Efficacy of rivastigmine transdermal therapy on low food intake in patients with Alzheimer’s disease: The Attitude Towards Food Consumption in Alzheimer’s Disease Patients Revive with Rivastigmine Effects study

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Aim: Most patients with Alzheimer’s disease (AD) experience poor food intake and/or loss of appetite, which accelerates cognitive impairment. Several reports have shown that rivastigmine improves appetite in AD patients. The present study investigated the efficacy of a rivastigmine transdermal patch for the treatment of low food intake in AD patients.

Methods: AD patients, recruited through the Attitude Towards Food Consumption in Alzheimer’s Disease Patients Revive with Rivastigmine Effects study, were recognized as experiencing either a loss of appetite or poor food intake. A rivastigmine transdermal patch was administered to study participants for 16 weeks. Patients’ food intake, bodyweight, Mini-Mental State Examination scores and any adverse events were recorded.

Results: A total of 38 patients with AD (age 86.2 ± 5.4 years) were examined. Their mean Mini-Mental State Examination score was 10.1 ± 7.0 at baseline. A significant increase in food intake amount (54.9 ± 98.0 g, P < 0.01) and food intake ratio (9.3% ± 17.6%, P < 0.01) was observed by week 1, improvements that were maintained throughout the study duration. A multiple linear regression analysis showed that no independent variables were significantly associated with changes in food intake amount or ratio. Patients in the higher Mini-Mental State Examination subgroup showed a trend change in food intake amount, although this did not reach statistical significance (P = 0.07).

Conclusions: The present study suggests that a rivastigmine transdermal patch might improve poor food intake or loss of appetite in patients with AD. Geriatr Gerontol Int 2019; 19: 571–576.

Keywords: Alzheimer’s disease, appetite, rivastigmine, transdermal patch.

Introduction

Worldwide, nearly 47 million people have Alzheimer’s disease (AD) or a related dementia, which is the leading cause of disability in later life.1 More than 80% of patients with AD manifest poor food intake or loss of appetite, which might increase their risk of further cognitive impairments, neuropsychiatric symptoms and malnutrition.2 As a result, a vicious cycle decreases the functionality and quality of life in patients with AD.

Cholinesterase inhibitors (ChEI), namely donepezil, galantamine and rivastigmine, are first-line drugs and are used globally for the treatment of mild-to-moderate AD. ChEI function by inhibiting the breakdown of acetylcholine, an important neurotransmitter associated with memory, by the enzyme cholinesterase.3 While donepezil and galantamine specifically inhibit acetylcholine esterase (AChE), rivastigmine inhibits both AChE and butyrylcholine esterase (BuChE), both of which act to hydrolyze intracerebral acetylcholine. BuChE is also known to degrade ghrelin, a gastrointestinal tract hormone5 that serves to increase appetite.6,7 Some clinical reports have shown that rivastigmine therapy in AD patients has beneficial effects on appetite.8–10 Loss of appetite in AD patients is thought to occur not only because of AD-associated cognitive impairments, but also because of additional comorbidities including depression, anxiety, gastrointestinal symptoms that accompany physical complications and disrupted swallowing caused by cerebrovascular complications. Rivastigmine was also reported to have beneficial effects on these symptoms.9,11–13

Although ChEI can have adverse effects on various cholinergic tissues, including both central and peripheral organs, these adverse effects are most evident in the gastrointestinal tract, where they result in symptoms such as nausea, vomiting or diarrhea.13 Rivastigmine is currently the only approved drug for transdermal patch administration for the treatment of AD symptoms. Transdermal administration provides for continuous drug delivery and reduced plasma level fluctuations.15 As such, the administration of rivastigmine through a transdermal patch makes it easier to achieve
optimal dosing, and might further offer improved tolerability and therapeutic advantages over other methods of administration. Considering these advantages and the problem of poor food intake among individuals with AD, the primary aim of the present study was to investigate the efficacy of a rivastigmine transdermal patch in the treatment of poor food intake in patients with AD.

**Methods**

**Study design**

The Attitude Towards Food Consumption in Alzheimer’s Disease Patients Revive with Rivastigmine Effects (FOOD-ARRIVE) study was designed as a multicenter, prospective, observational, single-arm trial. This study was registered at the University Hospital Medical Information Network Clinical Trial Registry (UMIN000018172), a non-profit organization in Japan that meets the requirements of the International Committee of Medical Journal Editors. The study protocol was approved by the ethics review board at each participating institution. The present study was carried out according to the Declaration of Helsinki and all current legal regulations in Japan. Data collection and management were carried out by a third-party contract research organization to avoid any possible bias.

**Study population**

The present study was carried out at 17 clinical sites across Japan. Inpatients with AD at the study sites were approached to participate in this study from May 2015 to August 2016. Participant inclusion criteria were as follows: (i) a diagnosis of AD per the Diagnostic and Statistical Manual of Mental Disorders, 5th edition criteria; (ii) recently commenced regular use of rivastigmine transdermal patch therapy, as provisioned by individual health insurance; (iii) a clinically-recognized loss of appetite or poor food intake necessitating nursing care for mealtime support; and (iv) written informed consent for study participation provided by patients themselves or by a family member proxy. The use of other ChEI (donepezil or galantamine) was prohibited during the study period, but patients who had already used donepezil or galantamine, but agreed to switch to rivastigmine transdermal patch therapy, were also included. The use of other agents for AD treatment (such as memantine, yohukansan and psychotropic agents) was allowed if they had been used before the study, but dose change or withdrawal of these agents were prohibited during the study period. Participant exclusion criteria were as follows: (i) a history of hypersensitivity to rivastigmine, any components of rivastigmine or carbamate derivatives; (ii) a movement disorder that might affect food intake; (iii) a serious disease, such as malignant neoplasm or pneumonia, that might increase mortality; (iv) a functional gastrointestinal transit disorder; and (v) active physician concern about being otherwise unsuitable for participation. All participants were required to reside in an inpatient care facility for the duration of the study.

**Rivastigmine administration**

A rivastigmine transdermal patch was administered once daily to participants who met inclusion and exclusion criteria guidelines, as described above. In general, rivastigmine doses were sequentially increased by 4.5 mg every 4 weeks, starting at 4.5 mg. When a maximal daily dose of 18 mg was reached, this maximal dosing was maintained to week 16. Physicians were allowed to titrate rivastigmine dosing according to the patients’ condition.

**Observation period data**

Participant data were recorded throughout a 16-week observation period. Data on participant food intake amount, food intake ratio, time spent eating lunch, bodyweight and study drug dosage were collected at baseline, and at weeks 1, 2, 3, 4, 6, 8, 12 and 16. Food intake amount (g) was measured by subtracting the after-meal total meal weight, including eating utensils, from that before meal. Similarly, a provided meal amount (g) was measured by subtracting the weight of eating utensils from the total meal weight (including eating utensils) before the meal. The food intake ratio was defined as the ratio of food intake amount to the provided meal amount. Food intake amount was measured at every mealtime of each time point, and mean food intake amount and food intake ratio of the day were calculated at each time point. Cognitive or neuropsychiatric function were assessed using the Neuropsychiatric Inventory-Nursing Home Version (NPI-NH)16,17 at baseline, and weeks 4, 8 and 16 and the Mini-Mental State Examination (MMSE)18 at baseline and week 16, respectively. All adverse events that occurred during the study observation period were recorded and reported.

**Study outcomes**

The primary end-points in the present study were changes to the mean food intake amount and ratio per day due to rivastigmine transdermal patch therapy. Secondary end-points were changes to the following outcomes: (i) time spent eating lunch; (ii) bodyweight; (iii) NPI-NH score; and (iv) MMSE score. Stratified analysis of the primary end-points by MMSE score was further carried out.

**Statistical analysis**

One-sample t-tests or Wilcoxon signed-rank tests were applied to continuous variables for detecting significant changes from baseline. A two-sample Student’s t-test was applied to all continuous variables for two-group comparisons. A multiple linear regression analysis was carried out, with changes in food intake as dependent variables, and age, bodyweight, MMSE score, use of psychotropic drugs at baseline and physical complications as independent variables. First, by using univariate linear regression analysis, we detected variables having a P-value <0.1. By using these factors as independent variables, multiple linear regression analysis was carried out. Anonymized data management and statistical analyses were outsourced to a third-party contract research organization to ensure impartiality (Soiken, Osaka, Japan). All statistical analyses were carried out using SAS software version 9.3 (SAS Institute, Cary, NC, USA).

**Results**

**Participant recruitment and clinical characteristics**

A total of 38 patients with AD were enrolled at 17 clinical sites during the study period. One patient was excluded for violation of inclusion criteria (use of prohibited concomitant drug). The study participants were 10 men (27%) and 27 women (73%), aged 86.2 ± 5.4 years (mean ± SD). The mean time since first AD diagnosis was 46.7 ± 46.2 months, and the mean MMSE score was 10.1 ± 7.0. Nine patients (24.3%) had a history of psychotropic drug use. One patient used memantine. A total of 18 patients dropped out of the study. This attrition was due to the occurrence of adverse events (n = 6), discharge from hospital or care facility (n = 9) and transfer to another hospital (n = 3). Most reasons for discharge or transfer to another hospital were clinical improvement of symptoms (e.g. neuropsychiatric symptom). A total of 19 patients completed the 16-week observation period. The mean dose of rivastigmine was 4.7 ± 1.0 mg at baseline and 14.8 ± 3.8 mg at week 16 (Table 1).

**Effect of rivastigmine through a transdermal patch on food intake**

Figure 1 shows changes in food intake amount and ratio from baseline. Both food intake amount (192.0 ± 139.5 g and
The higher MMSE score subgroup also showed a non-significant difference in time spent eating lunch, bodyweight or NPI-NH or swallowing by inhibiting BuChE.9 All of these potential mechanisms serve as targets for illumination by future studies.

Discussion

The present study shows that rivastigmine transdermal patch therapy increased the dietary food intake amount in AD patients experiencing loss of appetite symptomatology. Previous work has shown that a majority of AD patients experience a problematic loss of appetite.2 These eating problems occur even in mild AD,2 and represent one of the greatest sources of complications and mortality in advanced AD patients.1,7 AD patients who had a clinically-recognized loss of appetite or poor food intake, and who required nursing care, were enrolled in the present study. The mean MMSE score of enrolled participants was 10.1 ± 7.0, representing moderate-to-severe AD. Although the food intake amount significantly improved in the higher MMSE subgroup (MMSE ≥10), it did not in the lower MMSE subgroup (MMSE <10), and the difference in food intake amount between the MMSE severity subgroups did not reach statistical significance (Fig. 2). This suggests that the rivastigmine transdermal patch therapy might be more effective in mild AD than in moderate or severe AD for the treatment of appetite deficits. As the loss of appetite and weight loss have been shown to hasten the onset of AD and progression of cognitive impairments, we suggest that rivastigmine transdermal patch therapy should be administered to dementia patients who present with abnormal eating behaviors, a loss of appetite or significant weight loss.20,21 The present results showed that the food intake ratio is likely to improve at the beginning of the study period, particularly at weeks 1, 2, 3, 4 and 8 (Fig. 1). This raises the possibility that the rivastigmine transdermal patch might be more effective for poor appetite in lower doses. In contrast, a significant improvement of food intake amount tended to be maintained throughout the observation period. Although the present study did not detect the correlation between the dose of rivastigmine and improvement of poor appetite, further study might be required to ascertain this relationship.

Several reports have shown that rivastigmine bolsters appetite in AD patients.8–10 The present study further shows that the rivastigmine transdermal patch, when used in AD patients with a loss of appetite, significantly increased patient food intake amount and ratio (Fig. 1; Table 2). One potential underlying mechanism for this might be that rivastigmine suppresses the degradation of plasma ghrelin by inhibiting plasma BuChE.22 Ghrelin is a gastrointestinal tract hormone known to increase appetite.5,6 Further potential mechanisms for this improvement of appetite in patients with AD might be both the inflammatory effects of ChEi in cholinergic pathways, and their ability to improve smell and taste perception by increasing the acetylcholine concentration in olfactory mucosa and taste buds, respectively.24,25 In addition to rivastigmine's inhibition of ChE, it might further contribute to improved swallowing by inhibiting BuChE.5 All of these potential mechanisms serve as targets for illumination by future studies.
| Variable                  | baseline       | Week 1      | Week 2      | Week 3      | Week 4      | Week 6      | Week 8      | Week 12     | Week 16     |
|---------------------------|----------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| **Food intake amount (g)**| 192.0 ± 139.5  | 246.0 ± 160.4 | 247.3 ± 136.4 | 239.9 ± 143.5 | 255.5 ± 143.6 | 254.1 ± 145.3 | 258.9 ± 148.8 | 256.8 ± 160.5 | 304.3 ± 155.8 |
| Change                    | –              | 54.9 ± 98.0 (34) | 54.0 ± 118.7 (30) | 46.6 ± 135.8 (30) | 63.9 ± 125.7 (30) | 57.4 ± 128.8 (24) | 65.9 ± 117.7 (23) | 47.2 ± 153.4 (18) | 101.3 ± 177.3 (17) |
| P-value                   | –              | 0.003       | 0.019       | 0.07        | 0.009       | 0.039       | 0.014       | 0.21        | 0.032       |
| **Food intake ratio (%)** | 40.5 ± 26.9 (36) | 49.5 ± 28.6 (33) | 51.1 ± 27.3 (30) | 50.4 ± 30.2 (30) | 53.7 ± 29.9 (30) | 50.8 ± 28.6 (24) | 50.8 ± 28.2 (23) | 50.6 ± 30.1 (18) | 55.2 ± 24.5 (17) |
| Change                    | –              | 9.3 ± 17.6 (33) | 12.1 ± 20.9 (30) | 11.4 ± 27.7 (30) | 14.6 ± 25.8 (30) | 11.0 ± 26.4 (24) | 12.1 ± 25.0 (23) | 5.2 ± 31.5 (18) | 10.2 ± 31.1 (17) |
| P-value                   | –              | 0.005       | 0.004       | 0.032       | 0.004       | 0.05        | 0.030       | 0.50        | 0.19        |
| **time spent eating lunch (min)** | 27.4 ± 16.0 (33) | 28.7 ± 15.6 (31) | 31.2 ± 15.7 (28) | 28.9 ± 14.0 (26) | 27.1 ± 15.9 (26) | 28.5 ± 15.6 (23) | 30.6 ± 17.7 (21) | 33.0 ± 18.3 (18) | 33.4 ± 19.2 (17) |
| Change                    | –              | 0.6 ± 13.2 (29) | 2.3 ± 12.1 (26) | –1.7 ± 12.9 (25) | –1.8 ± 14.2 (25) | –2.5 ± 13.2 (20) | –0.9 ± 11.7 (18) | –2.5 ± 11.6 (15) | –4.3 ± 17.5 (15) |
| P-value                   | –              | 0.82        | 0.34        | 0.52        | 0.54        | 0.42        | 0.75        | 0.42        | 0.36        |
| **Bodyweight (kg)**       | 39.6 ± 5.9 (33) | 39.5 ± 5.8 (31) | 39.4 ± 5.5 (28) | 39.4 ± 5.4 (28) | 39.4 ± 4.6 (29) | 39.9 ± 4.5 (20) | 38.9 ± 4.5 (21) | 38.5 ± 4.7 (18) | 39.2 ± 3.9 (16) |
| Change                    | –              | −0.1 ± 1.2 (30) | −0.1 ± 1.6 (27) | −0.2 ± 2.0 (27) | −0.5 ± 2.6 (27) | −0.2 ± 2.0 (17) | −0.4 ± 2.0 (18) | 0.9 ± 3.2 (15)  | 0.2 ± 2.5 (13) |
| P-value                   | –              | 0.52        | 0.64        | 0.66        | 0.37        | 0.67        | 0.41        | 0.30        | 0.74        |
| NPI-NH score              | 13.4 ± 16.1 (36) | –             | –             | –             | 10.3 ± 11.3 (31) | –             | 10.9 ± 14.4 (22) | –             | 7.8 ± 8.1 (17) |
| Change                    | –              | –             | –             | –             | −3.8 ± 9.9 (31)  | –             | −4.2 ± 15.1 (22) | –             | −4.9 ± 13.8 (17) |
| P-value                   | –              | –             | –             | –             | 0.039        | –             | 0.20        | –             | 0.16        |
| Caregiver burden          | 4.9 ± 6.5 (36) | –             | –             | –             | 4.1 ± 5.0 (31) | –             | 3.8 ± 5.3 (22) | –             | 3.2 ± 4.6 (17) |
| Change                    | –              | –             | –             | –             | −1.2 ± 4.0 (31) | –             | −1.7 ± 4.7 (22) | –             | −2.1 ± 5.7 (17) |
| P-value                   | –              | –             | –             | –             | 0.12        | –             | 0.10        | –             | 0.16        |
| MMSE score                | 10.1 ± 7.0 (36) | –             | –             | –             | –             | –             | –             | –             | 11.9 ± 8.2 (19) |
| Change                    | –              | –             | –             | –             | –             | –             | –             | –             | 0.1 ± 3.6 (19) |
| P-value                   | –              | –             | –             | –             | –             | –             | –             | –             | 0.90        |

Data are presented as mean ± standard deviation (n). P-values show results of statistical tests for changes by one sample t-test. MMSE, Mini-Mental State Examination; NPI-NH, Neuropsychiatric Inventory in Nursing Home version.
Rivastigmine patch improves food intake

Table 3  Multiple linear regression for changes in food intake amount and ratio at week 16

| Independent variable | Food intake amount (g) | Food intake ratio (%) |
|----------------------|------------------------|-----------------------|
|                      | Regression coefficient (SE) | P-value | Regression coefficient (SE) | P-value |
| Age (years)          | −4.86 (14.42)           | 0.74    | 0.68 (2.54)                 | 0.79    |
| Baseline weight (kg) | 4.51 (10.90)            | 0.69    | 0.16 (1.99)                 | 0.94    |
| Baseline MMSE score  | 6.62 (5.92)             | 0.28    | 0.12 (1.08)                 | 0.92    |
| Baseline psychotropic drug use | −70.90 (95.75) | 0.47    | −10.54 (16.91)             | 0.54    |

Complications/comorbidity

|                          | Food intake amount (g) | Food intake ratio (%) |
|--------------------------|------------------------|-----------------------|
| Constipation             | 20.85 (92.79)          | 0.83                  | −8.20 (16.19)                 | 0.62    |
| Hypertension             | −59.66 (103.58)        | 0.57                  | −0.35 (18.39)                 | 0.98    |
| Reflux esophagitis       | −86.58 (136.04)        | 0.53                  | −14.92 (23.91)                | 0.54    |
| Osteoporosis             | 137.11 (133.24)        | 0.32                  | 29.52 (22.99)                 | 0.22    |
| Chronic gastritis        | 27.54 (136.41)         | 0.58                  | 13.97 (23.95)                 | 0.57    |
| Heart failure            | −136.55 (111.06)       | 0.24                  | −14.88 (20.10)                | 0.47    |
| Gastric ulcer            | −29.02 (137.66)        | 0.84                  | 8.88 (24.11)                  | 0.72    |
| Overactive bladder       | −25.51 (137.71)        | 0.86                  | 3.85 (24.20)                  | 0.88    |
| Asthma                   | −36.01 (188.55)        | 0.85                  | 10.04 (33.06)                 | 0.77    |
| Hypothyroidism           | 0.00 (−)               | -                    | 0.00 (−)                      | -       |
| Hyperuricemia            | −275.07 (174.91)       | 0.14                  | −41.83 (31.35)                | 0.20    |
| Prostatomegaly           | 0.00 (−)               | -                    | 0.00 (−)                      | -       |
| Diabetes                 | 0.00 (−)               | -                    | 0.00 (−)                      | -       |
| Cerebrovascular disease  | −69.52 (88.45)         | 0.44                  | −6.10 (15.78)                 | 0.70    |
| Psychiatric disorder     | 33.15 (89.85)          | 0.72                  | 6.56 (15.76)                  | 0.68    |

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