DOI:10.1111/j.1365-2125.2006.02696.x

Aliskiren, a novel orally effective renin inhibitor, exhibits similar pharmacokinetics and pharmacodynamics in Japanese and Caucasian subjects

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Keywords
aliskiren, ethnic differences, hypertension, renin inhibitor

Received
9 January 2006
Accepted
13 April 2006

Aims
Aliskiren is the first in a new class of orally effective renin inhibitors for the treatment of hypertension. This study compared the pharmacokinetic and pharmacodynamic properties of aliskiren in Japanese and Caucasian subjects.

Methods
In this open-label, single-centre, parallel-group, single- and multiple-dose study, 19 Japanese and 19 Caucasian healthy young male subjects received a single 300-mg oral dose of aliskiren on day 1 and then aliskiren 300 mg once daily on days 4–10. Blood samples were collected for the measurement of plasma aliskiren concentration, plasma renin concentration (PRC) and plasma renin activity (PRA).

Results
Pharmacokinetic parameters were comparable in Japanese and Caucasian subjects following administration of a single dose of aliskiren {ratio of geometric means: C_{max} 1.12 [90% confidence interval (CI) 0.88, 1.43]; $AUC_{0-72\,h}$ 1.19 [90% CI 1.02, 1.39]} and at steady state [mean ratio: C_{max} 1.30 (90% CI 1.00, 1.70); $AUC_{0-\tau}$ 1.16 (90% CI 0.95, 1.41)]. There was no notable difference in the plasma half-life of aliskiren between Japanese and Caucasian groups (29.7 ± 10.2 h and 32.0 ± 6.6 h, respectively). At steady state, peak PRC level and AUC for the concentration–time plot were not significantly different between Japanese and Caucasian subjects ($P = 0.64$ and $P = 0.80$, respectively). A single oral dose of aliskiren significantly reduced PRA to a similar extent in Japanese and Caucasian subjects (by 87.5% and 85.7%, respectively, compared with baseline; $P < 0.01$). Aliskiren was well tolerated by both ethnic groups.

Conclusions
The oral renin inhibitor aliskiren demonstrated similar pharmacokinetic and pharmacodynamic properties in Japanese and Caucasian subjects.

Introduction

Hypertension is the major treatable risk factor for cardiovascular disease, which remains the leading cause of death in the industrialized world. Despite the risks associated with the condition, the majority of patients with hypertension across the world do not have their blood pressure (BP) controlled to recommended target levels [1, 2].

The renin–angiotensin–aldosterone system (RAAS) plays a key role in the regulation of BP and body fluid

volume through the actions of the peptide angiotensin II (Ang II), but excessive RAAS activity may lead to hypertension and associated target organ damage [3]. Therapies that inhibit the RAAS, such as angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), have proven to be highly successful treatments for hypertension and related cardiovascular diseases [4]. However, ACE inhibitors and ARBs only partially suppress the RAAS, because they stimulate a compensatory increase in plasma renin activity (PRA), which may ultimately lead to increased levels of Ang II [5]. Indeed, increased levels of PRA have been associated with end organ damage and poorer clinical outcomes in patients with hypertension [6–8], probably due to the increase in Ang II levels associated with elevated PRA.

Inhibition of renin has long been proposed as the optimal means of inhibiting the RAAS, as renin catalyses the rate-limiting step in the pathway and has high specificity for a single naturally occurring substrate, angiotensinogen [9]. However, previous efforts to develop clinically effective renin inhibitors have been thwarted by the low potency and/or poor pharmacokinetic profiles of peptide-like compounds [10]. Aliskiren is the first in a new class of orally effective, nonpeptide renin inhibitors and is currently undergoing phase III clinical trials for the treatment of hypertension and related cardiovascular disorders. Aliskiren is a potent [*in vitro* IC_{50} 0.6 nmol l^{-1}] and highly specific inhibitor of human renin [11] and studies in healthy volunteers have demonstrated that aliskiren exhibits a long plasma half-life ($t_{1/2}$ 25–30 h) suitable for once-daily dosing [12, 13]. Indeed, once-daily doses of aliskiren of up to 640 mg were well tolerated and provided dose-dependent inhibition of renin [12]. Furthermore, clinical trials in patients with hypertension have shown that aliskiren provides antihypertensive efficacy comparable to the ARBs losartan and irbesartan, with similar tolerability [14, 15].

The effects of aliskiren have been investigated mainly in Caucasian subjects. However, it is well known that drug disposition and response may differ between ethnic groups, possibly due to genetic variation in drug-metabolizing enzymes, drug transporters and drug receptors [16]. The aim of the present study was to compare the single- and multiple-dose pharmacokinetic properties of aliskiren following oral administration of the drug to healthy male Japanese and Caucasian subjects. The pharmacodynamic effects of aliskiren were assessed by measurement of PRA and plasma renin concentration (PRC).

Methods

This was an open-label, parallel-group, single- and multiple-dose study of the pharmacokinetics and pharmacodynamics of aliskiren, 300 mg once daily, in healthy young male Japanese and Caucasian volunteers, conducted at a single study centre in the UK.

Subjects

Two parallel groups of healthy young male Japanese ($n = 19$) and Caucasian ($n = 19$) subjects, between 20 and 45 years old and matched for age (± 5 years) and weight (± 25%), were enrolled in the study. Japanese subjects were defined as having both parents of Japanese origin and citizenship, and as having been born in Japan and lived outside of Japan for ≤10 years. Caucasian subjects were defined as having both parents of Caucasian origin. This study was reviewed by one centre and one local ethical review board, carried out in accordance with Good Clinical Practice, and adhered to the principles of the Declaration of Helsinki of the World Medical Association. All subjects provided written informed consent before entering the study.

Procedures

After a 21-day screening period, all subjects underwent a baseline evaluation at day −1 and received a single 300-mg oral dose of aliskiren on day 1. From day 4, subjects received aliskiren 300 mg once daily for 7 days. Aliskiren was given as a single capsule with 200 ml of water at between 07.30 h and 09.00 h following an overnight fast of at least 10 h. Predose blood samples were taken for assessment of pharmacokinetic parameters on each dosing day (days 1–10 inclusive); a more intensive schedule of blood sampling was performed on days 1 and 10 (samples were taken at 0, 0.5, 1, 2, 4, 6, 8, 12 and 24 h postdosing). Blood samples for measurement of pharmacodynamic parameters were taken on days 1 and 10 only. Laboratory safety parameters were assessed at screening, baseline and at study completion. Subjects were domiciled in the study centre from day −1 (baseline) until the 24-h post last-dose evaluations were completed on day 11. Both groups received identical diets during the trial; intake of alcohol, grapefruit juice, and xanthine-containing foods and beverages was prohibited.

Pharmacokinetic and pharmacodynamic analysis

Plasma concentrations of aliskiren were measured by an LC/MS/MS method. The assay consisted of a solid-phase extraction on Oasis MCX cartridges using an automated system followed by reverse-phase high-performance liquid chromatography on a Metachem

MetaSil basic column using gradient elution with 10 mM aqueous ammonium acetate/acetonitrile. Detection was performed in MS/MS using electro spray ionization (ESI). The lower limit of quantification for the assay was approximately 0.5 ng ml^{-1} and the coefficient of variation was <10%. Pharmacokinetic parameters ($AUC_{0-\infty}$, AUC_{0-t}, C_{max}, t_{max} and $t_{1/2}$) for aliskiren were determined by noncompartmental methods using WinNonLin Pro (Version 4.0; Pharsight Corp., Mountain View, CA, USA). Noncompartmental analysis was considered appropriate because this approach allowed the pharmacokinetic parameters of aliskiren to be calculated without the introduction of any bias.

PRC was measured by immunoradiometric (sandwich technique) assay, using a commercially available kit (RENIN III GENERATION; CIS bio international, Schering SA, Gif/Yvette, France) according to the manufacturer's instructions. PRA was measured by indirect radioimmunoassay, using a commercially available kit (REN-CT2; CIS bio international) according to the manufacturer's instructions.

Safety and tolerability assessments

Safety and tolerability assessments were conducted in all subjects, and included the monitoring and recording of all adverse events (AEs) and serious adverse events and concomitant medications or significant nondrug therapies. Evaluations of routine blood chemistry, haematology and urine values, as well as a physical examination, ECG recordings and monitoring of vital signs, were performed at baseline and after completion of the study.

Data analysis

Log-transformed pharmacokinetic parameters (AUC and C_{max}) were analysed by an ANOVA model with race as a fixed factor and matched pair as a random factor. The resulting 90% confidence intervals (CI) of the ratios of the ethnic group means were used to evaluate relative differences between Japanese and Caucasian subjects. For the primary pharmacodynamic variable, PRC, peak concentration and the area under the 24-h concentration–time curve (AUC) were assessed and comparisons between groups made using an ANCOVA model adjusted for baseline values. PRA values following administration of aliskiren were compared with the baseline value (0 h) using one-way ANOVA with Dunnett's *post hoc* test [17].

Results

Baseline characteristics

Baseline characteristics for the 38 healthy male volunteers (19 Japanese and 19 Caucasian) recruited to the study are shown in Table 1. The two groups were well balanced with regard to the baseline characteristics of age, height and body mass index, although Japanese subjects had a lower weight than Caucasian subjects.

Table 1
Subject characteristics

Parameter	Study group: Japanese (n = 19)	Caucasian (n = 19)
Age, years	28.0 ± 4.9	27.7 ± 5.8
Height, cm	171.6 ± 5.2	176.8 ± 6.1
Body weight, kg	64.9 ± 5.6	73.4 ± 6.5
Body mass index, kg m^{-2}	22.0 ± 1.9	23.5 ± 1.9

Data are presented as mean ± SD.

Single-dose pharmacokinetics of aliskiren

Plasma concentration–time profiles for aliskiren following administration of a single 300-mg oral dose showed no major differences between Japanese and Caucasian subjects (Figure 1a). Median t_{max} occurred 2 h after dosing in both groups. Mean C_{max} and $AUC_{0-72\,h}$ values were comparable in Japanese and Caucasian subjects, although $AUC_{0-72\,h}$ was slightly higher in Japanese subjects [Table 2; ratio of geometric means: C_{max} 1.12 (90% CI 0.88, 1.43); $AUC_{0-72\,h}$ 1.19 (90% CI 1.02, 1.39)]. There were no notable differences in the $t_{1/2}$ or rate of absorption ($C_{max}/AUC_{0-72\,h}$) of aliskiren between the two groups (Table 2).

Steady-state pharmacokinetics of aliskiren

C_{max} and $AUC_{0-\tau}$ values for aliskiren at steady state were approximately twofold higher compared with the respective values following administration of a single oral dose in both Japanese and Caucasian subjects (Figure 1b; Tables 2 and 3). At steady state, mean C_{max} and $AUC_{0-\tau}$ values remained comparable in Japanese and Caucasian subjects [Figure 2; Table 3; ratio of geometric means: C_{max} 1.30 (90% CI 1.00, 1.70); $AUC_{0-\tau}$ 1.16 (90% CI 0.95, 1.41)].

Effects of aliskiren on plasma renin concentration

At baseline, PRC was slightly higher in Japanese subjects (15.3 ± 10.5 pg ml^{-1}) compared with Caucasian subjects (10.2 ± 9.7 pg ml^{-1}). A single 300-mg oral dose of aliskiren led to increases in PRC of 20-fold and 15-fold in Japanese and Caucasian subjects, respectively

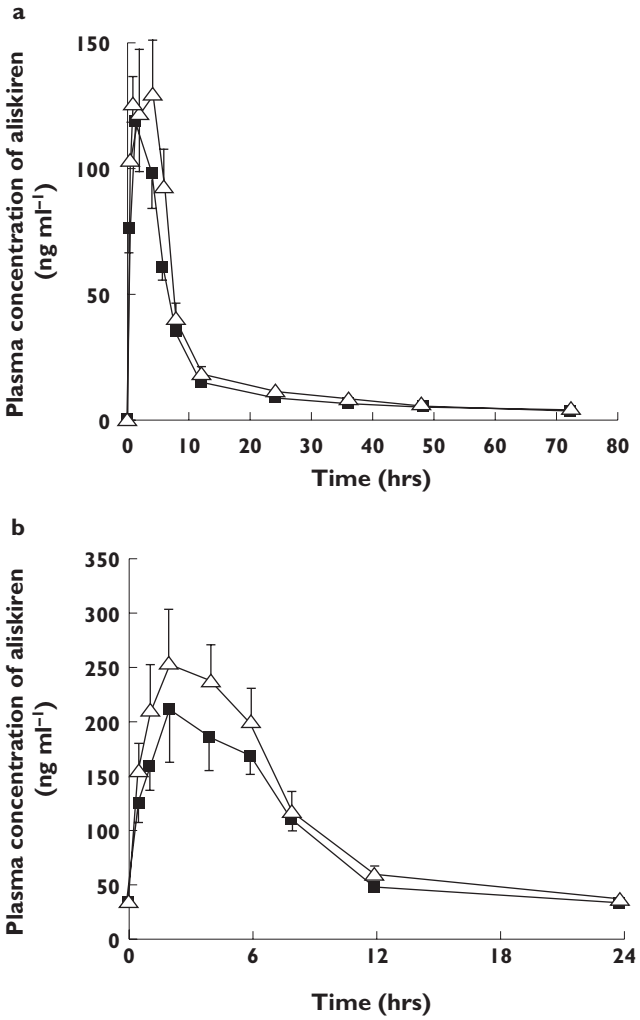

Figure 1
Plasma concentration–time profile of aliskiren in Japanese and Caucasian subjects (a) following administration of a single 300-mg oral dose and (b) at steady state. Plasma concentrations of aliskiren are presented for Japanese (△) and Caucasian (■) subjects. Data are presented as mean ± SEM

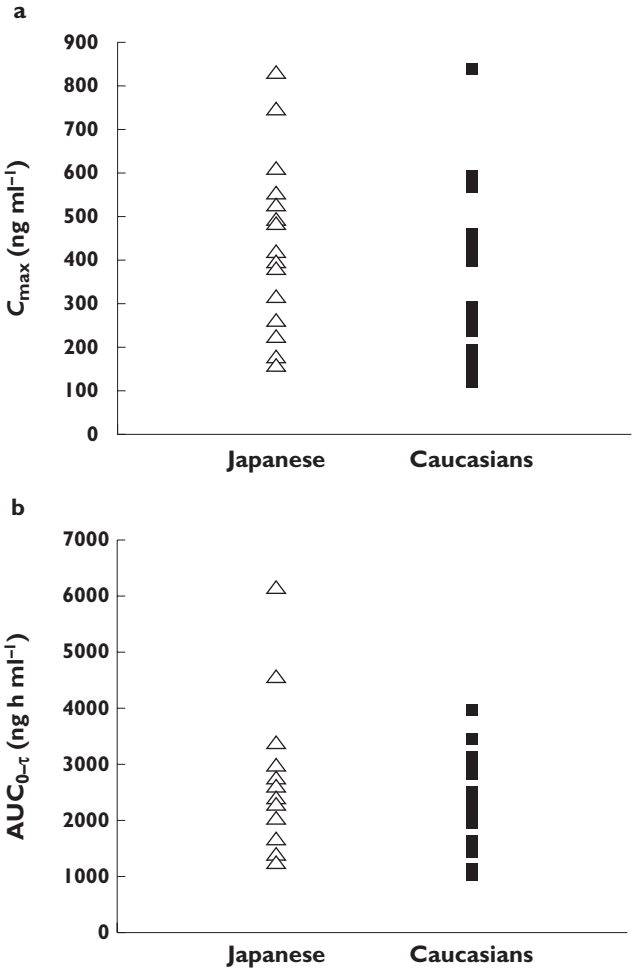

Figure 2
Individual values of (a) C_{max} and (b) $AUC_{0-\tau}$ for aliskiren at steady state in Japanese and Caucasian subjects. Individual C_{max} and $AUC_{0-\tau}$ values are presented for Japanese (△) and Caucasian (■) subjects. AUC, Area under the curve

Table 2
Pharmacokinetic parameters following the administration of a single oral dose of aliskiren 300 mg in Japanese and Caucasian subjects

Study group	C_{max} (ng ml^{-1})	t_{max} (h)	$AUC_{0-72\ h}$ (ng h ml^{-1})	$t_{1/2}$ (h)	$C_{max}/AUC_{0-72\ h}$ (h^{-1})
Japanese (n = 19)	215 ± 122	2.0 (0.5–4.0)	1387 ± 615	29.7 ± 10.2	0.16 ± 0.06
Caucasian (n = 19)	186 ± 91	2.0 (0.5–6.0)	1124 ± 339	32.0 ± 6.6	0.16 ± 0.05

Data are presented as mean ± SD for all parameters except t_{max}*, for which median (minimum–maximum) values are shown. AUC, Area under the curve.*

Table 3
Pharmacokinetic parameters at steady state following administration of aliskiren 300 mg once daily for 7 days to Japanese and Caucasian subjects

Study group	C_{max} (ng ml^{-1})	t_{max} (h)	$AUC_{0-\tau}$ (ng h ml^{-1})	C_{avg} (ng ml^{-1})
Japanese (n = 19)	403 ± 193	4.0 (1.0–6.0)	2519 ± 1179	105 ± 49
Caucasian (n = 19)	321 ± 189	2.0 (0.5–8.0)	2135 ± 791	89 ± 33

Data are presented as mean ± SD for all parameters except t_{max}, for which median (minimum–maximum) values are shown. AUC, Area under the curve.

($P < 0.01$ *vs.* baseline; Figure 3a), peaking at approximately 6 h after dosing. PRC remained significantly above baseline ($P < 0.05$) in both ethnic groups for at least 24 h after dosing. The peak PRC level and AUC for the concentration–time plot were significantly higher ($P = 0.0075$ and $P = 0.0003$, respectively) in Japanese subjects compared with Caucasian subjects following a single oral dose of aliskiren.

Compared with peak PRC levels observed after administration of a single dose of aliskiren, peak PRC levels at steady state were approximately 3.5-fold and threefold higher in Japanese and Caucasian subjects, respectively (Figure 3b). Although PRC values in Japanese subjects remained slightly higher compared with Caucasian subjects throughout the dose interval at steady state, there were no significant differences between groups in the peak level or AUC after adjusting for baseline values ($P = 0.64$ and $P = 0.80$, respectively).

Effects of aliskiren on plasma renin activity

Baseline PRA values were slightly higher in Japanese subjects (0.24 ± 0.21 ng ml^{-1} h^{-1} compared with 0.14 ± 0.14 ng ml^{-1} h^{-1} in Caucasians). A single 300-mg oral dose of aliskiren significantly ($P < 0.01$) reduced PRA by 87.5% in Japanese subjects (to 0.03 ± 0.02 ng ml^{-1} h^{-1} at 2 h postdose) and by 85.7% in Caucasians (0.02 ± 0.01 ng ml^{-1} h^{-1} at 2 h postdose; Figure 4a). PRA remained significantly inhibited ($P < 0.01$) for at least 24 h after administration of aliskiren in both groups. At steady state, peak suppression of PRA was observed approximately 2 h after dosing with aliskiren. Aliskiren suppressed PRA by at least 50% compared with pretreatment baseline levels throughout the 24-h dosing interval in both ethnic groups (Figure 4b).

Pharmacokinetic–pharmacodynamic relationship

Analysis of PRC levels and aliskiren plasma concentrations obtained in Japanese subjects at 0, 1, 2, 4, 6, 12 and 24 h after administration of a single 300-mg oral

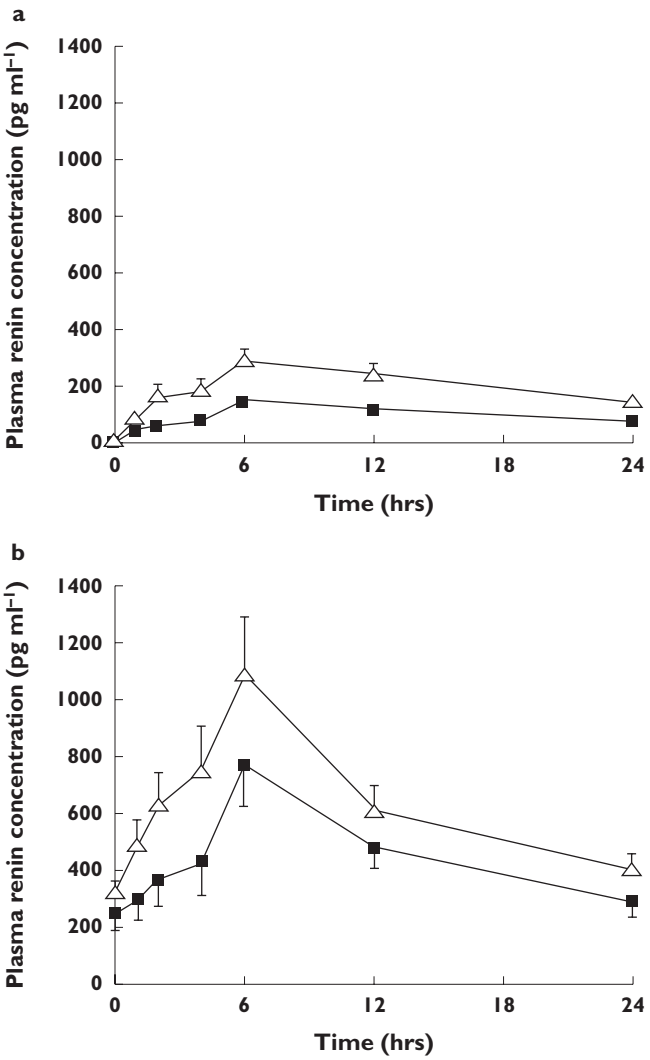

Figure 3
Effect of aliskiren on plasma renin concentration (PRC) in Japanese and Caucasian subjects (a) following administration of a single 300-mg oral dose and (b) at steady state. Mean PRC values are presented for Japanese (△) and Caucasian (■) subjects. Data are presented as mean ± SEM

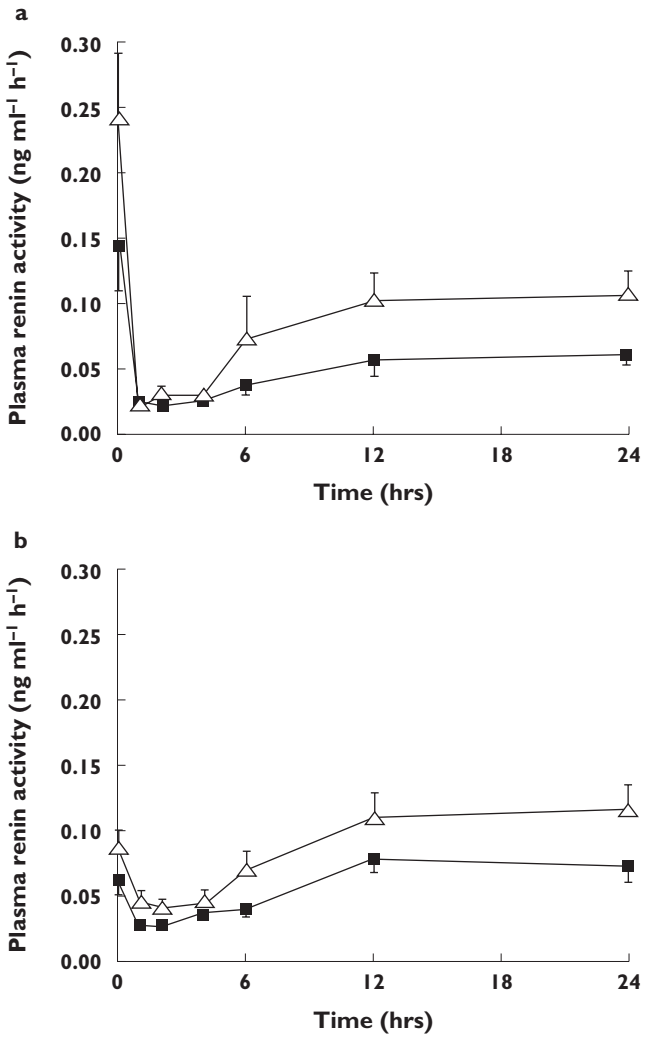

Figure 4
Effect of aliskiren on plasma renin activity (PRA) in Japanese and Caucasian subjects (a) following administration of a single 300-mg oral dose and (b) at steady state. Mean PRA values are presented for Japanese (△) and Caucasian (■) subjects. Data are presented as mean ± SEM

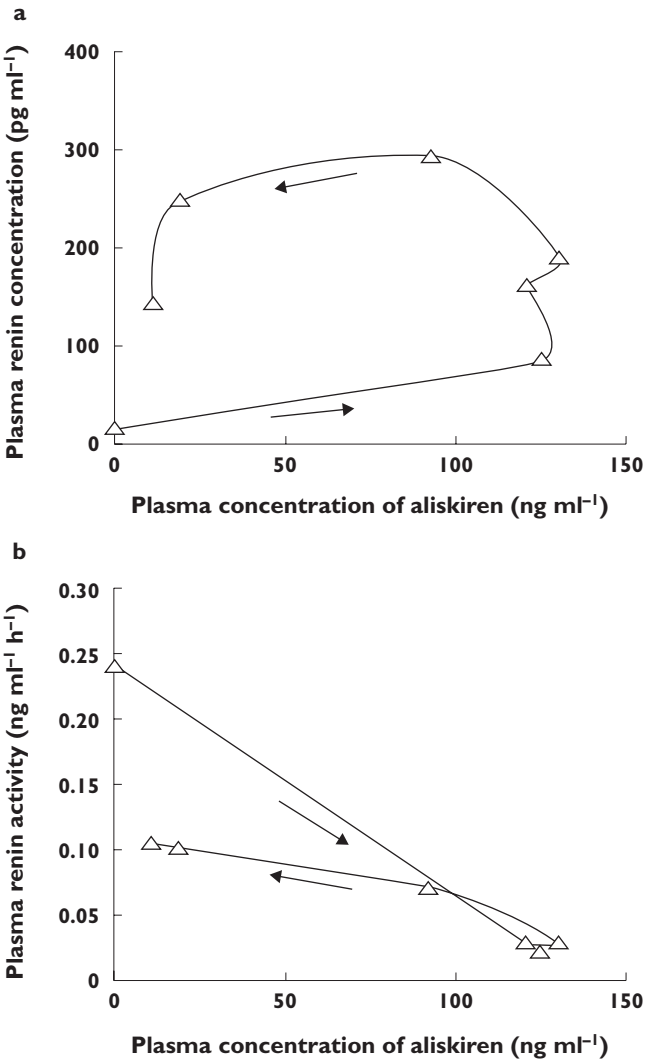

Figure 5
Relationship between plasma concentration of aliskiren and (a) plasma renin concentration (PRC) and (b) plasma renin activity (PRA) following administration of a single 300-mg oral dose in Japanese subjects. Graphs show mean plasma concentrations of aliskiren and respective values for (a) PRC and (b) PRA at 0, 1, 2, 4, 6, 12 and 24 h after administration of a single 300-mg oral dose of aliskiren in Japanese subjects. Arrows indicate time course of measurements

dose of aliskiren showed that although plasma concentrations of aliskiren declined towards zero at the end of the dose interval, PRC remained elevated (Figure 5a). Inhibition of PRA was also clearly evident in Japanese subjects 24 h after dosing, despite low plasma concentrations of aliskiren (Figure 5b). Similar marked elevations in PRC and inhibition of PRA were observed in Caucasian subjects at all time points after administration of a single 300-mg oral dose of aliskiren (data not shown).

Safety and tolerability

A total of 46 AEs were reported by 21 individuals. There were no notable differences in the distribution of AEs between the two study groups (20 in Japanese subjects and 26 in Caucasian subjects). Five AEs were judged to be related to study drug: three reports of dizziness, one of orthostatic hypotension and one of headache. All reported AEs were mild to moderate in intensity, with the exception of one case of dizziness reported in a Caucasian subject; this event was judged as unlikely to be related to the study drug.

A single 300-mg oral dose of aliskiren led to an approximately 10-mmHg reduction from baseline in mean standing systolic blood pressure (SBP) and an

approximately 2-mmHg reduction in mean standing diastolic blood pressure (DBP) in Japanese and Caucasian subjects (Table 4). However, there were no notable reductions in SBP or DBP compared with baseline at steady state. Aliskiren had no effect on pulse rate in either Japanese or Caucasian subjects (Table 4).

Discussion

Aliskiren is a renin inhibitor that has been shown to provide BP reductions comparable to ARBs in patients with hypertension [14, 15]. As studies conducted with aliskiren have primarily included Caucasian patients, this study assessed whether any differences in pharmacokinetics and pharmacodynamics could be observed between Caucasian and Japanese populations. The results show that the pharmacokinetics of the orally effective renin inhibitor aliskiren in healthy male Japanese and Caucasian subjects were comparable. The pharmacodynamic effects of aliskiren in the two ethnic groups were also comparable.

Ethnic differences in the pharmacokinetics and pharmacodynamics of drugs exist but are difficult to predict, due to the large number of genetic and environmental factors that may influence drug disposition [16, 18]. In the present study, although C_{max} and AUC values following a single oral dose or at steady state were slightly higher in Japanese subjects compared with Caucasians, this may be due to the difference in body weights of the two groups. Thus, the mean body weight of the Japanese subjects in this study was approximately 12% lower than that of the Caucasian subjects and exposure to a given dose of drug is expected to be higher in a subject of lower body weight. However, a <20% difference in AUC is unlikely to be of clinical relevance. It is noteworthy that metabolism of aliskiren is minimal (Novartis, data on file), hence genetic differences in cytochrome P450 isoenzymes between ethnic groups would be unlikely to contribute to differences in the disposition of aliskiren.

Exposure to aliskiren at steady state was approximately twofold higher compared with that following administration of a single dose of the drug in both ethnic groups; this observation reflects that fact that the $t_{1/2}$ of aliskiren is longer than the 24-h dose interval of the drug. It is notable that all pharmacokinetic parameters were associated with a high degree of variability (33–67% in Japanese subjects and 21–59% in Caucasians), a finding that is in accordance with previous studies of the disposition of aliskiren following oral administration to healthy volunteers [12, 13].

The long $t_{1/2}$ of aliskiren observed in the present study (29.7 h and 32.0 h in Japanese and Caucasian subjects,

Table 4
Blood pressure and pulse rate measurements at trough after the administration of a single 300-mg oral dose of aliskiren and at steady state following once-daily dosing with aliskiren 300 mg for 7 days in Japanese and Caucasian subjects

	Baseline (day −1)			Single dose*			Steady state*		
Study group	SBP (mmHg)	DBP (mmHg)	Pulse rate (bpm)	SBP (mmHg)	DBP (mmHg)	Pulse rate (bpm)	SBP (mmHg)	DBP (mmHg)	Pulse rate (bpm)
Japanese (n = 19)	114.5 ± 10.3	74.6 ± 6.1	74.4 ± 10.5	102.4 ± 8.5	72.4 ± 9.2	77.3 ± 12.3	113.5 ± 9.8	74.6 ± 6.6	76.5 ± 11.2
Caucasian (n = 19)	122.3 ± 12.0	74.9 ± 8.1	76.6 ± 9.9	112.3 ± 14.3	71.8 ± 7.5	79.7 ± 8.8	119.4 ± 12.9	78.2 ± 19.1	75.7 ± 8.4

**Blood pressure and pulse rate were measured 24 h postdose. Data are presented as mean ± SD. bpm, Beats per minute; DBP, standing diastolic blood pressure; SBP, standing systolic blood pressure.* n = *18 for BP measurements in Caucasian subjects.*

respectively) is consistent with the results of earlier studies [12, 13]. A $t_{1/2}$ of >24 h is of considerable clinical significance, as it allows aliskiren to be administered once daily. Moreover, it is well established that sustained BP control throughout the 24-h dosing interval is required for effective protection against end organ damage and cardiovascular events in patients with hypertension [19]. It is therefore important to note that an ambulatory BP monitoring study by Stanton and colleagues has demonstrated that once-daily aliskiren treatment provides sustained BP-lowering effects throughout the 24-h dosing interval in patients with hypertension [14]. Moreover, it is well established that patient adherence to antihypertensive therapy is greater with once-daily dosing compared with more frequent dosing regimens [20, 21].

The rise in PRC observed following administration of aliskiren is a well-known indicator of RAAS inhibition [22] and is caused by disruption of the feedback loop by which Ang II normally inhibits the release of renin from the kidney [23]. Despite the reactive rise in PRC, aliskiren inhibited PRA for at least 24 h in Japanese and Caucasian subjects. These results demonstrate that aliskiren is a highly effective oral renin inhibitor and confirm previous findings that the reactive rise in PRC does not compromise the ability of aliskiren to suppress the activity of renin [12, 13]. The ability of aliskiren to inhibit PRA is likely to be of clinical relevance, as studies have shown that elevated levels of PRA are associated with end organ damage and an increased risk of myocardial infarction in patients with hypertension [6–8], probably due to the increase in Ang II levels associated with increased PRA.

The magnitude of the reactive rise in PRC and the degree of inhibition of PRA observed with aliskiren were similar in Japanese and Caucasian subjects. Notably, analysis of the pharmacokinetic–pharmacodynamic relationship showed that in both ethnic groups, PRC remained elevated and PRA inhibited 24 h after treatment with a single dose of aliskiren, even though plasma concentrations of aliskiren were low. These results indicate that a single dose of aliskiren provides effective RAAS suppression throughout the 24-h dosing interval. Compared with Caucasians, PRC and PRA levels were slightly higher in Japanese subjects at baseline and during treatment with aliskiren; however, the differences were small and the number of subjects in the study was insufficient to determine whether this finding is indicative of a true difference between the two ethnic groups.

Consistent with previously reported studies [12–15], single and multiple doses of aliskiren were well tolerated in the present study. Of the 46 reported AEs, only five were judged to be possibly related to the study drug; all of these were AEs that might be expected following administration of an antihypertensive drug to normotensive subjects (orthostatic hypotension, dizziness and headache). A single 300-mg oral dose of aliskiren markedly reduced mean standing SBP in Japanese and Caucasian subjects, but there was no significant change from baseline in BP at steady state. There were no notable differences in the effects of aliskiren on BP and pulse rate between Japanese and Caucasian subjects.

In conclusion, the results of the present study show that the pharmacokinetic and pharmacodynamic properties of the oral renin inhibitor aliskiren are similar in healthy Japanese and Caucasian subjects, and suggest that no dose adjustment of aliskiren is necessary in Japanese patients compared with Caucasian patients. Further studies to investigate the antihypertensive effects of aliskiren in Japanese patients with hypertension are ongoing.

Competing interests

All authors are employees of Novartis Pharmaceuticals and, as such, are eligible for Novartis stock and stock options.

This study was supported by Novartis Pharma AG.

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