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Assessment of Ethnic Differences in the Pharmacokinetics and Pharmacodynamics of Valsartan

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Abstract

Objective: To assess the potential ethnic differences in pharmacokinetics and pharmacodynamics of valsartan between Japanese and Caucasian subjects.

Methods: This was an open-label, parallel-design study conducted in male Japanese (n=15) and Caucasian (n=15) subjects with similar age and body weight. All subjects received a single oral dose of 160 mg valsartan capsule, and the plasma levels of valsartan, aldosterone, and angiotensin II along with plasma renin activity (PRA) were determined at pre-set time intervals, post-dosing.

Key findings: The time to reach peak plasma concentrations of valsartan (T_{max}) was in the range of 1–6 h in both groups. The mean C_{max} of valsartan was 3.3 and 3.6 µg/ml; the mean plasma exposure ($AUC_{0-\infty}$) values were 23.0 and 23.8 µg.h/ml and the mean half-life ($t_{1/2}$) was 7.7 and 9.6 h in Japanese and Caucasian subjects, respectively. No significant difference (p>0.1) was found between two ethnic groups for PRA, angiotensin II and aldosterone at 2, 4 and 8 h, post dose.

Conclusion: Pharmacokinetics and pharmacodynamics of valsartan were not found to be associated with ethnic differences between healthy male Caucasian and Japanese subjects following single oral dose administration of valsartan and hence no dose adjustment is required for these groups.

Keywords: Caucasians; Japanese; Pharmacodynamics; Pharmacokinetics; Valsartan; Anti-hypertensive

Abbreviations: AE: Adverse Event; ANOVA: Analysis of Variance; ARB: Angiotensin Receptor Blocker; AUC: Area Under the Curve; BMI: Body Mass Index; CV: Coefficient of Variation; ESI: Electro Spray Ionization; OATP: Organic Ion Transport Polypeptide; PRA: Plasma Renin Activity; RIA: Radio Immuno Assay; SAE: Serious Adverse Event

Introduction

Ethnicity may influence efficacy and safety profile of drugs [1,2]. The differences in ethnically sensitive drug disposition may be either due to genetic (intrinsic) or extrinsic environmental factors or both [3,4]. Drugs that undergo significant metabolism/transport and have high plasma protein binding affinity are most likely to exhibit ethnic differences [5].

Valsartan, an angiotensin receptor blocker (ARB), is a widely used antihypertensive drug approved world-wide either as monotherapy or in combination with other antihypertensive agents [6-8]. The pharmacokinetics of valsartan is linear and dose proportional across a wide dose range (80–320 mg) [9,10]. Valsartan is rapidly absorbed after oral administration, reaching peak plasma concentration (C_{max}) at about 2–4 h post dose [11]. The oral bioavailability of valsartan is only 23% and about 95% is bound to serum proteins mainly albumin [12,13]. Plasma levels of valsartan decrease bi-exponentially with a half life ($t_{1/2}$) of 7–8 h [9,10]. Elimination is mostly in unchanged form and approximately 86% of the systemically available dose is excreted in the feces [11,14].

Owing to minimal metabolic conversion and hence unchanged excretion of the drug through feces, insignificant differences among ethnic groups are anticipated in the pharmacokinetics of valsartan [1]. The present study was conducted to evaluate for any potential differences in the pharmacokinetics and pharmacodynamics of valsartan after a single oral dose of 160 mg capsule (Diovan®) in healthy Japanese and Caucasian subjects.

Subjects and Methods

Study design

This was an open-label, parallel-group fasting study conducted at Royal Surrey County Hospital of Guildford Clinical Pharmacology Ltd (Guildford, Surrey, UK). The study was approved by the South West Surrey Local Research Ethics Committee. It was conducted in accordance to Good Clinical Practice and adhered to the Declaration of Helsinki. All study participants provided written informed consent before participating in the study.

Study participants

A total of 30 healthy male Japanese (n=15) and Caucasian (n=15) subjects aged 20–35 years with a body weight ranging from 55 to 75 kg and body mass index (BMI) of 20–25 kg/m^2 were included in the study. Japanese subjects were defined as those having both parents of Japanese origin, born in Japan and having left Japan not more than 10 years ago. All the study participants were in good health, as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at screening performed within 21 days prior to commencement of the study. Subjects were screened for nicotine and drugs of abuse, as well as hepatitis B/C and HIV.

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Subjects who had donated or lost ≥400 ml blood within 8 weeks prior to the study or with significant history of illness within 2 weeks; subjects with a history of clinically significant ECG abnormalities or a family history of prolonged QT-interval syndrome, autonomic dysfunction, history of acute or chronic bronchospasmic disease (including asthma and chronic obstructive pulmonary disease) or history of clinically significant drug allergy or atopic allergy, or a known hypersensitivity to the study drug or similar drugs; and subjects who reported smoking of more than 5 cigarettes per day were excluded from the study.

Study treatment

On Day 1, after overnight fasting for 10 h, all subjects were administered 160 mg valsartan capsule (Diovan®, Novartis Pharma AG, Basel, Switzerland), as a single oral dose with 200 ml of water between 07:30 and 09:00 AM. Valsartan capsules (Batch No. V0008) were purchased by the investigator from the local pharmacy. All the subjects continued to fast for an additional 4 h post-dose. Both the groups received identical diet during the study. The intake of alcohol, grapefruit juice, and xanthine-containing foods and beverages were prohibited.

Admission and accommodation

Subjects were admitted and housed in the Clinical Research Unit at least 14 h prior to dosing for baseline evaluations and were discharged 48 h after administration of the study drug.

Sampling schedule

For pharmacokinetic assessments, blood samples (5 ml) were collected into a lithium heparin tube by either direct venipuncture or an indwelling cannula inserted in a forearm vein at 0 h (pre-dose) and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, and 48 h after drug administration. Blood samples for measurement of pharmacodynamic parameters were collected at 0 h (pre-dose) and 2, 4, 8, and 24 h post-dose into EDTA-containing tubes.

The blood samples were centrifuged under refrigeration (3°C to 5°C) for 15 min at 800 *g* for pharmacokinetic assessments and for 10 min at 1600–1700 *g* for pharmacodynamic assessments. The plasma was then transferred into polypropylene screw-cap tubes and stored at ≤-20°C and at -70°C for pharmacokinetic and pharmacodynamic assessments, respectively, until analysis.

Pharmacokinetic assessments

Analytical method for measurement of plasma concentrations: The analysis of valsartan was performed in plasma using a validated LC/MS/MS method. The assay consisted of a liquid–liquid extraction of samples followed by HPLC using a Luna 5 µ phenyl-hexyl (2.0×50mm, Phenomenex) column with isocratic elution using 0.1% acetic acid/acetonitrile (45:55, v/v). Detection was performed by MS/MS with Electro Spray Ionization (ESI) using a TSQ700 mass spectrometer (Thermo Electron Corporation) in positive ion mode. The masses for valsartan were precursor ion m/z 432.2 and product ion m/z 291.2. The lower limit of quantification for the assay was 2.0 ng/ml using 500 µg/ml of plasma. The internal standard for this assay was [D9]VAL489 500 ng/ml. Within-study assay validation at nominal valsartan concentrations of 5, 80, and 800 ng/ml showed an assay precision of 2.6–7.7%.

Pharmacokinetic data analysis: Plasma concentration-time profiles were evaluated by standard non-compartmental methods using WinNonlin Pro (Version 4.0.1, Pharsight Corporation, Mountain View, CA, USA). Plasma concentrations below the limit of quantification were treated as 0 in all calculations. The following pharmacokinetic parameters were determined: C_{max} and T_{max} (time to reach C_{max}) were recorded from experimental observations. Area under the plasma concentration–time curve (AUC) was calculated using the linear trapezoidal method, and the following three AUC parameters were determined: $AUC_{0\text{-}24h}$ (AUC from time zero to 24 h); $AUC_{0\text{-}t}$ (AUC from time zero to the last measurable concentration); and $AUC_{0\text{-}\infty}$ (AUC from time zero to infinity; calculated using formula $(AUC_{(0\text{-}t)} + Ct/\lambda z$, where Ct is concentration at time t and λz is the terminal elimination rate constant). Terminal elimination rate constant (λz) was determined from slope of the regression line of lnC vs time with the constraints of at least three consecutive measurable concentrations, with all concentrations declining with time and the correlation coefficient (r) of regression of ≥0.95. The elimination half-life ($t_{1/2}$) was determined as 0.693/λz.

Pharmacodynamic assessments

Plasma renin activity (PRA), plasma aldosterone concentrations, and plasma Ang II concentrations were measured using radio immunoassay (RIA) kit(s) in Hachioji Laboratory, SRL, Inc., Tokyo, Japan. Relative PRA, aldosterone concentrations, and Ang II concentrations were calculated using the following formula: value at each sampling point/value at pre-dose×100.

Safety and tolerability assessments

Safety assessments comprised monitoring and recording all adverse events (AEs) and serious adverse events (SAEs). Routine blood chemistry, hematology, urinalysis, and vital signs were monitored; physical examination, ECG recordings, and blood pressure measurements were performed at baseline and after completion of the study.

Statistical analysis

A sample size of 30 subjects, 15 in each ethnic group, was needed to provide an 80% power to detect a significant difference (two-sided test at the 5% level) in AUC, if there is a 45% true difference between groups. Descriptive statistics for pharmacokinetic parameters were presented, which included mean, SD, coefficient of variation (CV), minimum, and maximum. Geometric means have been stated wherever presented. Because T_{max} was evaluated by a nonparametric method, the median values and ranges were given. Log-transformed pharmacokinetic parameters (AUC and C_{max}) were analyzed by a one-way ANOVA model. The resulting 90% confidence intervals of the mean ratios for AUC and C_{max} were used to evaluate relative differences between Japanese and Caucasian subjects.

Pharmacodynamic parameters

PRA, plasma aldosterone, and plasma Ang II concentrations were compared between the two ethnic groups at each post-dose time point using the analysis of covariance procedure, with the pre-dose value as a covariate.

Results

Demographics

All 30 subjects enrolled in the study completed all the study requirements. Baseline characteristics for the study subjects in both the groups were well matched with respect to age, height, body weight, and BMI (Table 1).

Pharmacokinetics

Mean (SD) plasma concentration–time profiles for valsartan

following administration of a single oral dose of 160 mg were similar for Caucasian and Japanese subjects (Figure 1). The mean C_{max} of valsartan, mean plasma exposure indicated by AUC_{0-24}, AUC_{0-t} and $AUC_{0-\infty}$ were also comparable between Japanese and Caucasian subjects (Table 2).

The mean C_{max} of valsartan was 3.55 and 3.30 µg/ml in Caucasians and Japanese subjects, respectively, and the corresponding mean plasma exposure ($AUC_{0-\infty}$) values were 23.0 and 23.8 µg.h/ml, respectively. The estimated geometric mean ratios (Japanese/Caucasian) of C_{max} and $AUC_{0-\infty}$ were 0.83 and 0.91, respectively, and the corresponding 90% confidence intervals were 0.64–1.07 and 0.73–1.13 (Table 3). The difference in means between the groups was not statistically significant ($p>0.05$).

Plasma concentrations of valsartan reached a maximum within a range of 1–6 h in both Japanese and Caucasian subjects with median T_{max} values of 2.5 and 4 h, respectively. Plasma levels declined with mean $t_{1/2}$ of 7.7 h in Japanese subjects and 9.6 h in Caucasian subjects. The inter-subject variability observed in this study was in the range of 20–60%.

Pharmacodynamics

The mean PRA, Ang II, and aldosterone concentration–time profiles are shown in Figure 2. The pharmacodynamic measures (PRA (ng/ml/h), plasma aldosterone (pg/ml), and plasma Ang II (pg/ml) obtained at 2, 4, 8, and 24 h post-dose were compared between the two ethnic groups after adjusting for the corresponding pre-dose values. No significant difference was found between Japanese and Caucasian populations at all time points, except for a significantly lower plasma aldosterone value observed for the Japanese population at 24 h post-dose. The adjusted mean difference for PRA, plasma aldosterone, and plasma Ang II was -0.2 (p=0.74), -38.0 (p=0.02), and -3.1 (p=0.17), respectively (Table 4).

There was a rise in PRA and plasma Ang II concentrations after 2 h of dosing. Peak PRA and plasma Ang II concentrations were reached around 8 h after dosing in most Japanese and Caucasian subjects. PRA and Ang II concentrations remained higher than baseline at 24 h after drug intake in both ethnic groups. At 2 h after dosing, plasma aldosterone concentrations showed a slight decrease in both ethnic groups and remained stable until 8 h after dosing. Twenty-four hours after dosing, plasma concentrations were similar to those measured at baseline in each ethnic group.

Variable Mean ± SD	Study groups	
	Japanese (N=15)	Caucasian (N=15)
Age (years)	26.5 ± 4.0	24.8 ± 4.5
Height (cm)	172.1 ± 7.5	175.5 ± 5.7
Body weight (kg)	65.8 ± 5.5	70.4 ± 4.7
Body mass index (kg/m²)	22.2 ± 1.5	22. 9 ± 1.6

Table 1: Demographics summary.

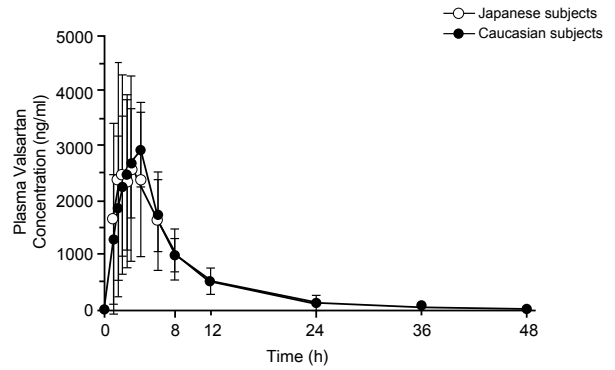

Figure 1: Mean (SD) plasma concentration versus time profiles of valsartan.

Study group	C_{max} (µg/ml)	AUC_{0-48} (µg·h/ml)	AUC_{0-24} (µg·h/ml)	$AUC_{0-\infty}$ (µg·h/ml)	$t_{1/2}$ (h)	T_{max} (h)
Japanese (N=15)	3.30 ± 1.97 (59.7%)	22.80 ± 9.38 (41.2%)	21.48 ± 9.12 (42.4%)	22.99 ± 9.44 (41.1%)	7.74 ± 1.55 (20.0%)	2.5 (1.5-6.0)
Caucasian (N=15)	3.55 ± 0.84 (23.7%)	23.51 ± 5.65 (24.0%)	22.10 ± 5.01 (22.7%)	23.83 ± 5.63 (23.6%)	9.57 ± 4.79 (50.0%)	4.0 (1.0 -6.0)

C_{max}: peak plasma concentration, AUC_{0-48}: Area under the plasma concentration versus time curve, T_{max}: time at which the C_{max} occurs, $t_{1/2}$: elimination half life
For T_{max} median and range is reported

Table 2: Summary of pharmacokinetic parameters of valsartan (Arithmetic Mean ± SD [CV%]).

Parameter	Ratio of geometric means (Japanese/Caucasian)	90% CI for ratio	p-value
Cmax	0.83	(0.64, 1.07)	0.217
AUC_{0-48}	0.91	(0.73, 1.14)	0.479
AUC_{0-24}	0.91	(0.73, 1.13)	0.461
$AUC_{0-\infty}$	0.91	(0.73, 1.13)	0.449

C_{max}: peak plasma concentration, AUC: Area under the plasma concentration versus time curve

Table 3: Summary of ratio of geometric means (Japanese/Caucasian) and the corresponding 90% confidence intervals and p-values.

Safety and tolerability

There were no AEs reported in the Japanese subjects and the incidence of AEs in Caucasians was low. Overall, 4 AEs (an episode of nausea, abnormal feeling, seasonal allergy, and myalgia) of mild intensity were reported in three Caucasian subjects. None of the AEs were suspected to be study drug related. There were no SAEs or discontinuations from the study due to AEs.

Discussion

The primary objective of this study was to assess the ethnic differences in the pharmacokinetics of valsartan in Japanese and Caucasians when administered as a single oral dose of 160 mg. In addition, pharmacodynamic effects, PRA, plasma aldosterone levels, and plasma Ang II levels on administration of valsartan were also monitored.

The results of this study indicated that the mean plasma concentration versus time profiles and pharmacokinetic parameters (AUC, C_{max}, T_{max}, and $t_{1/2}$) of valsartan were comparable between Japanese and Caucasian subjects. The estimates of AUC, C_{max}, T_{max}, and $t_{1/2}$ observed in this study were comparable to those observed in the previous studies [15-18]. The estimated geometric mean ratios (Japanese/ Caucasian) of AUC and C_{max} were 0.91 and 0.83, respectively. The corresponding 90% confidence intervals were 0.73–1.14 and 0.64–1.07, respectively. The inter-subject variability associated with the pharmacokinetic variables of valsartan was in the range of 20–50%, which is consistent with previous findings [9,18]. Considering this high variability of valsartan, the 90% confidence intervals of AUC and C_{max} were well within range. The range of T_{max} in Japanese and Caucasians were also similar (1.5–6.0 vs. 1.0–6.0).

After oral administration, valsartan is rapidly absorbed into systemic circulation and is primarily eliminated unchanged in feces via bile excretion. Hepatic uptake and biliary excretion of valsartan are also suggested via the use of organic ion transport polypeptide (OATP) family transporters, specifically OATP1B1 and OATP1B3 [19]. Moreover, genetic polymorphism in OATPs might have an effect

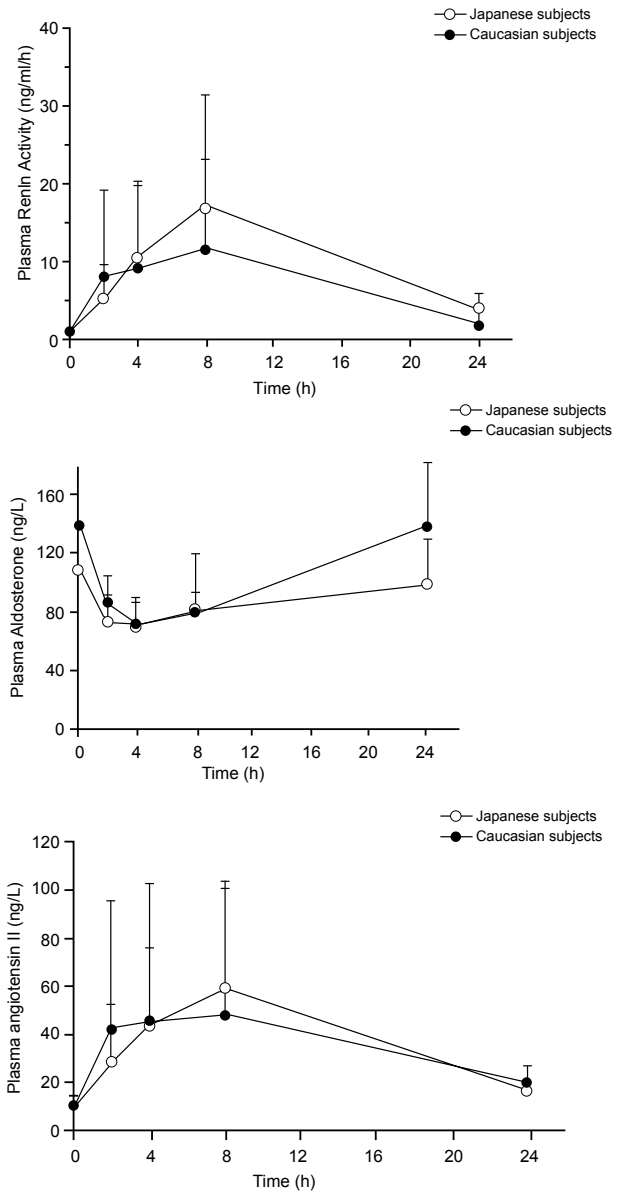

Figure 2: Pharmacodynamic effects of valsartan: (A) plasma renin activity (PRA) (B) plasma aldosterone and (C) plasma angiotensin II in Japanese and Caucasians.

Variable	Adjusted mean difference	p-value
Plasma aldosterone (pg/ml)	-38.0	0.02
Plasma angiotensin II (pg/ml)	-3.1	0.17
Plasma renin Activity (ng/ml/h)	-0.2	0.74

Table 4: Comparison of pharmacodynamic parameters between Japanese and Caucasian subjects at 24 h post dose.

on hepatic clearance of valsartan. The uptake of valsartan by hepatic cells seems to be related to OATP1B1*1b alleles, which may be one of the determinant factors governing the inter-subject variability in the pharmacokinetics of valsartan observed in both Japanese and Caucasian subjects in the present study [20]. Furthermore, valsartan is not metabolized via CYP-mediated oxidative pathway [8,24]. This suggests that significant difference with regard to pharmacokinetics of valsartan is not anticipated between Japanese and Caucasian population consistent to the results of this study.

The pharmacodynamic variables PRA, Ang II, and aldosterone concentrations also did not differ significantly between Japanese and Caucasian subjects. In both ethnic groups, PRA and plasma Ang II reached the maximum value at around 8 h. These results are consistent with the previous studies [16,17,21]. The blockade of renin–angiotensin system at the AT1 receptor level interrupts the negative feedback on renin secretion and causes an increase in the PRA and plasma Ang II in humans [22]. In addition, the duration of PRA activity and plasma concentrations of Ang II is prolonged relative to the plasma elimination kinetics of valsartan, as reported previously[22,23]. In the case of plasma aldosterone, the mean change in plasma aldosterone levels from baseline at 2, 4, and 8 h post dose is comparable between Japanese and Caucasian subjects. At the 24-h time point, the mean difference is statistically significant, with lower levels in Japanese subjects; however, this is not considered to be clinically relevant.

Valsartan 160 mg was well tolerated in both Japanese and Caucasian subjects. The incidence of AEs was low, and no AE was reported in the Japanese group. There were no SAEs or discontinuations because of AEs during the study.

In conclusion, pharmacokinetics and pharmacodynamics of valsartan were not ethnically sensitive among healthy Japanese and Caucasian men following single oral dose administration of valsartan, and hence no dose-adjustment is required based on ethnic differences.

Transparency

Declaration of interest: This study was supported by Novartis Pharmaceutical Corporation. All authors are employees of Novartis. None of the authors have any conflicts of interest with respect to the contents of this article. The authors thank Shivali Arora, PhD and Ashish Agarwal, PhD from Novartis, India for writing support. The authors also acknowledge all investigators and study coordinators at the participating centers, and all volunteers for their commitment to the study.

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