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Similar Rivastigmine Pharmacokinetics and Pharmacodynamics in Japanese and White Healthy Participants Following the Application of Novel Rivastigmine Patch

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The pharmacokinetics and pharmacodynamics of rivastigmine were compared in Japanese and white healthy participants who were given ascending single doses of the novel rivastigmine transdermal patch. Rivastigmine patch strengths were 4.6 mg/24 h (5 cm^2, 9 mg rivastigmine loaded dose), 9.5 mg/24 h (10 cm^2, 18 mg), and 13.3 mg/24 h (15 cm^2, 27 mg) (per label) or 7.0 mg/24 h (7.5 cm^2, 13.5 mg) as a fall-back dose. No relevant ethnic differences in the noncompartmental pharmacokinetics (parent and metabolite NAP226-90) and pharmacodynamics (plasma BuChE activity) of the rivastigmine patch were observed between Japanese and whites. However, drug exposure was slightly higher and inhibition of BuChE slightly more pronounced in Japanese participants than in whites, which was attributed to the lower body weight (ca. 11% less on average) of Japanese participants. Treatments were similarly well tolerated in both ethnic groups. In conclusion, no relevant ethnic differences in the intrinsic disposition or effects of rivastigmine delivered via transdermal route are expected between Japanese and white patients. The possible effect of body weight on drug exposure suggests that special attention should be paid to patients with very low body weight during up-titration.

Keywords: *Alzheimer's disease; Parkinson's disease; rivastigmine; pharmacokinetics; pharmacodynamics; ethnicity; Japanese; patch*

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Alzheimer's disease (AD) is the most common cause of progressive mental deterioration in people of advanced age. It is characterized by impaired neuronal signaling, leading to a slow and progressive decline in cognition functional activity and behavior. Although the etiology of the disease is not clearly established, several causes that contribute to the disease pathogenesis have been proposed, one of which is based on the cholinergic hypothesis. Acetylcholine (ACh) is the primary neurotransmitter that facilitates learning and increases attention.[1,2] Its deficiency (as seen in AD patients), which leads to dysfunctional cholinergic signaling in the cortex and hippocampus, is considered to be responsible for cognitive, behavioral, and functional impairment.

Among the different types of drugs that are used to enhance cholinergic neurotransmission, cholinesterase inhibitors (ChEIs) have been shown to be effective in treating symptoms of mild to moderate AD[3-8] in a

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dose-dependent relationship. Rivastigmine is distinct from other available cholinesterase inhibitors (donepezil and galantamine) in that it is a pseudo-irreversible inhibitor of both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) rather than a rapidly reversible inhibitor of AChE alone. In contrast to AChE, BuChE can be easily measured in plasma, and its enzymatic activity may be used as a marker of target enzyme inhibition over time. This is further supported by the correlation between BuChE (and AChE) inhibition in cerebral spinal fluid (CSF) and plasma and therapeutic effects.[9,10] Until recently, all approved pharmacological treatments for dementia were delivered orally. However, reports of centrally induced cholinergic gastrointestinal side effects (nausea, vomiting, diarrhea) with oral cholinesterase inhibitors have been associated with high maximum plasma concentrations (C_{max}) and short times to C_{max} (t_{max}).[11] Therefore, a transdermal delivery system for daily administration has been developed for rivastigmine with the primary goal to reduce C_{max} and increase C_{min} of the drug (ie, to reduce fluctuations in plasma levels), prolong t_{max} so as to achieve a more gradual increase in C_{max}, and avoid the rapid rise and fall of drug concentration.[12,13] This novel way of rivastigmine administration was developed to provide clinical effectiveness with a more favorable tolerability profile,[14] allowing a simple one-step titration to the recommended dose. Furthermore, the patch design may prove more convenient, be easier to use, and provide visual reassurance that the treatment has been administered, thus potentially improving compliance. This is a novel patch in the sense that, unlike early transdermal patches that used a "reservoir" of the drug dissolved in an adjunct (usually alcohol) to facilitate drug absorption through the skin, the rivastigmine patch uses a modern matrix design. This combines the drug, antioxidants, a polymer mixture that controls the drug delivery rate, and a silicone matrix adhesive to make a single "polymeric matrix" layer. This allows smooth, controlled delivery of the drug via diffusion from the matrix and enables the patches to be kept small, thin, and discrete. In 2007, the rivastigmine transdermal patch became the first patch to be approved in the United States for the treatment of AD and Parkinson's disease dementia (PDD) and in Europe for the treatment of AD. It is also approved in Latin America and Asia.

The aim of the current ethnic sensitivity study was to compare the pharmacokinetics and pharmacodynamics (BuChE activity) of rivastigmine following transdermal application of rivastigmine in Japanese and white healthy participants.

METHODS

Participants and Clinical Protocol

Forty nonsmoking healthy male participants (20 Japanese and 20 whites) gave written consent to participate in this study. Whites were defined as participants having both parents and all 4 grandparents of white descent. Japanese participants had to be born in Japan, having both parents and all 4 grandparents of Japanese origin and having left Japan not more than 10 years ago. White participants were matched pairwise according to age (±5 years) and weight (±25%) to their Japanese counterpart. Each participant had to undergo a screening period (–21 to –2 days), a baseline evaluation for each treatment period (in the day prior to each patch application), and 3 treatment periods of 3 days, each followed by at least a 3-day washout. The study completion evaluation was performed 7 days after the removal of the final patch application.

This study was a single-center, nonrandomized, open-label, 3-period, 3-treatment, 2-sequence ascending-dose study. The study was conducted at Richmond Pharmacology Ltd (London, UK), in accordance with the World Medical Association's Declaration of Helsinki, Venice, Hong Kong, and Somerset West amendments of 1983, 1989, and 1996, as well as good clinical practice. Ethical approval of the study protocol, consent form, and volunteer information document was granted by Ravenscourt Ethics Committee (London, UK).

The patch application (Exelon®, Novartis) was performed simultaneously for both ethnic groups. On day 1 of each treatment period, the patch was applied in the morning after an overnight fast of at least 10 hours. Each of the 3 treatment periods consisted of a 24-hour dermal single application on the upper scapular region of the back of rivastigmine patch: 4.6 mg/24 h (5 cm^2, 9 mg loaded dose of rivastigmine) in treatment period 1, 9.5 mg/24 h (10 cm^2, 18 mg) in period 2, and 13.3 mg/24 h (15 cm^2, 27 mg) in period 3 (strengths as per label). A fallback dose strength (not in label) of 7.0 mg/24 h (7.5 cm^2, 13.5 mg) was to be used in period 3 in the case of tolerability problems in period 2 with the 9.5-mg/24-h patch. A washout interval of at least 3 days was maintained between the treatment periods (from time of patch removal to time of next patch application). Participants were confined to the study site from day –1 (baseline, the day immediately preceding day 1) to day 3 of each treatment period. Participants were instructed not to consume alcohol or food or beverages containing caffeine or other xanthines 48 hours prior to dosing and while domiciled.

Drug Assay and Pharmacokinetic Evaluation

For each treatment period, a total of 13 venous blood samples (3 mL each) were collected on day 1 from the forearm vein using heparin tubes at time 0 (prepatch application) and then at 3, 6, 8, 12, 16, 24, 26, 28, 32, 36, 40, and 48 hours postpatch application. Each blood sample was immediately transferred to a tube containing physostigmine (10 µL of a 0.01 molar physostigmine solution per 1 mL blood) to inhibit the enzymatic breakdown of rivastigmine. Samples were then centrifuged within 30 minutes of collection at between 3°C and 5°C for 15 minutes at approximately 800 *g* (about 2000 rpm). Plasma was transferred to a cooled polypropylene screw-cap tube. The tubes were kept frozen at ≤–20°C pending bioanalysis.

Urine was collected at time 0 (prepatch application) and then during time intervals 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 36, and 36 to 48 hours postpatch application. Each participant voided his bladder before patch application and at the end of each urine sampling period. During each sampling interval, the urine portions were pooled in a polypropylene container stored at 4°C to 8°C in a refrigerator. Upon completion of the collection interval, the total volume of urine was determined, and a 30-mL aliquot was kept frozen at ≤–20°C pending bioanalysis.

Rivastigmine and its pharmacologically inactive major metabolite NAP226-90 were determined in plasma and urine by using liquid/liquid extraction followed by liquid chromatography analysis and tandem mass spectrometry with atmospheric pressure chemical ionization mode (limit of quantitation [LOQ] = 0.2 ng/mL in plasma and 5.0 ng/mL in urine).[15] The mean recovery of rivastigmine (percent coefficient of variation [CV%]) was 109% (5.0%) at 0.4 ng/mL, 110% (3.7%) at 5.0 ng/mL, and 112% (3.3%) at 25 ng/mL in plasma and was 92% (4.2%) at 15 ng/mL, 93.5% (3.5%) at 1 µg/mL, and 94.5% (3.9%) at 2 µg/mL in urine. The corresponding values for the metabolite were 99.3% (7.1%), 100% (5.9%), and 102 (5.0%) in plasma and 94% (8.8%), 98.6% (7.1%), and 99.5% (5.4%) in urine.

The following pharmacokinetic variables were derived using noncompartmental methods (WinNonlin Professional Version 4.0.1, Pharsight Corp, Mountain View, California): peak concentration (C_{max}), time to reach C_{max} (t_{max}), elimination half-life from plasma ($t_{1/2}$), area under the plasma concentration-time curve from time 0 to 24 hours ($AUC_{0\text{-}24\ h}$), time 0 to last time point (AUC_{last}), and time 0 to infinity (AUC_{∞}). Because a population analysis (with covariate analysis) in a large clinical trial showed body weight to affect the pharmacokinetics of rivastigmine patch,[13] dose and body weight normalized values ($C_{max,norm}$, $AUC_{0\text{-}24\ h,norm}$, and $AUC_{\infty,norm}$) were calculated by dividing by the dose of rivastigmine released from the patch (see below) per kg body weight. The amount excreted in urine and corresponding renal clearance (CL_R) were derived from urinary excretion data.

Residual Drug Content in Worn Patches

Patches applied in each treatment period were assayed for residual amounts of rivastigmine. The worn patches were stored between 2°C and 8°C until they were analyzed. The method of measurement was developed and validated at Lohmann Therapie-Systeme AG (Andernach, Germany) according to International Conference on Harmonization (ICH) guidelines Q2A and Q2B.

Each patch was transferred into a suitable Erlenmeyer flask, and a solvent mixture of methanol/ethyl-acetate/diethylamine 70:30:0.4 (v/v/v) was added. This was stirred on a magnetic stirrer with a frequency of about 200 min^{-1} for at least 16 hours (extraction was complete after 16 hours; ie, no drug was detectable after a second extraction of same patch). An aliquot volume of the sample solution was then centrifuged for at least 10 minutes at about 10 000 min^{-1} (in 2.0-mL micro test tubes with safety lid lock, Fa. Eppendorf). An aliquot (20 µL) of the supernatant solution was injected (2 mL/min) and measured using high-performance liquid chromatography (HPLC) with ultraviolet (262 nm) detection. The method accuracy was demonstrated by an average percent recovery value of 101.2% of nominal contents (n = 9) and a relative standard deviation <2.0%. The 95% confidence interval of the average percent recovery was 99.7% to 102.7%. Precision/repeatability was demonstrated by relative standard deviations within 1.1% to 3.0%.

Pharmacodynamic Analysis

As shown in vitro (postmortem human brain tissue) and ex vivo (rat), rivastigmine inhibits both AChE and BuChE with equal potency.[16-18] Only assessment of BuChE activity was considered in this study because it is predominantly present in plasma and is believed to be a good peripheral marker for the drug's action in the central nervous system. Blood samples for the determination of BuChE activity in plasma were collected in lithium-heparinate tubes

during each treatment period at the same times as pharmacokinetic (PK) samples. Plasma activity of BuChE was determined by a modified colorimetric method.[19]

Tolerability and Safety Analysis

Safety and tolerability assessments included the monitoring and recording of all adverse events and of concomitant medications, regular checks of routine blood chemistry, hematology and urine values, electrocardiogram (ECG) recordings, measurements of vital signs, physical examination, and local skin irritation evaluation. The test application sites were scored for skin irritation prior to application, as well as 30 minutes and 24 hours after patch removal according to the local skin irritation scale. The test sites were photographed before patch application and 30 minutes after patch removal. Participants had to have pretreatment scores of 0 on all test sites. Because in previous studies the current formulation of the patch showed good adhesiveness, no formal evaluation of adhesiveness was planned in this study. However, if the investigator found that the adhesiveness was unsatisfactory, a comment to this effect was documented.

Sample Size Calculation and Statistical Analysis

The sample size calculation was based on pharmacokinetic data from a previous study with the rivastigmine patch in whites and was performed using nQuery Advisor 4.0 "Linear Regression Confidence Interval for β_1-β_2" based on the width of the 90% confidence interval (CI) for the difference in the dose proportionality constants $\beta_{1\ (\text{whites})}$ and $\beta_{2\ (\text{Japanese})}$. A total sample size of 40 (20 Japanese, 20 whites) was required to ensure that the width of the 90% CI on the log scale for the difference between β_1 and β_2 was ±0.094.

The assessment of dose proportionality for $AUC_{0\text{-}24\ h}$, AUC_{last}, AUC_{∞}, and C_{max} was performed separately for each of the ethnic groups, using a power model.[20] In addition, an exploratory analysis was performed estimating the difference in the dose-proportionality slopes between Japanese and whites. At each dose level, the pharmacokinetic parameters (with and without normalization to actual dose per kg body weight) of Japanese and white participants were compared using ratios of geometric means and their 90% CIs. No formal analysis of safety and tolerability data was planned; these data were summarized by treatment for each of the ethnic groups.

RESULTS

Participant Disposition and Demographics

Forty healthy male participants were to be enrolled (20 whites and 20 Japanese), but 39 participants (20 whites and 19 Japanese) completed the study according to the study protocol. One Japanese participant withdrew consent prior to patch application on day 1 of treatment period 1 and was not replaced. Twenty white participants received the 4.6-mg/24-h (5-cm^2) and 9.5-mg/24-h (10-cm^2) patches, 12 received the 7.0-mg/24-h (7.5-cm^2) patches, and 8 received the 13.3-mg/24-h (15-cm^2) patches. Nineteen Japanese participants received the 4.6-mg/24-h (5-cm^2) and 9.5-mg/24-h (10-cm^2) patches, 10 received the 7.0-mg/24-h (7.5-cm^2) patches, and 9 received the 13.3-mg/24-h (15-cm^2) patches. The Japanese and white groups were well matched in terms of age, 26.9 ± 3.2 years (range, 20-33 years) and 24.9 ± 4.0 years (range, 20-24 years), respectively, and body mass index (range, 18.1-25.0 kg/m^2 and 19.4-24.3 kg/m^2, respectively). The Japanese group had, on average, an 11% lower body weight (63.2 ± 6.2 kg; range, 56-80 kg), compared with the white group (71.1 ± 5.6 kg; range, 58-80 kg).

Pharmacokinetics

The arithmetic mean plasma concentration-time profiles for rivastigmine and its metabolite NAP226-90 are shown in Figures 1 and 2, respectively. The corresponding pharmacokinetic parameters for both ethnic groups are summarized in Table I for rivastigmine and Table II for NAP226-90.

The plasma concentrations of rivastigmine rose similarly slowly in the 2 ethnic populations, reaching peaks at median t_{max} around 10 to 14 hours in whites and 16 hours in Japanese and providing sustained levels for the remainder of the 24-hour application period. The mean (± SD) maximum plasma concentrations (C_{max}) were very similar between the 2 ethnic groups and were in the range of 2.76 ± 1.23 ng/mL (4.6 mg/24 h) to 12.9 ± 4.27 ng/mL (13.3 mg/24 h) for whites and 2.73 ± 0.89 ng/mL (4.6 mg/24 h) to 12.5 ± 4.41 ng/mL (13.3 mg/24 h) for Japanese. Similarly, the areas under the concentration-time curve extrapolated to time infinity (AUC_{∞}) were comparable between the 2 groups and were in the range 52.4 ± 18.9 ng·h/mL (4.6 mg/24 h) to 239 ± 81.1 ng·h/mL (13.3 mg/24 h) for whites and 55.7 ± 18.1 ng·h/mL (4.6 mg/24 h) to 256 ± 93.9 ng·h/mL

Table I Arithmetic Mean ± SD (CV%) Pharmacokinetic Parameters of Rivastigmine in White and Japanese Healthy Participants Given a Single 24-Hour Application of a 4.6-, 7.0-, 9.5-, or 13.3-mg/24-h Rivastigmine Patch

	4.6 mg/24 h (5 cm^2)		7.0 mg/24 h (7.5 cm^2)		9.5 mg/24 h (10 cm^2)		13.3 mg/24 h (15 cm^2)	
Parameter	**White (n = 20)**	**Japanese (n = 19)**	**White (n = 12)**	**Japanese (n = 10)**	**White (n = 20)**	**Japanese (n = 19)**	**White (n = 8)**	**Japanese (n = 9)**
C_{max}, ng/mL	2.76 ± 1.23 (45)	2.73 ± 0.89 (33)	3.99 ± 1.47 (37)	4.58 ± 1.61 (35)	7.29 ± 3.79 (52)	6.73 ± 2.40 (36)	12.9 ± 4.27 (33)	12.5 ± 4.41 (35)
$C_{max,norm}$, (ng/mL)/(mg/kg)	37.5 ± 12.0 (32)	35.8 ± 8.16 (23)	39.9 ± 9.33 (23)	41.6 ± 11.4 (27)	48.4 ± 20.5 (42)	44.5 ± 12.7 (29)	57.6 ± 14.4 (25)	54.4 ± 13.8 (25)
t_{max}, h[a]	12.0 [3.0-24.08]	16.0 [6.0-16.02]	14.0 [6.0-24.08]	16.0 [8.0-16.03]	12.0 [6.0-24.08]	16.0 [8.0-16.07]	10.0 [8.0-16.0]	16.0 [8.02-16.03]
$AUC_{0\text{-}24\ h}$, ng·h/mL	45.6 ± 18.3 (40)	47.8 ± 16.7 (35)	66.1 ± 26.3 (40)	75.3 ± 26.5 (35)	119 ± 58.3 (49)	116 ± 42.7 (37)	204 ± 71.9 (35)	216 ± 79.2 (37)
$AUC_{0\text{-}24\ h,norm}$, (ng·h/mL)/(mg/kg)	624 ± 187 (30)	626 ± 157 (25)	655 ± 181 (28)	685 ± 188 (27)	794 ± 322 (41)	767 ± 218 (28)	916 ± 270 (29)	944 ± 256 (27)
AUC_{last}, ng·h/mL	50.3 ± 19.2 (38)	53.7 ± 18.7 (35)	76.7 ± 28.1 (37)	86.6 ± 29.7 (34)	136 ± 63.9 (47)	135 ± 49.1 (36)	237 ± 81.2 (34)	255 ± 93.7 (37)
AUC_{∞}, ng·h/mL	52.4 ± 18.9 (36)	55.7 ± 18.1 (32)	77.5 ± 27.9 (36)	88.1 ± 29.8 (34)	137 ± 63.8 (47)	136 ± 49.1 (36)	239 ± 81.1 (34)	256 ± 93.9 (37)
$AUC_{\infty,norm}$, (ng·h/mL)/(mg/kg)	723 ± 191 (26)	732 ± 171 (23)	773 ± 192 (25)	802 ± 212 (26)	918 ± 354 (39)	900 ± 253 (28)	1080 ± 314 (29)	1120 ± 312 (28)
$t_{1/2}$, h	2.89 ± 0.73 (25)	2.68 ± 0.54 (20)	2.10 ± 0.18 (9)	2.21 ± 0.29 (13)	2.25 ± 0.28 (12)	2.12 ± 0.21 (10)	2.90 ± 0.37 (13)	2.78 ± 0.31 (11)
CL_R, L/h	2.78 ± 1.05 (38)	3.25 ± 1.04 (32)	2.36 ± 0.58 (24)	3.43 ± 1.18 (34)	2.30 ± 0.91 (40)	2.59 ± 1.02 (39)	2.14 ± 0.78 (36)	1.95 ± 0.80 (41)

CV, coefficient of variation.
a. Median and [range].

Table II Arithmetic Mean ± SD (CV%) Pharmacokinetic Parameters of NAP266-90 in White and Japanese Healthy Participants Given a Single 24-Hour Application of a 4.6-, 7.0-, 9.5-, or 13.3-mg/24-h Rivastigmine Patch

	4.6 mg/24 h (5 cm^2)		7.0 mg/24 h (7.5 cm^2)		9.5 mg/24 h (10 cm^2)		13.3 mg/24 h (15 cm^2)	
Parameter	**White (n = 20)**	**Japanese (n = 19)**	**White (n = 12)**	**Japanese (n = 10)**	**White (n = 20)**	**Japanese (n = 19)**	**White (n = 8)**	**Japanese (n = 9)**
C_{max}, ng/mL	1.64 ± 0.69 (42)	1.48 ± 0.55 (37)	2.45 ± 1.08 (44)	2.09 ± 0.42 (20)	3.70 ± 1.51 (41)	3.20 ± 1.15 (36)	6.65 ± 2.30 (35)	5.76 ± 2.99 (52)
$C_{max,norm}$, (ng/mL)/(mg/kg)	22.3 ± 5.89 (26)	19.3 ± 4.23 (22)	24.2 ± 66.9 (28)	19.2 ± 2.67 (14)	24.7 ± 6.65 (27)	21.1 ± 5.09 (24)	29.4 ± 6.57 (22)	24.8 ± 8.27 (33)
t_{max}, h[a]	12.0 [8.0-16.0]	12.0 [6.0-16.0]	12.0 [6.0-26.0]	16.0 [6.0-16.03]	12.0 [8.0-26.0]	12.0 [8.0-26.00]	12.0 [12.0-16.0]	16.0 [12.0-26.00]
$AUC_{0\text{-}24\ h}$, ng·h/mL	26.9 ± 11.0 (41)	24.6 ± 8.16 (33)	40.2 ± 17.1 (43)	37.2 ± 8.31 (22)	62.0 ± 24.3 (39)	54.7 ± 18.8 (34)	108 ± 35.1 (33)	98.7 ± 51.7 (52)
$AUC_{0\text{-}24\ h,norm}$, (ng·h/mL)/(mg/kg)	366 ± 93.5 (26)	321 ± 64.9 (20)	399 ± 109 (27)	341 ± 55.2 (16)	415 ± 106 (26)	360 ± 80.7 (22)	477 ± 94.8 (20)	423 ± 144 (34)
AUC_{last}, ng·h/mL	32.5 ± 11.6 (36)	30.6 ± 9.17 (30)	52.6 ± 18.9 (36)	48.6 ± 9.41 (19)	79.8 ± 26.3 (33)	71.9 ± 21.7 (30)	142 ± 39.7 (28)	131 ± 57.2 (44)
AUC_{∞}, ng·h/mL	35.7 ± 11.3 (32)	32.8 ± 9.38 (29)	54.6 ± 18.6 (34)	50.3 ± 9.61 (19)	81.6 ± 26.3 (32)	73.5 ± 21.6 (29)	144 ± 39.4 (27)	133 ± 57.0 (43)
$AUC_{\infty,norm}$, (ng·h/mL)/(mg/kg)	491 ± 87.5 (18)	432 ± 79.5 (18)	550 ± 125 (23)	461 ± 61.2 (13)	552 ± 116 (21)	486 ± 93.3 (19)	645 ± 98.0 (15)	575 ± 159 (28)
$t_{1/2}$, h	5.06 ± 1.04 (21)	4.70 ± 0.94 (20)	5.27 ± 1.83 (35)	3.98 ± 0.43 (11)	4.13 ± 0.57 (14)	3.90 ± 0.49 (13)	4.31 ± 0.62 (14)	3.76 ± 0.50 (13)
$AUC_{\infty metab}/AUC_{\infty parent}$	0.70 ± 0.14 (20)	0.61 ± 0.13 (21)	0.74 ± 0.18 (24)	0.60 ± 0.09 (15)	0.65 ± 0.17 (26)	0.56 ± 0.12 (21)	0.63 ± 0.16 (25)	0.54 ± 0.19 (35)
CL_R, L/h	19.0 ± 4.72 (25)	18.3 ± 5.68 (31)	18.3 ± 4.17 (23)	17.2 ± 4.85 (28)	16.7 ± 3.12 (19)	15.4 ± 4.77 (31)	15.6 ± 4.21 (27)	13.4 ± 4.73 (35)

CV, coefficient of variation.

a. Median and [range].

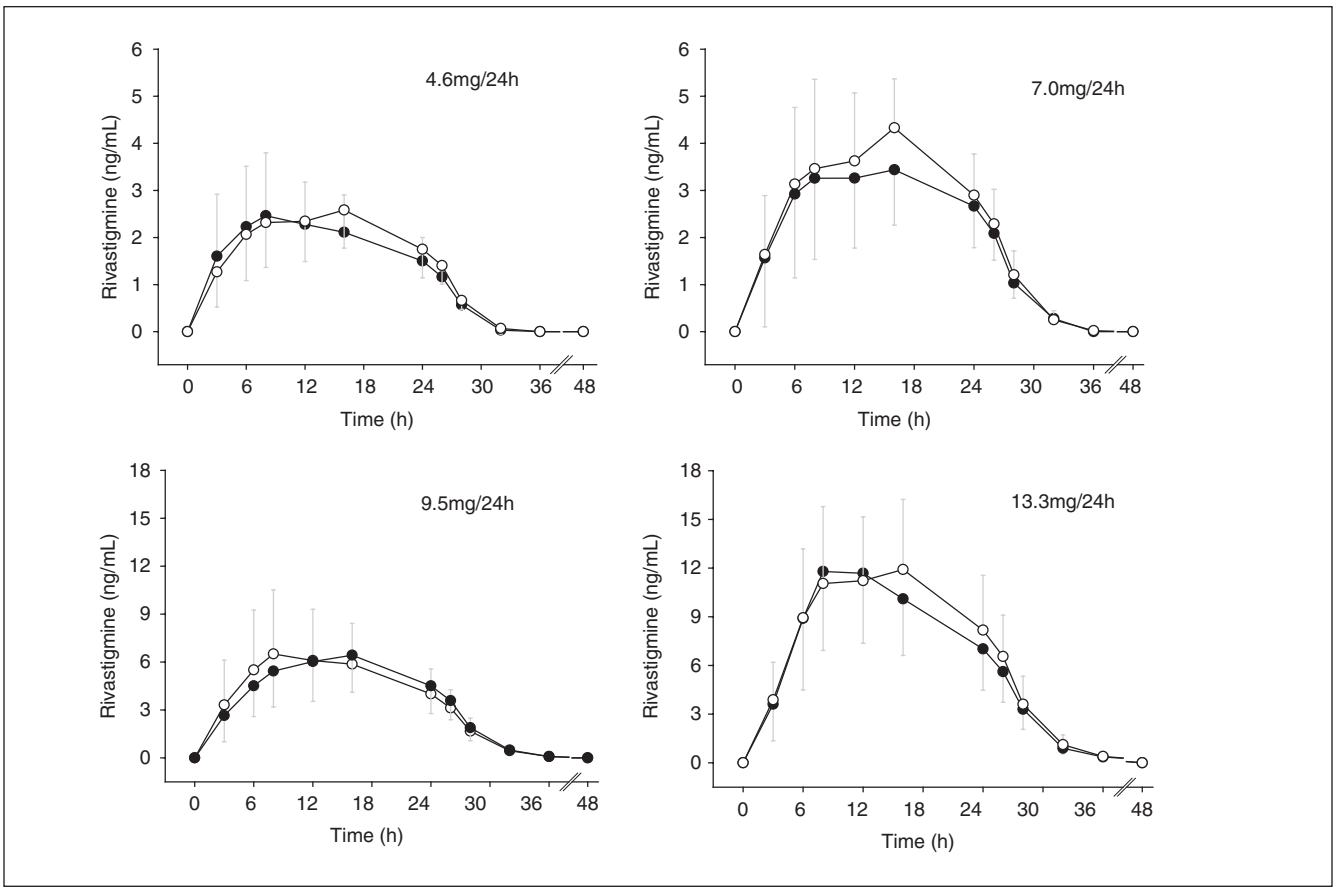

Figure 1. Arithmetic mean ± SD plasma concentration-time profiles of rivastigmine in white (●) and Japanese (○) healthy participants given a single 24-hour application of a 4.6-, 7.0-, 9.5-, or 13.3-mg/24-h rivastigmine patch.

(13.3 mg/24 h) for Japanese. The elimination half-life of rivastigmine from plasma was comparable in white (range, 2.10-2.90 hours) and Japanese participants (range, 2.12-2.78 hours). The intersubject variability associated with the pharmacokinetic parameters was comparable in both populations and was characterized by coefficients of variation of 33% to 52% (C_{max}) and 32% to 47% (AUC_{∞}).

The statistical evaluation showed that the ratios of geometric means for rivastigmine exposure parameters C_{max} and AUC_{∞} for all 4 patch strengths between Japanese and white participants ranged between 1.03 and 1.11, with the upper limits of the 90% CI ranging between 1.26 and 1.37 (Table III). However, when considering the same exposure values C_{max} and AUC_{∞}, each normalized (ie, $C_{max,norm}$ and $AUC_{\infty,norm}$) to the actual (ie, released from patch) rivastigmine dose per kg body weight, the ratios of geometric means between Japanese and white participants ranged between 0.97 and 1.06 with the 90% CI extending no lower than 0.84 and no higher than 1.22 for all doses (Table III). For NAP226-90, ratios ranged between 0.90 and 0.94 for the 4 patch sizes. The 90% CI for the ratio of geometric means of AUC_{∞} (and AUC_{last}) was within 0.80 to 1.09 for both 7.0- and 9.5-mg/24-h patches and was within 0.79 to 1.10 for 4.6- and 13.3-mg/24-h patches.

A similar over-proportional increase in exposure with dose was observed in the 2 ethnic groups (Figure 3), with C_{max} and AUC_{∞} values increasing slightly more than the rise in rivastigmine patch size/dose strength in both populations. However, the ratios of the dose-response slopes (ie, dose-rivastigmine parameter increase) between Japanese and white participants were 1.01 and 1.05 for C_{max} and AUC_{∞}, respectively, with 90% CIs of 0.90 to 1.15 and 0.94 to 1.16, respectively.

The relative difference between maximum (C_{max}) and minimum ($C_{min} = C_{24\,h}$) rivastigmine plasma concentrations was characterized by the mean (± SD)

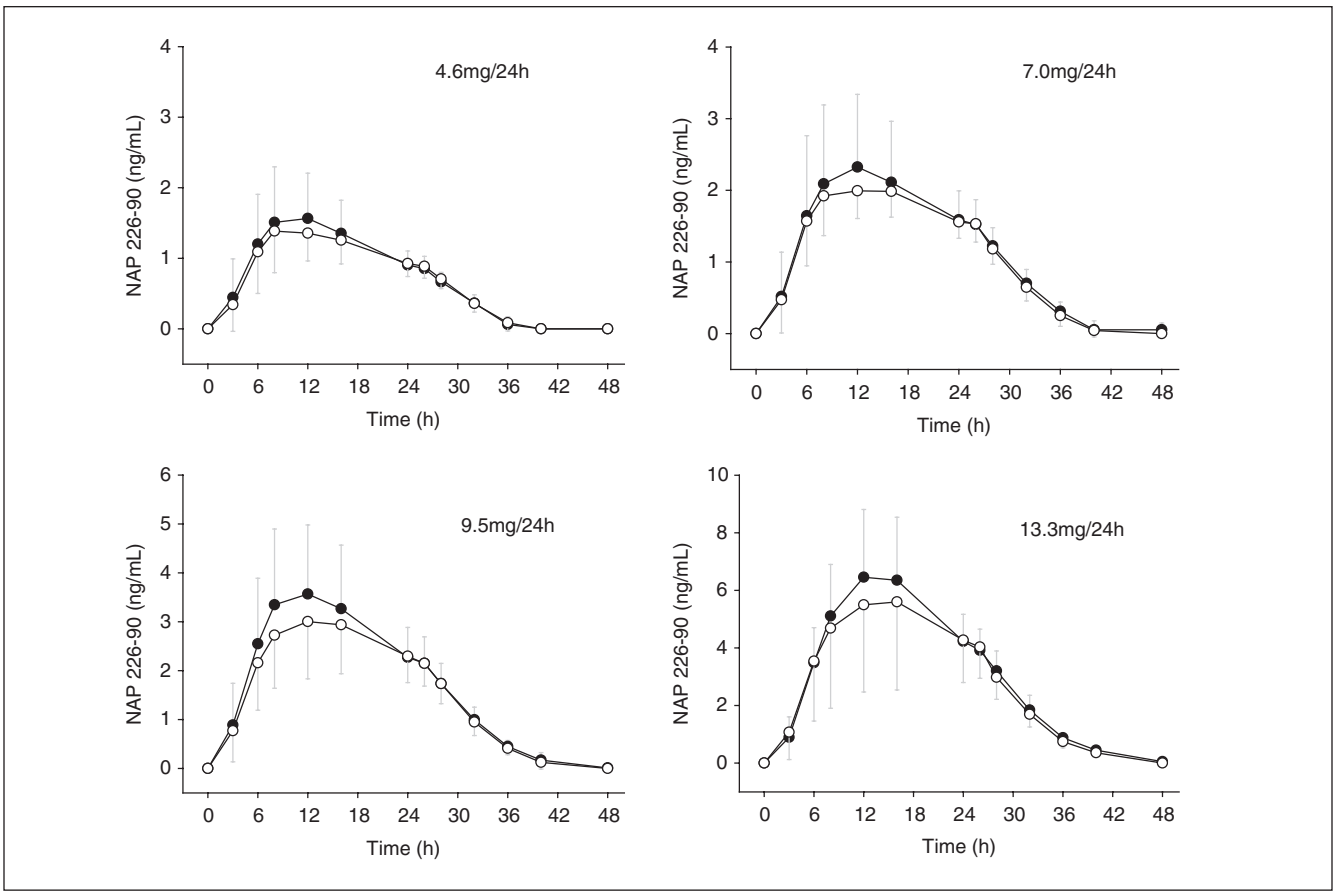

Figure 2. Arithmetic mean ± SD plasma concentration-time profiles of NAP226-90 in white (•) and Japanese (○) healthy participants given a single 24-hour application of a 4.6-, 7.0-, 9.5-, or 13.3-mg/24-h rivastigmine patch.

C_{max}/C_{min} ratios ranging from 1.59 ± 0.76 (7.0 mg/24 h) to 1.98 ± 1.24 (4.6 mg/24 h) in white participants and 1.53 ± 0.32 (9.5 mg/24 h) to 1.61 ± 0.51 (13.3 mg/24 h) in Japanese participants.

The metabolite-to-parent ratio ranged from 0.63 ± 0.16 (13.3 mg/24 h) to 0.74 ± 0.18 (7.0 mg/24 h) in whites and 0.54 ± 0.19 (13.3 mg/24 h) to 0.61 ± 0.13 (4.6 mg/24 h) in Japanese (Table II).

Urinary excretion of rivastigmine was 2.5% to 3.3% and 3.5% to 4.1% of the dose (released dose from patch) in white and Japanese participants, respectively. Renal clearance (CL_R) ranged from 2.14 to 2.78 L/h in whites and from 1.95 to 3.25 L/h in Japanese, with a trend to decrease with rising patch size in both populations (Table I). The excretion of metabolite NAP226-90 represented 17.7% to 20.0% of the dose (CL_R = 15.6-19.0 L/h) and 16.9% to 18.5% of the dose (CL_R = 13.4-18.3 L/h) in white and Japanese participants, respectively (Table II).

Drug Residual in the Transdermal System

Approximately 50% of the drug load was released from the transdermal systems. On average, the amount of drug released over 24 hours from the patch (mean ± SD) was 5.04 ± 0.89 mg (5 cm^2), 7.00 ± 1.37 mg (7.5 cm^2), 10.4 ± 1.86 mg (10 cm^2), and 15.5 ± 1.95 mg (15 cm^2) in whites and was 4.74 ± 0.69 mg (5 cm^2), 6.74 ± 0.66 mg (7.5 cm^2), 9.40 ± 1.20 mg (10 cm^2), and 14.4 ± 1.86 mg (15 cm^2) in Japanese. The amount of drug released from each individual transdermal system was used in the dose normalization of the corresponding pharmacokinetic parameter estimates.

Pharmacodynamics

The transdermal administration of rivastigmine exerted a very similar dose-related, albeit slightly underproportional, inhibition of the plasma BuChE

Table III Geometric Mean Ratios and 90% CI of Rivastigmine Exposure Parameters With and Without Normalization to the Dose Per kg Body Weight Between Japanese and White Participants at Each Patch Strength

Pharmacokinetic Parameter	Patch Strength, mg/24 h	Ratio of Geometric Means	Lower 90% Confidence Limit	Upper 90% Confidence Limit
C_{max}, ng/mL	4.6	1.03	0.836	1.259
	7.0	1.03	0.848	1.257
	9.5	1.04	0.850	1.264
	13.3	1.04	0.845	1.287
AUC_{∞}, ng·h/mL	4.6	1.06	0.876	1.276
	7.0	1.08	0.898	1.293
	9.5	1.09	0.909	1.312
	13.3	1.11	0.918	1.351
$C_{max,norm}$, (ng/mL)/(mg/kg)[a]	4.6	0.97	0.836	1.122
	7.0	0.98	0.849	1.122
	9.5	0.98	0.852	1.130
	13.3	0.99	0.848	1.153
$AUC_{\infty,norm}$, (ng·h/mL)/(mg/kg)[a]	4.6	1.00	0.867	1.145
	7.0	1.02	0.890	1.164
	9.5	1.03	0.903	1.183
	13.3	1.06	0.915	1.220

CV, coefficient of variation.
a. Pharmacokinetic parameters normalized to the actual dose (released from patch) per kg body weight.

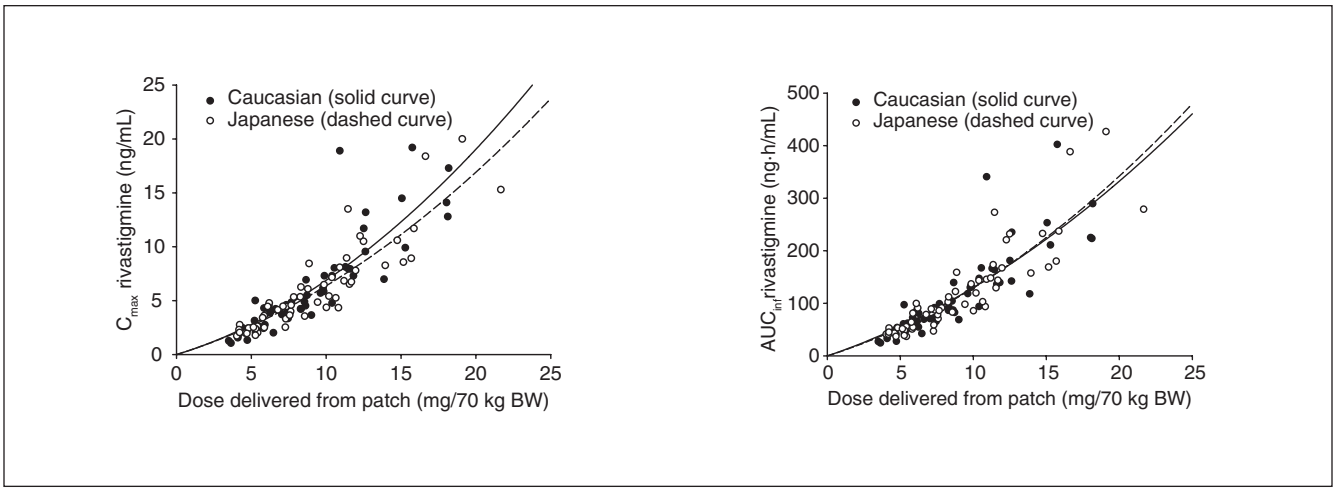

Figure 3. Dose-exposure relationship for rivastigmine C_{max} and AUC_{∞} in white and Japanese healthy participants given a single 24-hour application of a 4.6-, 7.0-, 9.5-, or 13.3-mg/24-h rivastigmine patch.

activity in both Japanese and white participants (Figure 4). The inhibition of BuChE activity by rivastigmine was evident at 3 hours after patch application and smoothly increased over the following 13 hours to reach its observed maximum (E_{max}, Table IV) at about 16 hours after application. The inhibitory effect at 24 hours was similar to 16 hours, and the BuChE activity then returned to the predose values 24 hours after patch removal (ie, 48 hours after patch application). The extent of inhibition was very similar for both ethnic groups, although the inhibition values (Figure 4, Table IV) suggested a slightly and consistently more pronounced inhibition in Japanese participants at all doses. The overall

inhibition of plasma BuChE activity, as assessed by the area under the inhibitory effect (AUE)-time curve values (expressed as percent inhibition of baseline activity·h [%IA·h]; Table IV), increased with rising doses that were almost identical in white and Japanese participants. The ratios of the geometric means of AUE for Japanese over white participants ranged from 1.08 to 1.15 for all dose levels. Japanese participants had almost the same estimated mean increase in AUE with rising dose as the white participants (ratio of slopes = 1.06).

Safety and Tolerability

No serious adverse events were reported. None of the participants enrolled in the study were taking concomitant medication at screening or baseline assessment, and no concomitant medication was administered throughout the study. There were no clinically significant changes in vital signs for any of the participants from the time of dosing up to and including the end of study evaluation. There were no clinically relevant ECG changes in both ethnic groups during the study, compared with screening or baseline evaluation.

The most frequently reported adverse events were gastrointestinal disorders (abdominal pain, nausea, and vomiting) by 45% of white and 26.3% of Japanese participants, with a trend toward a higher incidence with increasing doses. One case of diarrhea was observed in each ethnic group (at 13.3 mg/24 h in white and at 7.0 mg/24 h in Japanese participants). Nervous system disorders (dizziness, headache) were reported by 15.0% of white and 15.8% of Japanese participants.

Each of the included participants, independent of their ethnic affiliation, showed at least one sign of skin irritation. Five (25.0%) white and 4 (21.1%) Japanese participants experienced skin irritation defined as intense erythema or erythema associated with vesicles and skin induration at all patch sizes (rated at 24.5 and 48 hours postpatch application), which were resolved at study completion evaluation. None of the participants discontinued as a result of skin irritations. There were no reports of adhesiveness failures.

DISCUSSION

The pharmacokinetics of rivastigmine have been described extensively after intravenous and oral administrations,[12,13,21-24] and this is the first ethnic sensitivity study in Japanese compared to white participants that is described after administration of the novel rivastigmine patch.

The pharmacokinetics and pharmacodynamics (BuChE inhibition) of rivastigmine appeared to be similar in both the Japanese and white participants, although drug exposure for 3 of the 4 doses was numerically slightly higher and inhibition of BuChE slightly more pronounced in Japanese as compared with white participants. However, when rivastigmine C_{max} and AUC_{∞} values were normalized to the actual dose per kg body weight, the bioavailability was similar between Japanese and white participants for all 4 patch doses. It would thus appear that the differences in body weight (11% on average) between Japanese (63.2 ± 6.18 kg) and white participants (71.1 ± 5.6 kg) explained this apparent slight difference between the 2 groups. This is in agreement with a previous population analysis that showed body weight to affect the pharmacokinetic profile of rivastigmine.[13]

From these findings, no relevant ethnic differences in the intrinsic disposition and effect of rivastigmine are expected between Japanese and white patients. Theoretically, patients with a low body weight, as is more frequently observed in Asian populations, might show a higher rivastigmine exposure (and effect) as compared to the general population. However, as demonstrated in the multicountry 24-week IDEAL clinical trial in 1190 AD patients,[14] the rivastigmine patch has a significantly better tolerability profile than the conventional oral capsule dosing. Although initiation of treatment with the 4.6-mg/24-h (5-cm^2) patch is known to result in exposure (on the basis of AUC) that is substantially greater than for 1.5-mg bid capsule,[12] in the IDEAL trial, the patch appeared to have a markedly improved tolerability profile over the capsule, both in the global population and Asian subpopulation. The incidence of nausea and vomiting in the Asian subpopulation was lower or similar, respectively, to that in the global population. Therefore, the rivastigmine patch sizes (4.6 mg/24 h as starting dose and 9.5 mg/24 h as maintenance dose) are considered to be also suitable in patients with lower body weight, as is observed in Asian populations.

Rivastigmine has been shown to exhibit nonlinear pharmacokinetics because of capacity-limited elimination, which causes C_{max} and AUC to increase more than proportionally with rising doses following both oral and intravenous administrations.[21] Our findings following patch application similarly showed nonlinear pharmacokinetics consistent with the observation that

Table IV Arithmetic Mean ± SD (CV%) Pharmacodynamic Parameters of BuChE in White and Japanese Healthy Participants Given a Single 24-Hour Application of a 4.6-, 7.0-, 9.5-, or 13.3-mg/24-h Rivastigmine Patch

	4.6 mg/24 h (5 cm^2)		7.0 mg/24 h (7.5 cm^2)		9.5 mg/24 h (10 cm^2)		13.3 mg/24 h (15 cm^2)	
Parameter	**White (n = 20)**	**Japanese (n = 19)**	**White (n = 12)**	**Japanese (n = 10)**	**White (n = 20)**	**Japanese (n = 19)**	**White (n = 8)**	**Japanese (n = 9)**
Maximal inhibition, E_{max}, % change from predose	22.1 ± 9.8 (44)	24.1 ± 5.8 (24)	32.5 ± 7.9 (24)	34.6 ± 9.2 (27)	40.5 ± 10.4 (26)	43.6 ± 10.4 (24)	49.5 ± 8.4 (17)	55.1 ± 11.7 (21)
$AUE_{0\text{-}48\ h}$, %IA·h	621 ± 263 (42)	650 ± 203 (31)	883 ± 354 (40)	949 ± 274 (29)	1050 ± 331 (31)	1190 ± 298 (25)	1360 ± 158 (12)	1560 ± 388 (25)

CV, coefficient of variation; $AUE_{0\text{-}48\ h}$, area under the plasma inhibitory effect-time (0 to 48 h) curve expressed as percent inhibition baseline activity·h (%IA·h).

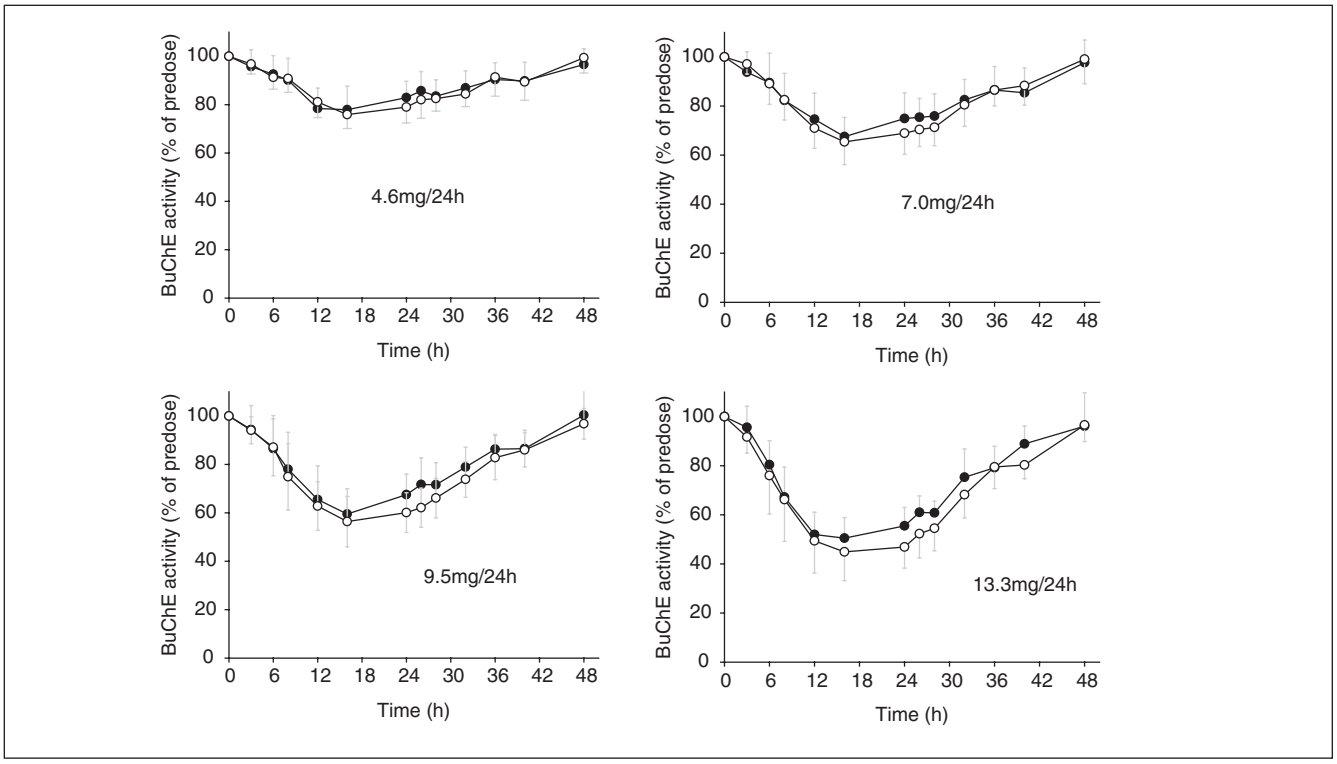

Figure 4. Arithmetic mean ± SD plasma BuChE activity-time profile in white (●) and Japanese (○) healthy participants given a single 24-hour application of a 4.6-, 7.0-, 9.5-, or 13.3-mg/24-h rivastigmine patch.

bioavailability of rivastigmine increases with rising doses and confirmed earlier findings with the patch.[12] This novel rivastigmine patch formulation demonstrated a much flatter rivastigmine concentration-time profile compared with the capsule formulation.[21] The fluctuation between maximum (C_{max}) and minimum (C_{min}) concentrations, as expressed by the ratio C_{max}/C_{min}, was markedly lower with the patch (around 1.6-2.0 in white and 1.5-1.6 in Japanese participants) than that previously observed with the oral capsule formulation (ratio = 55).[21] The metabolite-to-parent AUC_{∞} ratio with the patch administration (range, 0.54 ± 0.19 to 0.74 ± 0.18) was markedly lower than that previously observed with the oral administration (1.35 ± 1.0).[21] Less NAP226-90 is formed after the patch administration, presumably because of the lack of presystemic (first-pass) metabolism. After intravenous administration, the metabolite-to-parent AUC_{∞} ratio was reported to be 0.53 ± 0.15,[21] thus indicating that the extent of metabolism is similar after dermal and intravenous rivastigmine administrations. Transdermal administration may therefore decrease the burden of a pharmacologically inactive metabolite on the body and ensures a more efficient and targeted administration of the pharmacologically active moiety compared to the capsule.

Japanese and white participants showed a very similar dose-related inhibition of the plasma BuChE activity, with maximum inhibition reached at about 16 hours after application in both groups. BuChE activity returned to the predose values 24 hours after patch removal. The time course of BuChE inhibition followed the pharmacokinetic profile of rivastigmine closely, with maximum enzyme inhibition coinciding approximately with the t_{max} of rivastigmine in plasma (10-16 hours). Consistent with rivastigmine exposure that was slightly higher in Japanese participants, the extent of inhibition appeared to also be slightly more pronounced in this group. This indicates a similar exposure-response relationship in the 2 ethnic groups. The effect of rivastigmine on peripheral plasma BuChE activity, when delivered from a patch, appears to be a suitable noninvasive marker for the drug's pharmacodynamic activity.

Rivastigmine was well tolerated in both ethnic groups, particularly when taking into consideration that all doses were given in this study without

titration, which is usually not achievable with the capsule. The nature of adverse events was similar to what is known with oral administration of rivastigmine, with gastrointestinal and nervous system adverse events being the most frequent. The good tolerability of rivastigmine when given transdermally to healthy participants suggests that this formulation may also be better tolerated in patients with AD or PDD compared to oral drug dosing as it was demonstrated in a large pivotal clinical trial in AD patients.[14]

CONCLUSION

No relevant ethnic differences in the pharmacokinetics and pharmacodynamics (inhibition of plasma BuChE activity) of rivastigmine were observed between white and Japanese healthy participants following application of the novel rivastigmine patch formulation of 4.6 mg/24 h (9-mg dose load), 7.0 mg/24 h (13.5 mg), 9.5 mg/24 h (18 mg), or 13.3 mg/24 h (27 mg), with only a numerically slightly higher drug exposure and inhibitory effect in Japanese participants. This slight difference was attributed to the lower body weight in Japanese and thus suggests special attention to patients with very low body weight during up-titration. The rivastigmine patch was similarly well tolerated in white and Japanese healthy participants.

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REFERENCES

1. Gauthier S. Advances in the pharmacotherapy of Alzheimer's disease. *CMAJ*. 2002;166:616-623.

2. Wang HY, Lee DH, D'Andrea MR, Peterson PA, Shank RP, Reitz AB. Beta-amyloid (1-42) binds to alpha7 nicotinic acetylcholine receptor with high affinity: implications for Alzheimer's disease pathology. *J Bio Chem*. 2000;2075:5626-5632.

3. Alzheimer's disease: risk stratification, patient evaluation, and outcome-effective pharmacologic therapy—year 2004 clinical update. Available at: http://www.ahcpub.com.

4. American Psychiatric Association. Practice guideline for the treatment of patients with Alzheimer's disease and other dementias of late life. *Am J Psychiatry*. 1997;154:1-39.

5. Cummings JL, Frank JC, Cherry D, et al. Guidelines for managing Alzheimer's disease: part I. Assessment. *Am Fam Physician*. 2002;65:2263-2272.

6. Cummings JL, Frank JC, Cherry D, et al. Guidelines for managing Alzheimer's disease: part II. Treatment. *Am Fam Physician*. 2002;65:2525-2534.

7. Doody RS, Stevens JC, Beck RN, et al. Practice parameter: management of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2001;56:1154-1166.

8. Small GW, Rabins PV, Barry PP, et al. Diagnosis and treatment of Alzheimer disease and related disorders: consensus statement of the American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society. *JAMA*. 1997;278:1363-1371.

9. Darreh-Shori T, Almkvist O, Guan ZZ, et al. Sustained cholinesterase inhibition in AD patients receiving rivastigmine for 12 months. *Neurology*. 2002;59:563-572.

10. Giacobini E, Spiegel R, Enz A, Veroff AE, Cutler NR. Inhibition of acetyl- and butyryl-cholinesterase in the cerebrospinal fluid of patients with Alzheimer's disease by rivastigmine: correlation with cognitive benefit. *J Neural Transm*. 2002;109:1053-1065.

11. Imbimbo BP. Pharmacodynamic tolerability relationships of cholinesterase inhibitors for Alzheimer's disease. *CNS Drugs*. 2001;15:375-390.

12. Lefèvre G, Sędek G, Jhee S, et al. Pharmacokinetics and bioavailability of the novel daily rivastigmine transdermal patch compared with twice-daily capsules in patients with mild-to-moderate Alzheimer's disease. *Clin Pharmacol Ther*. 2008;83:106-114.

13. Mercier F, Lefèvre G, Huang A, Schmidli H, Amzal B, Appel-Dingemanse S. Rivastigmine exposure provided by a transdermal patch *versus* capsules. *Curr Med Res*. 2007;23:3199-3204.

14. Winblad B, Cummings J, Andreasen N, et al. A six-month double-blind, randomized, placebo-controlled study of a transdermal patch in Alzheimer's disease: rivastigmine patch versus capsule. *Int J Geriatr Psychiatry*. 2007;22:456-467.

15. Pommier F, Frigola R. Quantitative determination of rivastigmine and its major metabolite in human plasma by liquid chromatography with atmospheric pressure chemical ionization tandem mass spectrometry. *J Chromatogr B*. 2003;784:301-313.

16. Jann MW, Shirley KL, Small GW. Clinical pharmacokinetics and pharmacodynamics of cholinesterase inhibitors. *Clin Pharmacokinet*. 2002;41:719-739.

17. Jann MW. Rivastigmine, a new-generation cholinesterase inhibitor for the treatment of Alzheimer's disease. *Pharmacotherapy*. 2000;20:1-12.

18. Nordberg A, Svensson AL. Cholinesterase inhibitors in the treatment of Alzheimer's disease. *Drug Saf*. 1998;19:465-480.

19. Ellmann GL, Courtney KD, Andres V, Featherstone RM. A new and rapid colorimetric determination of acetylcholinesterase activity. *Biochem Pharmacol*. 1961;7:88-90.

20. Smith BP, Vandenhende FR, DeSante KA, et al. Confidence interval criteria for assessment of dose proportionality. *Pharm Res*. 2000;17:1278-1283.

21. Hossain M, Jhee SS, Shiovitz T, et al. Estimation of the absolute bioavailability of rivastigmine in patients with mild to moderate dementia of the Alzheimer's type. *Clin Pharmacokinet*. 2002;41:225-234.

22. Grossberg GT, Stähelin HB, Messina JC, Anand R, Veach J. Lack of adverse pharmacodynamic drug interactions with rivastigmine and twenty-two classes of medications. Int J Geriat Psychiatry. 2000;15:242-247.

23. Polinsky RJ. Clinical pharmacology of rivastigmine: a new-generation acetylcholinesterase inhibitor for the treatment of Alzheimer's disease. *Clin Ther*. 1998;20:634-647.

24. Lee L, Hossain M, Wang Y, Şedek G. Absorption of rivastigmine from different regions of the gastrointestinal tract in humans. *J Clin Pharmacol*. 2004;44:599-604.