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ABSTRACT

Purpose

This study aimed to investigate the effect of rifampicin, an inducer of CYP3A4 and P-glycoprotein, on the pharmacokinetics and pharmacodynamics of aliskiren, a renin inhibitor used in the treatment of hypertension.

Methods

In a randomized crossover study, twelve healthy volunteers took 600 mg rifampicin or placebo once daily for five days. On day six, they ingested a single 150 mg dose of aliskiren. Plasma aliskiren concentrations were measured up to 72 h and urine concentrations up to 12 h, pharmacodynamic variables were measured up to 24 h.

Results

Rifampicin reduced the peak plasma aliskiren concentration (C_{max}) by 39% (95% confidence interval 0.41, 0.90; P=0.017) and the area under the plasma aliskiren concentration-time curve ($AUC_{0-\infty}$) by 56% (95% confidence interval 0.35, 0.56; P<0.001). Rifampicin had no significant effect on aliskiren elimination half-life ($t_{½}$) or its renal clearance (Cl_{renal}). Plasma renin activity 24 h after aliskiren intake was 61% higher during the rifampicin phase than during the placebo phase (P=0.008).

Conclusions

Rifampicin considerably reduces the plasma concentrations and the renin-inhibiting effect of aliskiren by decreasing its oral bioavailability.

KEYWORDS Pharmacokinetics, Drug interaction, Aliskiren, Rifampicin, Multidrug resistance transporter 1 P-glycoprotein

INTRODUCTION

Aliskiren is a renin inhibitor, which belongs to a class of antihypertensive drugs acting on the renin-angiotensin-aldosterone system [1-3]. It has a low oral bioavailability of about 2-3%, probably mainly because of poor absorption [3-5]. The peak plasma aliskiren concentration (C_{max}) is reached within 1 to 3 h. Aliskiren is eliminated primarily in the unchanged form by biliary excretion into the feces and, to a lesser extent, by renal excretion of unchanged aliskiren (about 0.4% of oral dose) and by oxidative biotransformation (about 1.4% of oral dose), mainly via CYP3A4 [5]. The elimination half-life ($t_{½}$) of aliskiren is about 30-40 h.

Aliskiren is a substrate of the multidrug resistance transporter 1 (MDR1) P-glycoprotein, but not of breast cancer resistance protein or multidrug resistance-associated protein 2 [6]. P-glycoprotein efflux transporter is expressed on the apical membrane of small intestinal enterocytes, hepatocytes, and proximal tubule cells and can reduce the intestinal absorption and enhance the elimination of its substrates [7]. In addition, P-glycoprotein is expressed at blood-tissue barriers, such as blood-brain barrier, protecting tissues from potentially toxic xenobiotics [7]. The hepatic uptake of aliskiren is thought to be mediated by organic anion transporting polypeptide 2B1 (OATP2B1) [6]. Ketoconazole (an inhibitor of both CYP3A4 and P-glycoprotein [8-11]) and cyclosporine (a potent inhibitor of CYP3A4, P-glycoprotein, and OATP2B1 [12-14]) have raised the area under the plasma aliskiren concentration-time curve (AUC) 1.8-fold and 5-fold, respectively [6, 15].

Rifampicin is an inducer of several drug-metabolizing enzymes (including CYP3A4) and of some drug transporters (such as P-glycoprotein), and can markedly reduce the plasma concentrations and efficacy of several CYP3A4 and P-glycoprotein substrates [16-22]. However, there are no published studies on the interactions of aliskiren with inducers of CYP3A4 and P-glycoprotein. Our aim was to study the possible effects of rifampicin on the pharmacokinetics and pharmacodynamics of aliskiren. The hypothesis was that rifampicin may reduce the plasma concentrations and the renin-inhibiting effect of aliskiren.

METHODS

Subjects

Twelve healthy white Finnish volunteers (7 women, 5 men) participated in the study after giving written informed consent. Their mean ± SD age was 21 ± 2 years (range, 20-25 years), mean height 174 ± 10 cm (range, 156-187 cm), and mean weight 66 ± 11 kg (range, 50-89 kg). Participants were ascertained to be healthy by medical history, physical examination, and routine laboratory tests. Subjects with a systolic blood pressure less than 110 mm Hg were not included in the study. None of the participants was on any continuous medication, including oral contraceptives, and none was a tobacco smoker.

Study design

The study protocol was approved by the Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital District, and the National Agency for Medicines in Finland. In a randomized two-phase crossover study with a wash-out period of four weeks, the volunteers took 600 mg rifampicin (Rimapen; Orion Pharma, Espoo, Finland) or placebo once daily at 20.00 h for five days. On day six, after an overnight fast, a single oral dose of 150 mg aliskiren (Rasilez; Novartis, Horsham, Great Britain) was administered with 150 ml of water at 08.00 h. A standardized warm meal was served 4 h after the administration of aliskiren, and a standardized light meal after 7 h and 10 h. The participants were under direct medical supervision for 12 h after aliskiren ingestion. Fluids for intravenous infusion were available for immediate use in case of hypotension, but were not needed. Use of other drugs was prohibited for one week before and after,

and use of grapefruit products and alcohol for five days before and three days after aliskiren administration.

Blood sampling and pharmacodynamic measurements

On the days of the administration of aliskiren, a forearm vein of each subject was cannulated with a plastic cannula and kept patent with an obturator. Timed blood samples for drug concentration measurements (5 or 10 ml each) were drawn into tubes containing ethylenediaminetetraacetic acid (EDTA) prior to and 0.5, 1, 2, 3, 4, 5, 7, 9, 12, 24, 34, 48, and 72 h after aliskiren administration. Blood samples for the determination of plasma renin activity (5 ml each) were drawn before the administration of aliskiren and 4 h and 24 h thereafter into chilled EDTA tubes, which were placed on ice immediately after sampling. Plasma was separated within 30 min. Urine was collected up to 12 h after aliskiren ingestion. Urine aliquots and plasma were stored at -70ºC until analysis. Plasma renin activity was measured using a commercially available radioimmunoassay method (RENCTK; DiaSorin, Saluggia, Italy). Systolic and diastolic blood pressures, and heart rate were measured twice (mean value was used in the calculations) from the forearm with an automatic oscillometric blood pressure monitor (Omron M5-I; Omron Healthcare Europe BV, Hoofddorp, The Netherlands), with the subject in a sitting position, prior to and 2, 4, 7, 9, 12, and 24 h after the administration of aliskiren.

Determination of aliskiren concentrations

Plasma and urine concentrations of aliskiren were quantified using an Applied Biosystems SCIEX API 2000 Q Trap liquid chromatography-tandem mass spectrometry

(LC/MS/MS) system (Sciex Division of MDS Inc, Toronto, Ontario, Canada) [5]. Acebutolol served as an internal standard. The limit of quantification of plasma aliskiren was 0.25 ng/ml, and the intra-day coefficient of variation (CV) was 1.2% at 2 ng/ml, 1.0% at 20 ng/ml, and 1.2% at 200 ng/ml (*n*=6). The calibration curve for plasma aliskiren was linear over the range 0.25-500 ng/ml (r>0.999, weighting 1/x). The limit of quantification of aliskiren in urine was 9 ng/ml, and the intra-day CV was 4.8% at 9 ng/ml, 4.5% at 120 ng/ml, and 3.4% at 1200 ng/ml (*n*=6). The calibration curve for urine aliskiren was linear over the range 9-1800 ng/ml (r>0.999, weighting 1/x).

Pharmacokinetics

The pharmacokinetics of aliskiren were characterized by C_{max}, time to C_{max} (t_{max}), $t_{½}$, AUC_{0-72}, $AUC_{0-\infty}$, the amount of aliskiren excreted into urine from 0 to 12 h (Ae), and the renal clearance (Cl_{renal}). Pharmacokinetic parameters were calculated with non-compartmental methods using MK-Model, version 5.0 (Biosoft, Cambridge, United Kingdom). The terminal log-linear part of each concentration-time curve was identified visually. The elimination rate constant (k_e) was determined by linear regression analysis of the log-linear part of the plasma drug concentration-time curve. The $t_{½}$ was calculated by the equation $t_{½} = \ln 2/k_e$. The AUC values were calculated by a combination of the linear and log-linear trapezoidal rules with extrapolation to infinity, when appropriate, by division of the last measured concentration by k_e. The Cl_{renal} of aliskiren was calculated by the equation $Cl_{renal} = Ae/AUC_{0-12}$.

Pharmacodynamics

The pharmacodynamics of aliskiren were characterized by plasma renin activity at 4 h and 24 h after aliskiren intake, as well as average systolic and diastolic blood pressures, and heart rate. Average values of systolic and diastolic blood pressures and heart rate were calculated by dividing the area under the effect-time curve from 0 to 24 h by 24 h.

Statistical analysis

The results are expressed as geometric means (95% confidence interval), unless otherwise indicated. The C_{max}, AUC, Ae, and Cl_{renal} data were logarithmically transformed before statistical analysis. Statistical comparisons of the pharmacokinetic (other than t_{max}) and pharmacodynamic variables during the placebo and rifampicin phases were carried out using repeated-measures analysis of variance with treatment phase as a within-subjects factor and treatment sequence as a between-subjects factor. The t_{max} data were compared using the Wilcoxon signed rank test. The frequencies of individuals with a double-peak in aliskiren plasma concentration curve were compared between the phases using the McNemar test. Possible correlations between the pharmacokinetic variables of aliskiren and subject body weight were analyzed with the Pearson correlation coefficient. The data were analyzed using the statistical program SPSS 16.0 for Windows (SPSS, Chicago, IL, USA). Differences were considered statistically significant when P was <0.05. The number of subjects was estimated to be sufficient to detect a 40% difference in the $AUC_{0-\infty}$ of aliskiren between the placebo and rifampicin phases, with a power of 80% (α-level 5%) [4].

RESULTS

Effect of rifampicin on aliskiren pharmacokinetics

Rifampicin markedly reduced the plasma concentrations of aliskiren (Fig. 1, Table 1). The C_{max} of aliskiren was reduced by 39% (P=0.017) and its $AUC_{0-\infty}$ by 56% (P<0.001) by rifampicin. The Ae was decreased by 48% by rifampicin (P=0.001). Rifampicin had no significant effect on the t_{max}, $t_{½}$, or Cl_{renal} of aliskiren. The extent of the interaction showed marked interindividual variability: decrease in aliskiren $AUC_{0-\infty}$ ranged from 20% to 76% and the effect of rifampicin on the aliskiren C_{max} ranged from a 78% decrease to a 9% increase (Fig. 2). Plasma aliskiren concentration showed a double-peak in 11 out of 12 subjects during the placebo phase and 6 out of 12 subjects during the rifampicin phase (P=0.063). None of the pharmacokinetic variables of aliskiren correlated with subject body weight, during either the placebo or rifampicin phase ($|r|<0.38$, $P>0.23$).

Effect of rifampicin on aliskiren pharmacodynamics

Plasma renin activity 24 h after aliskiren intake was 61% higher during the rifampicin phase than during the placebo phase (P=0.008) (Fig. 3, Table 2). No significant difference existed in the systolic or diastolic blood pressure, or the heart rate between the rifampicin and placebo phases.

DISCUSSION

This study demonstrates that rifampicin markedly reduces the plasma concentrations of aliskiren. The C_{max} and $AUC_{0-\infty}$ of aliskiren were reduced by 39% and 56%, respectively. Marked interindividual variability was evident in the extent of the interaction. Plasma renin activity 24 h after aliskiren intake was 61% higher during the rifampicin phase than during the placebo phase. The interaction between rifampicin and aliskiren may result in a need to adjust aliskiren dose.

Aliskiren, a drug with a low oral bioavailability, is a substrate of P-glycoprotein efflux transporter and is slightly metabolized by CYP3A4 [3, 5, 6]. In the present study, rifampicin reduced the C_{max} and $AUC_{0-\infty}$ of aliskiren without affecting the $t_{½}$ or the Cl_{renal}, indicating that rifampicin increased mainly the first-pass elimination of aliskiren with no or minimal effect on its systemic clearance. Rifampicin has a strong inducing effect on intestinal and hepatic CYP3A4 with a smaller, though significant, effect on P-glycoprotein [16-22]. It is noteworthy that intestinal CYP3A4 and P-glycoprotein act synergistically to reduce the oral bioavailability of their joint substrates [23].

Because aliskiren has a low hepatic extraction ratio (0.10) [24], induction of its hepatic elimination unlikely explains this interaction observed during the first-pass phase. Moreover, significant change in the hepatic extraction of such a drug with a low hepatic extraction should result in a shortened elimination $t_{½}$. In addition, plasma aliskiren concentration data showed double-peaks characteristic of entero-hepatic circulation, particularly during the placebo phase. This phenomenon appeared to be diminished

during the rifampicin phase, consistent with reduced intestinal reabsorption of aliskiren due to induction of intestinal P-glycoprotein and CYP3A4. Taken together, the interaction between rifampicin and aliskiren is most likely caused by induction of P-glycoprotein-mediated efflux and CYP3A4-catalyzed biotransformation of aliskiren in the gut wall [16-22].

In this study, the renin-inhibiting effect of aliskiren was attenuated during the rifampicin phase. However, no differences in hemodynamic effects were observed between the rifampicin and placebo phases after a single dose of aliskiren in healthy volunteers. This can be explained by the delayed start of the blood pressure decreasing effect of aliskiren, which gradually reaches its maximum after four weeks treatment [15, 25]. Moreover, the pharmacodynamic response to aliskiren in patients with hypertension may be distinct from normotensive healthy individuals [3, 15]. On the other hand, the pharmacokinetics of aliskiren is similar in patients with hypertension and healthy individuals [3, 15]. According to pharmacokinetic theory, the dose-interval AUC at steady state is equal to the $AUC_{0-\infty}$ after a single dose [26]. However, the pharmacokinetics of aliskiren is slightly non-linear [3], interfering with the direct extrapolation of the present results to steady-state. Because aliskiren shows a dose-response relationship in the range 150-300 mg, but no clear effect on blood pressure with lower doses [15, 25], it is possible that rifampicin reduces the efficacy of aliskiren in patients with hypertension. Similarly to rifampicin, a high-fat meal has reduced the AUC of aliskiren by about 70% [3]. To minimize variability due to the food effect, aliskiren is recommended to be taken once daily with a light meal or in a routine pattern with regard to meals [15, 27].

In conclusion, rifampicin considerably reduces the plasma concentrations of aliskiren. Clinicians should be aware of the possibility that rifampicin may reduce the antihypertensive efficacy of aliskiren.

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COMPETING INTEREST

None to declare.

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Table 1 Pharmacokinetic variables of aliskiren in twelve healthy volunteers after a single 150 mg oral dose of aliskiren following a 5-day treatment with 600 mg rifampicin or placebo once daily

Variable	Placebo phase (control)	Rifampicin phase	Geometric mean ratio/ mean difference (95% CI)	*P* value
C_{max} (ng/ml)	137 (83, 226)	83 (59, 118)	0.61 (0.41, 0.90)	0.017
t_{max} (h)	1 (0.5-5)	0.5 (0.5-5)		0.254
$t_{½}$ (h)	28.4 ± 8.5	24.4 ± 7.4	-4.0 (-9.6, 1.6)*	0.143
AUC_{0-72} (ng·h/ml)	537 (349, 825)	244 (182, 325)	0.45 (0.36, 0.57)	<0.001
$AUC_{0-\infty}$ (ng·h/ml)	581 (376, 898)	258 (191, 349)	0.44 (0.35, 0.56)	<0.001
Ae (mg)	0.576 (0.403, 0.822)	0.299 (0.227, 0.394)	0.52 (0.38, 0.72)	0.001
Cl_{renal} (l/h)	1.52 (1.21, 1.91)	1.63 (1.38, 1.93)	1.07 (0.91, 1.26)	0.347

Data are given as geometric mean (95% CI), t_{max} data as median (range), and $t_{½}$ data as mean ± SD.

CI, Confidence interval; C_{max}, peak plasma concentration; t_{max}, time to C_{max}; $t_{½}$, elimination half-life; AUC_{0-72}, area under the plasma concentration-time curve from 0 to 72 h; $AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 to infinity; Ae, amount excreted into urine within 12 h; Cl_{renal}, renal clearance.

*Mean difference (95% CI).

Table 2 Pharmacodynamic variables of aliskiren in twelve healthy volunteers after a single 150 mg oral dose of aliskiren following a 5-day treatment with 600 mg rifampicin or placebo once daily

Variable	Placebo phase (control)	Rifampicin phase	Mean difference (95% CI)	*P* value
Plasma renin activity (ng/ml/h)				
Baseline	2.21 ± 1.95	2.20 ± 1.40	-0.01 (-1.04, 1.01)	0.980
At 4 h	0.01 ± 0.04	0.19 ± 0.39	0.18 (-0.09, 0.45)	0.166
At 24 h	1.27 ± 1.20	2.04 ± 1.11	0.77 (0.25, 1.29)	0.008
Systolic blood pressure (mm Hg)				
Baseline	124 ± 15	127 ± 15	4 (-1, 8)	0.078
$Average_{0\text{-}24h}$	126 ± 13	126 ± 16	0 (-4, 4)	0.847
$Average_{0\text{-}24h}$/Baseline	1.02 ± 0.06	0.99 ± 0.03	-0.03 (-0.07, 0.01)	0.093
Diastolic blood pressure (mm Hg)				
Baseline	77 ± 11	76 ± 9	0 (-5, 5)	0.926
$Average_{0\text{-}24h}$	74 ± 10	73 ± 8	-1 (-6, 3)	0.482
$Average_{0\text{-}24h}$/Baseline	0.97 ± 0.06	0.95 ± 0.06	-0.02 (-0.07, 0.04)	0.544
Heart rate (1/min)				
Baseline	63 ± 13	64 ± 7	1 (-5, 7)	0.729
$Average_{0\text{-}24h}$	70 ± 12	69 ± 9	0 (-5, 5)	0.888
$Average_{0\text{-}24h}$/Baseline	1.11 ± 0.09	1.08 ± 0.07	-0.03 (-0.08, 0.02)	0.233

Data are given as mean ± SD.

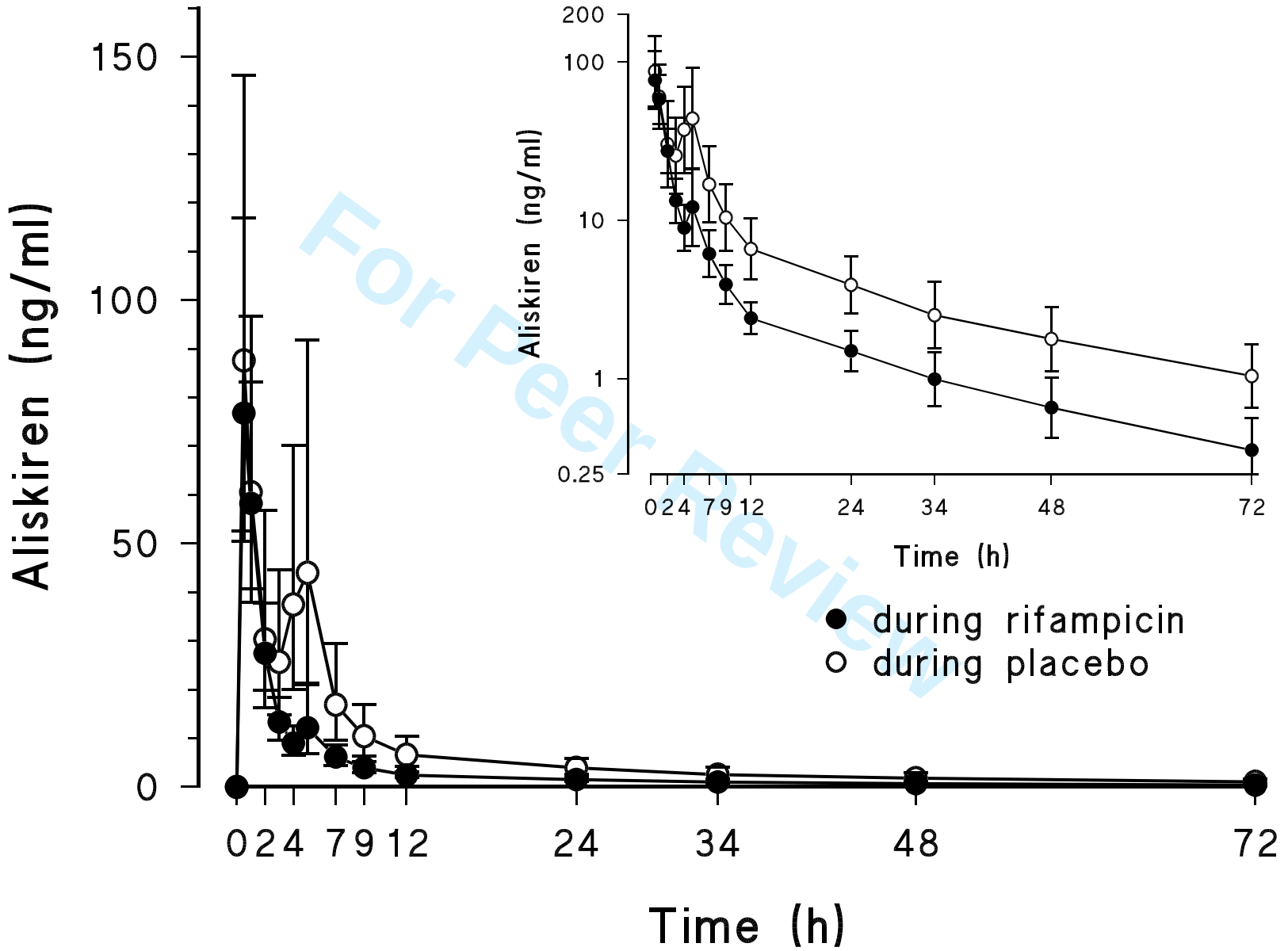
CI, Confidence interval; Baseline, before the administration of aliskiren.

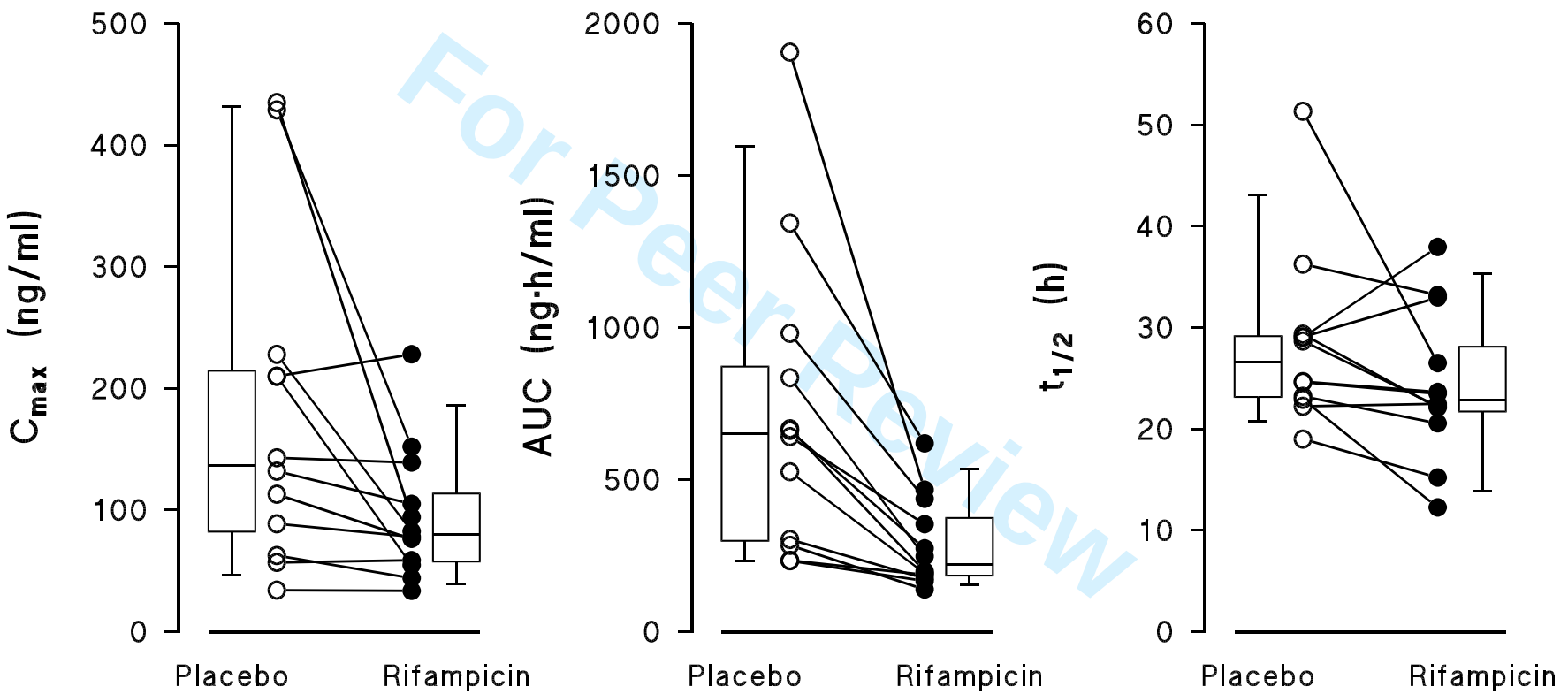
FIGURE LEGENDS

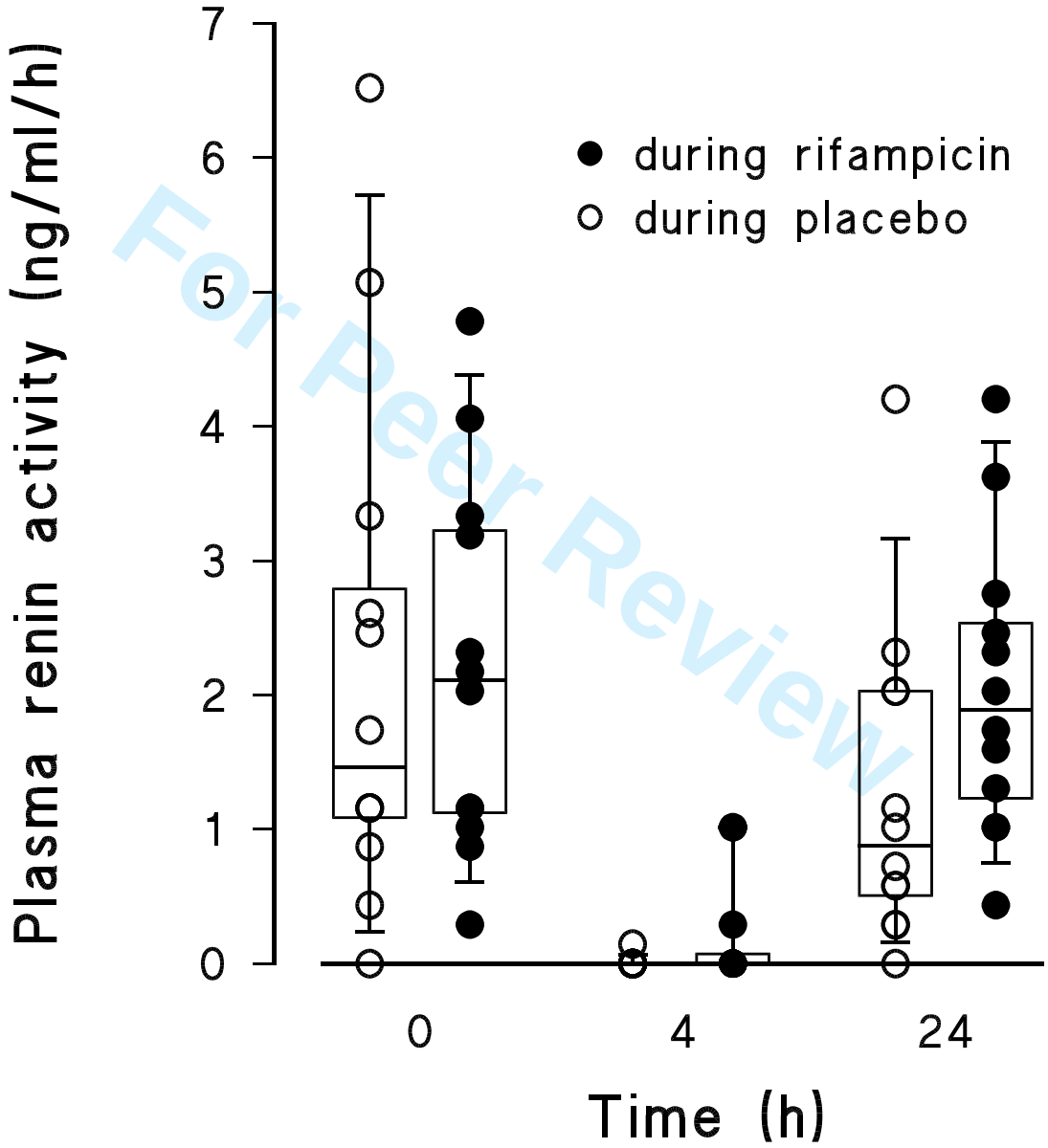
Fig. 1 Geometric mean (95% confidence interval) plasma concentrations of aliskiren in twelve healthy volunteers after a single 150 mg oral dose of aliskiren following a 5-day treatment with 600 mg rifampicin or placebo once daily. Inset depicts the same data on a semi-logarithmic scale

Fig. 2 Box-and-whisker plots of the C_{max}, AUC and $t_{½}$ values of aliskiren. A single 150 mg oral dose of aliskiren was given to twelve healthy volunteers following a 5-day treatment with 600 mg rifampicin or placebo once daily. The horizontal lines inside the boxes represent the median, the box edges show the lower and upper quartiles, and the whiskers show the 5th and 95th percentiles. Individual data points are given as open (placebo phase) and solid (rifampicin phase) circles

Fig. 3 Box-and-whisker plots of plasma renin activity in twelve healthy volunteers 0, 4, and 24 after a single 150 mg oral dose of aliskiren following a 5-day treatment with 600 mg rifampicin or placebo once daily. The horizontal lines inside the boxes represent the median, the box edges show the lower and upper quartiles, and the whiskers show the 5th and 95th percentiles. Individual data points are given as open (placebo phase) and solid (rifampicin phase) circles







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ABSTRACT

Purpose

This study aimed to investigate the effect of rifampicin, an inducer of CYP3A4 and P-glycoprotein, on the pharmacokinetics and pharmacodynamics of aliskiren, a renin inhibitor used in the treatment of hypertension.

Methods

In a randomized crossover study, twelve healthy volunteers took 600 mg rifampicin or placebo once daily for five days. On day six, they ingested a single 150 mg dose of aliskiren. Plasma aliskiren concentrations were measured up to 72 h and urine concentrations up to 12 h, pharmacodynamic variables were measured up to 24 h.

Results

Rifampicin reduced the peak plasma aliskiren concentration (C_{max}) by 39% (95% confidence interval 0.41, 0.90; P=0.017) and the area under the plasma aliskiren concentration-time curve ($AUC_{0-\infty}$) by 56% (95% confidence interval 0.35, 0.56; P<0.001). Rifampicin had no significant effect on aliskiren elimination half-life ($t_{½}$) or its renal clearance (Cl_{renal}). Plasma renin activity 24 h after aliskiren intake was 61% higher during the rifampicin phase than during the placebo phase (P=0.008).

Conclusions

Rifampicin considerably reduces the plasma concentrations and the renin-inhibiting effect of aliskiren by decreasing its oral bioavailability.

KEYWORDS Pharmacokinetics, Drug interaction, Aliskiren, Rifampicin, Multidrug resistance transporter 1 P-glycoprotein

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INTRODUCTION

Aliskiren is a renin inhibitor, which belongs to a class of antihypertensive drugs acting on the renin-angiotensin-aldosterone system [1-3]. It has a low oral bioavailability of about 2-3%, probably mainly because of poor absorption [3-5]. The peak plasma aliskiren concentration (C_{max}) is reached within 1 to 3 h. Aliskiren is eliminated primarily in the unchanged form by biliary excretion into the feces and, to a lesser extent, by renal excretion of unchanged aliskiren (about 0.4% of oral dose) and by oxidative biotransformation (about 1.4% of oral dose), mainly via CYP3A4 [5]. The elimination half-life ($t_{½}$) of aliskiren is about 30-40 h.

Aliskiren is a substrate of the multidrug resistance transporter 1 (MDR1) P-glycoprotein, but not of breast cancer resistance protein or multidrug resistance-associated protein 2 [6]. P-glycoprotein efflux transporter is expressed on the apical membrane of small intestinal enterocytes, hepatocytes, and proximal tubule cells and can reduce the intestinal absorption and enhance the elimination of its substrates [7]. In addition, P-glycoprotein is expressed at blood-tissue barriers, such as blood-brain barrier, protecting tissues from potentially toxic xenobiotics [7]. The hepatic uptake of aliskiren is thought to be mediated by organic anion transporting polypeptide 2B1 (OATP2B1) [6]. Ketoconazole (an inhibitor of both CYP3A4 and P-glycoprotein [8-11]) and cyclosporine (a potent inhibitor of CYP3A4, P-glycoprotein, and OATP2B1 [12-14]) have raised the area under the plasma aliskiren concentration-time curve (AUC) 1.8-fold and 5-fold, respectively [6, 15].

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Rifampicin is an inducer of several drug-metabolizing enzymes (including CYP3A4) and of some drug transporters (such as P-glycoprotein), and can markedly reduce the plasma concentrations and efficacy of several CYP3A4 and P-glycoprotein substrates [16-22]. However, there are no published studies on the interactions of aliskiren with inducers of CYP3A4 and P-glycoprotein. Our aim was to study the possible effects of rifampicin on the pharmacokinetics and pharmacodynamics of aliskiren. The hypothesis was that rifampicin may reduce the plasma concentrations and the renin-inhibiting effect of aliskiren.

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METHODS

Subjects

Twelve healthy white Finnish volunteers (7 women, 5 men) participated in the study after giving written informed consent. Their mean ± SD age was 21 ± 2 years (range, 20-25 years), mean height 174 ± 10 cm (range, 156-187 cm), and mean weight 66 ± 11 kg (range, 50-89 kg). Participants were ascertained to be healthy by medical history, physical examination, and routine laboratory tests. Subjects with a systolic blood pressure less than 110 mm Hg were not included in the study. None of the participants was on any continuous medication, including oral contraceptives, and none was a tobacco smoker.

Study design

The study protocol was approved by the Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital District, and the National Agency for Medicines in Finland. In a randomized two-phase crossover study with a wash-out period of four weeks, the volunteers took 600 mg rifampicin (Rimapen; Orion Pharma, Espoo, Finland) or placebo once daily at 20.00 h for five days. On day six, after an overnight fast, a single oral dose of 150 mg aliskiren (Rasilez; Novartis, Horsham, Great Britain) was administered with 150 ml of water at 08.00 h. A standardized warm meal was served 4 h after the administration of aliskiren, and a standardized light meal after 7 h and 10 h. The participants were under direct medical supervision for 12 h after aliskiren ingestion. Fluids for intravenous infusion were available for immediate use in case of hypotension, but were not needed. Use of other drugs was prohibited for one week before and after,

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and use of grapefruit products and alcohol for five days before and three days after aliskiren administration.

Blood sampling and pharmacodynamic measurements

On the days of the administration of aliskiren, a forearm vein of each subject was cannulated with a plastic cannula and kept patent with an obturator. Timed blood samples for drug concentration measurements (5 or 10 ml each) were drawn into tubes containing ethylenediaminetetraacetic acid (EDTA) prior to and 0.5, 1, 2, 3, 4, 5, 7, 9, 12, 24, 34, 48, and 72 h after aliskiren administration. Blood samples for the determination of plasma renin activity (5 ml each) were drawn before the administration of aliskiren and 4 h and 24 h thereafter into chilled EDTA tubes, which were placed on ice immediately after sampling. Plasma was separated within 30 min. Urine was collected up to 12 h after aliskiren ingestion. Urine aliquots and plasma were stored at -70ºC until analysis. Plasma renin activity was measured using a commercially available radioimmunoassay method (RENCTK; DiaSorin, Saluggia, Italy). Systolic and diastolic blood pressures, and heart rate were measured twice (mean value was used in the calculations) from the forearm with an automatic oscillometric blood pressure monitor (Omron M5-I; Omron Healthcare Europe BV, Hoofddorp, The Netherlands), with the subject in a sitting position, prior to and 2, 4, 7, 9, 12, and 24 h after the administration of aliskiren.

Determination of aliskiren concentrations

Plasma and urine concentrations of aliskiren were quantified using an Applied Biosystems SCIEX API 2000 Q Trap liquid chromatography-tandem mass spectrometry

(LC/MS/MS) system (Sciex Division of MDS Inc, Toronto, Ontario, Canada) [5]. Acebutolol served as an internal standard. The limit of quantification of plasma aliskiren was 0.25 ng/ml, and the intra-day coefficient of variation (CV) was 1.2% at 2 ng/ml, 1.0% at 20 ng/ml, and 1.2% at 200 ng/ml (n=6). The calibration curve for plasma aliskiren was linear over the range 0.25-500 ng/ml (r>0.999, weighting 1/x). The limit of quantification of aliskiren in urine was 9 ng/ml, and the intra-day CV was 4.8% at 9 ng/ml, 4.5% at 120 ng/ml, and 3.4% at 1200 ng/ml (n=6). The calibration curve for urine aliskiren was linear over the range 9-1800 ng/ml (r>0.999, weighting 1/x).

Pharmacokinetics

The pharmacokinetics of aliskiren were characterized by C_{max}, time to C_{max} (t_{max}), $t_{½}$, AUC_{0-72}, $AUC_{0-\infty}$, the amount of aliskiren excreted into urine from 0 to 12 h (Ae), and the renal clearance (Cl_{renal}). Pharmacokinetic parameters were calculated with non-compartmental methods using MK-Model, version 5.0 (Biosoft, Cambridge, United Kingdom). The terminal log-linear part of each concentration-time curve was identified visually. The elimination rate constant (k_e) was determined by linear regression analysis of the log-linear part of the plasma drug concentration-time curve. The $t_{½}$ was calculated by the equation $t_{½} = \ln 2/k_e$. The AUC values were calculated by a combination of the linear and log-linear trapezoidal rules with extrapolation to infinity, when appropriate, by division of the last measured concentration by k_e. The Cl_{renal} of aliskiren was calculated by the equation $Cl_{renal} = Ae/AUC_{0-12}$.

Pharmacodynamics

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The pharmacodynamics of aliskiren were characterized by plasma renin activity at 4 h and 24 h after aliskiren intake, as well as average systolic and diastolic blood pressures, and heart rate. Average values of systolic and diastolic blood pressures and heart rate were calculated by dividing the area under the effect-time curve from 0 to 24 h by 24 h.

Statistical analysis

The results are expressed as geometric means (95% confidence interval), unless otherwise indicated. The C_{max}, AUC, Ae, and Cl_{renal} data were logarithmically transformed before statistical analysis. Statistical comparisons of the pharmacokinetic (other than t_{max}) and pharmacodynamic variables during the placebo and rifampicin phases were carried out using repeated-measures analysis of variance with treatment phase as a within-subjects factor and treatment sequence as a between-subjects factor. The t_{max} data were compared using the Wilcoxon signed rank test. The frequencies of individuals with a double-peak in aliskiren plasma concentration curve were compared between the phases using the McNemar test. Possible correlations between the pharmacokinetic variables of aliskiren and subject body weight were analyzed with the Pearson correlation coefficient. The data were analyzed using the statistical program SPSS 16.0 for Windows (SPSS, Chicago, IL, USA). Differences were considered statistically significant when P was <0.05. The number of subjects was estimated to be sufficient to detect a 40% difference in the $AUC_{0-\infty}$ of aliskiren between the placebo and rifampicin phases, with a power of 80% (α-level 5%) [4].

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RESULTS

Effect of rifampicin on aliskiren pharmacokinetics

Rifampicin markedly reduced the plasma concentrations of aliskiren (Fig. 1, Table 1). The C_{max} of aliskiren was reduced by 39% (P=0.017) and its $AUC_{0-\infty}$ by 56% (P<0.001) by rifampicin. The Ae was decreased by 48% by rifampicin (P=0.001). Rifampicin had no significant effect on the t_{max}, $t_{½}$ or Cl_{renal} of aliskiren. The extent of the interaction showed marked interindividual variability: decrease in aliskiren $AUC_{0-\infty}$ ranged from 20% to 76% and the effect of rifampicin on the aliskiren C_{max} ranged from a 78% decrease to a 9% increase (Fig. 2). Plasma aliskiren concentration showed a double-peak in 11 out of 12 subjects during the placebo phase and 6 out of 12 subjects during the rifampicin phase (P=0.063). None of the pharmacokinetic variables of aliskiren correlated with subject body weight, during either the placebo or rifampicin phase (|r|<0.38, P>0.23).

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Effect of rifampicin on aliskiren pharmacodynamics

Plasma renin activity 24 h after aliskiren intake was 61% higher during the rifampicin phase than during the placebo phase (P=0.008) (Fig. 3, Table 2). No significant difference existed in the systolic or diastolic blood pressure, or the heart rate between the rifampicin and placebo phases.

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DISCUSSION

This study demonstrates that rifampicin markedly reduces the plasma concentrations of aliskiren. The C_{max} and $AUC_{0-\infty}$ of aliskiren were reduced by 39% and 56%, respectively. Marked interindividual variability was evident in the extent of the interaction. Plasma renin activity 24 h after aliskiren intake was 61% higher during the rifampicin phase than during the placebo phase. The interaction between rifampicin and aliskiren may result in a need to adjust aliskiren dose.

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Aliskiren, a drug with a low oral bioavailability, is a substrate of P-glycoprotein efflux transporter and is slightly metabolized by CYP3A4 [3, 5, 6]. In the present study, rifampicin reduced the C_{max} and $AUC_{0-\infty}$ of aliskiren without affecting the $t_{½}$ or the Cl_{renal}, indicating that rifampicin increased mainly the first-pass elimination of aliskiren with no or minimal effect on its systemic clearance. Rifampicin has a strong inducing effect on intestinal and hepatic CYP3A4 with a smaller, though significant, effect on P-glycoprotein [16-22]. It is noteworthy that intestinal CYP3A4 and P-glycoprotein act synergistically to reduce the oral bioavailability of their joint substrates [23].

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Because aliskiren has a low hepatic extraction ratio (0.10) [24], induction of its hepatic elimination unlikely explains this interaction observed during the first-pass phase. Moreover, significant change in the hepatic extraction of such a drug with a low hepatic extraction should result in a shortened elimination $t_{½}$. In addition, plasma aliskiren concentration data showed double-peaks characteristic of entero-hepatic circulation, particularly during the placebo phase. This phenomenon appeared to be diminished

during the rifampicin phase, consistent with reduced intestinal reabsorption of aliskiren due to induction of intestinal P-glycoprotein and CYP3A4. Taken together, the interaction between rifampicin and aliskiren is most likely caused by induction of P-glycoprotein-mediated efflux and CYP3A4-catalyzed biotransformation of aliskiren in the gut wall [16-22].

In this study, the renin-inhibiting effect of aliskiren was attenuated during the rifampicin phase. However, no differences in hemodynamic effects were observed between the rifampicin and placebo phases after a single dose of aliskiren in healthy volunteers. This can be explained by the delayed start of the blood pressure decreasing effect of aliskiren, which gradually reaches its maximum after four weeks treatment [15, 25]. Moreover, the pharmacodynamic response to aliskiren in patients with hypertension may be distinct from normotensive healthy individuals [3, 15]. On the other hand, the pharmacokinetics of aliskiren is similar in patients with hypertension and healthy individuals [3, 15]. According to pharmacokinetic theory, the dose-interval AUC at steady state is equal to the $AUC_{0-\infty}$ after a single dose [26]. However, the pharmacokinetics of aliskiren is slightly non-linear [3], interfering with the direct extrapolation of the present results to steady-state. Because aliskiren shows a dose-response relationship in the range 150-300 mg, but no clear effect on blood pressure with lower doses [15, 25], it is possible that rifampicin reduces the efficacy of aliskiren in patients with hypertension. Similarly to rifampicin, a high-fat meal has reduced the AUC of aliskiren by about 70% [3]. To minimize variability due to the food effect, aliskiren is recommended to be taken once daily with a light meal or in a routine pattern with regard to meals [15, 27].

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In addition to rifampicin, also other inducers of CYP3A4 and the P-glycoprotein may interact with aliskiren. The antiepileptic drugs carbamazepine and phenytoin are approximately similarly potent inducers of CYP3A4 as rifampicin [19, 20, 25], whereas St John's wort has a smaller, though significant, effect [26]. Carbamazepine and phenytoin have reduced the AUC of the orally given CYP3A4 probe substrate midazolam (not a substrate of the P-glycoprotein [27]) by 94% and rifampicin by 96-98% [19, 20, 25, 28]. Phenytoin has reduced the AUC of oral digoxin (a substrate of the P-glycoprotein but not of CYP3A4 [21, 29, 30]) by 23% and rifampicin by 30% [21, 31], but carbamazepine treatment has not affected the oral bioavailability of digoxin [32]. St John's wort extract has reduced the AUC of oral midazolam by 52% and the AUC of oral digoxin by 25% [26, 33].¶
Deleted: Aliskiren is approved for the treatment of hypertension at once daily oral doses of 150 mg and 300 mg, and its antihypertensive effect is attained in two weeks [15]. Blood pressure reduction with 75-mg aliskiren has not been consistently greater than with placebo [15, 34, 35]. Therefore, during continuous treatment it is probable that rifampicin reduces the antihypertensive effect of aliskiren.
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In conclusion, rifampicin considerably reduces the plasma concentrations of aliskiren.

Clinicians should be aware of the possibility that rifampicin may reduce the antihypertensive efficacy of aliskiren.

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COMPETING INTEREST

None to declare.

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Table 1 Pharmacokinetic variables of aliskiren in twelve healthy volunteers after a single 150 mg oral dose of aliskiren following a 5-day treatment with 600 mg rifampicin or placebo once daily

Variable	Placebo phase (control)	Rifampicin phase	Geometric mean ratio/ mean difference (95% CI)	*P* value
C_{max} (ng/ml)	137 (83, 226)	83 (59, 118)	0.61 (0.41, 0.90)	0.017
t_{max} (h)	1 (0.5-5)	0.5 (0.5-5)		0.254
$t_{½}$ (h)	28.4 ± 8.5	24.4 ± 7.4	-4.0 (-9.6, 1.6)*	0.143
AUC_{0-72} (ng·h/ml)	537 (349, 825)	244 (182, 325)	0.45 (0.36, 0.57)	<0.001
$AUC_{0-\infty}$ (ng·h/ml)	581 (376, 898)	258 (191, 349)	0.44 (0.35, 0.56)	<0.001
Ae (mg)	0.576 (0.403, 0.822)	0.299 (0.227, 0.394)	0.52 (0.38, 0.72)	0.001
Cl_{renal} (l/h)	1.52 (1.21, 1.91)	1.63 (1.38, 1.93)	1.07 (0.91, 1.26)	0.347

Data are given as geometric mean (95% CI), t_{max} data as median (range), and $t_{½}$ data as mean ± SD.

CI, Confidence interval; C_{max}, peak plasma concentration; t_{max}, time to C_{max}; $t_{½}$, elimination half-life; AUC_{0-72}, area under the plasma concentration-time curve from 0 to 72 h; $AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 to infinity; Ae, amount excreted into urine within 12 h; Cl_{renal}, renal clearance.

*Mean difference (95% CI).

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Table 2 Pharmacodynamic variables of aliskiren in twelve healthy volunteers after a single 150 mg oral dose of aliskiren following a 5-day treatment with 600 mg rifampicin or placebo once daily

Variable	Placebo phase (control)	Rifampicin phase	Mean difference (95% CI)	*P* value
Plasma renin activity (ng/ml/h)				
Baseline	2.21 ± 1.95	2.20 ± 1.40	-0.01 (-1.04, 1.01)	0.980
At 4 h	0.01 ± 0.04	0.19 ± 0.39	0.18 (-0.09, 0.45)	0.166
At 24 h	1.27 ± 1.20	2.04 ± 1.11	0.77 (0.25, 1.29)	0.008
Systolic blood pressure (mm Hg)				
Baseline	124 ± 15	127 ± 15	4 (-1, 8)	0.078
$Average_{0\text{-}24h}$	126 ± 13	126 ± 16	0 (-4, 4)	0.847
$Average_{0\text{-}24h}$/Baseline	1.02 ± 0.06	0.99 ± 0.03	-0.03 (-0.07, 0.01)	0.093
Diastolic blood pressure (mm Hg)				
Baseline	77 ± 11	76 ± 9	0 (-5, 5)	0.926
$Average_{0\text{-}24h}$	74 ± 10	73 ± 8	-1 (-6, 3)	0.482
$Average_{0\text{-}24h}$/Baseline	0.97 ± 0.06	0.95 ± 0.06	-0.02 (-0.07, 0.04)	0.544
Heart rate (1/min)				
Baseline	63 ± 13	64 ± 7	1 (-5, 7)	0.729
$Average_{0\text{-}24h}$	70 ± 12	69 ± 9	0 (-5, 5)	0.888
$Average_{0\text{-}24h}$/Baseline	1.11 ± 0.09	1.08 ± 0.07	-0.03 (-0.08, 0.02)	0.233

Data are given as mean ± SD.

CI, Confidence interval; Baseline, before the administration of aliskiren.

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FIGURE LEGENDS

Fig. 1 Geometric mean (95% confidence interval) plasma concentrations of aliskiren in twelve healthy volunteers after a single 150 mg oral dose of aliskiren following a 5-day treatment with 600 mg rifampicin or placebo once daily. Inset depicts the same data on a semi-logarithmic scale

Deleted: Mean ± SEM

Fig. 2 Box-and-whisker plots of the C_{max}, AUC and $t_{½}$ values of aliskiren. A single 150 mg oral dose of aliskiren was given to twelve healthy volunteers following a 5-day treatment with 600 mg rifampicin or placebo once daily. The horizontal lines inside the boxes represent the median, the box edges show the lower and upper quartiles, and the whiskers show the 5th and 95th percentiles. Individual data points are given as open (placebo phase) and solid (rifampicin phase) circles

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Fig. 3 Box-and-whisker plots of plasma renin activity in twelve healthy volunteers 0, 4, and 24 after a single 150 mg oral dose of aliskiren following a 5-day treatment with 600 mg rifampicin or placebo once daily. The horizontal lines inside the boxes represent the median, the box edges show the lower and upper quartiles, and the whiskers show the 5th and 95th percentiles. Individual data points are given as open (placebo phase) and solid (rifampicin phase) circles

Deleted: Mean ± SEM plasma renin activity in twelve healthy volunteers after

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Table 1 Pharmacokinetic variables of aliskiren in twelve healthy volunteers after a single 150 mg oral dose of aliskiren following a 5-day treatment with 600 mg rifampicin or placebo once daily

Variable	Placebo phase (control)	Rifampicin phase	% of control (range)	Geometric mea mean differe (95% CI
C_{max} (ng/ml)	179 ± 134	95 ± 55	53% (22-109%)	0.61 (0.41, 0
t_{max} (h)	1 (0.5-5)	0.5 (0.5-5)		
$t_{½}$ (h)	28.4 ± 8.5	24.4 ± 7.4	86% (52-131%)	-4.0 (-9.6, 1
AUC_{0-72} (ng·h/ml)	661 ± 457	270 ± 138	41% (24-81%)	0.45 (0.36, 0
$AUC_{0-\infty}$ (ng·h/ml)	718 ± 501	288 ± 150	40% (24-80%)	0.44 (0.35, 0
Ae (mg)	0.662 ± 0.365	0.326 ± 0.144	49% (27-104%)	0.52 (0.38, 0
Cl_{renal} (l/h)	1.60 ± 0.44	1.69 ± 0.45	106% (74-184%)	1.07 (0.91, 1

Data are given as mean ± SD, t_{max} data as median (range).

CI, Confidence interval; C_{max}, peak plasma concentration; t_{max}, time to C_{max}; $t_{½}$, elimination half-life; AUC_{0-72}, area under the plasma concentration-time curve from 0 to 72 h; $AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 to infinity; Ae, amount excreted into urine within 12 h; Cl_{renal}, renal clearance.

*Mean difference (95% CI).