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Full Paper

Effect of Renal Impairment on the Pharmacokinetics of Memantine

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Abstract. The effect of renal impairment on the pharmacokinetics of a single oral dose of memantine (10 mg) was determined in Japanese subjects. Subjects were assigned to four groups based on baseline creatinine clearance (CL_{CR}): normal renal function (> 80 mL/min, n = 6), and mild (50 to ≤ 80 mL/min, n = 6), moderate (30 to < 50 mL/min, n = 6), and severe renal impairment (5 to < 30 mL/min, n = 7). Mean memantine maximum plasma concentration (C_{max}) was similar in the groups (12.66, 17.25, 15.75, and 15.83 ng/mL, respectively), as was mean time to C_{max} (6.2, 5.2, 4.3, and 5.4 h, respectively). However, exposure to memantine determined from mean area under the plasma concentration–time curve was 1.62-, 1.97-, and 2.33-times higher in subjects with mild, moderate, and severe renal impairment, respectively, as compared to controls with normal renal function. Mean memantine plasma elimination half-life increased according to increasing renal impairment (61.15, 83.00, 100.13, and 124.31 h, respectively), while mean cumulative urinary recovery of unchanged memantine in 72 h after dosing decreased according to increasing renal impairment (33.68%, 33.47%, 23.60%, and 16.17%, respectively). These results are the same as those in the previous study on caucasian individuals, when compared per body weight. It is suggested that the dose of memantine should be halved in patients with renal impairment.

Keywords: memantine, renal impairment, pharmacokinetics, dose, dementia

Introduction

Memantine hydrochloride (3,5-dimethyltricyclo [3.3.1.1^{3,7}]decan-1-aminemonohydrochloride) is a glutamatergic (NMDA receptor) antagonist (NMDA open-

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channel inhibitor) that has been used since 1982 for the treatment of patients with dementia showing concentration impairment in thinking, poor motivation, decreased activities of daily living, and mild to moderate symptoms of depression as well as for patients with spastic cerebral palsy and parkinsonism (1 – 4). In a double-blind placebo-controlled trial, memantine improved clinical symptoms of dementia evaluated using the SIB-J subscale in Japanese patients with no difference in the incidence of adverse effects among the groups that received placebo, memantine at 10 mg/day, and memantine at 20 mg/day (data on file; Asubio Pharma Co., Ltd., Kobe).

Memantine is primarily excreted unchanged via the kidney (5), so blood memantine concentrations are expected to be increased in patients with renal impairment, especially in the elderly. We determined the pharmacokinetics of memantine in Japanese healthy subjects and subjects with renal insufficiency and compared the results with those in Caucasians to determine any potential differences between the races.

Materials and Methods

Subjects

Japanese adult subjects (age 20 – 80 years) of either gender were eligible for entry into the study. Subjects with normal renal function and those with mild, moderate, or severe renal impairment were enrolled on informed consent. The subjects with dialysis, taking charcoal, a history of myocardial infarction, stroke, uncontrolled hypertension, or diabetic mellitus were excluded.

Study design

The study protocol received Independent Review Board approval at each of the participating institutions where the trial was conducted. All subjects provided written informed consent prior to participation in the study, which adhered to the ethical principles of the Declaration of Helsinki.

This was an open-label, non-randomized, single-sequence study to determine the pharmacokinetics of a single 10-mg tablet of memantine hydrochloride (Memary®; Asubio Pharma Co., Ltd.) after oral administration in subjects with varying degrees of renal impairment. A total of 25 subjects were recruited into four groups according to their renal function based on creatinine clearance (CL_{CR}) estimated by the Cockcroft-Gault formula using screening serum creatinine (6). Group stratification was as follows: Group I, Normal renal function (CL_{CR} > 80 mL/min) [n = 6]; Group II, Mild renal impairment (CL_{CR} 50 to ≤ 80 mL/min) [n = 6]; Group III, Moderate renal impairment (CL_{CR} 30 to < 50 mL/min) [n = 6]; Group IV, Severe renal impairment (CL_{CR} 5 to < 30 mL/min) [n = 7].

All subjects received memantine administered with 150 mL of water in the morning at 9:00 am after overnight fasting. Subjects were required to refrain from consumption of any food or beverages containing alcohol, grapefruit, St. John's wort, or caffeine (e.g., coffee, tea, chocolate) during the study period.

Subjects were required not to receive any drugs with NMDA-receptor inhibitory activity (e.g., amantadine hydrochloride, ketamine hydrochloride, riluzole, ifenprodil tartrate, haloperidol, milnacipran hydrochloride, dextromethorphan hydrobromide) or agents that could possibly alter urinary pH or affect the renal cation transport system (OCT-2) in the week prior to study initiation and during the study. Subjects were not allowed to start any new drug therapy or change the dose of existing concurrent medication in the week prior to study initiation and during the study.

Screening and safety assessments

The following screening assessments were performed immediately prior to study entry: physical examination, medical history, height, weight, body mass index, vital signs (temperature, BP, pulse rate); 12-lead electrocardiogram for QTc determination; pregnancy test; routine blood tests [red blood cell count, hemoglobin, hematocrit, platelet count, total protein, albumin, total bilirubin, direct bilirubin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, leucine aminopeptidase, alkaline phosphatase, gamma-glutamyltranspeptidase, creatine kinase, total cholesterol, trigycerides, glucose, glycosylated hemoglobin, uric acid, blood urea nitrogen, creatinine, and electrolytes (calcium, sodium, potassium, chloride, and inorganic phosphate)], and urinalysis (specific gravity, pH, ketones, glucose, urobilinogen, bilirubin, protein, occult blood, and sediment). All treatment-emergent adverse events were recorded irrespective relationship to memantine and graded with respect to severity.

Blood and urine sample collection

Blood samples were collected at 0 (pre-dose), 1, 2, 3, 4, 6, 10, 24, 48, 72, 144, 216, 312, 384, and 480 h after the administration of memantine. Plasma was separated by standard procedures for determination of memantine concentration and percentage binding of memantine to plasma protein. Total urine was collected daily for 3 days (0 – 24, 24 – 48, and 48 – 72 h after taking memantine) and the total amount of unchanged memantine in urine was measured. Serum and urinary creatinine concentrations were also measured to determine creatinine clearance.

Pharmacokinetic measurements

Unchanged memantine concentrations in plasma and urine were measured using a gas chromatographic/mass spectrometry method (TRACE GC2000/MS) with detection limits of 0.50 and 5.00 ng/mL in plasma and urine, respectively, at Mitsubishi Chemical Medience, Ltd. (Tokyo).

Pharmacokinetic parameters were calculated using WinNonlin Professional (Version 4.0.1; Pharsight Corporation, CA, USA) using standard non-compartmental methods. C_{max} (maximum observed plasma concentration), T_{max} (time to reach C_{max}), AUC_{0-t} [area under the plasma concentration–time curve (AUC) from time zero to the last measurable concentration (C_t) calculated by the linear trapezoidal method], and $t_{1/2}$ (apparent first-order terminal elimination half-life) were determined. $Ae_{0-72\ h}$ (urinary recovery of unchanged memantine over 72 h post-dose) was also determined. Statistical Analysis (SAS), version 9.1 (SAS Institute Inc., Cary, NC, USA), was applied for statistical analysis. Results are expressed as mean values ± standard deviation (S.D.). Statistical significance was accepted for *P*-values < 0.05. WinNonlin, version 4.0.1 was used for simulation of steady-state plasma memantine concentrations.

Results

Subjects

All of the 25 subjects were used for the safety and pharmacokinetic analysis. The clinical and demographic characteristics of the subjects are shown in Table 1. There were no differences between the groups with respect to age, height, and body weight. There was high degree of correlation between the estimated CR_{CL} and the measured CR_{CL} (R = 0.879, data not shown).

Plasma pharmacokinetics

Mean plasma memantine concentrations over time for the different groups are shown in Fig. 1. Mean memantine pharmacokinetic parameters for the groups are summarized in Table 2. There were no significant differences in mean C_{max} or T_{max} among the 4 groups. However, compared to subjects with normal renal function, mean memantine AUC_{0-t} was 1.62-, 1.97-, and 2.33-times higher in subjects with mild, moderate, and severe renal impairment, respectively ($P < 0.05$). Exposure to memantine increased in relation to declining renal function (Fig. 2). Mean memantine $t_{1/2}$ was prolonged in relation to declining renal function (Fig. 3).

Urinary pharmacokinetics

The renal clearance of memantine decreased in rela-

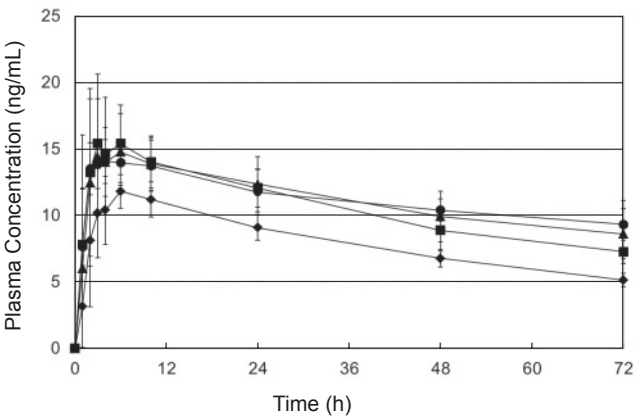

Fig. 1. Plasma memantine concentrations in each group. Values each represent a mean ± S.D. Closed diamonds, no renal impairment; closed squares, mild renal impairment; closed triangles, moderate renal impairment; closed circles, severe renal impairment.

Table 1. Subject demographic and clinical characteristics

Characteristic	Degree of renal impairment			
	none (n = 6)	mild (n = 6)	moderate (n = 6)	severe (n = 7)
Gender, n (%)				
Male	4 (66.7)	3 (50.0)	3 (50.0)	6 (85.7)
Female	2 (33.3)	3 (50.0)	3 (50.0)	1 (14.3)
Mean ± S.D. age (year)	67.0 ± 7.0	69.8 ± 2.6	65.5 ± 7.2	67.8 ± 6.8
Mean ± S.D. height (cm)	162.05 ± 6.53	159.60 ± 10.28	157.05 ± 10.08	162.79 ± 6.78
Mean ± S.D. weight (kg)	59.00 ± 7.13	56.57 ± 8.03	56.38 ± 5.87	59.66 ± 5.78
Mean ± S.D. estimated CL_{CR} (mL/min)	91.05 ± 13.57	62.70 ± 5.94	40.93 ± 6.01	19.11 ± 6.81
Mean ± S.D. measured CL_{CR} (mL/min)	125.46 ± 43.17	93.97 ± 16.86	56.88 ± 10.67	19.31 ± 9.71

CL_{CR}, creatinine clearance; S.D., standard deviation.

Table 2. Memantine pharmacokinetic parameters

Pharmacokinetic parameter	Mean ± S.D.			
	degree of renal insufficiency			
	none (n = 6)	mild (n = 6)	moderate (n = 6)	severe (n = 7)
C_{max} (ng/mL)	12.66 ± 2.14	17.25 ± 3.94	15.75 ± 3.70	15.83 ± 0.62
T_{max} (h)	6.2 ± 3.4	5.2 ± 3.8	4.3 ± 1.9	5.4 ± 3.4
$t_{1/2}$ (h)	61.15 ± 7.45	83.00 ± 16.97*	100.13 ± 16.25**	124.31 ± 21.00**
AUC_{0-t} (ng·h/mL)	963.0 ± 105.9	1560.7 ± 182.9**	1935.5 ± 479.3**	2257.3 ± 382.0**
Plasma protein binding (%)	40.83 ± 5.90	49.45 ± 10.83	41.23 ± 12.75	31.77 ± 10.10
$Ae_{0-72\ h}$ (%)	33.68 ± 8.30	33.47 ± 3.40	23.60 ± 2.86	16.17 ± 6.05

*$P < 0.05$, **$P < 0.001$ (*t*-test vs. normal controls). $Ae_{0-72\ h}$, urinary recovery over 72 h post-dose; AUC_{0-t}, area under the plasma concentration–time curve from time zero to the last measurable concentration; C_{max}, maximum plasma concentration; S.D., standard deviation; T_{max}, time to C_{max}; $t_{1/2}$, apparent first-order terminal elimination half-life.

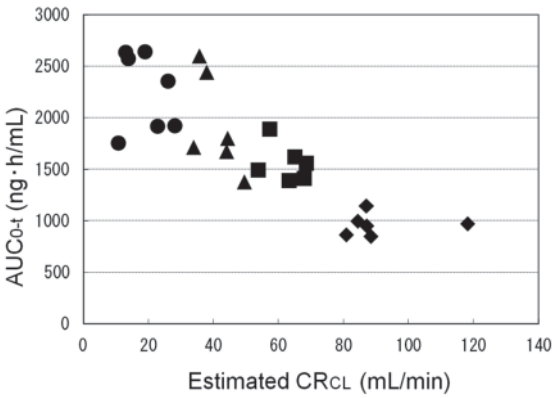

Fig. 2. Correlation between AUC_{0-t} and estimated CR_{CL} (R = 0.829). Closed diamonds, no renal impairment; closed squares, mild renal impairment; closed triangles, moderate renal impairment; closed circles, severe renal impairment.

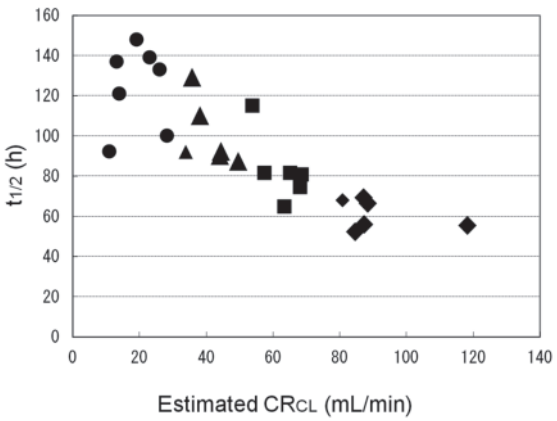

Fig. 3. Correlation between $t_{1/2}$ and estimated CR_{CL} (R = 0.842). Closed diamonds, no renal impairment; closed squares, mild renal impairment; closed triangles, moderate renal impairment; closed circles, severe renal impairment.

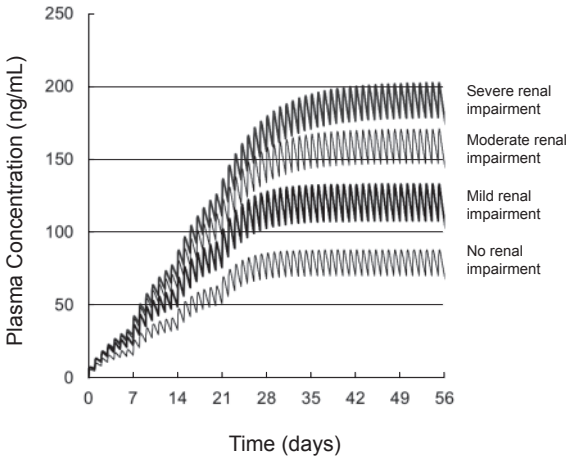

Fig. 4. Simulated steady-state plasma memantine concentrations according to the degree of renal impairment for each group.

tion to declining renal function and the mean urinary recovery of memantine over 72 h after dosing decreased according to increased renal insufficiency. There were no differences in the percentage plasma protein binding of memantine among the groups (Table 2).

Predicted steady-state memantine plasma concentrations

Steady-state plasma memantine concentrations were extrapolated using the present single-dose data. The estimated mean C_{max} at steady state was 85, 125, 165, and 195 ng/mL in groups with no, mild, moderate, and severe renal impairment, respectively (Fig. 4).

Safety

Twenty-three treatment-emergent adverse events were observed in 12 subjects, none of which were severe or

serious. None of these adverse effects were considered related to memantine (Table 3).

Discussion

The pharmacokinetics of a single dose of memantine (20 mg) have been studied in 32 Caucasian subjects (7). Mean memantine $AUC_{0-\infty}$ increased by 60% and 115% in patients with moderate and severe renal insufficiency, respectively, as compared to subjects with normal renal function, while mean memantine $t_{1/2}$ increased by 41% and 95%, respectively. There were seven adverse events in 10 subjects. In our study on Japanese subjects, mean memantine AUC_{0-t} increased by 97% and 133% in subjects with moderate and severe renal impairment, respectively, and mean memantine $t_{1/2}$ increased by 64% and 103%, respectively, as compared to subjects with normal renal function. There were 23 adverse events in 12 of 25 subjects, showing a similar incidence and type to the study in Caucasian subjects. No severe adverse events were observed in either study. With respect to estimation of renal function, the correlation between calculated CR_{CL} and measured CR_{CL} was high, which is the same as in previous reports (8).

Amantadine, another NMDA antagonist used in the treatment of CNS disorders, is also excreted unchanged via the kidney and shows marked increases plasma concentrations according to increasing renal insufficiency. Patients showed severe adverse effects such as myoclonus or excitement in cases where plasma amantadine concentrations exceeded 3000 ng/mL (9). The concentration of amantadine causing severe adverse effects seems to be lower in Japanese compared to Caucasian subjects during the treatment of dyskinesia in cases with Parkinson's disease. However, there were no differences between Japanese and Caucasian subjects in sensitivity to adverse effects in patients with renal failure (10, 11).

Memantine is used in the treatment of dementia of Alzheimer's disease or multiple cerebral infarction, which is common in the elderly who frequently have concurrent renal impairment. Mean memantine AUC_{0-t} increased 1.2- and 1.3-fold in subjects with moderate and severe renal impairment, respectively, as compared controls with normal renal function following a single

Table 3. Adverse events

Adverse events	No. of subjects (%)			
	degree of renal impairment			
	none (n = 6)	mild (n = 6)	moderate (n = 6)	severe (n = 7)
Total	1 (16.7)	3 (50.0)	3 (50.0)	5 (71.4)
Color-blindness	0	0	1 (16.7)	0
Conjunctivitis	0	1 (16.7)	0	0
Visual acuity reduced	0	0	1 (16.7)	0
Constipation	0	1 (16.7)	1 (16.7)	1 (14.3)
Diarrhea	1 (16.7)	0	0	0
Nausea	0	0	0	1 (14.3)
Periodontitis	0	0	1 (16.7)	0
Feeling abnormal	0	1 (16.7)	1 (16.7)	0
Edema, peripheral	0	0	0	1 (14.3)
Nasopharyngitis	0	1 (16.7)	1 (16.7)	0
Blood glucose increased	0	0	0	1 (14.3)
Blood pressure increased	0	0	1 (16.7)	0
Back pain	0	1 (16.7)	0	0
Dizziness	0	1 (16.7)	0	0
Dizziness, postural	0	0	0	1 (14.3)
Headache	0	0	1 (16.7)	0
Upper respiratory tract infection	0	0	1 (16.7)	0
Pruritus	0	0	1 (16.7)	1 (14.3)

dose of memantine. However, corresponding steady-state AUC_{0-t} increases were estimated at 2- and 2.3-fold higher, respectively, using simulated data. The blood concentration of memantine was around 120 ng/ml in the clinical trials in Japan at the dose of 20 mg a day, which was the recommended dose in patients with Alzheimer's Disease (Insert package, http://www.info.pmda.go.jp/go/pack/1190018F1023_1_03/). Memantine is primarily excreted via the kidney and there may be induction of other routes of memantine metabolism or excretion in patients with severe renal insufficiency (12). According to our present results, it is recommended that the normal dose of memantine should be halved in patients with renal impairment.

References

1 Reisberg B, Doody R, Stöffler A, Schmitt F, Ferris S, Möbius HJ; Memantine Study Group. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med. 2003;348:1333–1341.

2 Kavirajan H, Schneider LS. Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomised controlled trials. Lancet Neurol. 2007;6:782–792.

3 Emre M, Tsolaki M, Bonuccelli U, Destée A, Tolosa E, Kutzelnigg A, et al; 11018 Study Investigators. Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2010;9:969–977.

4 Merello M, Nouzeilles MI, Cammarota A, Leiguarda R. Effect of memantine (NMDA antagonist) on Parkinson's disease: a double-blind crossover randomized study. Clin Neuropharmacol. 1999;22:273–276.

5 Wesemann W, Sonntag K-M, Maj J. [Pharmacodynamics and pharmacokinetics of memantine]. Drug Res. 1983;33:1122–1134. (text in German with English abstract)

6 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31–41.

7 Periclou P, Ventura D, Rao N, Abramowitz W. Pharmacokinetic study of memantine in healthy and renally impaired subjects. Clin Pharmacol Ther. 2006;79:134–143.

8 Büchler M, Bretagnol A, Desaldeleer C, Garreau P, Halimi JM, Al-Najjar A, et al. Estimation of the glomerular filtration rate through different methods in kidney transplant recipients: correlation with the creatinine clearance measurement. Transplant Proc. 2006;38:2289–2291.

9 Nishikawa N, Nagai M, Moritoyo T, Yabe H, Nomoto M. Plasma amantadine concentrations in patients with Parkinson's disease. Parkinsonism Relat Disord. 2008;15:351–353.

10 Verhagen Metman L, Del Dotto P, van den Munckhof P, Fang J, Mouradian MM, Chase TN. Amantadine as treatment for dyskinesias and motor fluctuations in Parkinson's disease. Neurology. 1998;50:1323–1326.

11 Hanlon JT, Aspinall SL, Semla TP, Weisbord SD, Fried LF, Good CB, et al. Consensus guidelines for oral dosing of primarily renally cleared medications in older adults. J Am Geriatr Soc. 2009;57:335–340.

12 Zhang Y, Zhang L, Abraham S, Apparaju S, Wu TC, Strong JM, et al. Assessment of the impact of renal impairment on systemic exposure of new molecular entities: evaluation of recent new drug applications. Clin Pharmacol Ther. 2009;85:305–311.