse relationship between BW and AESI occurrence, possibly by preventing a sharp increase in the peak concentration of high-dose donepezil.

Generally, low BW increases the risk of AEs, which are more prominent in cases of direct dose escalation to high-dose donepezil [21, 22]. In the low BW group, the maximum concentration could be increased, although the time to maximum concentration might be decreased; consequently, the drug clearance might be delayed based

### Table 3. Incidences of adverse events according to baseline body weights (all groups)

| Variable                        | Male (n = 62) | Female (n = 98) | p value | T1 (n = 35) | T2 (n = 31) | T3 (n = 32) | p value |
|---------------------------------|---------------|-----------------|---------|-------------|-------------|-------------|---------|
|                                | Q1 (n = 16)   | Q2 (n = 17)     | Q3 (n = 15) | Q4 (n = 14) | T1 (n = 35) | T2 (n = 31) | T3 (n = 32) | p value |
| Age, years                      | 76.9±7.8      | 73.4±8.8        | 69.8±12.0 | 75.1±7.8    | 0.229       | 79.1±6.3    | 73.3±10.2 | 75.7±6.8 | 0.014  |
| Education (low/mid/high, n)     | 4/5/7         | 5/5/7           | 3/5/7    | 2/6/6       | 0.974       | 25/8/2      | 22/4/5   | 23/8/1  | 0.349  |
| Baseline K-MMSE                 | 14.1±6.2      | 13.1±5.1        | 13.6±4.7 | 15.4±4.7    | 0.660       | 12.8±4.7    | 13.9±4.5 | 13.9±4.4 | 0.858  |
| Baseline CDR                   | 1.9±0.7       | 1.4±0.5         | 2.0±0.0  | 1.3±0.5     | 0.082       | 1.7±0.6     | 1.6±0.7  | 1.7±0.6  | 0.768  |
| Baseline GDS                   | 4.7±0.6       | 4.7±0.7         | 4.7±0.6  | 4.9±0.9     | 0.926       | 4.9±0.6     | 4.9±0.7  | 4.9±0.7  | 0.267  |
| Donepezil duration, month      | 16.5±16.6     | 24.3±26.2       | 23.7±25.0| 19.8±19.3   | 0.734       | 26.2±28.2   | 22.3±23.5| 22.9±28.2| 0.809  |
| AESI (n, %)                     | 10, 62.5      | 6, 35.3         | 6, 40    | 2, 14.3     | 0.060       | 16, 45.7    | 19, 61.3 | 8, 25    | 0.015  |

| Variable                        | Male (n = 62) | Female (n = 98) | p value | T1 (n = 35) | T2 (n = 31) | T3 (n = 32) | p value |
|---------------------------------|---------------|-----------------|---------|-------------|-------------|-------------|---------|
| |
| Group (1/2/3, n)                | 5/6/5         | 15/16/15        | 1.000   | 20/20/26    | 75.7±6.8    | 0.376       |
| Age, years                      | 76.9±7.8      | 72.7±9.7        | 0.167   | 74.5±8.7    | 23/8/1      | 0.403       |
| Education (low/mid/high, n)     | 4/5/7         | 10/16/20        | 1.000   | 47/12/7    | 13.9±4.4    | 0.531       |
| Baseline K-MMSE                 | 14.1±6.2      | 13.9±4.8        | 0.900   | 13.3±4.6    | 1.7±0.6     | 0.683       |
| Baseline CDR                   | 1.9±0.7       | 1.6±0.5         | 0.249   | 1.6±0.7     | 4.9±0.7     | 0.799       |
| Baseline GDS                   | 4.7±0.6       | 4.8±0.7         | 0.846   | 4.9±0.7     | 22.9±28.2   | 0.792       |
| Donepezil duration, month      | 16.5±16.6     | 22.7±23.5       | 0.334   | 24.4±26.0   | 8, 25       | 0.010       |
| AESI (n, %)                     | 10, 62.5      | 14, 30.4        | 0.036   | 35, 53      | 8, 25       |

K-MMSE, Korean version of mini-mental state examination; CDR, clinical dementia rating; GDS, global deterioration scale; AESI, adverse events of special interest. Male: Q1 (lower 25%) ≤58 kg, 58 kg < Q2 ≤ 65 kg, 65 kg < Q3 ≤ 69 kg, 69 kg < Q4. Female: T1 (lower 33%) ≤ 50 kg, 50 kg < T2 ≤ 57 kg, 57 kg < T3.
on the fact that BW can contribute to the hepatic clearance variability and metabolic rate [23, 24]. In our study, BW was a more sensitive indicator than was BMI for predicting the occurrence of AEs. Therefore, in Asian patients with dementia, BW seems to be more relevant to the risk of AEs that are associated with the use of cholinesterase inhibitors. In addition, lower BW showed significantly increased AESIs than higher BW groups, thus, we can assume that AD patients with lower BW (≤57 kg in female and ≤58 kg in male) need cautious dose escalations to donepezil 23 mg. It is interesting that increase of AESI incidences was more prominent in female participants with lower BW (≤57 kg) of the no-titration group. Failure to reach statistical significance in the male participants of no-titration group might also be explained by the small sample size in each group (n = 5 in Q1 group; n = 15 in Q2–4 groups).

Our study had some limitations that should be considered when interpreting the results. First, we studied a relatively small sample size and included only Korean patients with dementia with moderate to severe AD, which could limit the generalizability of our results. Given that the safety assessments reported in a US-based population were different from those in a non-US population [11], safety outcomes related to BW might require cautious interpretation when generalizing to other populations. Second, we did not investigate long-term safety outcomes. However, considering that the incidence of AEs dropped rapidly after the first 4 weeks in previous trials that used high-dose donepezil [8], and given that patients with moderate to severe dementia might have higher rates of physical disabilities and comorbidities, longer follow-up studies could be difficult in this population. Despite these limitations, our study does reveal an inverse relationship between baseline BW and the occurrence of AEs based on the first clinical trial to investigate the efficacy of dose titration prior to escalating to donepezil 23 mg. To our knowledge, this is the first study to demonstrate that dose titration before escalation to high-dose donepezil might weaken these negative associations.

Conclusion

In this study, baseline BW was the most important factor related to cholinergic AEs during the first 12 weeks of high-dose especially in direct dose escalation without titration. Among patients with moderate to severe AD patients who consider dose escalation to 23 mg/day, patients with low BW might experience an increased risk of cholinergic AEs. Hence, stepwise dose titration is recommended prior to direct escalation to the high dose to enhance drug adherence and to weaken the inverse relationship between BW and the risk of AEs, particularly in AD patients with low BW.

Statement of Ethics

This study was conducted in accordance with the Declaration of Helsinki and the guidelines on good clinical practice. All eligible patients who had signed the consent form were included in the study. The study protocol was validated by the Asan Medical Center’s Ethics Committee, Seoul, South Korea (Approval No. #2014-0576).

Conflict of Interest Statement

The authors declare that they have no competing interests.

Funding Sources

This research was supported by a Grant (#2014-0576) from the Asan Institute for Life Sciences, Asan Medical Center and a grant from the Eisai Korea Inc., Seoul, South Korea. The funder did not have a role in the study design, data collection, analysis, interpretation of the data, writing the manuscript, or decision to submit the manuscript for publication.

Author Contributions

J.H.L. and S.Y.K. contributed to the study concept and design. Y.J.H. and H.J.K. analyzed and interpreted the results. Y.J.H. and J.H.L. drafted the manuscript. H.J.H., Y.C.Y., K.W.P., D.W.Y., S.Y.K., H.J.K., M.S.K., Y.L., and J.H.L. were involved in data collection, recruitment, and evaluation of the patients. All the authors read and approved the final manuscript.

Data Availability Statements

All data generated or analyzed during this study are included in this article and the online supplementary material file. Further enquiries can be directed to the corresponding author.
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