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Pharmacokinetics of Repeated Oral Doses of Amlodipine and Amlodipine plus Telmisartan in Healthy Volunteers

Joachim Stangier, PhD, and Chung-An P. F. Su, MD

This open-label, crossover study was performed to establish if there is evidence for interaction between telmisartan, an angiotensin II antagonist, and amlodipine, a class II (dihydropyridine) calcium channel antagonist, on the basis of pharmacokinetics and safety. In a two-way crossover trial, 12 healthy Caucasian males were randomized to receive once daily for 9 days oral amlodipine 10 mg with or without oral telmisartan 120 mg. After a washout period of ≥ 13 days, the subjects were switched to the other medication regimen. The geometric means of the primary pharmacokinetic parameters at steady state (day 9) for amlodipine when given alone were the following: maximum plasma concentration (C_{max}) 17.7 ng/mL, area under the plasma concentration-time curve (AUC) 331 ng•h/mL, and renal clearance 39.5 mL/min, with 8% of the total amlodipine dose being excreted. When concomitant telmisartan was given, the respective values were 18.7 ng/mL, 352 ng•h/mL, and 43.0 mL/min, with 9.4% of the total amlodipine dose being excreted renally. The limits

of the 90% confidence intervals (CIs) for the ratios of these steady-state parameters were 0.97 to 1.14 for C_{max} and 0.98 to 1.16 for AUC; both were within the predefined reference range (0.8 to 1.25) for bioequivalence. The high intersubject variability in urinary amlodipine excretion resulted in bioequivalence not being demonstrated for renal clearance. Adverse effects were few, mild to moderate in intensity, and transient whether amlodipine was given alone or with telmisartan. Vital signs, except for blood pressure, and clinical laboratory values were unaffected by either medication. The findings of this study show that concomitant telmisartan and amlodipine may be administered as there is no clinically significant variation in primary pharmacokinetic parameters of amlodipine in the presence of telmisartan, and the safety of the combination is comparable to that of amlodipine alone.

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Hypertension is a widespread condition for which there are a variety of pharmacologic treatments, including diuretics, β -blockers, α_1 -adrenergic receptor antagonists, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II antagonists. The latter two classes of drugs target the renin-angiotensin system, which is known to have a key role in the control of blood pressure and fluid and electrolyte balance.^{1,2} The release of renin from the kidneys, in response to a reduction in blood pressure or plasma sodium concentration, sets off a cascade culminating in the ACE-mediated conversion of angiotensin I

to angiotensin II. Angiotensin II, acting mainly via angiotensin II type 1 (AT_1) receptors, increases blood pressure and also brings about the release of aldosterone, which stimulates sodium retention and therefore increases blood pressure.

Blocking the production of angiotensin II by inhibiting ACE, using drugs such as captopril and lisinopril, provides clinically effective treatment for hypertension,³ but patients can experience side effects. The most frequent of these is a persistent dry cough, which may compromise patient compliance. The cough is thought to be caused by ACE inhibitors preventing the breakdown of bradykinin and substance P to inactive peptides.^{4,5}

An alternative therapeutic approach is to block the pressor effects of the renin-angiotensin system more specifically, thus eliminating the adverse side effects resulting from accumulation of bradykinin and sub-

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stance P.⁶ Angiotensin II receptor antagonists prevent angiotensin II binding to the receptors in arterioles that bring about vasoconstriction.⁷ Telmisartan is a new nonpeptide AT₁ receptor antagonist. It was developed to be active without requiring transformation from an inactive prodrug.⁸ Other features of telmisartan are its long duration of action permitting once-daily dosing and high lipophilicity enabling good tissue penetration.⁸ The chemical structure of telmisartan, which is a substituted benzimidazole rather than a substituted imidazole such as losartan (the first angiotensin II receptor antagonist to be licensed), is such that it binds strongly but reversibly to the AT₁ receptor.^{9,10}

Studies in animals have established that telmisartan has significant antihypertensive, renoprotective, and cardioprotective activity.¹¹⁻¹³ Pharmacokinetic evaluation of telmisartan in young and elderly healthy volunteers and in hypertensive patients has shown that the drug achieves therapeutic concentrations that are maintained with once-daily dosing, owing to the long elimination half-life of approximately 24 hours.¹⁴ Telmisartan is detected almost exclusively as the parent compound in the feces, which is the primary route of excretion.¹⁵ Only about 0.5% of the telmisartan dose is detected in the urine, mainly as the glucuronide conjugate rather than the parent compound. Pharmacokinetic studies also showed that telmisartan is well tolerated when given orally up to a dose of 320 mg, with any treatment-related side effects being generally mild in intensity and transient.^{14,15} As with other angiotensin II receptor antagonists,¹⁶ headache is the most commonly reported treatment-related side effect potentially associated with telmisartan; however, it occurs at a lower incidence than with placebo (telmisartan 9.7% vs. placebo 17.4%).¹⁷

Calcium channel blockers exert their antihypertensive action by preventing the influx of calcium ions into cells. This reduces the availability of calcium for muscular contraction and, consequently, brings about decreased peripheral vascular resistance and reduced blood pressure. Calcium channel blockers also have negative inotropic effects on myocardial cells. The class II agents (i.e., dihydropyridines, such as amlodipine and nifedipine) have a greater selectivity for the vasculature over the myocardium compared with class I agents (i.e., phenylalkylamines, such as verapamil).¹⁸

Amlodipine has a slow onset of action that is believed to be the reason for the lack of treatment-associated reflex tachycardia and lower incidence of vasodilator side effects compared with earlier dihydropyridines. In humans, orally administered amlodipine is readily absorbed (bioavailability 60% to 80%), and peak plasma

concentration is reached within 6 to 8 hours.¹⁸ The volume of distribution is large (21 L/kg), and the drug is 98% bound to plasma proteins.¹⁹ It also has a long duration of action as a result of its slow elimination (in the range of 40 to 60 hours) that permits once-daily dosing.^{19,20} In addition to hypertension, amlodipine is indicated for the treatment of myocardial ischemia associated with stable or vasospastic angina.

As it is possible that telmisartan and amlodipine might be used concomitantly, it is important to establish that there is no pharmacokinetic interaction between the two drugs. The primary pharmacokinetic endpoints used to identify any potential interaction were maximum plasma concentration (C_{max}) of amlodipine, area under the amlodipine plasma concentration-time curve (AUC) at steady state, and renal clearance (CL_r) of amlodipine. This study was also designed to assess the tolerability of a combination of once-daily oral telmisartan 120 mg and amlodipine 10 mg; these doses are the highest doses to be used clinically.

SUBJECTS AND METHODS

Study Population

The 12 healthy male Caucasian volunteers required for the study were enrolled at a single center (Human Pharmacology Center, Boehringer Ingelheim Pharma KG, Biberach, Germany). The participants, who provided written informed consent before enrollment, were free to withdraw from the study at any point. Exclusion criteria were the following: age < 18 or > 50 years; overweight or underweight (BROCA \geq 20%); use of any drugs that might affect the results of the trial within the 5 days preceding administration of the study medications; participation in a trial with an investigational drug within the previous 2 months; drug abuse; alcoholism; heavy smoking, defined as 15 or more cigarettes or three or more pipes per day; inability to abstain from smoking on study days; excessive physical activity within the 5 days preceding administration of study medication; donation of blood within the 2 months preceding study drug administration; previous gastrointestinal tract surgery, other than appendectomy; any clinically relevant deviation in electrocardiogram (ECG); supine systolic blood pressure < 110 mmHg or diastolic blood pressure < 60 mmHg at screening; subjective symptoms of orthostatic events; hypersensitivity to telmisartan or amlodipine or to related drugs; any clinical laboratory value outside the clinically accepted reference range; and any other disease or abnormality of clinical relevance.

Study Design

The study was carried out in accordance with the principles of the Declaration of Helsinki and all applicable German and European Community regulatory requirements. Medical ethics committee approval was obtained before the study began. The study was open label and of a two-way, crossover, randomized design. The subjects were screened 7 to 14 days before their admission to the study center, which was on the day before administration of the first dose of medication. Starting on day 1, the subjects received single daily oral doses of either amlodipine 10 mg, given as two 5 mg tablets, or amlodipine 10 mg plus telmisartan 120 mg (one 80 mg plus one 40 mg tablet) for 9 days; the medication was randomly assigned. Tablets were taken, under supervision, with 150 mL tap water and had to be swallowed within 40 seconds. The subjects, who remained in the study center until they had received the fourth dose on the morning of day 4 of the study, received standardized meals at set times. Thereafter, they returned to the study center in the morning on days 5, 6, 7, and 8. In the evening of day 8, they were readmitted to the center and remained there until discharge on the morning of day 10. After a washout period of ≥ 13 days, the subjects were switched to the other medication, and the procedure was repeated. Subjects also returned to the center for an examination on either day 12 or 13 of the second medication period.

During the study, the only concurrent therapy permitted was for emergency or symptomatic purposes. In the event of severe arterial hypotension, catecholamines were to be given.

Sample Collection and Analysis

Blood samples (9 mL) were collected in EDTA via an indwelling catheter inserted into an antecubital vein. Plasma was isolated by centrifugation and stored at -20°C until assay. Samples were taken for assay of telmisartan and amlodipine on day 1 (immediately before and at 0.5, 1, 1.5, 2, 4, 6, 8, 10, and 12 hours after administration of medication) and on day 9 (before and at 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 24, 48, 72, and 96 hours after administration). On the morning of days 2 to 8, samples were obtained to determine trough levels. Telmisartan concentrations were assessed using validated, automated column-switching high-performance liquid chromatography. Amlodipine concentrations were determined using gas chromatography/mass spectrometry with negative-ion chemical ionization and single-ion recording.

Other Tests

All subjects underwent a complete medical examination at screening, and this was repeated on day 12 or 13 after the second medication period. Blood and urine samples for hematology, clinical chemistry, and urinalysis were collected at screening, before the administration of the first dose in each of the two periods of the study, and on day 12 or 13 after the second medication period. Standard clinical laboratory variables were assessed. Laboratory variables outside the reference range at the final examination (day 12/13) were followed up until they had returned to normal or had been otherwise explained. Blood pressure, pulse rate, and ECG were monitored at regular intervals throughout the study.

The occurrence of adverse events, which were defined as all complaints of reduced well-being, subjective and objective symptoms, clinically significant changes in laboratory results, intercurrent diseases, and accidents, was assessed by investigator observation and volunteered information provided by subjects when interviewed at each visit to the study center. All events were recorded whether or not they were considered to be related to the study medications.

Pharmacokinetic Parameters

Measured plasma concentrations of telmisartan and amlodipine were used to derive the following pharmacokinetic parameters: the AUC within one steady-state interval, calculated using the trapezoid rule (AUC_{ss} , $\text{ng}\cdot\text{h}/\text{mL}$); AUC from 0 to 24 hours, calculated using the trapezoid rule (AUC_{0-24} , $\text{ng}\cdot\text{h}/\text{mL}$); C_{max} on day 1 of the medication period ($C_{\text{max,D1}}$, ng/mL); C_{max} at steady state ($C_{\text{max,ss}}$, ng/mL); time after the first, single extravascular dose to C_{max} ($t_{\text{max,D1}}$, h); time after a single extravascular dose at steady state to reach $C_{\text{max,ss}}$ ($t_{\text{max,ss}}$, h); elimination half-life associated with the terminal slope (λ_z) of the semilogarithmic drug concentration-time curve, calculated using the formula $t_{1/2} = \ln 2/\lambda_z$ ($t_{1/2}$, h); mean residence time of drug molecules in the body (MRT, h); total clearance of the drug from plasma after oral dose (CL_{tot}/f , mL/min); apparent volume of distribution during the terminal λ_z phase (oral administration) (V_z/f , L); and accumulation factors, that is, ratio of $\text{AUC}_{\text{ss}}/\text{AUC}_{0-24}$ ($R_{\text{A(AUC)}}$) and of $C_{\text{max,ss}}/C_{\text{max,D1}}$ ($R_{\text{A(Cmax)}}$). In addition, the following parameters were assessed for amlodipine only: proportion of drug excreted renally within one steady-state interval ($A_{\text{e,ss}}$, % dose) and CL_r (mL/min). All pharmacokinetic parameters, other than C_{max} and t_{max} , which were directly observed, were

derived by the noncompartmental methods in the program TopFit (Gustav Fischer Verlag, Stuttgart, Germany).

Statistical Analysis

The primary endpoints of the study were $C_{\max,ss}$, AUC_{ss} , and CL_r for amlodipine. The secondary endpoints were $C_{\max,ss}$ and AUC_{ss} for telmisartan and C_{\max} , t_{\max} , MRT_{tot} , $R_{A(AUC)}$, $R_{A(C_{\max})}$, t_{\max} , and AUC_{0-24} for both amlodipine and telmisartan. A multiplicative model was used for the analysis of variance (ANOVA).²¹⁻²³ All pharmacokinetic parameters, except t_{\max} , were log transformed prior to ANOVA. Treatment, period, sequence, and subject within sequence were included in the ANOVA model. The 90% confidence intervals (CIs) for the treatment ratios of amlodipine + telmisartan/ amlodipine of the primary endpoints ($C_{\max,ss}$, AUC_{ss} , and CL_r for amlodipine) were calculated. The predefined criterion set for demonstrating the absence of an interaction between telmisartan and amlodipine was a 90% CI for the treatment ratios of between 0.8 and 1.25 for primary endpoints of amlodipine. An alpha adjustment was not performed. The 90% CIs for t_{\max} were calculated using a nonparametric test.²⁴

All mean values of pharmacokinetic parameters were calculated as geometric means.

RESULTS

Subject Demographics

A total of 12 healthy Caucasian males were enrolled and completed the study. The demographic characteristics of these subjects are shown in Table I.

Pharmacokinetics of Amlodipine

Mean trough plasma concentrations of amlodipine when given alone increased from 3.0 ng/mL on day 2 to 10.2 ng/mL on day 9 of the study and from 3.4 ng/mL on day 2 to 11.5 ng/mL on day 9 when coadministered with telmisartan, indicating accumulation of amlodipine. Figure 1 shows a comparison of mean plasma amlodipine concentration-time profiles on days 1 and 9 when given with or without telmisartan.

Values of amlodipine pharmacokinetic parameters are shown in Table II. When amlodipine 10 mg was given alone, the geometric mean $C_{\max,D1}$ was 5.4 ng/mL, with a median t_{\max} of 7.0 hours and a mean AUC_{0-24} of 90.5 ng•h/mL. On the morning of day 9, before drug administration, the degree of steady state reached was calculated as 90%. On day 9, mean $C_{\max,ss}$ was 17.7 ng/mL

Table I Mean Demographic Data of the 12 Healthy Male Caucasian Volunteers Who Were Enrolled in and Completed the Study

	Mean	SD	Range
Age (years)	34.7	9.8	21-49
Height (cm)	181.2	4.5	175-180
Weight (kg)	82.7	10.8	64-102
BROCA (%)	1.9	12.4	-16-25 ^a

a. One subject exceeded the BROCA index limit of 20% by 5% (+25%), but this was considered a minor deviation by the investigator, so the subject was not excluded.

and the $R_{A(C_{\max})}$ was 3.3, indicating significant accumulation of amlodipine. At steady state, mean AUC_{ss} was 331 ng•h/mL with a ratio of accumulation ($R_{A(AUC)}$) of 3.7. Elimination of the drug was slow; the geometric mean terminal elimination half-life was 55.9 hours. Of the total dose given over the 9 days of the study, 8.0% was excreted via the urine over a 24-hour period.

When amlodipine was coadministered with telmisartan 120 mg, the mean $C_{\max,D1}$ of amlodipine was 5.6 ng/mL. The mean value of $C_{\max,ss}$ was 18.7 ng/mL, with a median t_{\max} of 8.0 hours and a mean AUC_{0-24} of 95.8 ng•h/mL. The mean AUC_{ss} was 352 ng•h/mL, and the $R_{A(AUC)}$ was 3.7. Mean terminal elimination half-life was 52.0 hours, and 9.4% of the total dose of amlodipine was excreted in urine over one steady-state interval on day 9 of the study.

Ratios comparing the values of two of the three primary endpoint pharmacokinetic parameters for amlodipine with and without coadministration of telmisartan— $AUC_{ss(amlodipine + telmisartan)}/AUC_{ss(amlodipine)}$ (1.06) and $C_{\max,ss(amlodipine + telmisartan)}/C_{\max,ss(amlodipine)}$ (1.06)—gave 90% CIs of 0.98 to 1.16 and 0.97 to 1.14, respectively, which were within the accepted range (0.8 to 1.25) for bioequivalence (i.e., no interaction); the range of values for these and other pharmacokinetic variables is shown in Table III. The ratio for the third primary endpoint parameter, $CL_{r(amlodipine + telmisartan)}/CL_{r(amlodipine)}$, was 1.09, with a 90% CI of 0.79 to 1.50. Due to the high intersubject variability in the urinary excretion of amlodipine, the bioequivalence criterion was not met for this parameter.

Pharmacokinetics of Telmisartan

Plasma concentrations of telmisartan were highly variable. Figure 2 shows a comparison of mean plasma telmisartan concentrations on days 1 and 9 of the medication period. After the first dose of telmisartan, the

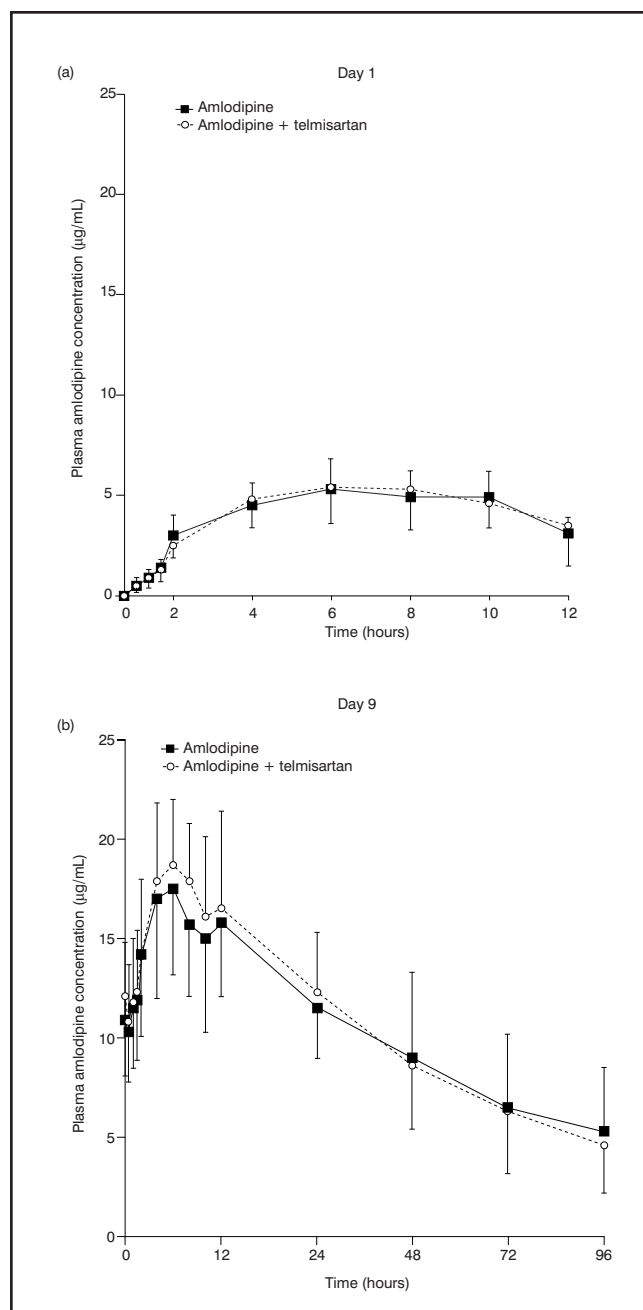


Figure 1. Geometric mean plasma amlodipine concentrations-time profiles on (a) day 1 and (b) day 9 of administration in subjects receiving once-daily amlodipine 10 mg with or without once-daily telmisartan 120 mg.

mean $C_{\max, D1}$ was 311 ng/mL (range: 58.1-1310 ng/mL); the median $t_{\max, D1}$ was 1.25 hours. Steady state was reached after 5 days of telmisartan administration. On day 9, $C_{\max, ss}$ was 494 ng/mL. The mean trough plasma

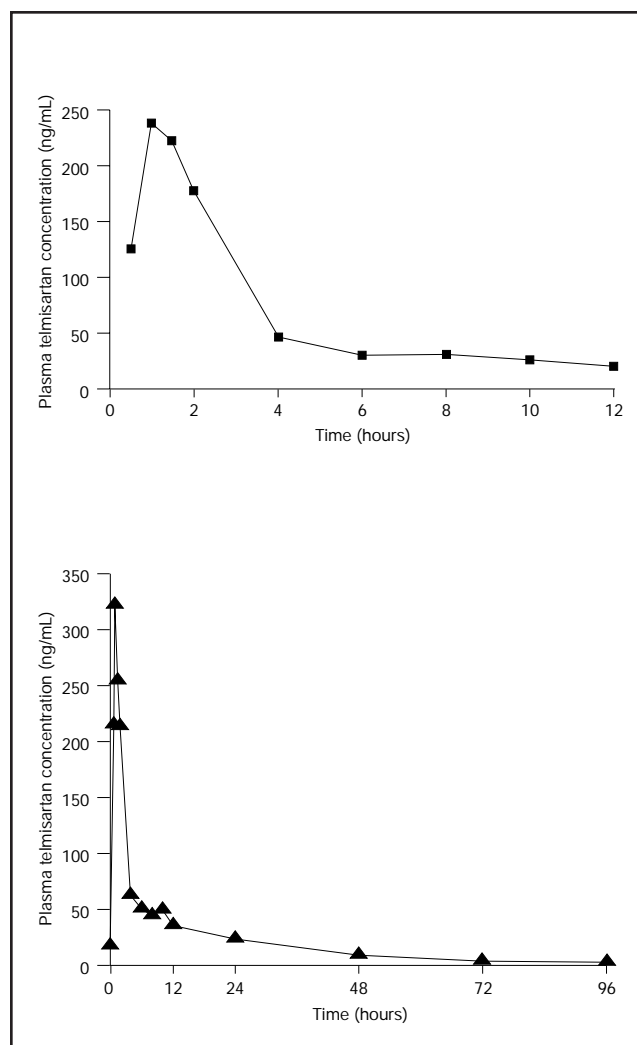


Figure 2. Geometric mean plasma telmisartan concentration-time profiles on (top) day 1 and (bottom) day 9 in subjects receiving once-daily amlodipine 10 mg plus telmisartan 120 mg.

telmisartan concentration on day 9 (i.e., immediately before the last dose) was 17.4 ng/mL. The AUC_{0-24} on day 1 was 1000 ng•h/mL, whereas AUC_{ss} at day 9 was 1590 ng•h/mL. The R_A ratios calculated using AUC and C_{\max} values were both 1.6. The mean $t_{1/2}$ was 19 hours (range: 10.9-26.6 hours). The mean total clearance (CL_{tot}/f) was 1260 mL/min.

Evaluation of Safety

All 12 subjects, who completed both medication periods and received 18 doses of amlodipine 10 mg and 9 doses of telmisartan 120 mg, were included in the eval-

Table II Geometric Mean Pharmacokinetic Parameters for Amlodipine Given Alone or in Combination with Telmisartan

Parameter	Amlodipine (n = 12)		Amlodipine + Telmisartan (n = 12)	
	Geometric Mean	gCV (%)	Geometric Mean	gCV (%)
$C_{\max,D1}$ (ng/mL)	5.4	27.0	5.6	31.8
$t_{\max,D1}$ (h)	7.0 ^a	—	8.0 ^a	—
$C_{\max,ss}$ (ng/mL) ^b	17.7	29.6	18.7	29.6
$t_{\max,ss}$ (h)	6.0 ^a	—	6.0 ^a	—
AUC_{0-24} (ng•h/mL)	90.5	22.9	95.8	27.0
AUC_{ss} (ng•h/mL) ^b	331	32.1	352	30.9
$t_{1/2}$ (h)	55.9	39.2	52.0	33.0
MRT (h)	77.7	34.5	70.4	27.8
CL_{tot}/f (mL/min)	504	32.1	474	31.0
V_z/f (L)	2440	38.4	2130	32.0
$R_{A(AUC)}$	3.7	22.8	3.7	18.4
$R_{A(C_{\max})}$	3.3	27.0	3.4	18.6
$A_{e,ss}$ (% dose)	8.0	51.6	9.4	33.2
CL_r (mL/min)	39.5 ^b	51.0	43.0	37.8

gCV, coefficient of variation of the geometric mean; AUC_{ss} , area under concentration-time curve within one steady-state interval; AUC_{0-24} , AUC from 0 to 24 hours, calculated using the trapezoid rule; $C_{\max,D1}$, C_{\max} on day 1 of the medication period; $C_{\max,ss}$, C_{\max} at steady state; $t_{\max,D1}$, time after the first single extravascular dose to C_{\max} ; $t_{\max,ss}$, time after a single extravascular dose at steady state to reach $C_{\max,ss}$; MRT, mean residence time of drug molecules in the body; CL_{tot}/f , total clearance of drug from plasma after oral dose; V_z/f , apparent volume of distribution during the terminal phase; $R_{A(AUC)}$, AUC_{ss}/AUC_{0-24} ; $R_{A(C_{\max})}$, ratio of $C_{\max,ss}/C_{\max,D1}$; $A_{e,ss}$, proportion of drug excreted renally within one steady-state interval; CL_r (mL/min). All pharmacokinetic parameters, other than C_{\max} and t_{\max} , which were directly observed, were derived by noncompartmental methods.

a. Median values.

b. Primary endpoint parameters.

uation of safety. One subject with conjunctivitis required concomitant drug therapy (tramazolin), but this was not considered sufficient reason for the exclusion of this subject.

During the study, a total of 36 adverse events were experienced by 11 subjects; 1 subject did not report any such events. All the events were described as being mild to moderate in intensity, and there were no serious adverse events. Of these 36 adverse events, 31 were deemed by the investigators to be related to study medications. The most commonly reported adverse event was headache, reported by 11 subjects while receiving a combination of amlodipine and telmisartan and by 10 when amlodipine was administered alone; all these events were considered by the investigator to be related to study medication.

Adverse events that in the opinion of the investigator were related to study medication were more common with the combination medication: amlodipine given with telmisartan, 19 events; amlodipine administered alone, 12 events. All adverse events abated without sequelae.

Hematologic screening did not reveal any clinically significant outlying values; deviations observed were

Table III Ratios of Primary Amlodipine Pharmacokinetic Parameters for Amlodipine plus Telmisartan: Amlodipine and 90% Confidence Interval (CI) Limits by ANOVA

Parameter	Ratio	Upper Limit ^a	Lower Limit ^a
$C_{\max,ss}$	1.06	0.97	1.14
AUC_{ss}	1.06	0.98	1.16
CL_r	1.09	0.79	1.50

a. Criterion predefined for bioequivalence of amlodipine under the two treatments was a 90% CI range of 0.8 to 1.25 for ratios of the primary endpoint parameters.

few and minor and were within seasonal influences or normal daily variations. Similarly, blood chemistry and urinalysis variables showed only a few single outlying values that were not considered clinically significant. No changes indicative of an effect of the study medications on any parameter were evident. Monitoring of ECG did not reveal any clinically relevant abnormalities. At the time points tested, most subjects showed a decrease in blood pressure that was some-

times sustained and not always associated with an increase in pulse rate; however, the blood pressure response was highly variable between individuals and appeared to be independent of medication type or the sequence of medication. Comparison of physical examinations conducted at baseline and after the study did not reveal any clinically significant changes.

DISCUSSION

This study was designed to establish whether concomitant administration of telmisartan 120 mg affects the pharmacokinetics of once-daily amlodipine given at a dose of 10 mg.

An increase in the AUC of amlodipine was detected on day 9 in comparison with day 1, and the $R_{A(AUC)}$ was 3.7. There was also a greater than threefold increase in C_{max} values between days 1 and 9. The accumulation of amlodipine can be explained by its slow elimination: the terminal $t_{1/2}$ in previous studies has been found to be in the range 40 to 60 hours^{20,25} and in this study was in excess of 50 hours when given with or without telmisartan.

The primary endpoint variables of amlodipine on which the assessment of interaction was based were AUC_{ss} , $C_{max,ss}$, and CL_r . Values for the pharmacokinetic parameters in this study are consistent with previously reported values. Prior studies, for example, have shown that amlodipine steady state is achieved after 7 to 8 days' administration.^{20,25} The statistical criterion, which was set before conducting the study to indicate a lack of interaction, was met for both AUC_{ss} and $C_{max,ss}$.²¹⁻²³ On the basis of these findings, it can be concluded that telmisartan when given concurrently does not increase plasma concentrations of amlodipine to a clinically relevant extent. Because of the high variability of amlodipine renal excretion within and between individuals (intraindividual coefficient of variation 48%), the slightly increased urinary excretion of amlodipine (9%) when telmisartan was concomitantly administered was not considered to be of any clinical significance.

The pharmacokinetic profile of telmisartan in this study, when given with amlodipine, corresponded well with that seen in previous studies.^{14,15} Although the study was not designed specifically to assess whether concomitant amlodipine therapy alters the pharmacokinetics of telmisartan, there was no evidence of any marked effect of amlodipine on telmisartan's pharmacokinetic profile. The elimination half-life was in the range of 10.9 to 26.6 hours, which is consistent with a value of approximately 24 hours ob-

served at steady state in mild to moderate hypertensive patients.²⁶

Amlodipine, whether given alone or in combination with telmisartan, was well tolerated, with only few minor, transient adverse effects. This is to be expected on the basis of clinical experience with amlodipine²⁷⁻²⁹ and earlier studies with telmisartan.¹⁷ In clinical trials involving more than 1500 patients treated with telmisartan at doses of 20 to 160 mg for up to 26 weeks, the overall incidence of adverse events (irrespective to their causal relationship to the medication) reported with telmisartan was comparable to those for placebo, atenolol, lisinopril, and enalapril (Boehringer Ingelheim, data on file). Headache has consistently been shown to be the most frequently experienced adverse event, but it occurred no more frequently in the patients treated with telmisartan than in those receiving placebo. The current study provides evidence that combining telmisartan and amlodipine at high doses did not have any detrimental effect on the safety of either medication. As would be expected, amlodipine and amlodipine in combination with telmisartan lowered blood pressure, but individual responses varied and were not related to the treatment regimen (i.e., whether the subject was receiving amlodipine alone or in combination with telmisartan) or the sequence of treatment. Close observation of the subjects throughout the present study did not reveal any evidence of reflex tachycardia and rhythm disorders, which are typical signs of amlodipine overdosing.³⁰

From the findings of this study, it can be concluded that there is no pharmacokinetic evidence of any clinically relevant interaction between amlodipine and telmisartan when administered concomitantly. Monitoring of the safety profiles of amlodipine when given alone and in combination with telmisartan also suggests that there is no interaction between the two antihypertensive agents and that the combination medication is well tolerated. The results suggest that, if given in combination, both amlodipine and telmisartan may be administered once daily without any need to adjust the dose of either agent.

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