Pharmacokinetics and Bioequivalence of Memantine Tablet and a New Dry Syrup Formulation in Healthy Japanese Males: Two Single-Dose Crossover Studies

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ABSTRACT

Introduction: Memantine hydrochloride, an N-methyl-D-aspartate receptor antagonist, is used to treat Alzheimer’s disease (AD). A new dry syrup formulation containing memantine hydrochloride has been developed to improve medication adherence in AD patients and to reduce family and caregiver burden. This study was conducted to assess the bioequivalence of this new formulation to the tablet.

Methods: Two single-dose, randomized, open-label, two-period, two-group, crossover studies were conducted to assess the bioequivalence of a test product [dry syrup, 2%, 1 g (containing 20 mg of memantine hydrochloride)] to a reference product (film-coated tablet) under two dosing conditions: administration of the test product as a suspension in water (Study I) and as granules taken with water (Study II). Blood samples were collected at specified time intervals, and memantine plasma concentrations were determined using a validated liquid chromatography tandem mass spectrometry method. The pharmacokinetic parameters of memantine were calculated using non-compartmental analysis. The maximum concentration ($C_{\text{max}}$) and area under the concentration–time curve up to the last sampling time ($AUC_{\text{all}}$) were used to assess the bioequivalence of the two formulations.

Results: The geometric least square mean (GLSM) ratios [90% confidence interval (CI)] of $C_{\text{max}}$ and $AUC_{\text{all}}$ of memantine for the test product to the reference product were 0.981 (0.943–1.020) and 0.978 (0.955–1.001) in Study I, and 0.973 (0.944–1.003) and 1.004 (0.983–1.025) in Study II, respectively. In both studies, the 90% CI values of the GLSM ratios of $C_{\text{max}}$ and $AUC_{\text{all}}$ were within the prespecified bioequivalence range (0.80–1.25). The safety of the test product under both dosing conditions and that of the reference product were not different.

Conclusions: The new dry syrup formulation containing memantine hydrochloride showed bioequivalence to the film-coated tablet under the two dosing conditions. Thus, the new dry syrup is suitable under either dosing condition for patients with AD.

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Keywords: Bioequivalence; Dry syrup; Memantine; Pharmacokinetics
INTRODUCTION

Alzheimer’s disease (AD) is a degenerative brain disease with multiple progressive symptoms, such as memory loss, communication impairment, disorientation, behavioral changes, and swallowing impairment, and is the most common cause of dementia [1, 2]. AD is a very burdensome disease, as it imposes a heavy burden on not only the patients but also their families and caregivers [2, 3]. Generally, dementia, including that associated with AD, is most prevalent in the elderly (>65 years) [2]; therefore, due to the increasing global elderly population, its incidence is expected to increase [4, 5].

Memantine hydrochloride is an N-methyl-D-aspartate receptor antagonist indicated for the treatment of moderate to severe dementia in AD. Currently, two orally administered dosage formulations [a film-coated tablet and an oral disintegrating (OD) tablet] at three strengths (5, 10, and 20 mg) have been approved in Japan. OD tablets are easy to take, especially by patients with swallowing impairment [6]. In contrast, several factors other than cognitive impairment affect medication adherence by patients with dementia [7, 8]. Therefore, a new dry syrup formulation of memantine hydrochloride has been developed to add another option, which will improve medication adherence and reduce the family and caregiver burden.

After oral administration, memantine is highly absorbed, reaching the observed maximum concentration ($C_{\text{max}}$) in 3–8 h [9]. The pharmacokinetics (PK) of memantine is proportional in a wide dose range and the apparent elimination half-life ($T_{1/2}$) is approximately 60–70 h [9, 10]. Memantine is mainly excreted from the kidney, and hardly metabolized in the liver [9, 10]. Multidrug and toxin extrusion protein contributes to renal secretion of memantine [11].

The primary objective of this study was to assess the bioequivalence between the test (dry syrup containing 20 mg of memantine hydrochloride) and reference (20 mg film-coated tablet) products in healthy adult Japanese males.

METHODS

The study was conducted in accordance with the Good Clinical Practice guidelines, locally applicable laws and regulations, and ethical principles originating in or derived from the Declaration of Helsinki. The study protocol was developed per the guideline for Bioequivalence Studies of Generic Products [12], and the study was conducted at Tokyo Heart Center (Tokyo, Japan). The study protocol, its amendments, and the informed consent form were approved by the 124th Institutional Review Board of the study site on December 16, 2015 (Protocol number: SUN Y7017-G-J101). This study was not registered at any registry databases because at the time it was conducted, the registration of healthy subject trials was not required by the Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases by the International Federation of Pharmaceutical Manufacturers and Associations. Prior to study execution, all subjects provided written informed consent.

Subjects

Healthy Japanese males aged 20–40 years with 25.0 kg/m$^2$ > BMIs ≥ 18.5 kg/m$^2$ at screening, were eligible for inclusion. The exclusion criteria included: (1) any medical history of central nervous, cardiovascular, respiratory, gastrointestinal, urinary, or blood/hematopoiesis system disorders, or hepatic/renal impairment, thyroid dysfunction, pituitary malfunction, adrenal dysfunction; (2) any clinically significant deviation from the normal range in a physical examination, vital signs (e.g., blood pressure, heart rate, and body temperature), 12-lead electrocardiogram, or clinical laboratory determinations; (3) history of epilepsy or convulsions; (4) incompletely healed oral cavity wound; (5) hypersensitivity or idiosyncratic reactions to any drug; (6) history of alcohol or drug abuse; (7) presence of an infection; (8) previous participation in a memantine hydrochloride clinical study; (9) current or planned receipt of any medical intervention after screening; (10) whole blood collection of
> 800 mL within 1 year, > 400 mL within 84 days, or > 200 mL within 28 days, or blood component collection within 14 days of the study; (11) previous clinical trial participation and investigational drug administration within 120 days of the study; (12) current or planned use of other drugs or supplements 14 days prior to hospitalization for the study and until study completion; (13) consumption of grapefruit (juice or pulp) within 7 days prior to hospitalization; (14) not consenting effective contraception use; and (15) investigator-determined ineligibility. Subjects could withdraw from the study at any time after a request.

**Study Design**

Two single-dose, randomized, open-label, two-period, two-group, crossover studies were conducted under two dosing conditions: test product [dry syrup, 2%, 1 g (containing 20 mg of memantine hydrochloride); Daiichi Sankyo, Tokyo, Japan] administration as a suspension in water (Study I) and as granules with water (Study II), because the dry syrup will be marketed to be administered in both conditions. Thirty days prior to treatment commencement, subjects were screened for eligibility. Subjects were confined to the study site for 5 days, from the day before treatment commencement (Day -1) until 72-h post-dosing (Day 4). After discharge, the 120- and 192-h post-dosing procedures were conducted during ambulatory visits to the study site on Days 6 and 9. On Day -1 of each treatment period, the study drugs were administered, with a 20- to 24-day washout period between administrations. On Day -1 of the first treatment period of each study, subjects were randomly assigned (1:1 ratio) to either a test–reference or reference-test sequence. The follow-up assessment was conducted after 20-24 days of the last administration in the second treatment period.

Randomization was conducted by the investigators in accordance with a randomization schedule, which was created using a computer-generated randomization scheme by the contract research organization.

**Sample Collection and Bioanalytical Methods**

Blood samples (5 mL) were collected in vacuum tubes containing the anti-coagulant, sodium heparin, at pre-dosing, and at 1, 3, 4, 5, 6, 8, 12, 24, 48, 72, 120, and 192 h post-dosing in each treatment period of both studies. Plasma was separated by centrifugation and stored at −20 °C until analysis.

Memantine was extracted from 100-μL plasma samples via liquid–liquid extraction with diethyl ether. The organic layer was transferred and then evaporated under a nitrogen stream at approximately 40 °C. The remaining residue was reconstituted with 600 μL of reconstitution solution [0.76:600:400:2 (ammonium formate/water/methanol/formic acid), v/v/v/v]. The final solution was analyzed using a validated liquid chromatography tandem mass spectrometry method. Chromatographic separation was performed using an Inertsil ODS-SP column (2.1 mm I.D. × 50 mm, 3 μm; GL Sciences, Tokyo, Japan). Detection was performed using an API 4000 or 4000 QTRAP (AB SCIEX, Framingham, MA, USA) tandem mass spectrometer with a TurboIonSpray source by electrospray ionization in the positive ion mode, and multiple-reaction monitoring of memantine (m/z 180–163) and its internal standard (memantine-d6, m/z 186–169). The intra-study assay precisions for 1.60, 8.00, and 80.0 ng/mL memantine were 2.6, 1.4, and 0.4%, respectively. Assay
accuracy ranged from −3.1 to −2.5%, with a lower limit of quantification of 0.500 ng/mL.

**Pharmacokinetic Analysis**

PK parameters were calculated from the plasma concentration–time data of memantine of each subject by a non-compartment analysis using Phoenix WinNonlin (v.6.3; Certara G.K, Tokyo, Japan).

The primary PK parameters were \( C_{\text{max}} \) and area under the concentration–time curve (AUC) up to the last sampling time (AUC\(_{\text{all}}\)), whereas the secondary PK parameters were the observed time to \( C_{\text{max}} \) (\( T_{\text{max}} \)), \( T_{1/2} \), and AUC up to infinity (AUC\(_{\text{inf}}\)).

**Statistical Analysis**

Logarithmically-transformed values of the primary PK parameters (\( C_{\text{max}} \) and AUC\(_{\text{all}}\)) were compared for the two dosage formulations, and the test product versus the reference product. A mixed-effect model that included treatment group, treatment period, and formulation as fixed effects, and subject within sequence as random effect, was used for all comparisons. The ratios of geometric least-squares means (GLSM) of the primary PK parameters and their 90% confidence intervals (CIs) were calculated. Subjects whose AUC\(_{\text{all}}\) could not be properly calculated were excluded from the calculation of GLSM and their 90% CIs. Bioequivalence of the test and reference products was concluded if the 90% CIs of the ratios of GLSM of the primary PK parameters were within the predefined acceptance range of 0.80–1.25. Statistical analyses were performed using SAS\textsuperscript{®} (v.9.2; SAS Institute Japan, Tokyo, Japan).

The sample size for this study was calculated by the reported approach [13] using previous memantine studies (data on file). The intra-individual geometric coefficient of variations of \( C_{\text{max}} \) and AUC\(_{\text{all}}\) of memantine were approximately 10%; thus, 18 evaluable subjects were necessary to provide a 90% power to demonstrate bioequivalence of the two dosage formulations in each study. To ensure that we obtained the PK data of ≥ 18 subjects at study procedure completion, 24 subjects were enrolled in each study.

**Safety Assessments**

Drug safety was assessed using data of adverse events (AEs), vital signs (body temperature, blood pressure, and pulse rate), body weight, 12-lead electrocardiograms, and laboratory tests (including hematology, serum chemistry, and urinalysis). The intensity, duration, relationship to the study drugs, outcome, and severity of all AEs that occurred after the first administration of study drugs until study completion were recorded.

**RESULTS**

**Disposition and Baseline Clinical characteristics**

In Study I, 24 healthy subjects were enrolled; 19 completed the study and five withdrew after drug administration in the first treatment period (four due to AEs and one due to deviation from the exclusion criteria).

In Study II, 24 healthy subjects were enrolled; 21 completed the study and two dropped out during the first treatment period (one due to an AE and one due to deviation from the exclusion criteria) and one dropped out during the second treatment period after withdrawing consent.

The subject demographics and baseline characteristics of both studies are shown in Table 1.

**Pharmacokinetics**

**Study I (Test Product Administration: Suspension in Water)**

The mean plasma memantine concentration–time profile is shown in Fig. 1. A summary of memantine’s PK parameters are presented in Table 2. The \( C_{\text{max}} \) and AUC\(_{\text{all}}\) of memantine in the test and reference products were similar, with mean [standard deviation (SD)] values of 27.3 (3.89) ng/mL and 1890 (315) ng h/mL, and 27.9 (3.81) ng/mL and 1950 (288) ng h/mL, respectively. The \( T_{\text{max}} \), \( T_{1/2} \), and AUC\(_{\text{inf}}\) of the
test and reference products were also similar. The GLSM ratios (90% CI) of the $C_{\text{max}}$ and $AUC_{\text{all}}$ were 0.981 (0.943–1.020) and 0.978 (0.955–1.001), respectively (Table 3). Both 90% CIs of the ratios of GLSM were within the pre-specified bioequivalence range (0.80–1.25).

Study II (Test Product Administration: Granule with Water)
The mean plasma memantine concentration–time profile is shown in Fig. 2. A summary of memantine’s PK parameters are presented in Table 2. The $C_{\text{max}}$ and $AUC_{\text{all}}$ of memantine in the test and reference products were similar, with mean (SD) values of 27.7 (3.94) ng/mL and 1890 (266) ng h/mL, and 28.5 (3.70) ng/mL and 1880 (271) ng h/mL, respectively. The $T_{\text{max}}$, $T_{V/2}$, and $AUC_{\text{inf}}$ of the test and reference products were also similar. The GLSM ratios (90% CI) of the $C_{\text{max}}$ and $AUC_{\text{all}}$ were 0.973 (0.944–1.003) and 1.004 (0.983–1.025), respectively (Table 3). Both 90% CIs of the ratios of GLSM were within the pre-specified bioequivalence range (0.80–1.25).

Safety
All AEs that occurred during this study are listed in Table 4.
Fig. 1 Mean (standard deviation) plasma concentration–time profiles of memantine after a single oral administration of dry syrup 2%, 1 g (containing 20 mg of memantine hydrochloride) and a tablet with linear (a) and semi-logarithmic (b) scales in Study I (administration of the dry syrup as a suspension in water). The mean plasma concentration of the dry syrup at 192-h post-dosing was calculated using $n = 18$. 
In both Studies I and II, the 90% CIs of the GLSM ratios of $C_{\text{max}}$ and $AUC_{\text{all}}$ for memantine were within the prespecified bioequivalence range, suggesting that patients with AD can take this new dry syrup under either dosing condition. These results are owed to the physicochemical properties of memantine hydrochloride, classified as a class I (high solubility/permeability) drug, according to the Bio- pharmaceutical Classification System [17, 18]. Additionally, the results of the in vitro dissolution tests performed in accordance with local guidelines [19], using the paddle method at 50 rpm with 900 mL of Japanese Pharmacopoeia first Fluid for Dissolution Test (JP1, pH 1.2), diluted McIlvaine buffer (pH 4.0), Japanese Pharmacopoeia second Fluid for Dissolution Test (JP2, pH 6.8), and water, elucidated the similarity between the dry syrup and the film-coated tablet (data on file). These findings suggest that the dissolution of memantine hydrochloride from each formulation in the gastrointestinal tract was similar, and that the fraction absorbed after oral administration of each formulation was comparable.

With regards to the safety of the formulations, all reported AEs were of mild or moderate intensity, with no deaths, and subjects recovered or relieved from all AEs. The AEs after administration of the dry syrup under both dosing conditions were not notably different.

### Table 2
Summary of pharmacokinetic (PK) parameters of memantine in Study I (administration of the dry syrup as a suspension in water) and Study II (administration of the dry syrup as granules with water)

|                   | Dry syrup       | Tablet          |
|-------------------|-----------------|-----------------|
|                   | Study I (n = 19)| Study II (n = 22)|
|                   | $C_{\text{max}}$ (ng/mL) | 27.3 (3.89) | 27.7 (3.94) |
|                   | $AUC_{\text{all}}$ (ng h/mL) | 1890 (315)$^b$ | 1890 (266)$^c$ |
|                   | $AUC_{\text{inf}}$ (ng h/mL) | 2170 (459) | 2100 (319)$^c$ |
|                   | $T_{\text{max}}$ (h)$^a$ | 6.00 (1.00, 8.00) | 5.00 (3.00, 8.00) |
|                   | $T_{\frac{1}{2}}$ (h) | 60.6 (12.5) | 57.1 (7.68)$^c$ |

Data are presented as mean (SD)

$AUC_{\text{all}}$ area under the concentration–time curve up to the last sampling time, $AUC_{\text{inf}}$ area under the concentration–time curve up to infinity, $C_{\text{max}}$ observed maximum concentration, $max$ maximum, $min$ minimum, SD standard deviation, $T_{\frac{1}{2}}$ apparent elimination half-life, $T_{\text{max}}$ observed time to $C_{\text{max}}$

$^a$ Median (min, max)
$^b$ $n = 18$ (number of subjects with reportable $AUC_{\text{all}}$
$^c$ $n = 21$ (number of subjects with reportable $AUC_{\text{all}}$

### Table 3
Statistical analysis of pharmacokinetic (PK) parameters of memantine in Studies I and II

| GLSM ratio (dry syrup/tablet) | 90% CI lower | 90% CI upper |
|-------------------------------|-------------|-------------|
| Study I (n = 19)              |             |             |
| $C_{\text{max}}$ (ng/mL)     | 0.981       | 1.020       |
| $AUC_{\text{all}}$ (ng h/mL)$^a$ | 0.978       | 1.001       |
| Study II (n = 22)             |             |             |
| $C_{\text{max}}$ (ng/mL)     | 0.973       | 1.003       |
| $AUC_{\text{all}}$ (ng h/mL)$^b$ | 1.004       | 1.025       |

$AUC_{\text{all}}$ area under the concentration–time curve up to the last sampling time, CI confidence interval, $C_{\text{max}}$ observed maximum concentration, GLSM geometric least squares mean

$^a$ $n = 18$ (number of subjects with reportable $AUC_{\text{all}}$
$^b$ $n = 21$ (number of subjects with reportable $AUC_{\text{all}}$

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Fig. 2 Mean (standard deviation) plasma concentration–time profiles of memantine after a single oral administration of dry syrup 2%, 1 g (containing 20 mg of memantine hydrochloride) and a tablet with linear (a) and semi-logarithmic (b) scales in Study II (administration of the dry syrup as granules with water). The mean plasma concentration of the dry syrup at 120- and 192-h post-dosing was calculated using \( n = 21 \).
from those of the conventional film-coated tablet [20].

Easy to administer formulations are desirable for patients with AD because of the associated low medication compliance [6]. OD tablets were developed for improved medication compliance compared with traditional tablets. Similarly, the dry syrup was developed to further improve medication compliance in patients with AD, and reduce family and caregiver burden. The dry syrup formulation containing donepezil hydrochloride has been approved for AD treatment in Japan [21], as it is relatively easier to administer to some patients than tablets.

The existence of few limitations in this study is owed to the study design, subjects, PK sample points, bioanalytical method, and PK analysis being planned and performed in accordance with the Guideline for Bioequivalence Studies of Generic Products [12]. However, because all

| Study I | Study II |
|---------|---------|
| Dry syrup | Tablet | Dry syrup | Tablet |
| No. of subjects evaluated | $n = 22$ | $n = 21$ | $n = 22$ | $n = 24$ |
| No. of subjects with AEs | 6 (27.3) | 5 (23.8) | 4 (18.2) | 7 (29.2) |
| Infections and infestations | | | |
| Influenza | 1 (4.5) | 0 | 0 | 1 (4.2) |
| Pharyngitis | 0 | 1 (4.8) | 0 | 0 |
| Nervous system disorders | | | |
| Dizziness | 1 (4.5) | 0 | 1 (4.5) | 2 (8.3) |
| Gastrointestinal disorders | | | |
| Diarrhoea | 1 (4.5) | 0 | 0 | 0 |
| Toothache | 2 (9.1) | 0 | 0 | 0 |
| Faeces soft | 0 | 0 | 0 | 1 (4.2) |
| Stomatitis | 0 | 0 | 0 | 1 (4.2) |
| Investigations | | | |
| Alanine aminotransferase increased | 1 (4.5) | 0 | 1 (4.5) | 0 |
| Blood bilirubin increased | 0 | 1 (4.8) | 0 | 0 |
| Blood cholesterol increased | 0 | 1 (4.8) | 0 | 0 |
| Blood triglycerides increased | 2 (9.1) | 2 (9.5) | 0 | 1 (4.2) |
| Gamma-glutamyltransferase increased | 1 (4.5) | 0 | 0 | 0 |
| Aspartate aminotransferase increased | 0 | 0 | 1 (4.5) | 0 |
| Blood creatine phosphokinase increased | 0 | 0 | 1 (4.5) | 0 |
| Myoglobin blood increased | 0 | 0 | 1 (4.5) | 0 |
| Neutrophil count increased | 0 | 0 | 0 | 1 (4.2) |
| White blood cell count increased | 0 | 0 | 1 (4.5) | 1 (4.2) |

$n$ (%), MedDRA/J v.19.0

$\Delta$ Adis
study subjects were healthy, it remains unclear whether the new dry syrup formulation is beneficial to actual AD patients, and their families and caregivers. Notwithstanding, because of the benefits of the dry syrup formulation containing donepezil hydrochloride, we believe the memantine hydrochloride dry syrup will also be beneficial in AD treatment.

CONCLUSION

The new dry syrup formulation containing memantine hydrochloride is bioequivalent to the marketed film-coated tablet in healthy adult Japanese males, and is expected to improve patient medication adherence and to reduce family and caregiver burden.

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Authorship. All authors of this article meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship, and take responsibility for the work as a whole, including the integrity of the data and accuracy of the data analysis. All named authors approve the publication of this version.

Disclosures. Yutarō Maekawa is an employee of Daiichi Sankyo Co. Tomoko Ishizuka is an employee of Daiichi Sankyo Co. Kazuhito Shiosakai is an employee of Daiichi Sankyo Co. Hitoshi Ishizuka is an employee of Daiichi Sankyo Co., Ltd. Setsuo Hasegawa has nothing to disclose.

Compliance with Ethics Guidelines. All procedures performed in this study were in accordance with local regulations, Good Clinical Practice guidelines, and the Declaration of Helsinki and its later amendments. Informed consents were obtained from all eligible and willing study subjects.

Data Availability. All generated and/or analyzed study data are available upon reasonable request from the corresponding author.

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