Effect of the oral renin inhibitor aliskiren on the pharmacokinetics and pharmacodynamics of a single dose of warfarin in healthy subjects

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Aims

To investigate the effects of aliskiren, an oral renin inhibitor, on the pharmacokinetics and pharmacodynamics of warfarin.

Methods

In a single-blind, placebo-controlled, randomized, two-period crossover study, 15 healthy male and female subjects received a single oral dose of 25 mg racemic warfarin twice, once in the morning of the 8th day of treatment with 150 mg aliskiren and once at the same time point during treatment with placebo. Blood samples were collected for the measurement of prothrombin time (PT) and activated thromboplastin time (aPTT) and for determination of plasma concentrations of (R)- and (S)-warfarin.

Results

Aliskiren treatment had no effect on the blood coagulation parameters (PT, INR and aPTT). The ratios of least square means (90% CI) of pharmacokinetic parameters in the presence and absence of aliskiren for (R)- and (S)-warfarin were $C_{\max}$ 0.89 (0.82, 0.96) and 0.88 (0.80, 0.97), $AUC(0,\infty)$ 1.00 (0.94, 1.07) and 1.06 (0.96, 1.16) and $t_{1/2}$ 0.99 (0.92, 1.07) and 1.05 (0.96, 1.14).

Conclusions

Multiple doses of aliskiren had no detectable effect on the pharmacokinetics or pharmacodynamics of a single dose of warfarin in healthy subjects.

Introduction

Aliskiren (2(S),4(S),5(S),7(S)-N-(2-carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]-octanamid hemifumarate), is the first known representative of a new class of orally effective nonpeptide, low molecular weight, renin inhibitors [1]. The renin-angiotensin system (RAS) plays an important role in the regulation of blood pressure and volume homeostasis [2, 3]. Renin is secreted by the kidney and cleaves its substrate, angiotensinogen, to form the inactive decapeptide angiotensin

I (Ang I) which is then converted to the active octapeptide Ang II by angiotensin converting enzyme (ACE). Ang II interacts with cellular receptors inducing vascular constriction, and release of catecholamines from the adrenal medulla and prejunctional nerve endings. It promotes aldosterone secretion and sodium reabsorption, and inhibits renin release, thus providing a negative feedback to the system. Ang II acts at various sites to increase vascular resistance and blood pressure [4].

The RAS may be blocked by pharmacological agents at various sites. Renin inhibitors block the RAS at a

higher level in the cascade than ACE inhibitors and have a different effect on the components of the RAS. Following administration of a renin inhibitor, the formation of both Ang I and Ang II is blocked, whereas after ACE inhibition only Ang II formation is impaired and concentrations of Ang I increase. Thus the latter is available to be converted to Ang II by other pathways, such as the chymase system. These effects have the potential to give renin inhibitors a therapeutic profile distinct from ACE inhibitors [5].

Aliskiren has been shown to be generally well tolerated in healthy subjects and in patients with hypertension, when given as single and multiple oral doses [6]. Aliskiren inhibits the RAS to an extent comparable with or better than enalapril [7] and is effective as a once daily oral treatment for hypertension [6].

Warfarin is the most widely used oral anticoagulant and is prescribed as chronic therapy to decrease risk of thrombosis and embolism in high-risk patients. Warfarin is a classic example of a narrow therapeutic window drug. This and its elimination by cytochrome P450 makes warfarin prone to potentially life-threatening drug–drug interactions [8]. The drug is a racemic mixture of its R(+)- and S(–)-enantiomers, and the S-enantiomer is approximately two- to fivefold more potent than the R-enantiomer with respect to anticoagulant activity [9]. The metabolism of warfarin is stereoselective [10].

As the two drugs are likely to be administered together, the effect of aliskiren on the pharmacokinetics and pharmacodynamics of warfarin requires investigation. For this reason an interaction study was performed in healthy volunteers who received a single high oral dose of warfarin once together with aliskiren under steady-state conditions and once together with placebo.

Methods

Subjects

Thirteen subjects were males (11 Caucasian and 2 Black) and three were females (all Caucasian). The study was approved by the Ethics Committee in Madison, Wisconsin, USA. All subjects gave written informed consent before prestudy screening. The mean age and weight of the 15 subjects (12 males and 3 females) who completed the study were 29 years (range 20–43 years) and 75.4 kg (range 59.6–94.5 kg), respectively.

Study protocol

This was a single-blind, placebo-controlled, randomized, balanced, two-period crossover study. Subjects received once daily doses of aliskiren (150 mg) or placebo in the fasted state for 11 days, with a single dose

of warfarin (25 mg; five × 5 mg Coumadin®) given on day 8 of each treatment period, separated by a washout period of at least 21 days. One subject dropped out for administrative reasons.

Blood samples (5 ml) for analysis of the prothrombin time (PT), the associated international normalized ratio (INR) and the activated partial thromboplastin time (aPTT) were taken by venepuncture at specific times during the study.

Blood samples (7 ml) for analysis of warfarin were taken by venepuncture at specific times during the study and were centrifuged at approximately 2000 g for 15 min at approximately 5 °C, within 1 h of collection. Plasma was stored at approximately –70 °C.

Drug analysis

Plasma concentrations of R- and S-warfarin were determined by liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) [11]. Aliskiren did not interfere with this assay. The limit of quantification was 1.00 ng ml^{–1} for both enantiomers. The interassay precision of quality control samples was 6.9% at 3.5 ng ml^{–1}, 5.8% at 15 ng ml^{–1}, 5.2% at 75 ng ml^{–1} and 13.7% at 400 ng ml^{–1} for (R)-warfarin and 4.8% at 3.5 ng ml^{–1}, 4.8% at 15 ng ml^{–1}, 4.0% at 75 ng ml^{–1} and 7.1% at 400 ng ml^{–1} for (S)-warfarin. The interassay accuracy varied between –10.8% and 2.5% and –13.8% and 2.0% for (R)- and (S)-warfarin, respectively.

The determination of PT, the associated international normalized ratio (INR), and aPTT, was performed according to standard clinical laboratory methodology.

Pharmacokinetic and pharmacodynamic evaluation

The pharmacokinetic parameters calculated using model-independent methods were peak plasma concentration ($C_{\max}$), time to reach $C_{\max}$ ($t_{\max}$), area under the plasma concentration–time curve from time zero to the last quantifiable concentration ($AUC(0, t_{\text{last}})$) and from time zero to infinity ($AUC(0, \infty)$) and apparent terminal elimination half-life ($t_{1/2,z}$).

$C_{\max}$ and $t_{\max}$ were taken directly from the observed plasma concentration time data. The area under the curve ($AUC(0, t_{\text{last}})$) was estimated using the linear trapezoidal rule to the last measured concentration value. Extrapolation to infinity was performed by dividing the last measurable concentration by the apparent terminal elimination rate constant λ_z . The $t_{1/2,z}$ was calculated by dividing $\ln 2$ by λ_z .

Maximum PT ($R_{\max,PT}$) and INR ($R_{\max,INR}$), time to reach maximum PT ($t_{(t,\max,PT)}$) and INR ($t_{(t,\max,INR)}$), the area under the PT vs time curve up to 144 h ($AUC(0, 144 \text{ h}, PT)$) following the warfarin dose, and the

equivalent area under the aPTT vs time curve (AUC(0,144 h,INR)) were calculated using the above pharmacokinetic methods. Changes from baseline (pre-dose) were calculated for PT, INR and aPTT.

Statistical evaluation

Logarithmic transformed data of pharmacokinetic (except $t_{\max}$) and pharmacodynamic variables were subjected to analysis of variance (ANOVA), followed by calculation of the confidence intervals (CI) on the ratio of the aliskiren relative to the placebo treatment. $t_{\max}$ was analyzed nonparametrically using the method outlined by Hauschke *et al.* [12], which takes period effects into account. The median difference between the test and reference treatments and the corresponding 90% CI were calculated. All the tests were two-sided and used the 5% level of significance.

Results

All subjects completed the study without serious adverse events and the treatments were well tolerated.

Both (R)- and (S)-warfarin were rapidly absorbed, with a slightly lower mean maximum plasma concentration being attained when co-administered with aliskiren compared with placebo (Table 1). The mean apparent elimination half-lives of (R)- and (S)-warfarin were similar for each treatment. The $t_{1/2,z}$ of (R)-warfarin ranged from 32 to 57 h after aliskiren co-administration and 36–52 h after placebo. The corresponding values for

(S)-warfarin ranged from 24 to 50 h and 25–48 h. Absorption and the disposition kinetics of both enantiomers did not differ statistically following the two treatments.

During both treatments, the AUC(0,144 h) and $R_{\max}$ values did not differ statistically for PT and INR (Table 2), and following $R_{\max}$, PT and INR decreased steadily, to reach approximately baseline values at 144 h post-dose. The administration of warfarin on day 8 induced an initial decrease in aPTT, followed by an increase, with a similar maximum response occurring at 48 h postdose for each treatment. Thereafter, aPTT declined steadily to reach approximately baseline values at 144 h postdose, for both treatments.

Discussion

We investigated the effect of aliskiren dosed to steady-state on the pharmacodynamic and pharmacokinetic properties of a single oral dose of warfarin.

Aliskiren had no detectable effect on the pharmacodynamic properties of warfarin assessed by measuring PT, INR and aPTT over a period of 144 h post-dose. The overall response to warfarin was also very similar for both treatments.

Systemic exposure to both (R)- and (S)-warfarin was unaffected by the co-administration of aliskiren. (R)- and (S)-warfarin were rapidly absorbed, with maximum plasma concentrations generally occurring at 0.5 or 1 h post-dose, followed by a predominantly monophasic

Table 1

Pharmacokinetic parameters and associated statistical analysis for (R-) and (S-) warfarin in healthy volunteers after a single oral dose of the racemic mixture on the 8th day of an 11-day treatment period with aliskiren or placebo

	150 aliskiren and 25 mg warfarin (A) (n = 15)	Placebo and 25 mg warfarin (B) (n = 15)	Ratio of least squares means 90% CI (A/B)
<i>Parameters for (R+)-warfarin</i>			
AUC(0, t_{last}) (ng ml ⁻¹ h)	56247 (27.3)	56003 (24.5)	1.00 (0.95, 1.06)
AUC(0, ∞) (ng ml ⁻¹ h)	62139 (29.1)	61680 (26.0)	1.00 (0.94, 1.07)
$C_{\max}$ (ng ml ⁻¹)	1353 (29.4)	1528 (23.3)	0.89 (0.82, 0.96)
$t_{\max}$ (h)†	1.00 (0.50–4.00)	0.500 (0.50–8.00)	0.24 (–0.25, 0.50)
$t_{1/2,z}$ (h)	41.5 (15.7)	41.7 (12.8)	0.99 (0.92, 1.07)
<i>Parameters for (S-)-warfarin</i>			
AUC(0, t_{last}) (ng ml ⁻¹ h)	38442 (25.5)	36673 (21.9)	1.04 (0.96, 1.13)
AUC(0, ∞) (ng ml ⁻¹ h)	40361 (27.8)	38081 (23.1)	1.06 (0.96, 1.16)
$C_{\max}$ (ng ml ⁻¹)	1397 (27.6)	1586 (23.6)	0.88 (0.80, 0.97)
$t_{\max}$ (h)†	1.00 (0.50–4.00)	0.500 (0.50–1.00)	0.25 (0.00, 1.00)
$t_{1/2,z}$ (h)	30.9 (23.1)	29.5 (16.6)	1.05 (0.96, 1.14)

Geometric mean (CV%) data presented. †Median (min-max); Median difference (90% CI) (A-B); n = number of subjects studied.

Table 2

Pharmacodynamic parameters and associated statistical analysis for PT and INR in healthy subjects after a single oral dose of racemic warfarin on the 8th day of an 11-day treatment period with aliskiren or placebo

	150 mg aliskiren and 25 mg warfarin (A) (n = 15)	Placebo and 25 mg warfarin (B) (n = 15)	Ratio of least squares means 90% CI (A/B)
<i>Parameters for PT</i>			
AUC(0,144 h) (s h)	2195 (12.1)	2270 (13.5)	0.97 (0.93, 1.00)
R _{max} (s)	19.5 (20.4)	19.8 (22.0)	0.99 (0.95, 1.02)
t _{max} (h)†	47.9 (23.9–48.1)	47.9 (23.9–48.0)	0.00 (0.00, 0.03)
<i>Parameters for INR</i>			
AUC(0,144 h) (INR h)	185 (15.4)	192 (18.0)	0.96 (0.93, 1.00)
R _{max} (s)	1.75 (26.7)	1.79 (28.4)	0.98 (0.94, 1.02)
t _{max} (h)†	47.9 (23.9–48.1)	47.9 (23.9–48.0)	0.00 (0.00, 0.00)

Geometric mean (CV%) data are presented; †Median (min-max); Median difference (90% CI) (A-B); n = Number of subjects studied.

decline, with a terminal half-life of approximately 42 and 30 h for the (R)- and (S)-isomers, respectively. C_{max} was slightly lower (up to 12%) when warfarin was co-administered with aliskiren, compared with placebo. However, this difference was not considered to be clinically important.

In summary, no pharmacodynamic or pharmacokinetic interaction was observed between aliskiren and a single oral dose of warfarin.

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