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Lack of pharmacokinetic interactions of aliskiren, a novel direct renin inhibitor for the treatment of hypertension, with the antihypertensives amlodipine, valsartan, hydrochlorothiazide (HCTZ) and ramipril in healthy volunteers

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SUMMARY

Aliskiren is a novel, orally active direct renin inhibitor that lowers blood pressure alone and in combination with existing antihypertensive agents. As aliskiren does not affect cytochrome P450 enzyme activities, is minimally metabolised, and is not extensively protein bound, the potential for drug interactions is predicted to be low. Four open-label studies investigated the pharmacokinetic interactions between aliskiren 300 mg and the antihypertensive drugs amlodipine 10 mg ($n = 18$), valsartan 320 mg ($n = 18$), hydrochlorothiazide 25 mg (HCTZ, $n = 22$) and ramipril 10 mg ($n = 17$) in healthy subjects. In each study, subjects received multiple once-daily doses of aliskiren and the test antihypertensive drug alone or in combination in two dosing periods separated by a drug-free washout period. Plasma concentrations of drugs were determined by liquid chromatography and mass spectrometry methods. At steady state, relatively small changes in exposure to aliskiren were observed when aliskiren was co-administered with amlodipine (AUC_τ increased by 29%, $p = 0.032$), ramipril ($C_{max,ss}$ increased by 31%, $p = 0.043$), valsartan (AUC_τ decreased by 26%, $p = 0.002$) and HCTZ ($C_{max,ss}$ decreased by 22%, $p = 0.039$). Co-administration with aliskiren resulted in small changes in exposure to ramipril (AUC_τ increased by 22%, $p = 0.002$), valsartan (AUC_τ decreased by 14%, $p = 0.062$) and HCTZ (AUC_τ decreased by 10% and $C_{max,ss}$ by 26%, both $p < 0.001$). All other changes in pharmacokinetic parameters were also small, and not statistically significant. None of the observed pharmacokinetic changes was considered clinically relevant. Aliskiren inhibited plasma renin activity (PRA) and also prevented the reactive rise in PRA induced by valsartan. The most commonly reported adverse events were headache, dizziness and gastrointestinal symptoms (all mild in severity), which were similar in frequency during antihypertensive drug treatment alone and in combination with aliskiren except for an increase in dizziness during treatment with the combination of aliskiren and HCTZ. In conclusion, aliskiren shows no clinically relevant pharmacokinetic interactions and is generally well tolerated when administered in combination with amlodipine, valsartan, HCTZ or ramipril.

Keywords: Aliskiren; angiotensin receptor blocker; combination therapy; drug interaction; hypertension; renin-angiotensin system

INTRODUCTION

Hypertension is a major risk factor for cardiovascular disease, and affects nearly a quarter of the adult population worldwide (1). Despite the known risks associated with uncontrolled blood pressure (BP) and the availability of current antihypertensive agents, recent data from the World Health Organization MONICA project (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) show that in most countries fewer than one-third of patients with hypertension receive drug treatment, and less than half of those treated achieve adequate BP control (to <140/90 mmHg) (2). The majority of patients with hypertension require two or more agents from different drug classes to lower BP effectively (3,4). It is therefore important to determine whether potential novel antihypertensive drugs do not

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exhibit clinically significant pharmacokinetic interactions with existing drug classes that may increase the risk of side effects or require adjustment of doses.

Renin system inhibitors [e.g. angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)], diuretics and calcium channel blockers are widely used for the treatment of hypertension (4). However, ACE inhibitors, ARBs and diuretics all cause a reactive rise in plasma renin activity (PRA) that elevates levels of angiotensin II, the peptide hormone that mediates the effects of the renin system (5,6). Blockade of the renin system is not optimal with existing drug treatments, and so inhibiting the renin system at its point of activation by direct inhibition of renin has long been a therapeutic goal (7).

Aliskiren is the first in a new class of orally effective direct renin inhibitors for the treatment of hypertension. *In vitro*, aliskiren is a potent inhibitor of human renin ($IC_{50} = 0.6$ nmol/l) (8,9), while studies in patients with hypertension have shown that aliskiren provides highly effective suppression of PRA when administered alone (10) or in combination with hydrochlorothiazide (HCTZ) or the ACE inhibitor ramipril (11,12). Furthermore, once-daily treatment with aliskiren has demonstrated antihypertensive efficacy comparable to ramipril (13) and the ARBs losartan (14) and irbesartan (15).

The aim of the four open-label studies reported here was to determine in healthy subjects if there are any clinically relevant pharmacokinetic interactions between aliskiren and representative agents of four main classes of antihypertensive drugs with which aliskiren may be combined, namely the calcium channel blocker amlodipine, the ARB valsartan, the diuretic HCTZ and the ACE inhibitor ramipril. The safety and tolerability of co-administration of aliskiren with the four antihypertensive agents was also assessed. The potential for pharmacokinetic drug–drug interactions with aliskiren is predicted to be low for several reasons: (i) aliskiren is eliminated primarily unchanged via the hepatobiliary route following oral administration, with hepatic metabolism and renal excretion playing only a minor role in drug elimination; (ii) aliskiren does not inhibit the activity of cytochrome P450 (CYP450) isoenzymes (16); and (iii) aliskiren is not extensively protein bound (17).

METHODS

Study Designs

Aliskiren/amlodipine study

After a screening period of up to 21 days, subjects underwent a baseline evaluation on day −1, followed by two open-label treatment periods. In period 1, subjects received once-daily treatment with amlodipine 10 mg for 14 days, followed by a washout period of 7 days (Figure 1A). In period 2, subjects received once-daily oral doses of aliskiren 300 mg for 14 days, followed by aliskiren co-administered with amlodipine for 14 days. Subjects were discharged the morning after the first dose and returned to the clinic on a daily basis thereafter for drug administration. Subjects were admitted on the days when blood samples were collected for drug concentration measurements.

Aliskiren/valsartan study

After a screening period of up to 21 days, subjects underwent a baseline evaluation on day −1, followed by two open-label treatment periods. In period 1, subjects received once-daily treatment with valsartan 320 mg for 4 days, followed by a washout period of 3 days (Figure 1B). In period 2, subjects received once-daily aliskiren 300 mg for 7 days, followed by aliskiren co-administered with valsartan for 4 days. Subjects were admitted for the entire study.

Aliskiren/HCTZ study

After a screening period of up to 21 days, subjects underwent a baseline evaluation on day −1, followed by two treatment periods. In period 1, subjects received once-daily treatment with HCTZ 25 mg for 4 days, followed by a washout period of 4 days (Figure 1C). In period 2, subjects received once-daily aliskiren 300 mg for 7 days, followed by aliskiren co-administered with HCTZ for 4 days. Subjects were admitted for the entire study.

Aliskiren/ramipril study

After a screening period of up to 21 days, subjects underwent a baseline evaluation on day −1, followed by two treatment periods. In period 1, subjects received ramipril 2.5 mg once daily titrated to ramipril 10 mg once daily (Figure 1D). Period 1 was followed by a 4-day washout. In period 2, subjects received aliskiren 300 mg once daily for 7 days, followed by aliskiren 300 mg and ramipril 2.5 mg once daily titrated to aliskiren 300 mg and ramipril 10 mg once daily. Subjects visited the study centre on a daily basis and were admitted during co-administration of aliskiren and ramipril (last 6 days of period 2).

Objectives

The primary objective of these studies was to determine the effect of co-administration of aliskiren with amlodipine, valsartan, HCTZ or ramipril on the steady-state pharmacokinetics of each of the drugs in healthy subjects. In the aliskiren/ramipril study, the effects of aliskiren on the pharmacokinetics of ramiprilat (the active metabolite of ramipril)

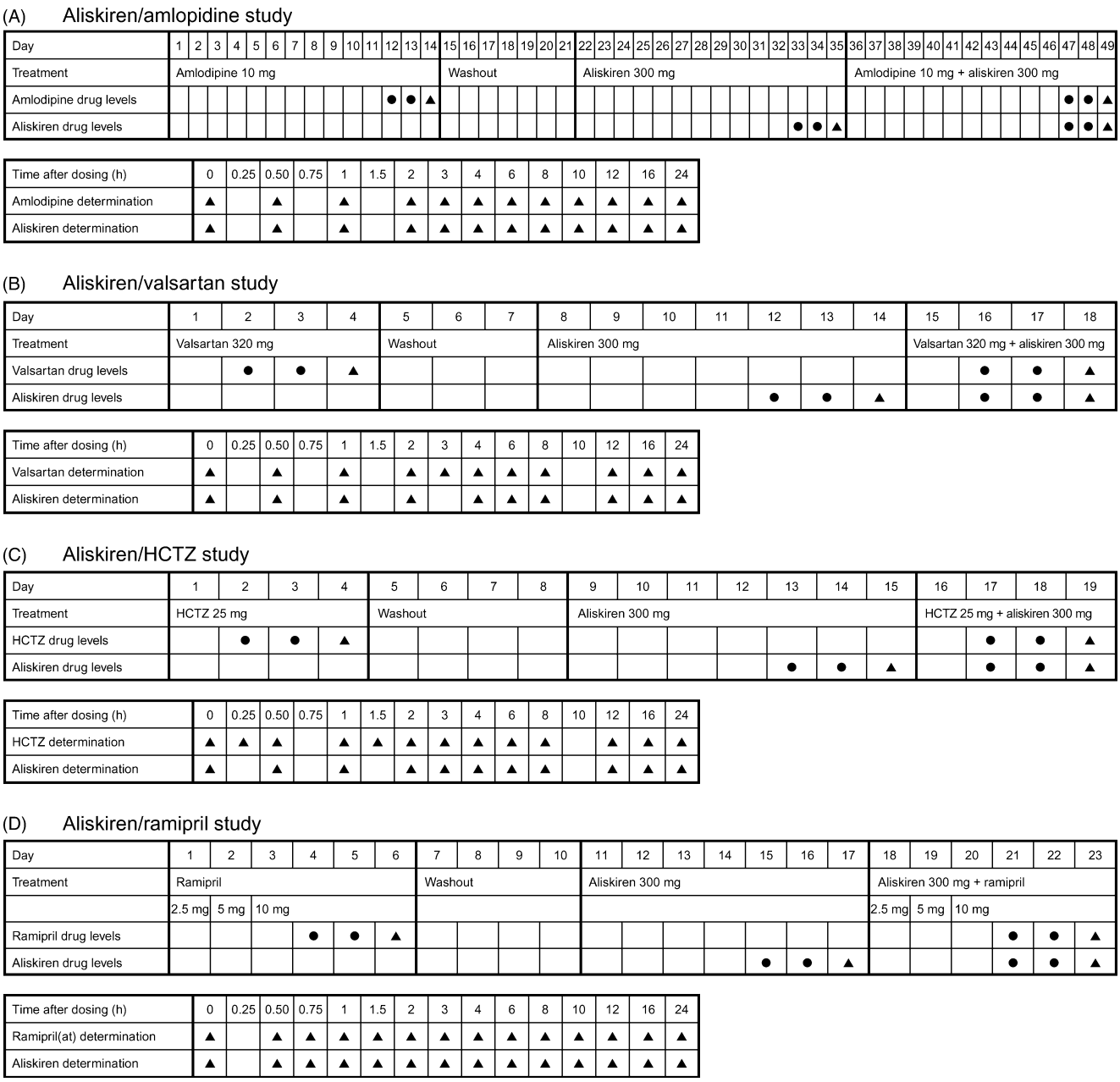

Figure 1 Study design and blood sampling schedules for studies investigating the interaction of aliskiren with (A) amlodipine, (B) valsartan, (C) hydrochlorothiazide and (D) ramipril. Filled circles indicate predose blood sample only; triangles indicate blood sampling throughout the 24-h postdose interval according to the schedules shown

were also determined. In the aliskiren/valsartan study, the pharmacodynamic effects on the renin system (PRA, renin concentration and aldosterone) were also evaluated. A secondary objective of the studies was to assess the safety and tolerability of co-administration of aliskiren with amlodipine, valsartan, HCTZ or ramipril. All studies used the highest anticipated daily dose of aliskiren (300 mg) for the treatment of hypertension. The highest daily doses of valsartan and amlodipine used in clinical practice (320 and 10 mg, respectively) (18,19) were employed. The 25 mg daily dose of HCTZ chosen is the standard dose given for the treatment of hypertension in adults, and the usual maximum dose used in combination with other antihypertensive agents (20). The 10 mg daily dose of ramipril is the usual maximum dose used for the treatment of hypertension (21), and the standard maintenance dose indicated for the reduction in risk of myocardial infarction, stroke and death from cardiovascular causes (22). All drugs were administered with 240 ml of water in the morning following an overnight fast of at least 10 h.

Study Population

All four studies enrolled male and female subjects ages 18–45 years in good health as determined by medical history,

physical examination, vital signs (oral body temperature 35.0–37.5 °C, supine systolic BP 90–140 mmHg, diastolic BP 50–90 mmHg and pulse rate 40–90 bpm with no evidence of postural hypotension), ECG, and laboratory tests. Subjects had a body weight within ±15% (HCTZ and ramipril studies) or ±20% (amlodipine and valsartan studies) of normal for their height and frame size according to the Metropolitan Life Insurance Tables.

Exclusion criteria for all four studies included smoking (use of tobacco product in the previous 3 months); use of any prescription drug or over-the-counter medication within 2 weeks prior to study drug administration (with the exception of acetaminophen); clinically significant ECG abnormalities or a family history of prolonged QT-interval syndrome; significant illness within 2 weeks prior to study drug administration; history of acute or chronic bronchospastic disease; history of clinically significant drug allergy or history of atopic allergy; a known hypersensitivity to the study drugs or drugs similar to the study drugs; and any condition that might significantly alter the absorption, distribution, metabolism or excretion of study drugs.

Subjects were not permitted to take part in any strenuous physical exercise for 7 days before dosing until after the study completion evaluation, or to take alcohol for 72 h before dosing until after the study completion evaluation. Intake of xanthine-containing food or beverages was discontinued 48 h before dosing and was not permitted at any time while the subjects were admitted.

All subjects provided written informed consent prior to study participation, and all four studies were performed in accordance with Good Clinical Practice and adhered to the principles of the Declaration of Helsinki of the World Medical Association.

Pharmacokinetic Assessments

In each study, blood samples for analysis of drug concentrations were collected pre-dose on the final 3 days of each treatment period, and at frequent intervals for up to 24-h post-dose on the final day of each treatment period (Figure 1A–D). In each study, inspection of mean trough plasma concentrations of each drug indicated that steady-state conditions had been reached at the time at which pharmacokinetic parameters were assessed (data not shown).

All blood samples were taken either by direct venipuncture or by an indwelling cannula inserted in a forearm. Samples were collected into heparinised tubes and plasma was extracted by centrifugation at 2500 rpm between 3 °C and 5 °C for 15 min. Plasma samples were then frozen at ≤−70 °C (aliskiren/ramipril study), or ≤−20 °C (aliskiren/amlodipine study, aliskiren/HCTZ study) until analyses were performed. In the aliskiren/valsartan study, plasma samples were stored at ≤−70 °C for assessment of aliskiren concentrations and −20 °C for assessment of valsartan plasma concentrations until analyses were performed.

Plasma concentrations of aliskiren were determined by an LC/MS/MS assay, consisting of a solid phase extraction on Oasis® MCX cartridges (Waters Corp., Milford, MA, USA) using an automated system followed by reversed-phase HPLC on a Metachem MetaSil™ (Varian Inc., Palo Alto, CA, USA) basic column using gradient elution with 10 mM aqueous ammonium acetate/acetonitrile. Detection was performed in MS/MS by using electro spray ionisation. The lower limit of quantification was 0.5 ng/ml.

Determination of plasma concentrations of amlodipine, HCTZ and ramipril were performed by CEPHAC (St Benoît, France) according to validated methods. Briefly, plasma concentrations of amlodipine were determined by an LC/MS/MS method, consisting of a solid-phase extraction on Oasis® MCX plates (Waters Corp.) followed by reversed-phase liquid chromatography (with isocratic separation using a mobile phase of 0.01 mol/l ammonium acetate containing 0.08% acetic acid–methanol 40 : 60 v/v). The lower limit of quantification was 0.5 ng/ml.

Plasma concentrations of HCTZ and ramipril were determined by solid-phase extraction on Oasis® HLB 96-well plate (Waters Corp.) followed by reversed-phase liquid chromatography with tandem mass spectrometric detection. Separation during HPLC was by isocratic elution with methanol–water (30 : 70 v/v) for HCTZ and by gradient elution with methanol–water (75 : 25 v/v) with 0.025% formic acid for ramipril and ramiprilat. The lower limit of quantification was 2 ng/ml for HCTZ and 0.1 ng/ml for ramipril and ramiprilat.

Plasma concentrations of valsartan were determined at Novartis Pharma SAS (Rueil-Malmaison, France) by using an automated 96-well solid-phase extraction procedure followed by analysis by liquid chromatography (isocratic elution with methanol–acetonitrile–TFA 0.1%, 35 : 20 : 45 v/v/v) with tandem mass spectrometry (HPLC/MS/MS) in turbo ion spray (TIS) positive ion mode. The lower limit of quantification was 20 ng/ml.

Pharmacodynamic Effects on the Renin System

In the aliskiren/valsartan study, pharmacodynamic effects on the renin system were evaluated. Blood samples were collected for measurement of PRA and plasma renin and aldosterone concentrations on days 4 (valsartan alone), 14 (aliskiren alone) and 18 (aliskiren/valsartan co-administration). All blood samples were taken either by direct venipuncture or by an indwelling cannula inserted in a forearm after the subjects had been in the supine position for at least 20 min. Samples (5 ml per time point) were collected into EDTA

tubes and plasma was extracted by centrifugation at 2500 ***g*** at room temperature (25 °C) for 10 min. Plasma samples were then frozen at ≤−20 °C until analyses were performed. Samples were sent to CRL Medinet Inc. (Lenexa, KS, USA) for analysis. PRA was determined by using a radioimmunoassay of generated angiotensin I (DiaSorin, Stillwater, MN, USA). Plasma renin and aldosterone concentrations were measured by using immunochemiluminescence assay kits (Nichols Institute Diagnostics, San Clemente, CA, USA).

Safety and Tolerability Assessments

Safety and tolerability assessments included the regular monitoring and recording of all adverse events (AEs) and concomitant medications or significant non-drug therapies. Evaluations of routine blood chemistries, blood counts with white cell differential, and urine analyses, as well as a physical examination, ECGs and monitoring of vital signs, were performed at regular intervals in each study.

Statistical Analyses

Pharmacokinetic parameters at steady state (AUC_τ; $C_{max,ss}$; C_{min}; $t_{max,ss}$; and CL/F) were determined by non-compartmental methods by using WINNONLIN PRO (Version 4.1, Pharsight Corp., Mountain View, CA, USA). In sample size estimation, the intra-subject coefficient of variation for aliskiren AUC and C_{max} was assumed to be between 0.50 and 0.70. In all four studies, a sample size of 18 completed subjects therefore provided 80% power that the 90% CI for the ratio of aliskiren pharmacokinetic parameters (for co-administration compared with aliskiren alone) would have an upper CI within 80% and a lower CI within 44% of the true mean ratio.

Log-transformed pharmacokinetic parameters (AUC_τ and $C_{max,ss}$) were analysed by a linear mixed effect model with treatment as a fixed factor and subject as a random factor. The resulting 90% CI for the ratio of means (co-administration vs. administration alone) was used to examine potential drug–drug interactions.

In the aliskiren/valsartan study, peak plasma levels and the area under the concentration–time curve were determined for renin concentrations, and summary statistics were calculated for PRA values at each timepoint. Comparisons between treatments were made by using the non-parametric Wilcoxon signed-rank test; a p-value of <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 87 healthy male and female subjects ages 18–45 years were enrolled in the four studies (aliskiren/amlodipine $n = 25$; aliskiren/valsartan $n = 19$; aliskiren/HCTZ $n = 22$; aliskiren/ramipril $n = 21$), of whom 75 completed the studies (aliskiren/amlodipine $n = 18$; aliskiren/valsartan $n = 18$; aliskiren/HCTZ $n = 22$; aliskiren/ramipril $n = 17$). Reasons for discontinuation were protocol violations (four subjects in the amlodipine study and one subject in the ramipril study), withdrawal of consent (three subjects in the ramipril study, two subjects in the amlodipine study and one subject in the valsartan study) and loss to follow-up (one subject in the amlodipine study). All available pharmacokinetic data were included in the analyses.

Baseline characteristics for healthy subjects across the four studies are shown in Table 1. The four studies were well balanced with respect to age, body weight, height and gender. Race was predominantly Caucasian in the HCTZ and ramipril studies (50.0% and 61.9%) and 'other' (neither Caucasian, Black nor Oriental) in the amlodipine and valsartan studies (92.0% and 57.9%, respectively).

Table 1 Subject baseline and demographic characteristics

Characteristic	*Aliskiren/amlodipine study ($n = 25$)*	*Aliskiren/valsartan study ($n = 19$)*	*Aliskiren/HCTZ study ($n = 22$)*	*Aliskiren/ramipril study ($n = 21$)*
Age, years,	33.7 ± 8.2	31.7 ± 9.3	28.1 ± 6.8	26.6 ± 7.0
Gender, male/female	10/15	14/5	9/13	14/7
Race, *n*, **(%)**				
Caucasian	1 (4%)	6 (31.6%)	11 (50.0%)	13 (61.9%)
Black	1 (4%)	2 (10.5%)	2 (9.1%)	0 (0.0%)
*Other	23 (92%)	11 (57.9%)	9 (40.9%)	8 (38.1%)
Body weight, kg	69.6 ± 9.2	74.9 ± 9.2	68.7 ± 11.0	71.2 ± 9.8
Height, cm	162 ± 8	172 ± 8	172 ± 11	173 ± 7
BMI, kg/m^2	26.4 ± 2.7	25.4 ± 2.8	23.1 ± 2.5	23.8 ± 2.7

Data are presented as mean ± SD unless otherwise stated. BMI, body mass index; HCTZ, hydrochlorothiazide.
*'Other' refers to all subjects who were neither Caucasian, Black nor Oriental.

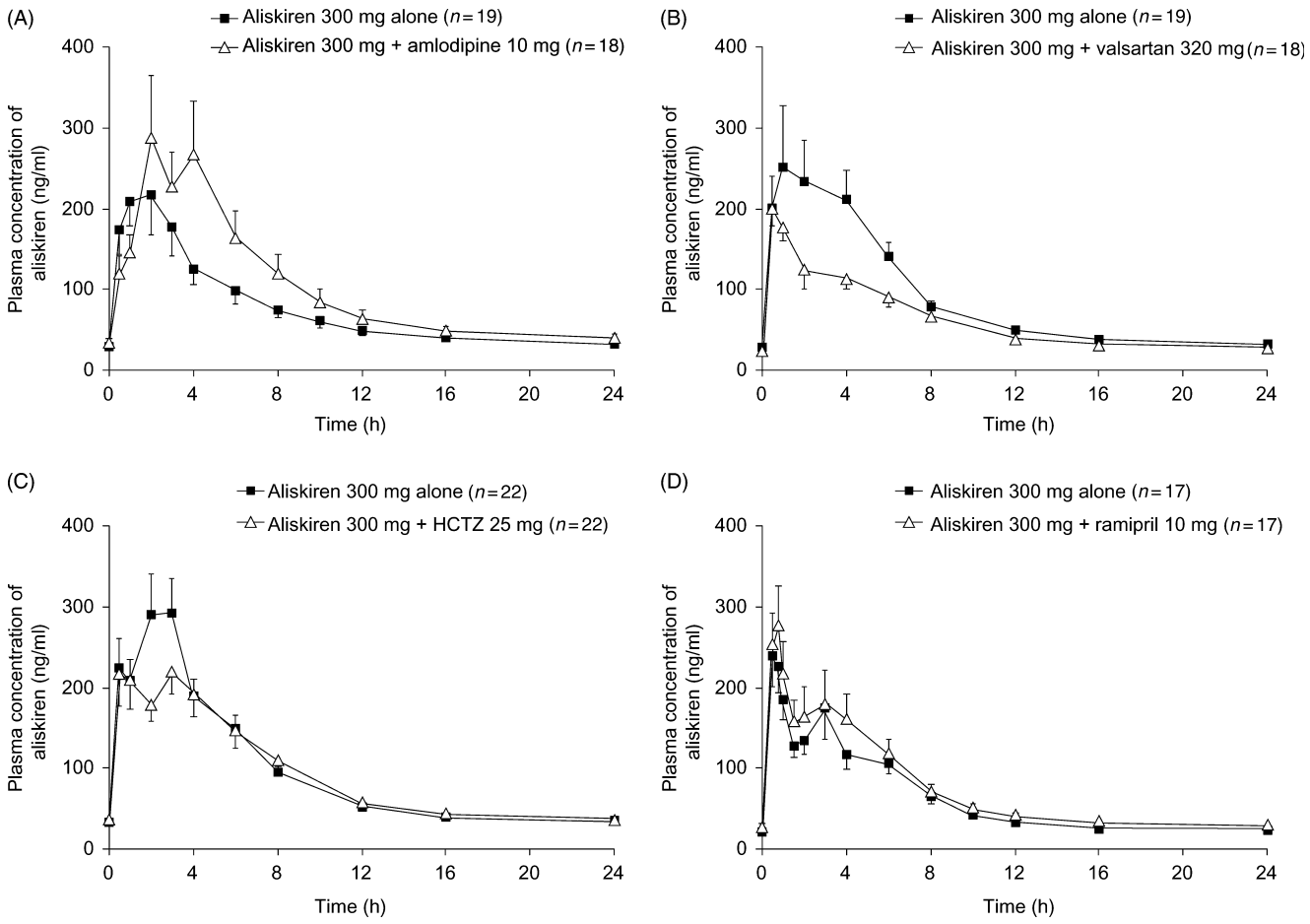

Figure 2 Plasma concentration–time profiles for aliskiren following once-daily administration of aliskiren alone or in combination with (A) amlodipine, (B) valsartan, (C) hydrochlorothiazide (HCTZ) or (D) ramipril in healthy subjects. Figure shows plasma concentrations of aliskiren at steady state. Data are presented as mean ± SEM

Pharmacokinetic Analyses

Aliskiren/amlodipine study

Co-administration of aliskiren with amlodipine increased aliskiren AUC_τ by 29% [geometric mean ratio 1.29 (90% CI 1.07, 1.55); p = 0.032], with no significant change in aliskiren $C_{max,ss}$ [geometric mean ratio 1.18 (0.83, 1.69); p = 0.426; Figure 2A, Table 2]. Median $t_{max,ss}$ was increased from 1.0 h (aliskiren alone) to 3.0 h (co-administration of aliskiren/amlodipine), indicating a slower rate of absorption (Table 2).

Co-administration of aliskiren with amlodipine had no significant effect on amlodipine AUC_τ [geometric mean ratio 0.98 (90% CI 0.92, 1.05); p = 0.610], $C_{max,ss}$ [geometric mean ratio 0.98 (0.93, 1.05); p = 0.669] or median $t_{max,ss}$ (Figure 3A; Table 3).

Aliskiren/valsartan study

Co-administration of aliskiren with valsartan decreased aliskiren AUC_τ by 26% [geometric mean ratio 0.74 (0.63, 0.85); p = 0.002] and $C_{max,ss}$ by 28% [geometric mean ratio 0.72 (0.52, 0.99); p = 0.090; Figure 2B, Table 2] with no effect on median $t_{max,ss}$ (Table 2).

Co-administration of aliskiren with valsartan slightly decreased valsartan AUC_τ by 14% [geometric mean ratio 0.86 (0.75, 0.98); p = 0.062] and $C_{max,ss}$ by 12% [geometric mean ratio 0.88 (0.74, 1.04); p = 0.210], with no change in median $t_{max,ss}$ (Figure 3B; Table 3).

Aliskiren/HCTZ study

Co-administration of aliskiren with HCTZ decreased aliskiren $C_{max,ss}$ by 22% [geometric mean ratio 0.78 (0.64, 0.95); p = 0.039] with no change in AUC_τ [geometric mean ratio 0.93 (0.83, 1.05); p = 0.315; Figure 2C, Table 2] or median $t_{max,ss}$ (Table 2).

Co-administration of aliskiren with HCTZ decreased HCTZ AUC_τ by 10% [geometric mean ratio; 0.90 (0.87, 0.93); p < 0.001] and $C_{max,ss}$ by 26% [geometric mean ratio 0.74 (0.69, 0.79); p < 0.001; Figure 3C, Table 3] with no change in median $t_{max,ss}$ (Table 3).

Table 2 Pharmacokinetic parameters for aliskiren administered alone and in combination with amlodipine, valsartan, hydrochlorothiazide (HCTZ) or ramipril

	Aliskiren/amlodipine study		*Aliskiren/valsartan study*		*Aliskiren/HCTZ study*		*Aliskiren/ramipril study*	
Parameter	*Aliskiren alone* ($n = 19$)	*Aliskiren + amlodipine* ($n = 18$)	*Aliskiren alone* ($n = 19$)	*Aliskiren + valsartan* ($n = 18$)	*Aliskiren alone* ($n = 22$)	*Aliskiren + HCTZ* ($n = 22$)	*Aliskiren alone* ($n = 17$)	*Aliskiren + rampril* ($n = 17$)
$C_{max,ss}$, ng/ml	336 ± 179	448 ± 318	420 ± 328	249 ± 96	425 ± 216	309 ± 150	296 ± 167	382 ± 187
$t_{max,ss}$, h	1.0 (0.5–4.0)	3.0 (0.5–8.0)	2.0 (0.5–6.0)	1.0 (0.5–6.0)	2.2 (0.5–6.0)	1.5 (0.5–4.4)	0.5 (0.5–6.0)	0.85 (0.5–6.0)
AUC_τ, ng/h/ml	1809 ± 827	2470 ± 1425	2107 ± 867	1502 ± 425	2310 ± 934	2210 ± 1157	1522 ± 613	1774 ± 864
$C_{min,ss}$, ng/ml	27.2 ± 14.2	33.6 ± 17.8	27 ± 11	24 ± 9	35.0 ± 12.7	41.2 ± 19.5	20.1 ± 7.6	25.5 ± 10.8
CL/F, mL/h	$2.1 \times 10^5 \pm 1.0 \times 10^5$	$1.6 \times 10^5 \pm 8.5 \times 10^4$	$1.7 \times 10^5 \pm 7.6 \times 10^4$	$2.2 \times 10^5 \pm 7.3 \times 10^4$	ND	ND	ND	ND

Data are shown as mean ± SD except for $t_{max,ss}$ values, which are presented as median (minimum–maximum).
HCTZ, hydrochlorothiazide; ND, not determined.

Aliskiren/ramipril study

Co-administration of aliskiren with ramipril increased aliskiren $C_{max,ss}$ by 31% [geometric mean ratio 1.31 (1.06, 1.62), $p = 0.043$] and AUC_τ by 12% [geometric mean ratio 1.12 (0.98, 1.28), $p = 0.169$; Figure 2D, Table 2] with no change in median $t_{max,ss}$ (Table 2).

Co-administration of aliskiren with ramipril increased ramipril AUC_τ by 22% [geometric mean ratio 1.22 (1.11, 1.34), $p = 0.002$] with no change in $C_{max,ss}$ or median $t_{max,ss}$ (Figure 3D; Table 3). $C_{max,ss}$ for ramiprilat was decreased by 15% [geometric mean ratio 0.85 (0.76, 0.95), $p = 0.02$] with no change in AUC_τ [geometric mean ratio 1.00 (0.95, 1.07), $p = 0.892$].

Pharmacodynamic Analyses

Plasma renin activity

Normal values for PRA in healthy subjects on a normal sodium diet (150 mmol sodium/day) are <7 ng/ml/h. During treatment with aliskiren alone at steady state, PRA (mean ± SD) averaged 0.4 ± 0.5 ng/ml/h immediately before dosing and was reduced by 58% ($p < 0.001$) 2 h after dosing. In contrast to the low values of PRA observed with aliskiren, during administration of valsartan alone, PRA averaged 12.7 ± 5.6 ng/ml/h immediately before dosing ($p < 0.001$ vs. aliskiren pre-dose PRA) and was increased by 166% 6 h after dosing (Figure 4A).

PRA measured immediately before dosing with co-administration of aliskiren/valsartan averaged 3.5 ± 4.8 ng/ml/h, and was decreased by 74% from baseline by aliskiren/valsartan. PRA was significantly suppressed relative to values observed following the administration of valsartan alone ($p < 0.05$) for 12 h after dosing (Figure 4A).

Plasma renin concentration

The normal range for plasma renin concentration in healthy subjects is 2.4–29 mU/l on a normal sodium diet. During treatment with aliskiren or valsartan alone at steady state, plasma renin concentration (mean ± SD) immediately before dosing was elevated (327 ± 247 mU/l and 332 ± 560 mU/l, respectively) and was increased further following the administration of aliskiren or valsartan (Figure 4B).

The peak renin concentration observed with the aliskiren/valsartan combination was significantly greater than that achieved with either drug administered alone ($p < 0.001$ vs. aliskiren or valsartan alone; Figure 4B). The area under the renin concentration–time curve for aliskiren/valsartan co-administration was 54,594 ± 36,669 mU/h/l, which was larger than that observed following the administration of

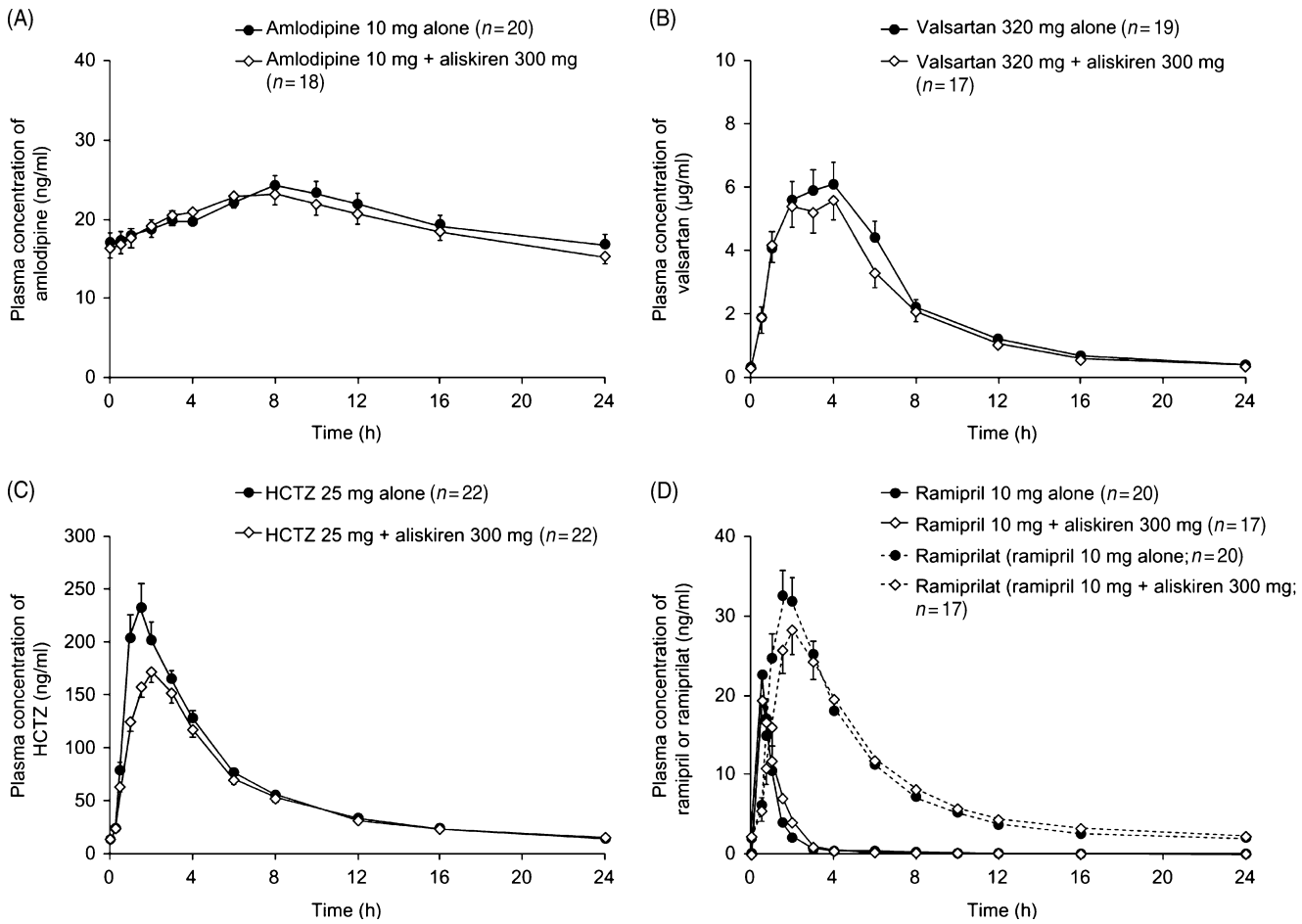

Figure 3 Plasma concentration–time profiles for (A) amlodipine, (B) valsartan, (C) hydrochlorothiazide (HCTZ) and (D) ramipril and ramiprilat, following once-daily administration alone or in combination with aliskiren in healthy subjects. Figure shows plasma concentrations at steady state. Data are presented as mean ± SEM

either aliskiren (14,247 ± 12,292 mU/h/l, $p < 0.001$) or valsartan (17,241 ± 23,913 mU/h/l, $p < 0.001$) alone, and also larger ($p < 0.01$) than the sum of the areas under the curve for aliskiren and valsartan administered alone.

Plasma aldosterone

The normal range for plasma aldosterone levels in healthy subjects is 2–14 ng/dl on a normal sodium diet. During treatment with either valsartan or aliskiren at steady state, aldosterone concentrations tended to decrease for up to 12 h after dosing (Figure 4C). Co-administration of aliskiren/valsartan led to slightly greater reductions in plasma aldosterone compared with either drug administered alone, but differences between treatments were small.

Safety and Tolerability

Aliskiren 300 mg once daily was generally well tolerated when administered alone or in combination with amlodipine 10 mg, valsartan 320 mg, HCTZ 25 mg or ramipril 10 mg once daily, with the exception of an increase in dizziness with aliskiren/HCTZ as described below. All AEs were mild to moderate in severity with the exception of one severe AE in the aliskiren/ramipril study (a case of menstrual cramps that was not suspected to be related to study drugs). There were no discontinuations because of AEs in any of the four studies. The majority of patients had at least one laboratory value or vital sign measurement outside the normal range in each of the four studies, but no trends were noted (with the exception of the aliskiren/HCTZ combination as noted below). As expected, most subjects experienced small decreases in BP during treatment with the antihypertensive drugs. One subject in the aliskiren/amlodipine study exhibited a clinically significant increase in creatine kinase from a value at screening of 198 U/l (normal range: 45–235 U/l) to 3820 U/l on study day 1, before administration of the first dose of amlodipine. On day 2, creatine kinase had decreased to 1647 U/l, but remained significantly above the normal range. This subject indicated that he had exercised while participating in the study and was therefore discontinued for a protocol viol-

Table 3 Pharmacokinetic parameters for amlodipine, valsartan, hydrochlorothiazide (HCTZ) and ramipril administered alone and in combination with aliskiren

	Aliskiren/amlodipine study		*Aliskiren/valsartan study*		*Aliskiren/HCTZ study*		*Aliskiren/ramipril study*	
Parameter	*Amlodipine alone* ($n = 20$)	*Aliskiren + amlodipine* ($n = 18$)	*Valsartan alone* ($n = 19$)	*Aliskiren + valsartan* ($n = 17$)	*HCTZ alone* ($n = 22$)	*Aliskiren + HCTZ* ($n = 22$)	*Ramipril alone* ($n = 20$)	*Aliskiren + ramipril* ($n = 17$)
$C_{max,ss}$, ng/ml	24.5 ± 6.0	24.0 ± 6.2	7.0 ± 2.8	6.4 ± 2.7	260 ± 86	187 ± 43	23.9 ± 9.9	22.6 ± 9.7
$t_{max,ss}$, h	8.0 (6.0–10.0)	8.0 (6.0–12.0)	3.0 (1.0–6.0)	3.0 (2.0–4.0)	1.50 (1.0–4.0)	2.0 (1.0–3.4)	0.5 (0.5–1.0)	0.5 (0.5–1.5)
AUC_{τ}, ng/h/ml	480 ± 128	466 ± 120	51 ± 21	46 ± 23	1411 ± 316	1273 ± 297	21.2 ± 9.7	25.8 ± 9.6
$C_{min,ss}$, ng/ml	15.7 ± 5.1	14.9 ± 4.2	0.3 ± 0.2	0.3 ± 0.2	15.0 ± 6.1	20.0 ± 7.1	0.0 ± 0.0	0.01 ± 0.03
CL/F, mL/h	22,547 ± 7508	22,947 ± 6572	$7.5 \times 10^6 \pm 3.2 \times 10^6$	$8.4 \times 10^6 \pm 3.4 \times 10^6$	ND	ND	ND	ND

Data are shown as mean ± SD except for $t_{max,ss}$ values, which are presented as median (minimum–maximum).
HCTZ, hydrochlorothiazide; ND, not determined.

ation. There were no clinically significant ECG abnormalities in any of the four studies.

The most frequently observed AEs were headache or dizziness, which were mild in severity, and nausea, diarrhoea or vomiting. There were no notable differences in either the incidence or type of AEs observed during co-administration of aliskiren with other antihypertensive agents compared with administration of these agents alone (Table 4) with the exception of HCTZ. There was a higher overall incidence of AEs during aliskiren/HCTZ co-administration compared with either drug administered alone (14 subjects reporting AEs vs. eight each for aliskiren or HCTZ alone). This was due to an increased incidence of dizziness, which was reported by eight subjects receiving aliskiren/HCTZ compared with two subjects during the administration of aliskiren or HCTZ alone. Of the eight subjects who experienced dizziness with aliskiren/HCTZ co-administration, seven exhibited numerically lower average supine SBP values (maximum supine SBP decreases 5–20 mmHg), and five of the eight subjects had higher pulse rates (maximum pulse rate increases 7–19 bpm) compared with treatment with either drug alone.

DISCUSSION

More than two-thirds of patients with hypertension require treatment with two or more antihypertensive drugs from different classes to optimally lower BP towards the target values (3,4). It is therefore of clinical importance that individual antihypertensive drugs do not exhibit large pharmacokinetic interactions that may decrease efficacy or increase drug-related side effects. Aliskiren, a direct renin inhibitor, promises to be a useful adjunct to existing antihypertensive treatments as it possesses a novel, complementary mode of action to lower BP, and a pharmacological profile that would predict a low rate of drug–drug interactions.

Aliskiren targets the renin system at its point of activation by binding to the catalytic site of renin (8), inhibiting PRA and preventing generation of angiotensin I, and thus suppressing the entire renin system. Whereas ACE inhibitors, ARBs and diuretics all cause a reactive rise in renin and PRA (5,6), aliskiren reduces PRA when used as monotherapy and in combination with these drug classes (11,12,23). The main conclusion from this study is that aliskiren shows no major pharmacokinetic interactions with other commonly used classes of antihypertensive drugs, and is well tolerated when co-administered with them in healthy subjects.

Some of the 90% CI of the geometric mean ratios for AUC_{τ} or $C_{max,ss}$ for the test antihypertensive agents during co-administration with aliskiren fell outside the range: 0.8–1.25, which is generally considered the criterion for lack of interaction. In several instances, the 90% CI spanned unity, given the relatively small sample sizes and high intra-subject

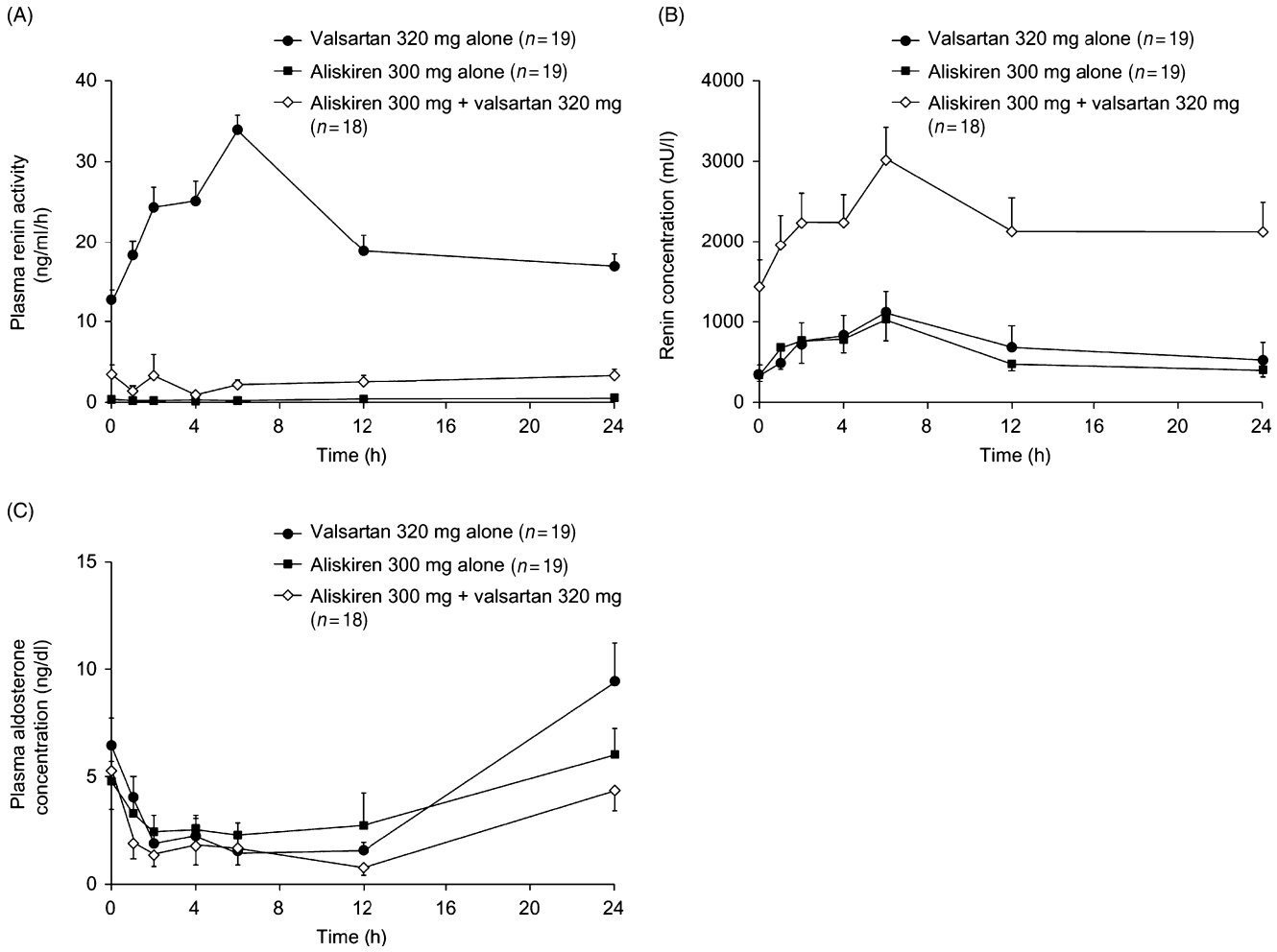

Figure 4 Effect of aliskiren and valsartan alone or in combination on (A) plasma renin activity, (B) renin concentration and (C) plasma aldosterone in healthy subjects. Figure shows mean plasma concentrations at steady state after once-daily administration of aliskiren 300 mg (6-day treatment) or valsartan 320 mg alone (3-day treatment) or co-administration of aliskiren/valsartan (3-day treatment). Data are presented as mean ± SEM

variability, one cannot conclude that true differences exist in such cases. In all instances where the 90% CI did not span unity, the absolute magnitude of the change was relatively small and the differences were not considered to be clinically relevant. Thus, the decreases in AUC_{τ} and $C_{max,ss}$ for valsartan (by 14% and 12%, respectively) are small and unlikely to alter the therapeutic effect of valsartan because the dose–response curve for valsartan is relatively shallow (24) (as is the case for all renin system inhibitors, including aliskiren). Similarly, one would not expect the observed 22% increase in the AUC_{τ} of ramipril to impact on the therapeutic effect. Moreover, the safety and tolerability of ramipril are unlikely to be altered by this small increase in exposure, because although 10 mg/day is the usual maximum maintenance dosage for ramipril for the treatment of hypertension, the drug is well tolerated at dosages of up to 20 mg/day (21). Co-administration of aliskiren also had no significant effect on the pharmacokinetics of ramiprilat (the active metabolite of ramipril), indicating that aliskiren does not alter the metabolism of ramipril. Finally, the 26% decrease in the $C_{max,ss}$ of HCTZ observed during co-administration with aliskiren does not have a negative impact on the pharmacodynamic effects of the aliskiren/HCTZ combination, as a study in patients with mild-to-moderate hypertension has shown that aliskiren/HCTZ combinations provided additive reductions in BP superior to those achieved with either drug administered alone (25).

Slight decreases in the AUC_{τ} and $C_{max,ss}$ for aliskiren were observed during co-administration with HCTZ and valsartan, whereas concomitant therapy with ramipril and amlodipine led to small increases in exposure to aliskiren. The changes in AUC_{τ} and $C_{max,ss}$ observed for aliskiren when administered with the other antihypertensive agents are unlikely to lead to clinically relevant changes in the efficacy of aliskiren, as aliskiren exhibits a shallow dose–response curve for BP lowering with a plateau beyond the 300 mg daily dose (10,15). Aliskiren exhibits a safety profile comparable with that of placebo at once-daily doses of up

Table 4 Safety and tolerability of study treatments

	Aliskiren/amlodipine study			*Aliskiren/valsartan study*			*Aliskiren/HCTZ study*			*Aliskiren/ramipril study*		
	Aliskiren (*n* = 19)	*Amlodipine* (*n* = 25)	*Aliskiren + amlodipine* (*n* = 19)	*Aliskiren* (*n* = 19)	*Valsartan* (*n* = 19)	*Aliskiren + valsartan* (*n* = 18)	*Aliskiren* (*n* = 22)	*HCTZ* (*n* = 22)	*Aliskiren + HCTZ* (*n* = 22)	*Aliskiren* (*n* = 19)	**Ramipril* (*n* = 21)	**Aliskiren + ramipril* (*n* = 17)
Any AE	5 (26.3)	9 (36.0)	3 (15.8)	10 (52.6)	13 (68.4)	10 (55.6)	8 (36.4)	8 (36.4)	14 (63.6)	7 (36.8)	12 (57.1)	9 (52.9)
Discontinuations because of AEs	0	0	0	0	0	0	0	0	0	0	0	0
AEs by body system												
Gastrointestinal	0	1 (4.0)	1 (5.3)	5 (26.3)	6 (31.6)	4 (22.2)	4 (18.2)	3 (13.6)	5 (22.7)	2 (10.5)	3 (14.3)	3 (17.6)
†General/admin. site	1 (5.3)	0	1 (5.3)	2 (10.5)	5 (26.3)	2 (11.1)	0	2 (9.1)	4 (18.2)	0	1 (4.8)	1 (5.9)
Infections	0	0	0	1 (5.3)	0	0	1 (4.5)	1 (4.5)	3 (13.6)	0	0	2 (11.8)
Metabolism/nutrition	0	0	0	1 (5.3)	1 (5.3)	4 (22.2)	0	0	1 (4.5)	0	0	0
Nervous system	3 (15.8)	6 (24.0)	1 (5.3)	2 (10.5)	5 (26.3)	3 (16.7)	4 (18.2)	7 (31.8)	9 (40.9)	5 (26.3)	8 (38.1)	5 (29.4)
Respiratory	0	0	1 (5.3)	0	4 (21.1)	0	0	0	1 (4.5)	1 (5.3)	3 (14.3)	1 (5.9)
Skin/subcutaneous	0	0	1 (5.3)	2 (10.5)	2 (10.5)	0	0	0	0	0	0	0
AEs by preferred term												
Headache	3 (15.8)	6 (24.9)	1 (5.3)	1 (5.3)	4 (21.1)	0	2 (9.1)	5 (22.7)	1 (4.5)	1 (5.3)	6 (28.6)	2 (11.8)
Dizziness	0	0	0	1 (5.3)	0	2 (11.1)	1 (4.5)	2 (9.1)	8 (36.4)	3 (15.8)	3 (14.3)	1 (5.9)
Nausea	0	0	0	2 (10.5)	1 (5.3)	0	1 (4.5)	2 (9.1)	3 (13.6)	0	0	1 (5.9)
Diarrhoea	0	1 (4.0)	0	3 (15.8)	2 (10.5)	2 (11.1)	0	0	0	0	0	0
Vomiting	0	0	1 (5.3)	2 (10.5)	0	1 (5.6)	0	2 (9.1)	0	0	2 (9.5)	0
Fatigue	0	0	0	2 (10.5)	1 (5.3)	0	0	1 (4.5)	2 (9.1)	0	0	0

Table shows all body system classes (MedDRA classification) for which AEs were reported by more than one subject in more than one treatment period, and the most frequently reported individual AEs across the four studies. Values are presented as the number (%) of patients reporting at least one AE in the respective category. Subjects with multiple occurrences of the same AE are counted only once in the respective AE category. AE, adverse event; HCTZ, hydrochlorothiazide.

*Ramipril and aliskiren + ramipril groups include combined AEs for ramipril 2.5, 5 and 10 mg. †General disorders and administration site conditions.

to 300 mg (10,15), and so small increases in exposure to aliskiren when co-administered with other antihypertensives would not be expected to affect the safety or tolerability of aliskiren. It should be noted that the 600 mg daily dose of aliskiren is associated with an increase in the incidence of diarrhoea (10). However, as aliskiren exhibits linear pharmacokinetics up to 600 mg (26), the small increase in exposure to aliskiren observed following the administration of a 300-mg dose in combination with amlodipine or ramipril (aliskiren AUC_{τ} increased by 29% and 12%, respectively) would be well below the exposure achieved at a dose of 600 mg. Indeed, the present study provided no evidence for an increased rate of diarrhoea with combinations of aliskiren/amlodipine or aliskiren/ramipril compared with each drug administered alone. We conclude that aliskiren shows no clinically significant drug–drug interactions with amlodipine, valsartan, HCTZ or ramipril. Modification of the initial dosage of aliskiren is therefore not needed when aliskiren is administered in combination with these other major classes of antihypertensive agent.

The observed lack of clinically significant pharmacokinetic interactions between aliskiren and other antihypertensive drugs is consistent with data demonstrating that aliskiren is eliminated primarily unchanged in the faeces, with hepatic metabolism and renal excretion playing only a minor role (Novartis, data on file). Aliskiren does not inhibit the activity of CYP450 isoenzymes (16), and renal clearance accounts for only 7.5% of total clearance. In addition, plasma protein binding of aliskiren is only 47–51% and concentration-independent. Therefore, the free concentration of aliskiren is unlikely to be affected by changes in protein concentrations and drug–drug interactions based on the changes in protein binding are unlikely. The predominant racial background of subjects varied across the individual studies reported in this paper. Although differences in the disposition of aliskiren among ethnic subgroups have not been identified to date, caution should nevertheless be exercised in extrapolating the results to specific ethnic subpopulations.

Patients with hypertension frequently have concomitant cardiovascular risk factors and other chronic diseases (e.g. dyslipidaemia, diabetes and heart failure) that require treatment with multiple medications, increasing the likelihood of drug–drug interactions (27). More than 50% of drugs currently used in clinical practice are metabolised by CYP450 isoenzymes (28). It is thus advantageous that aliskiren at therapeutic concentrations has no significant effect on CYP450 isoenzyme activity *in vitro* (16), and has demonstrated no significant pharmacokinetic interactions with drugs that are metabolised by CYP450 isoenzymes in healthy volunteers (29–31). By contrast, many antihypertensive agents, including most calcium channel blockers, the ARBs losartan and irbesartan and the beta-blockers carvedilol, metoprolol and propanolol, are substrates for CYP450 enzymes and can exhibit drug interactions with other agents that modify CYP450 activity (32).

In the aliskiren/valsartan study, renin concentrations and PRA were assessed for 24 h after administration of aliskiren 300 mg and valsartan 320 mg, alone or in combination. Peak renin concentrations and the area under the renin concentration–time curve at steady state following the co-administration of aliskiren and valsartan were greater than the sum of the values for each drug administered alone. This indicates synergistic inhibition of the renal renin system (positive juxtaglomerular feedback) by the combination of aliskiren and valsartan, consistent with previous findings in healthy volunteers (23). Despite the increase in renin concentrations, co-administration of aliskiren with valsartan effectively suppressed the reactive rise in PRA observed when the ARB was administered alone, confirming the results of a previous study (23). Co-administration with aliskiren has also been shown to prevent the reactive rise in PRA stimulated by HCTZ in patients with hypertension (11) and by ramipril in patients with diabetes and hypertension (12). Aliskiren therefore offers the prospect of improved renin system suppression when combined with existing antihypertensive drug therapies.

Aliskiren was generally well tolerated when administered alone or in combination with amlodipine, valsartan, HCTZ and ramipril, with the exception of an increase in the rate of mild cases of dizziness with the aliskiren/HCTZ combination. Almost all AEs across the four studies were mild to moderate in severity and there were no serious AEs. The frequency of AEs when aliskiren was co-administered with amlodipine, valsartan or ramipril was comparable with that of each agent administered alone. The increased incidence of dizziness during co-administration of aliskiren/HCTZ might be anticipated with two highly effective BP-lowering agents in normotensive, healthy subjects. The lower supine SBP levels and higher pulse rates seen with the combination compared with aliskiren or HCTZ alone suggest that the dizziness is likely due to the combined effect of BP lowering and sodium/volume depletion in healthy, normotensive subjects. Two studies investigating the effect of aliskiren administered alone and in combination with HCTZ in a total of 4727 patients with mild-to-moderate hypertension showed no differences in the rate of dizziness with aliskiren/HCTZ combinations compared with the respective monotherapies after 2 months of treatment (aliskiren/HCTZ 2.4%; HCTZ 2.3%; aliskiren 0.9%) (25) or 12 months of treatment (aliskiren/HCTZ 5.6%; aliskiren monotherapy 5.3%) (33). The incidence of dizziness with aliskiren/HCTZ combinations in these studies is similar to that observed with ARB/HCTZ combinations such as valsartan/HCTZ and eprosartan/HCTZ in patients with hypertension (34,35). Aliskiren/HCTZ combinations were more effective

than the respective monotherapies in lowering BP in the setting of hypertension and were well tolerated (25,33).

In conclusion, the results of this study indicate that there are no clinically significant pharmacokinetic interactions between aliskiren and the calcium channel blocker amlodipine, the ACE inhibitor ramipril, the ARB valsartan or the diuretic HCTZ. Aliskiren is therefore a convenient, once-daily treatment option for patients with hypertension, and can be combined with other classes of antihypertensive agents without the need for dosage modification.

CONFLICTS OF INTEREST

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

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